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Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players

OBJECTIVE: Cerebral concussion is common in collision sports such as football, yet the chronic neurological effects of recurrent concussion are not well understood. The purpose of our study was to investigate the association between previous head injury and the likelihood of developing mild cognitive impairment (MCI) and Alzheimer's disease in a unique group of retired professional football players with previous head injury exposure.

METHODS: A general health questionnaire was completed by 2552 retired professional football players with an average age of 53.8 (±13.4) years and an average professional football playing career of 6.6 (± 3.6) years. A second questionnaire focusing on memory and issues related to MCI was then completed by a subset of 758 retired professional football players (≥50 yr of age). Results on MCI were then cross-tabulated with results from the original health questionnaire for this subset of older retirees.

RESULTS: Of the former players, 61% sustained at least one concussion during their professional football career, and 24% sustained three or more concussions. Statistical analysis of the data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, $df = 2$, $P = 0.02$) and self-reported significant memory impairments ($\chi^2 = 19.75$, $df = 2$, $P = 0.001$). Retired players with three or more reported concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of reported significant memory problems compared with retirees without a history of concussion. Although there was not an association between recurrent concussion and Alzheimer's disease, we observed an earlier onset of Alzheimer's disease in the retirees than in the general American male population

CONCLUSION: Our findings suggest that the onset of dementia-related syndromes may be initiated by repetitive cerebral concussions in professional football players.

KEY WORDS: Alzheimer, Concussion, Mild cognitive impairment, Retired professional football players

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Traumatic brain injury (TBI) is an important public health concern, as each year more than 1.2 million Americans suffer head injury (26). More than 50,000 head-related injuries result in a fatality each year in the United States, whereas the overwhelming majority of head injuries are classified as mild traumatic brain injuries that can result in significant cognitive, emotional, and functional disabilities (26). TBI has been identified as a potential risk factor for the occurrence (or early expression) of neurodegenerative dementing disorders, including Alzheimer's disease (AD) disease and Parkinson's syndrome, and other psychiatric disorders such as clinical depression (8, 13, 21, 25, 28, 31, 35–37, 40). Still, other research findings have not shown this association between TBI and dementia (1, 3, 6, 7, 17, 19, 33, 42). Guo et al. (9) suggested that the severity of head injury is related to the magnitude of AD risk, and that the risk of AD associated with head injury involving loss of consciousness was approximately double that associated with head injury without loss of consciousness. However, they reported that even head injury without loss of conscious-

ness significantly increased the risk of AD relative to no head injury (9).

Mild cognitive impairment (MCI) is a recently established diagnostic classification typically applied to older individuals who exhibit some evidence of cognitive decline (usually in the domain of memory) and perform below expected levels on formal neurocognitive testing, but who have not exhibited a sufficient degree of impairment and/or functional decline to meet diagnostic criteria for dementia (30). MCI is often conceptualized as a transitional state between the cognitive changes of normal aging and dementia, with most recent studies estimating that 10 to 20% of MCI patients convert to a more advanced stage labeled as "dementia" each year, compared with healthy controls who convert at a rate of 1 to 2% per year (5, 22, 39). The majority of patients with MCI who convert to dementia are subsequently diagnosed with probable AD, although a significant percentage is diagnosed with vascular dementia (23). The identification of risk factors for the onset of MCI, and for the conversion of MCI to dementia, is an important step in developing strategies for the prevention and early treatment of these disorders, especially with the emergence of various dementia treatment agents thought to provide the greatest therapeutic yield earliest in the disease process. Although head trauma has been linked to irreversible cognitive deficits (24, 29, 30), its role in causing eventual MCI or AD is less clear. Mayeux et al. (20) reported a 10-fold increase in the risk of developing AD among those individuals who tested positive for the ApoE e4 gene and had a history of TBI, compared with only a two-fold increase in risk with the ApoE e4 gene alone. Other authors have described a genetic vulnerability and redistribution of neurofilaments after TBI resulting from rotational acceleration of the head in the nonathletic population (12, 27).

The relatively high rate of concussive brain injuries in contact sports affords a unique opportunity for exploring both the immediate and long-term consequences of concussion. More than 300,000 sport-related concussions, many of which are recurrent injuries, occur annually in the United States (38). Unfortunately, the long-term effects of these concussions remain largely unclear. Organized sports, however, provides for a unique laboratory for studying the influence of recurrent mild TBI on dementia-related syndromes such as MCI and AD. The sports literature has connected ApoE e4 with chronic TBI in boxers (16), and other studies have shown that the repeated head trauma experienced by boxers can lead to the development of dementia pugilistica—punch drunk syndrome (32). This literature has also carefully defined the neuropathology of dementia pugilistica as involving numerous neurofibrillary tangles in the absence of plaques, in contrast to the profusion of tangles and plaques seen in AD. Lower cognitive performance has also been found in older football players with the ApoE e4 gene, suggesting that there may be an association between these dementia syndromes and either recurrent TBI or recurrent subconcussive contacts to the head (18). The purpose of our study was to investigate the association between previous head injury and the likelihood of developing MCI and/or AD in a unique group of individuals, namely retired professional football players, who have previous head injury exposure.

PATIENTS AND METHODS

A diverse group of retired professional football players were studied, including recent retirees and those who played professional football before World War II. All participants played a minimum of two seasons of professional football. We studied this group using two self-report questionnaires: a general health survey and a follow-up instrument specifically targeting cognitive decline. It was explained at the beginning of the survey that participants would not be identified and that research records would be kept confidential. By completing and submitting the survey, participants were acknowledging that they agreed to take part in this research study.

General Health Questionnaire

The general health questionnaire was first sent to all living members of the National Football League Retired Player's Association (n = 3683) through the Center for the Study of Retired Athletes. The questionnaire asked a variety of questions about musculoskeletal, cardiovascular, and neurological conditions that the retired player experienced during and after his football career. It included questions about the number of concussions sustained during their professional football career (concussion history) and the prevalence of diagnosed medical conditions such as depression, Parkinson's disease, AD, and schizophrenia. Previous concussion was based on the player's retrospective recall of injury events and was defined on the questionnaire as an injury resulting from a blow to the head that caused an alteration in mental status and one or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, trouble sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, and difficulty concentrating. Additionally, the questionnaire included the SF-36 Measurement Model for Functional Assessment of Health and Well-Being, which addresses how well the retired athlete functions with activities of daily living (41). From the SF-36, we calculated a physical health composite score, which includes scores of physical functioning, role physical, bodily pain, and general health, as well as a mental health component score, which includes scores of vitality, social functioning, role emotional, and mental health. These scores were compared with age- and gender-specific population-based norms established by previous researchers (41).

We initially mailed the general health questionnaire in May 2001, followed by remailings to nonrespondents in August 2001 and February 2002. We then began telephoning nonrespondents at different times of the day and completed the questionnaire over the telephone. We then conducted a reliability check of the general health questionnaire by readministering the instrument to 25 of the original respondents 18 to

24 months later to establish a high level of agreement between selected responses.

Mild Cognitive Impairment Instrument

Approximately 4 months later, a second questionnaire focusing on memory and issues related to MCI was sent to a subset of 1754 retirees. The subset comprised all respondents from the original health questionnaire who were aged 50 years or older. The same instrument was also sent to an informant (spouse or close relative) to collect data on any cognitive problems exhibited by the retiree that were not reported on the retiree's instrument. Results from the MCI questionnaire were then cross-tabulated with results from the original general health questionnaire. MCI was defined according to the following, outlined in the American Academy of Neurology Practice Parameter (30): memory complaint corroborated by a family member; objective memory impairment as determined by neurocognitive testing; intact activities of daily living; and does not meet accepted diagnostic criteria for probable AD or other forms of dementia.

Statistical Analysis

X^2 tests of association were used to compare proportions in tables; Fisher's exact test was used when 80% of expected cell counts were less than five. Analysis of variance models were used to determine differences among the groups on selected variables. The groups were stratified by concussion history (none, one, two, and three or more). Because of the sample size, some analyses required us to collapse respondents with one and two previous concussions into a single group (one to two previous concussions). We used the Cochran-Armitage trend test to assess linear trends in the proportion of retirees reporting memory impairments and problems across strata of concussion history. Level of significance for all analyses was set a priori at $P < 0.05$. Estimates of the prevalence of AD in the general population of American men, stratified by age, were provided by researchers at the Johns Hopkins University (2).

RESULTS

General Health Questionnaire

Of the original 3683 general health surveys sent to retired players, 2552 (69.3%) were completed. The age of the respondents averaged 53.8 (±13.4) years, with an average professional football playing career of 6.6 (±3.6) years. Respondents reported having played organized football (junior high school, high school, college, armed service, and professional) for an average of 15.1 (± 4.3) years. When considering the prevalence of previous concussions, 1513 (60.8%) of the retired players reported having sustained at least one concussion during their professional playing career, and 597 (24%) reported sustaining three or more concussions. Of those retired players who had sustained a concussion during their professional career, more than half reported experiencing loss of consciousness (n = 817, 54.0%) or memory loss (n = 787, 52.0%) from at least one of their concussive episodes. We asked the retired athletes for their subjective assessment of the long-term consequences of their injuries. Of the retirees who sustained at least one concussion, 266 (17.6%) reported that they perceived the injury to have had a permanent effect on their thinking and memory skills as they have gotten older.

Only 33 (1.3%) retired players reported being diagnosed by a physician as having AD; 15 were undergoing medical treatment for the disease. We observed a higher prevalence of AD in the study population relative to the general American male population (*Fig. 1*). The overall age-adjusted prevalence ratio for AD was 1.37 (95% confidence interval 0.98–1.56), which indicates that the football retirees have higher prevalence than other American men of the same age. The AD prevalence in the football retirees was particularly increased in the younger age groups (≤70 yr), which suggests that this group may have an earlier onset of AD than the general American male population. The average age of the retired players with AD was 71.7 (± 7.62) years (range, 52–83 yr). There was, however, no association between number of concussions sustained as a professional player (none, one, two, and three or more) and a diagnosis of AD (Fisher's exact test, $P = 0.24$).

Mental Component Scale (MCS) scores on the SF-36 were similar between the NFL retirees and population-based normative values for all age groups ($P > 0.05$) (*Fig. 2*); however, retired players with a history of concussion, especially recurrent concussion, scored lower (worse) on the MCS than those without a history of recurrent concussion (F [3,2146] = 19.29, $P = 0.001$). The lowest MCS scores were observed in those with the most reported concussions (*Table 1*). The group who experienced three or more concussions also scored significantly worse than the normative group on the age-matched MCS (50.31 versus 52.42).

Mild Cognitive Impairment Instrument

Results of the follow-up MCI and memory questionnaires were analyzed based on responses from 758 retired players (average age, 62.4 yr) and 641 retired players' spouses or close relatives. Our findings revealed 22 cases of physician-diagnosed MCI and 77 cases of retirees who have significant

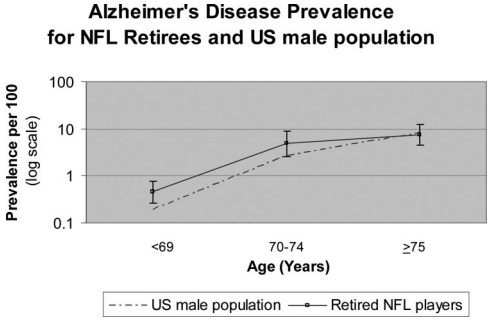

FIGURE 1. *Alzheimer's disease prevalence ratios for the American male population and National Football League (NFL) retirees.* Error bars *indicate 95% confidence intervals.*

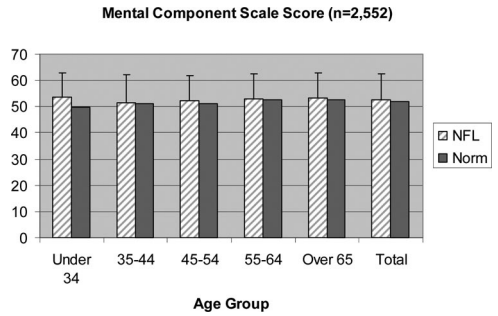

FIGURE 2. *MCS scores for the NFL retirees and population norms by age. "Total" is age-standardized;* error bars *indicate 95% confidence intervals.*

TABLE 1. Mental Component Scale score by concussion history in retired National Football League players aged 50 years or older[a]

No. of previous concussions	Mean MCS score and 95% CI	Standard deviation
0 (n = 814)	54.35 (53.77, 54.94)	(8.50)
1 (n = 429)	52.63 (51.73, 53.52)	(9.47)
2 (n = 374)	52.97 (52.03, 53.91)	(9.22)
3+ (n = 533)	50.31 (49.35, 51.27)	(11.26)

[a] MCS, mental component scale; CI, confidence interval. $P < 0.001$; β -1.51 (0.26).

memory impairment as determined by their spouse or close relative. Further analyses of these data identified an association between recurrent concussion and clinically diagnosed MCI ($\chi^2 = 7.82$, df = 2, $P = 0.02$); self-reported significant memory impairments ($\chi^2 = 19.75$, df = 2, $P = 0.001$); and spouse/relative-reported significant memory impairments ($\chi^2 = 6.05$, df = 2, $P = 0.04$). Retired players with three or more reported concussions had a fivefold prevalence of being diagnosed with MCI and a threefold prevalence of reported significant memory problems compared with those players without a history of concussion (*Fig. 3*). There was no association between MCI and other systemic factors such as coronary heart disease, hypertension, diabetes, or osteoarthritis. Although we found an association between diagnosis of MCI and stroke, this association does not detract from the association between MCI and concussion history. Only three (13.6%) of the 22 MCI cases involved stroke, and we do not know which diagnosis came first.

DISCUSSION

These data suggest that a history of concussion, particularly recurrent concussion, may be a risk factor for the expression of late-life memory impairment, MCI, and AD. Although the

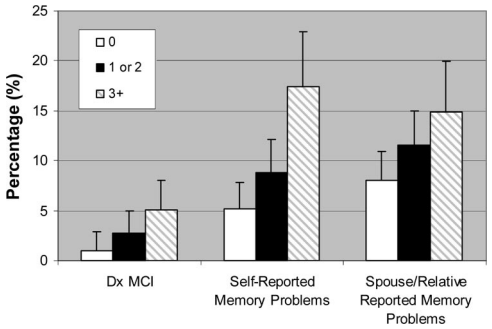

FIGURE 3. *Percentage of retired players aged 50 years or older with a diagnosis of MCI and memory problems (self-reported and reported by a spouse or close relative) by concussion history (none, one, two, and three or more).* Error bars *indicate 95% confidence intervals.* $P < 0.007$.

clinical samples studied are relatively small, retired professional football players were found to have a progressive decline in mental health functioning and a higher rate of memory problems and cognitive decline associated with a history of concussion. Retired players with a history of three or more concussions were at highest risk of being diagnosed by a physician as having MCI and of having significant memory problems based on their own account and the observations of their spouse or caregiver.

Data from a small sample of retired athletes medically diagnosed with probable AD also suggests a trend toward earlier disease onset and higher disease prevalence in younger cohorts relative to the general population (*Fig. 1*). Despite the earlier onset of AD, we failed to find an association between previous concussion and lifetime onset of AD. The cumulative effect of sub-concussive and concussive contacts to the head sustained by professional football players may promote an earlier expression of AD; however, the factor of age eventually overwhelms this factor and prevents it from becoming an independent predictor of lifetime onset of AD. Thus, the lines in *Figure 1* representing the two groups (American male population and retired NFL players) eventually converge.

The number of individuals in the United States with AD was estimated at 2.32 million in 1997, and it is projected that the prevalence will nearly quadruple in the next 50 years, by which time 1 in 45 Americans will be afflicted with the disease (2). As a result, AD is sure to place a large burden on the country's health care system in the decades ahead. For this reason, identification of factors associated with precursor conditions to AD are of interest. The pathology is characterized by cerebral atrophy most severe in frontal, temporal, and parietal lobes resulting in a dramatic reduction of brain weight (normal, 1500–1800 g; AD, 850–1250 g). Microscopic findings include senile plaques, neurofibrillary tangles, and granulovascular degeneration. Biomechanically, there is a 50 to 90% reduction in choline acetyltransferase (5, 15, 17, 23, 36, 37, 39). Clinically, AD presents with a progressive decline in cortical functions principally affecting memory, language, and executive functioning, followed by increasing neurobehavioral and

neuropsychiatric deficits in more advanced stages of the disease (2, 5, 6).

The study of MCI and AD is challenging because of the difficulties in diagnosing the conditions. Both conditions can be evaluated using several measures, but they cannot be diagnosed solely on neuropsychological assessment. Petersen et al. (29, 30) state that the usefulness of any neuropsychological battery for identifying cases of MCI depends on its composition, size, and supporting data. The battery should include measures of new learning, delayed recall, attention, and executive function. Neuroimaging is also considered a powerful tool for the differential diagnosis of cognitive impairment and tracking change (30). Hippocampal atrophy has been identified in amnestic MCI relative to cognitively intact controls, and it is believed that volumetric measurement of this atrophy can predict the rate of conversion from MCI to AD (15).

The human ApoE gene encodes a cholesterol carrier lipoprotein (apolipoprotein E) that is made in the liver and brain and is important in the transport of lipids in the brain. There are three allelic forms (ApoE e2, e3, e4) that give rise to six possible genotype combinations. ApoE plays an important role in the response of the brain to injury. After accelerator forces are imparted to the brain, there is an accumulation of beta amyloid and tau proteins within hours of injury within the neuronal body (12). Possession of the e2 allele is now believed to be underrepresented in AD and may be protective (22). On the other hand, possession of ApoE e4 increases the risk of AD, shifts onset to an earlier age, increases the accumulation of amyloid beta protein in AD and TBI, and decreases recovery after TBI (6, 7, 12, 19, 20).

The sports literature also suggests that possessing the ApoE e4 allele results in greater cognitive impairment after mild repetitive head injury. Older professional football players with the ApoE e4 allele score lower on cognitive tests than players without the allele or less experienced players of any genotype (18). The study clearly suggests that the cognitive status of athletes with repeated head trauma is influenced by age, inherited factors such as ApoE e4, and cumulative exposure to head contact.

Jordan et al. (16) came to similar conclusions in their study of boxers. The boxers with higher exposure (defined by number of bouts) had significantly higher chronic brain injury scores than those with low exposure. Boxers with low exposure had low chronic brain injury scores irrespective of ApoE e4 allele genotype, whereas those with high exposure and the ApoE e4 allele had higher chronic brain injury scores than boxers with high exposure and no ApoE e4 allele. Possession of the ApoE e4 allele was associated with an increased severity of neurological deficits in the high-exposure boxers.

To our knowledge, our study is unique in evaluating the risk of recurrent mild TBI in the development of later-life memory disorders and MCI. These data describe a significant association between recurrent concussion and MCI, as well as with self-reported memory impairments confirmed by a spouse or close relative. Retired professional football players with three or more concussions were twice as likely to be diagnosed with MCI as those with one or two previous concussions, and five times more likely than those with no previous concussions. This trend continued with respect to self-reported significant memory problems. These findings suggest that the clinical features of dementia-related syndromes, such as reductions in synaptic density, loss of neurons, and granulovacuolar degeneration, may be initiated by repetitive cerebral concussions. Other recent peer-reviewed studies of recurrent concussion have identified an acute cumulative effect of concussion as measured by increased symptomatology or slowed recovery on symptom checklists and neuropsychological tests after subsequent injuries in high school and collegiate athletes (4, 10, 11, 14). These acute or short-term consequences of recurrent concussion should be of great interest to the sports medicine community, especially given that they parallel our findings of more chronic consequences after years of playing football.

Our study is influenced by the limitations of any retrospective self-report study. The study is limited by the uncertainty of how well the retired players recalled the concussions sustained during their careers and the accuracy of reporting memory problems and diagnosis of MCI. Recent literature has reported selective preservation of older information in subjects with AD-related dementia, which suggests that recollection of events involving previous injuries is not unlikely in these retired athletes (34). The purpose of the spouse or close relative questionnaire was to confirm the retired players' memory status and any physician-diagnosed MCI. For cases in which there was disagreement in the responses of the retiree and the spouse or relative, phone calls and medical records were used to confirm the diagnosis. When the difference in responses could not be reconciled, the case was eliminated from the analyses. Another limitation of our study is that we do not currently know the ApoE allele form of these retired players, which might help to better understand some of these relationships.

CONCLUSIONS

Despite the limitations, these data suggest some very interesting findings—that a history of recurrent concussions, and probably sub-concussive contacts to the head, may be risk factors for the expression of late-life memory impairment, MCI, and AD. Our findings demonstrate a dose-response relationship between concussion and an increased lifetime burden; however, prospective longitudinal cohort studies are necessary to determine causality. Future prospective studies should implement genetic testing, more rigorous diagnostic criteria, historical documentation, and extensive serial evaluations (e.g., neuropsychological testing, functional neuroimaging) to clarify the direct or mitigating effects of concussion on lifetime risk of dementia or other neurological disorders.

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COMMENTS

The significance of repeated concussions is a question of great interest to all athletes, from players in grade schools to professionals. Anecdotes suggest that repetitive concussions may have a detrimental effect, but more rigorous analyses of this question have been less conclusive. In this report, Dr. Guskiewicz et al. surveyed retired professional football players, first by asking them to complete a general health questionnaire and subsequently by sending them a second questionnaire focusing on memory problems and cognitive impairment. Their data suggest that recurrent concussions seem to be related to mild cognitive impairment diagnosed by a physician and to be related to self-reported memory problems. These associations seemed to be stronger in patients with three or more reported concussions. Alzheimer's disease may have occurred at an earlier age in former National Football League players than in the population as a whole, but the number of patients with this diagnosis was quite small.

Like all retrospective studies that rely upon self-reported medical histories and health problems, this one is subject to bias in the accuracy with which problems were recalled and reported. Nevertheless, these results are of considerable interest. The authors make appropriate recommendations for further prospective studies to include such factors as genetic testing, standardized diagnostic criteria, and more extensive evaluation of players with concussion, perhaps including neuropsychological testing and functional neuroimaging.

Alex B. Valadka
Houston, Texas

The safety of contact sports and likelihood of neurologic impairment occurring after retiring from the sport are of obvious concern to athletes and to parents deciding on which sports they should allow their kids to participate in. Studies such as this have the potential to provide important information in this regard. Unfortunately, this particular study is confounded by a critical design flaw of relying on retired athletes to accurately recall events from decades earlier and relating those events to their current memory problems. The study would have been much stronger had the authors corroborated the frequency and severity of concussions sustained with independent sources.

Donald Marion
Boston, Massachusetts

Thank you for the opportunity to comment on this excellent and extremely important study. The authors have used the tremendous resource of a database of the National Football League Retired Players Association, which contains 3683 individuals who played football at a high level for an average of 15 years (minimum six yrs of professional-level football). Using carefully constructed retrospective questionnaires, they have shown a strong association between three or more concussions sustained during a players' professional football career and mild cognitive impairment.

Although this evidence was the most compelling, they also showed an earlier onset and increased incidence of Alzheimer's disease in this group of professional football players who received concussions frequently than in the general age-matched male population in the United States.

This study has important and far-reaching implications. To my knowledge, this is one of few studies to show a positive association between repetitive concussion and long-term cognitive impairment and Alzheimer's disease (1–4). Therefore, this study documents the dangers of contact sports, such as professional football. As professional football evolves, the speed of the plays appears to be increasing, the prowess, strength, and size of the athletes is measurably increasing, and, therefore, the potential for concussions, especially higher-impact energy concussions, is increasing. It is important to know whether the incidence of multiple concussions per player each year is increasing over time, and this invaluable cohort provides such details by including players with a history as far back as pre-World War II.

What are the implications for the future of the game? Possibly, rules could be tightened to limit the types of dangerous plays, but, in the "heat of the game," this may be unlikely. Helmet design has evolved tremendously in recent years (3), and clearly, studies with kinematic accelerometers of the type used in crash-test dummies by the auto industry should be performed and correlated with the "action replays," which are such an exciting facet of modern televised football. In this way, it may be possible to modify the game in ways that are compatible with increased safety without decreasing the spectator appeal of the game. New types of energy-absorbing foam and plastic are becoming available for football helmets.

However, as with professional boxing, athletes who undertake high-impact sports need to be fully and demonstrably informed of the risks that they undertake in pursuit of their vocation. This important study will provide a basis upon which players' associations and teams can formulate decisions.

Do the implications of these data go further? Many have called for apolipoprotein E genotyping of professional boxers to reduce the risk of precipitating Alzheimer's disease in apolipoprotein E e4 homozygous boxers. Should the same apply to professional football players, ice hockey players, and rugby players?

The authors have demonstrated that they have access to an enormous "data mine" to test the role of long-term physical fitness upon the development of delayed degenerative joint disease, low back disorders, and cardiovascular mortality. Do the cumulative effects of strains, sprains, and fractures, which are the inevitable consequence of professional football, outweigh the beneficial effect of many years of peak physical fitness upon the musculoskeletal system?

M.R. Ross Bullock
Richmond, Virginia

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Dr. Guskiewicz et al. have assessed by questionnaire a large number of retired professional football players to assess the incidence of concussions and more serious head injuries sustained during their playing careers and to determine whether such injuries influenced the subsequent development of Alzheimer's disease or mild cognitive impairment. Their results indicated that football players with repetitive concussion injuries (three or more) have a fivefold prevalence of mild cognitive impairment and a threefold increase in self-reported

memory problems. The authors also suggest a 'soft' association between concussion and Alzheimer's disease.

This is an interesting paper that poses an intriguing hypothesis regarding the consequences of recurrent concussion, not only to create short-term problems, but also to accelerate the decline of cognitive function in later years. While tantalizing, the findings are soft. This data is derived from a questionnaire administered to a group that may have substantial bias, especially considering the recent reports and concerns expressed by physicians and the media. How did the authors pare down the original 2552 respondents to 758 whose memory questionnaires were analyzed? Figure one suggests an earlier onset of Alzheimer's disease in respondents aged less than 69 years, but the trend corrects by the age of 75. If the hypothesis is correct, why shouldn't this early separation persist or widen over time?

As usual, the data in sports medicine is difficult to control. Despite its shortcomings, it is reasonable that this paper should be published, not on the basis of its science, but on its conjecture and the need for neurosurgeons to be more aware of the current information in this area.

Arthur L. Day
Boston, Massachusetts

This latest manuscript on the relationship between cognitive impairment and recurrent concussion focuses on players from the National Football League. As in previous studies, there is an association between the frequency of recurrent concussion, the development of mild cognitive impairment, and the suggestion that Alzheimer's disease develops earlier in such patients. This trend is potentially of interest, but a larger sample is necessary.

One concern with the manuscript is the lack of controls in other sports where aggressive behavior is common but concussion is relatively rare, such as in wrestling. There may be genetic linkage to aggressive behavior and cognitive impairment later in life, which is separate from concussion. Perhaps the link is unlikely, but such controls in future studies would help support the hypothesis. Clearly, this is an area of continuing interest and the authors work is important.

Lawrence F. Marshall
San Diego, California

Unfortunately, this manuscript reflects the low priority our society places on the prevention of head injuries and the major sequelae. It attempts to address the significant concern that repeated head injury leads to brain damage. Injury prevention programs, such as ThinkFirst, confront the lack of accurate studies on the potential damage of head trauma such as those sustained by both amateur and professional athletes.

The present study does not dispel uncertainties regarding the relationship between repeated concussions and subsequent onset of brain disorders, most importantly Alzheimer's disease. The study suffers from lack of professionally obtained prospective data. The glaring deficiency of this study is its reliance on questionnaires from patients and relatives that were obtained retrospectively. Society must provide the author with the necessary funds and incentive to do the study correctly based on professionally obtained prospective data. Regrettably, the questions raised by the authors are of great importance to society and remain unanswered.

Charles H. Tator
Toronto, Ontario, Canada

This is an extremely valuable contribution. Most concussion studies focus on the days and weeks following the injury with the implicit assumption that recovery to preinjury levels is the end of the issue. The present paper provides strong suggestion that some residua of a concussion may not become manifest until decades after the injury. The study also provides a strong rationale for future studies focusing on the effects of concussion on cognitive reserves, rather than simply on performance in the immediate aftermath of injury. Moreover, because the present study demonstrates a dose-response relation between concussion and future cognitive disorder, it highlights the importance of reducing lifetime burden of concussion in athletes.

The authors are to be commended for clearly stating the limitations of their retrospective self-report experimental design. However, the 'gold-standard' methodology would require a multi-decade prospective study. While I think the present findings support the need for a prospective inception-cohort study on this question, this should not overshadow the importance of the present findings and the importance of additional follow-up studies exploring the pathophysiological underpinnings of the present findings.

Joseph Bleiberg
Neuropsychologist
Washington, D.C.

This is an important paper on the relationship between cerebral concussion and subsequent cognitive impairment in retired professional football players. Its major flaw, as the authors acknowledge, is that the history of previous concussion was based on the players' 'retrospective recall of injury events.' Nonetheless, their data strongly suggests there is a cumulative deleterious effect of repeated concussion on later cognitive function. It further emphasizes the need to enhance protective measures that minimize concussion in contact sports and to carefully follow players by documenting the number and severity of concussive events throughout their careers. Finally, given the increasing data concerning the long-term risk of greater cognitive impairment for concussed individuals carrying the apolipoprotein E e4 allele, genetic screening and counseling of individuals about to embark on a potentially long career of contact sports should be considered.

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