Disputes & Debates: Editors' Choice

Editors' Note: Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players

In their retrospective autopsy series of 35 former football and hockey players, Schwab and colleagues found that half (49%) had histopathologic evidence of chronic traumatic encephalopathy (CTE) based on 2015 NINDS consensus criteria. Among their findings, the investigators reported no significant association between CTE risk and surrogate markers for lifetime exposure to sport and aggressive role/style of play, although the study was limited by its small sample size. The investigators conclude that factors other than cumulative physical contact and injury insufficiently explain the risk of CTE. Dr. Mez and colleagues compared these results from their recently published autopsy series of 266 former football players, in which the odds of CTE increased by 30% for every year of football played. In their work, Mez et al. also report no effect of player position (similar to the results of Schwab et al.); however, Mez et al. indicate that the findings reported here were too underpowered to detect any significant relationship between CTE and position or exposure duration. Furthermore, comments by Mez as well as Dr. Dams-O'Connor highlight important limitations in selection of the independent variables, particularly that the surrogate marker for duration of exposure (age at retirement) inadequately captures preprofessional duration of play. Preprofessional exposure and head injury have been shown in some studies to pose considerable risk as injuries accumulate in the developing brains of children and adolescents. The investigators acknowledge the limitation in statistical power, but reiterate a major conclusion that even subjects with relatively brief exposure to contact sports remain at risk of this histopathologic diagnosis, whereas others with protracted exposure may not develop this brain pathology.

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Reader Response: Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players

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Schwab et al.[1] did not find a statistically significant association between position played and career duration and autopsy-confirmed chronic traumatic encephalopathy (CTE) in elite football and ice hockey players. The study's limitations associated with statistical power, measurement error, and sample selection hinder interpretation of the presented data. The authors state that a sample size of about 14 is required "to detect a 50% difference in CTE diagnoses between groups with 80% power."[1] Player position is unlikely to account for a 50% difference in CTE status based on work by Mez et al.,[2] which indicates no effect for player position in >250 former

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football players. Assuming that player position accounts for a much smaller effect in CTE status, such as 10%, a sample size of approximately 400 would be needed. In Mez et al., each additional year of football play accounted for a 30% increase in odds of CTE. Given the sample size and standard deviation reported for career duration in this article, the authors were only 80% powered to detect an effect 2.4 times larger and were only 55% powered to detect the effect presented in Mez et al.

In addition, career duration was problematically measured. The authors state that "age of retirement was used as an indicator of overall career duration."[1] However, 2 elite athletes can retire at the same age, but have very different career lengths—specifically in football, where players begin tackling as early as age 4 years and as late as age 20 years.[3] Furthermore, the authors equate football players with ice hockey players, which are 2 sports with very different repetitive head impact (RHI) exposure profiles.[4] Given these concerns with statistical power and appropriate measurement of RHI exposure, we question the validity of the reported results.

1. Schwab N, Wennberg R, Grenier K, Tartaglia C, Tator C, Hazrati LN. Association of position played and career duration and chronic traumatic encephalopathy at autopsy in elite football and hockey players. *Neurology.* 2021;96(14):e1835-e1843.
2. Mez J, Daneshvar DH, Abdolmohammadi B, et al. Duration of American football play and chronic traumatic encephalopathy. *Ann Neurol.* 2020;87(1):116-131.
3. Alosco ML, Mez J, Tripodis Y, et al. Age of first exposure to tackle football and chronic traumatic encephalopathy. *Ann Neurol.* 2018; 83(5):886-901.
4. O'Connor KL, Rowson S, Duma SM, Broglio SP. Head-impact-measurement devices: a systematic review. *J Athl Train.* 2017;52(3): 206-227.

Author Response: Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players

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We have no difference of opinion with Mez et al. regarding the statistical power issues, and their description of the relevant limitations is an accurate recapitulation of our own.[1] We did not intend to suggest, with a cohort of this size, that there could not be some small differences in chronic traumatic encephalopathy (CTE) risk based on position; of course, smaller differences might be found with larger sample sizes. Whether differences <50% would have practical relevance for elite collision sport athletes is an open question. With respect to career duration measurement, we also analyzed career duration at the highest level played, but this analysis was removed from the article in response to reviewers' reasonable suggestions that the information was redundant to the age of retirement data. However, a summary line remains in table 1.[1]

Our sport-specific interest in this area has been drawn to the level of the individual athlete, and the inexplicable fact that some players in our cohort with no more than a 4-year university football or hockey career developed CTE, whereas others who played the same position in the same sport did not, despite professional careers lasting 10–15 seasons, in some cases.

Mez et al. state that we "equate football players with ice hockey players," which is certainly not the case. The fact that former elite athletes in these 2 very different collision sports should show the same 50% prevalence of CTE at autopsy is something we interpret as further support for our main conclusion that individual susceptibility to CTE may be a risk factor of paramount importance.

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1. Schwab N, Wennberg R, Grenier K, Tartaglia C, Tator C, Hazrati LN. Association of position played and career duration and chronic traumatic encephalopathy at autopsy in elite football and hockey players. *Neurology.* 2021;96(14):e1835-e1843.

Reader Response: Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players

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Schwab et al.[1] rigorously describe postmortem neuropathology in 35 elite athletes. Brain tissue from well-characterized cases remains scarce, demanding creative approaches to data collection. The inadequacy of web-based methods alone is evident in the authors' inability to define their primary exposure, career duration, as well as incomplete characterization of isolated traumatic brain injury (TBI). Open-ended questions yielded 0% prevalence of more severe TBI—a stark contrast to population-based studies that report >20% prevalence of TBI with loss of consciousness.[2] The authors assumed, but did not quantify mild TBI exposure, suggesting an accommodation of rigor to data available. That lifetime head trauma exposure is so poorly enumerated obscures investigation into the contributions of isolated TBI to the neuropathology of repetitive trauma and the exposure thresholds that confer elevated neurodegenerative disease risk. The value of a structured TBI screening tool cannot be understated,[3] particularly for identification of remote events. Retrospective family interview is sometimes the best, and often the only method for postmortem characterization, and has contributed greatly to our understanding of clinical dementia and cerebrovascular disease.[4,5] Common Data Elements for postmortem characterization of TBI exposure are now under development; their adoption will invite replication of this study's results with more complete data and an even greater scientific impact.

1. Schwab N, Wennberg R, Grenier K, Tartaglia C, Tator C, Hazrati LN. Association of position played and career duration and chronic traumatic encephalopathy at autopsy in elite football and hockey players. *Neurology.* 2021;96(14):e1835-e1843.
2. Yi H, Corrigan JD, Singichetti B, et al. Lifetime history of traumatic brain injury and current disability among OH adults. *J Head Trauma Rehabil.* 2018;33(4):E24-E32.
3. Dams-O'Connor K, Cantor JB, Brown M, Dijkers MP, Spielman LA, Gordon WA. Screening for traumatic brain injury: findings and public health implications. *J Head Trauma Rehabil.* 2014;29(6):479-489.
4. Au R, Seshadri S, Knox K, et al. The Framingham Brain Donation Program: neuropathology along the cognitive continuum. *Alzheimer Res.* 2012;9(6):673-686.
5. Halanych JH, Shuaib F, Parmar G, et al. Agreement on cause of death between proxies, death certificates, and clinician adjudicators in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Am J Epidemiol.* 2011;173(11):1319-1326.

Author Response: Association of Position Played and Career Duration and Chronic Traumatic Encephalopathy at Autopsy in Elite Football and Hockey Players

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We completely share Dr. Dams-O'Connor's hope for replication studies and increasingly complete and accurate data.[1] In our cohort of 35 former elite athletes, we did not think it surprising to have uncovered no history of moderate-severe traumatic brain injury (TBI)—as commonly defined[2]—nor did we find it to be in stark contrast to population-based studies. Indeed, our reading of the study cited to suggest a high (>20%) prevalence in the general population of more severe TBI is that only 192/6,998 respondents (2.7%) recollected a TBI

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with loss of consciousness >30 minutes—the definition used in that study for moderate-severe TBI.[3] At that rate (about 1/37), it would not be unexpected to find 0% prevalence in a cohort of 35 individuals. Moreover, from the data cited on intercollegiate athletes using the Brain Injury Screening Questionnaire, showing that 12/90 recollected a TBI with loss of consciousness lasting several minutes to an hour, interpreted as clinically significant TBI, it cannot be ascertained whether any of those individuals had a moderate, as opposed to a mild, TBI.[4] In our common quest for scientific rigor, it is important that the value of a structured TBI screening tool be neither understated nor overstated.

1. Schwab N, Wennberg R, Grenier K, Tartaglia C, Tator C, Hazrati LN. Association of position played and career duration and chronic traumatic encephalopathy at autopsy in elite football and hockey players. *Neurology*. 2021;96(14):e1835-e1843.
2. Wennberg R, Hiploylee C, Tai P, Tator CH. Is concussion a risk factor for epilepsy? *Can J Neurol Sci*. 2018;45(3):275-282.
3. Yi H, Corrigan JD, Singichetti B, et al. Lifetime history of traumatic brain injury and current disability among Ohio adults. *J Head Trauma Rehabil*. 2018;33(4):e24-e32.
4. Dams-O'Connor K, Cantor JB, Brown M, Dijkers MP, Spielman LA, Gordon WA. Screening for traumatic brain injury: findings and public health implications. *J Head Trauma Rehabil*. 2014;29(6):479-489.

CORRECTIONS

Convexity Subarachnoid Hemorrhage in Lobar Intracerebral Hemorrhage

A Prognostic Marker

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In the article "Convexity Subarachnoid Hemorrhage in Lobar Intracerebral Hemorrhage: A Prognostic Marker" by Raposo et al.,[1] the fourth author's name should appear as "Michelle A. Onyekaba," with no degree listed. The authors regret the error.

Reference

1. Raposo N, Charidimou A, Roongpiboonsopit D, et al. Convexity subarachnoid hemorrhage in lobar intracerebral hemorrhage: a prognostic marker. *Neurology*. 2020;94(9):e968-e977.

Association of Gray Matter Atrophy Patterns With Clinical Phenotype and Progression in Multiple Sclerosis

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In the article "Association of Gray Matter Atrophy Patterns With Clinical Phenotype and Progression in Multiple Sclerosis" by Rocca et al.,[1] the first sentence of the Abstract under Objectives should read "Gray matter (GM) involvement is clinically relevant in multiple sclerosis (MS)." The publisher regrets the error.

Reference

1. Rocca MA, Valsasina P, Meani A, et al. Association of gray matter atrophy patterns with clinical phenotype and progression in multiple sclerosis. *Neurology*. 2021;96(11):e1561-e1573.

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