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Bias-Adjusted Prevalence of Chronic Traumatic Encephalopathy Among Deceased National Football League Players

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Abstract

IMPORTANCE The majority of knowledge regarding chronic traumatic encephalopathy (CTE) in National Football League (NFL) players is derived from autopsy-based studies on voluntarily donated brains. Because these cohorts are highly vulnerable to selection bias (specifically registry bias), population-level prevalence of CTE among former NFL players is unknown, limiting understanding of the impact of this disease.

OBJECTIVE To estimate the selection-bias adjusted prevalence of CTE neuropathology in deceased NFL players.

DESIGN, SETTING, AND PARTICIPANTS This population-based cross-sectional study used Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) brain bank data combined with National Death Index records on former NFL players. Both brain donor and nondonor NFL players who died between January 2008 and December 2023 were included. Data were analyzed from November 2025 to April 2026.

EXPOSURE Playing in at least 1 regular or postseason NFL game.

MAIN OUTCOMES AND MEASURES The main outcomes of this study were bias-adjusted prevalence of CTE neuropathology and all-cause dementia among the target population, both of which were measured in donors prior to this study. A cognitive symptom–related brain donation selection ratio (probability of donation given CTE divided by the probability of donation given no CTE) was estimated using Poisson regression and was applied to adjust donor-observed prevalence of CTE neuropathology at death and all-cause dementia during life. The prevalence estimates were adjusted for bias using the estimated selection ratio.

RESULTS The cohort consisted of 2362 deceased former NFL players (mean [SD] years played, 5.1 [3.9]; 971 [41.1%] aged ≥80 years at death), of whom 396 were brain donors and 1966 were nondonors. Of 387 donors, 362 (93.5%) had CTE. The median selection ratio was 4.97 (95% CI, 4.72-5.26). Bias-adjusted population prevalence of CTE at death was 74.5% (95% CI, 69.6%-78.3%), with a conservative lower-bound analysis estimating 63.7% (57.2%-68.9%). Bias-adjusted population prevalence of all-cause dementia history during life was 27.2% (95% CI, 22.6%-31.6%).

CONCLUSIONS AND RELEVANCE The findings of this cross-sectional study suggest that selection bias materially inflates donor-based prevalence estimates but is unlikely to fully explain the high burden of CTE neuropathology among this population. Further research is required to understand the clinical impact of this disease.

Key Points

Question After adjusting for selection bias, what is the prevalence of chronic traumatic encephalopathy (CTE) in deceased National Football League (NFL) players?

Findings In this cross-sectional study of 2362 former NFL players who died between 2008 and 2023, 93.5% of players who were brain donors with neuropathologic evaluation had CTE. After adjustment for differential brain donation, the estimated prevalence of CTE neuropathology among all 2362 decedents was 74.5%.

Meaning These findings suggest that selection bias materially inflates donor-based estimates but is unlikely to fully explain the high burden of CTE neuropathology among deceased former NFL players.

+ Supplemental content

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Introduction

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease[1] associated with exposure to repetitive head impacts (RHIs), such as those from contact sport participation,[2-4] military combat exposure,[5] intimate partner violence,[6] and other sources. At present, CTE can only be definitively diagnosed through neuropathological examination using published diagnostic criteria.[7] CTE has been neuropathologically diagnosed most frequently among deceased American football players[3,4,8] across all levels of play. There is also evidence of a dose-response association of football-related RHI exposure with CTE status and severity.[4] Because millions of individuals participate in global contact sports each year, CTE has emerged as a public health concern.[9,10] However, the prevalence of CTE remains uncertain because available estimates are derived from studies affected by a specific form of selection bias, sometimes termed registry bias, which arises when participation in a brain bank is itself related to the disease under study.

Current knowledge regarding CTE neuropathology in American football players is derived from autopsy-based studies, particularly from brain donors enrolled in the Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) Brain Bank.[11] Autopsy studies are inherently susceptible to registry bias, which may distort estimates of both disease prevalence and associations of exposures with outcomes. Brain donation has been shown to be influenced by age, sex, race, marital status, depression, and dementia in the general community.[12] Estimating disease prevalence in the presence of selective autopsy participation represents a broad methodological challenge in neurodegenerative disease research.

In the context of CTE, selection mechanisms may be amplified because both RHI exposure history and symptoms can influence brain donation decisions.[13-15] For example, individuals with higher RHI exposure (eg, college or professional football players) who experienced cognitive, mood, or behavioral symptoms during life may be more likely to participate in brain donation, potentially inflating the prevalence of CTE neuropathology. For instance, a 2017 study reported CTE was neuropathologically diagnosed in 110 of 111 (99%) former National Football League (NFL) players.[3] This rate does not represent the prevalence in the entire NFL population because it is calculated from a selected, likely biased, subset. These concerns underscore the need for quantitative evaluation of the magnitude and direction of selection bias in population-level disease prevalence estimates derived from brain bank cohorts. Prior efforts to address this issue include estimating a wide range of possible NFL prevalence values[16] and estimating risk ratios for CTE in NFL players compared with college and high school players.[17] However, population-level estimates of CTE prevalence at death among all deceased former professional football players have not yet been done.

In this study, we estimated the prevalence of CTE neuropathology at death among all former NFL players who died between 2008 and 2023 while explicitly accounting for brain donation registry bias. To do so, we combined data from the UNITE brain bank with population-level mortality records for all deceased NFL players identified through the National Death Index (NDI). We first quantified the association of a derived clear cognitive symptoms variable with brain donation status and used this estimate to derive a selection ratio representing the relative probability of brain donation by CTE status. We then used this ratio to estimate the prevalence of CTE neuropathology among all deceased NFL players. We hypothesized that individuals with CTE would be more likely to donate their brain than those without CTE, but after accounting for this bias, the prevalence of CTE in former NFL players would remain high. To our knowledge, this study is the first to estimate population-level prevalence of CTE neuropathology at death. Additionally, we used the same method to estimate the bias-adjusted prevalence of all-cause dementia history during life among former deceased NFL players. Estimating the population-level prevalence of CTE neuropathology at death and dementia in life is essential for understanding findings from autopsy studies in a public health context.

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Methods

Study Data

Institutional review boards from Boston University and the VA Bedford Healthcare System approved brain donation, postmortem clinical record review, neuropathological evaluation, and clinical interviews with donor family members for this cross-sectional study. All informants of brain donors and participants provided written informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

NDI Data

Our target population consisted of all former NFL players who died between 2008 and 2023 because the UNITE brain bank began in 2008 and the NDI data for our population of interest was last extracted in 2023. The NDI is a centralized database of death record information in the US. Most of the data used in this study came from the NDI because it provides data on all deceased NFL players (brain donors and nondonors alike), allowing us to determine factors that are associated with donation status. Using the NDI data, we derived a binary dementia-related cause of death variable for all donors and nondonors using *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes (eTable 1 in Supplement 1). Further details on the NDI data are provided in eAppendix 1 in Supplement 1.

UNITE Brain Bank

The sample included NFL players from the UNITE brain bank as of December 31, 2023. The details of the UNITE study have been described previously.[18] Only consensus all-cause dementia history in life and neuropathological CTE status after death were used from the UNITE dataset. More details on the UNITE data, including procedures for CTE and dementia diagnoses, are provided in eAppendix 1 in Supplement 1.

Statistical Analysis

Analyses were conducted from November 2025 to April 2026. All analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing). Significance was defined as a 2-sided $P < .05$.

General Approach

To estimate the prevalence of CTE neuropathology at death, we adjusted the observed donor prevalence in the UNITE brain bank for the registry bias inherent in brain donation.[12,17] We estimated the likelihood of brain donation for someone with CTE compared with someone without CTE by calculating the selection ratio. The selection ratio is defined as the ratio of the probabilities of brain donation among individuals with CTE to those individuals without CTE. The observed CTE prevalence was then adjusted by weighting the observed number of CTE cases by the inverse of the selection ratio. The mathematical derivation of these calculations is provided in eAppendix 2 in Supplement 1. The same methodological approach was applied to estimate the prevalence of all-cause dementia history in our target population.

Calculation of the Selection Ratio: Dementia Cause of Death and Mild Cognitive Impairment Expansion

To estimate the selection ratio, we assumed that selection into the brain bank was principally influenced by the presence of cognitive symptoms in an NFL player observed by family members. The aforementioned NDI-derived binary dementia cause of death variable allowed us to estimate how much more likely individuals with a dementia-related cause of death were to donate compared with those without such a cause of death. We used dementia cause of death as proxy for CTE to allow us to calculate the selection ratio because CTE neuropathology alone has a large magnitude of

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association with dementia and cognitive symptoms.[3,10] While dementia-related cause of death captures a portion of those experiencing clear cognitive symptoms in life, it likely underestimates this number because many people with dementia or mild cognitive impairment (MCI) will have clear cognitive symptoms present but will die from a non–dementia-related cause; this introduces a level of measurement error when using this proxy variable, specifically in the direction of undercounting those with cognitive symptoms and thus underestimating the selection ratio and amount of bias and overestimating the overall CTE prevalence. With limited individual-level data on nondonors to expand our definition of clear cognitive symptoms, we turned to population-level estimates of MCI and dementia in former NFL players older than 50 years reported in 2022 by the Neurologic Function Across the Lifespan: A Prospective, Longitudinal, and Translational Study for Former NFL Players (NFL-LONG)[19] shown in eTable 2 in Supplement 1. From this study, we used prevalence of self-reported physician-diagnosed MCI and dementia. We then calculated age-specific ratios of MCI to dementia and smoothed these ratios using a natural cubic spline model to reduce the potential effect of sampling variability across age groups. Using these smoothed ratios, we expanded the number of dementia-related cases to include MCI cases within the donor strata and within the nondonor strata by multiplying by the appropriate ratio for each age group. This enrichment strategy aims to reduce underascertainment of clinically meaningful cognitive impairment when dementia was not recorded as the underlying cause of death. We provide an illustrative example of these calculations in eAppendix 3 in Supplement 1 and eTable 3 in Supplement 1. Circumstantial modifications to this methodology are described in eAppendix 4 in Supplement 1.

Calculation of the Selection Ratio: Poisson Modeling

To estimate the final selection ratio, we fit a Poisson regression model with robust variance estimates, with brain donation status as the outcome; clear cognitive symptoms as the main independent variable; and age of death, family-reported race, player position and years played in the NFL, number of Pro Bowl appearances, and Pro Football Hall of Fame status as additional independent variables to limit confounding. This procedure was repeated across 1000 simulations to incorporate uncertainty in the reclassification of MCI cases. The effect size estimate of the clear cognitive symptoms variable, interpreted as a risk ratio, was used as the selection ratio estimate. We reported the median selection ratio and the 2.5 and 97.5 percentiles of the simulated distribution as the 95% CI. Race was categorized as White and any reported race other than White, and was included as an additional independent variable because race is a known determinant of brain donation.

Calculating Bias-Adjusted Prevalence

To calculate the bias-adjusted CTE neuropathology prevalence, we adjusted the observed prevalence of CTE neuropathology in the UNITE brain bank using the selection ratio (formulas in eAppendix 2 in Supplement 1) and reported the median, 2.5, and 97.5 percentiles. We used the same distribution of selection ratios to estimate the prevalence of all-cause dementia history among all deceased NFL players.

We conducted 9 sensitivity analyses to evaluate the robustness of the results. These included age-restricting the sample (analyses 2-5) and using the unsmoothed MCI-to-dementia ratios originally reported in the NFL-LONG study (analyses 1, 3, and 5). We also performed sensitivity analyses using the overall non–age-stratified MCI-to-dementia ratio reported in the NFL-LONG study,[19] and then assigned age based on the distribution of MCI in the age strata (analyses 6 and 7). We also expanded the symptoms group to include individuals who died by suicide because death by suicide is highly predictive of brain donation in this population (analysis 8). Finally, we used the same methodology for nondonors but used the postmortem consensus-based dementia diagnosis as well as the premortem physician MCI diagnosis for donors as a high-bias, lower-bound estimate of prevalences (analysis 9).

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Results

Our cohort consisted of 2362 deceased former NFL players (mean [SD] years played, 5.1 [3.9]; 971 [41.1%] aged ≥80 years at death), of whom 396 were brain donors and 1966 were nondonors. Demographic information on brain donors and nondonors (from the NDI data) is provided in **Table 1**. Also provided in Table 1 are the bias-unadjusted prevalences of CTE neuropathology and all-cause dementia diagnosis in life from the UNITE brain bank (donors only). Five participants were missing age at death and Pro Bowls played, 17 were missing years played, 6 were missing position, and 53 were missing Hall of Fame status and cause of death. Among brain donors, CTE status was undetermined for 9 participants (2.3%) and dementia history was unavailable for 48 participants (12.1%); these individuals were excluded from the corresponding prevalence calculations. The Poisson regression model was fit on 2298 complete cases. Compared with nondonors, brain donors tended to die at younger ages (mean [SD] age of death, 67.0 [15.2] years vs 74.7 [14.9] years), played

Table 1. Characteristics of Sample

Characteristic	Participants, No. (%)		
	Overall (N = 2362)[a]	Nondonor (n = 1966)[a]	Donor (n = 396)[a]
Age at death, y			
<50	213 (9.0)	153 (7.8)	60 (15.2)
50-54	74 (3.1)	53 (2.7)	21 (5.4)
55-59	93 (3.9)	71 (3.6)	22 (5.6)
60-64	152 (6.4)	118 (6.0)	34 (8.7)
65-69	203 (8.6)	161 (8.2)	42 (10.6)
70-74	300 (12.7)	236 (12.0)	64 (16.2)
75-79	351 (14.9)	283 (14.4)	68 (17.2)
≥80	971 (41.1)	891 (45.3)	80 (20.2)
Years played in NFL, mean (SD)	5.1 (3.9)	4.7 (3.8)	7.1 (4.0)
Binary race			
White	1646 (69.7)	1392 (70.8)	254 (64.1)
Any race other than White	716 (30.3)	574 (29.2)	142 (35.9)
Position			
Offensive lineman	320 (13.5)	272 (13.8)	48 (12.1)
Tight end	62 (2.6)	47 (2.4)	15 (3.8)
Quarterback	109 (4.6)	94 (4.8)	15 (3.8)
Running back	279 (11.8)	235 (12.0)	44 (11.1)
Wide receiver	69 (2.9)	57 (2.9)	12 (3.1)
Defensive line	208 (8.8)	167 (8.5)	41 (10.4)
Linebacker	183 (7.8)	140 (7.1)	43 (10.9)
Defensive back	258 (10.9)	212 (10.8)	46 (11.6)
Punter	18 (0.8)	15 (0.8)	3 (0.8)
Kicker	25 (1.1)	22 (1.1)	3 (0.8)
Multiple	825 (34.9)	704 (35.8)	121 (30.9)
No. of Pro Bowls played, mean (SD) [range]	0.6 (1.5) [0-14]	0.5 (1.4) [0-14]	1.0 (1.9) [0-9]
Hall of Fame status	72 (3.1)	52 (2.7)	20 (5.5)
Dementia-related cause of death	291 (12.3)	221 (11.2)	70 (19.3)
CTE, No./total No. (%)			
No	Unknown	Unknown	25/387 (6.5)
Yes	Unknown	Unknown	362/387 (93.5)
Dementia history in life			
No	Unknown	Unknown	122 (35.1)
Yes	Unknown	Unknown	226 (64.9)

Abbreviations: CTE, chronic traumatic encephalopathy; NFL, National Football League.

[a] Not all numbers may add to column total due to missing data.

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longer in the NFL (mean [SD], 7.1 [4.0] vs 4.7 [3.8] years), had more Pro Bowl appearances (mean [SD], 1.0 [1.9] vs 0.5 [1.4] games), and were more likely to be members of the Pro Football Hall of Fame (20 players [5.5%] vs 52 players [2.7%]). Brain donors were also more likely to have a dementia cause of death than nondonors (70 of 363 players [19.3%] vs 221 of 1966 players [11.2%]). The prevalence of CTE neuropathology in the UNITE brain donor population (unadjusted for bias) was 93.5% (362 of 387 players). The prevalence of an all-cause dementia history in life in the UNITE brain donor population (unadjusted for bias) was 64.9% (226 of 348 players).

The results from the Poisson model using NDI data to estimate the selection ratio are displayed in **Table 2**. The median risk ratio estimates and corresponding 95% empirical intervals across all 1000 iterations are reported. The median selection ratio was 4.97 (95% CI, 4.72-5.26; $P < .001$). Additional variables that were significantly associated with brain donation were age at death (risk ratio estimate, 0.95; 95% CI, 0.94-0.95; $P < .001$), years played in the NFL (risk ratio estimate, 1.13; 95% CI, 1.10-1.16; $P < .001$), and White race compared with any race other than White (risk ratio estimate, 1.47; 95% CI, 1.12-1.92; $P = .005$).

After accounting for differential selection in brain donation, the estimated bias-adjusted prevalence of CTE neuropathology among all former NFL players who died between 2008 and 2023 was 74.5% (95% CI, 69.6%-78.3%). The bias-adjusted prevalence of an all-cause dementia history during life for the same population was 27.2% (95% CI, 22.6%-31.6%).

Across all sensitivity analyses using the MCI-enrichment estimation approach for both donors and nondonors (analyses 1-8), the CTE neuropathology prevalence estimates ranged from 70.3% (95% CI, 64.9%-75.2%) to 86.1% (95% CI, 83.3%-88.4%), and the all-cause dementia history in life prevalence estimates ranged from 28.2% (23.6%-32.7%) to 44.2% (95% CI, 39.0%-49.3%). These results are displayed in **Table 3**. The sensitivity analysis, which included consensus dementia or MCI history for donors, provided lower-bound estimates by using the MCI-enrichment estimates in nondonors and consensus-based dementia history and MCI diagnoses in donors; the resulting CTE neuropathology prevalence was 63.7% (95% CI, 57.2%-68.9%) and the all-cause dementia history prevalence was 18.3% (95% CI, 14.6%-22.1%). As a final comprehensive sensitivity analysis, the **Figure** displays the association between the selection ratio, CTE neuropathology prevalence, and all-cause dementia prevalence.[16]

Table 2. Median Exponentiated Risk Ratio Estimates from 1000 Replicates of Poisson Model for Donation

Variable	Median exponentiated risk ratio estimate (95% CI)	*P* value
Clear cognitive symptoms	4.97 (3.77-6.55)	<.001
Age at death	0.95 (0.94-0.95)	<.001
Position		
Tight end	1.34 (0.73-2.46)	.34
Quarterback	0.75 (0.41-1.36)	.34
Running back	1.29 (0.84-2.00)	.25
Wide receiver	1.14 (0.58-2.23)	.71
Defensive line	1.19 (0.75-1.88)	.46
Linebacker	1.14 (0.74-1.77)	.55
Defensive back	1.27 (0.83-1.94)	.27
Punter	0.85 (0.26-2.74)	.78
Kicker	0.73 (0.23-2.36)	.60
Multiple	1.03 (0.72-1.47)	.83
Years played in NFL	1.13 (1.10-1.16)	<.001
White race (compared with any race other than White)	1.47 (1.12-1.92)	.005
No. of Pro Bowls played	0.99 (0.92-1.07)	.74
Hall of Fame status	0.90 (0.42-1.94)	.73

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Discussion

The objective of this cross-sectional study was to estimate the prevalence of CTE neuropathology at death and all-cause dementia history among former NFL players while accounting for the bias inherent in brain bank studies. Using population-level NDI mortality data on all deceased NFL players between 2008 and 2023, we estimated the differential probability of brain donation among individuals with vs without clear cognitive symptoms. After adjusting for this selection process, we estimated that approximately 74.5% (95% CI, 69.6-78.3%) of deceased former NFL players had CTE neuropathology at death between 2008 and 2023. The corresponding estimated prevalence of dementia history during life was 27.2% (95% CI, 22.6%-31.6%).

Our findings extend prior work attempting to quantify the impact of selection bias in CTE brain bank studies. Binney et al[16] used bounding analyses under minimal assumptions and demonstrated

Table 3. CTE and Dementia Prevalence Adjusted for Selection Bias

Analysis	Selection ratio (95% CI)	Estimated prevalence, % (95% CI)	
		CTE pathology at death (n = 2362)	Dementia history in life (n = 2362)
Main analysis	4.95 (4.01-6.33)[a]	74.5 (69.6-78.3)	27.2 (22.6-31.6)
Sensitivity analysis			
MCI-to-dementia (ratios unsmoothed)	4.72 (3.81-6.01)	75.4 (70.7-79.2)	28.2 (23.6-32.7)
Age of death: ≥55 y (ratios smoothed)	5.50 (4.40-7.05)	73.2 (68.0-77.3)	35.1 (29.6-40.3)
Age of death: ≥55 y (ratios unsmoothed)	5.26 (4.22-6.77)	74.0 (68.9-78.1)	36.1 (30.5-41.3)
Age of death: ≥60 y (ratios smoothed)	5.87 (4.58-7.53)	70.3 (64.9-75.2)	36.7 (31.2-42.7)
Age of death: ≥60 y (ratios unsmoothed)	5.76 (4.44-7.41)	70.7 (65.2-75.8)	37.2 (31.5-43.4)
Nonstratified ratios (MCI present <50 y)	2.34 (1.91-2.89)	86.1 (83.3-88.4)	44.2 (39.0-49.3)
Nonstratified ratios (no MCI <50 y)	2.89 (2.36-3.52)	83.4 (80.5-86.0)	39.1 (34.5-43.9)
Suicide cause of death included	4.12 (3.44-5.07)	77.8 (74.0-80.8)	31.0 (26.7-35.0)
Consensus dementia history or MCI for donors	8.27 (6.54-10.85)	63.7 (57.2-68.9)	18.3 (14.6-22.1)

Abbreviations: CTE, chronic traumatic encephalopathy; MCI, mild cognitive impairment.

[a] The selection ratio estimate reported in this table for the main analysis differs slightly from that reported in Table 2 and throughout the manuscript (4.95 vs 4.97) because the Table 3 selection ratio estimates use a random draw process from a normal distribution defined by the risk ratio estimate for each iteration as the mean and the robust standard error for each risk ratio estimate as the standard deviation. This process was implemented to induce additional randomness and ensure the robustness of our findings.

Figure. Line Graph of Chronic Traumatic Encephalopathy (CTE) and Dementia Prevalence Under a Range of Brain Donation (Selection) Ratios

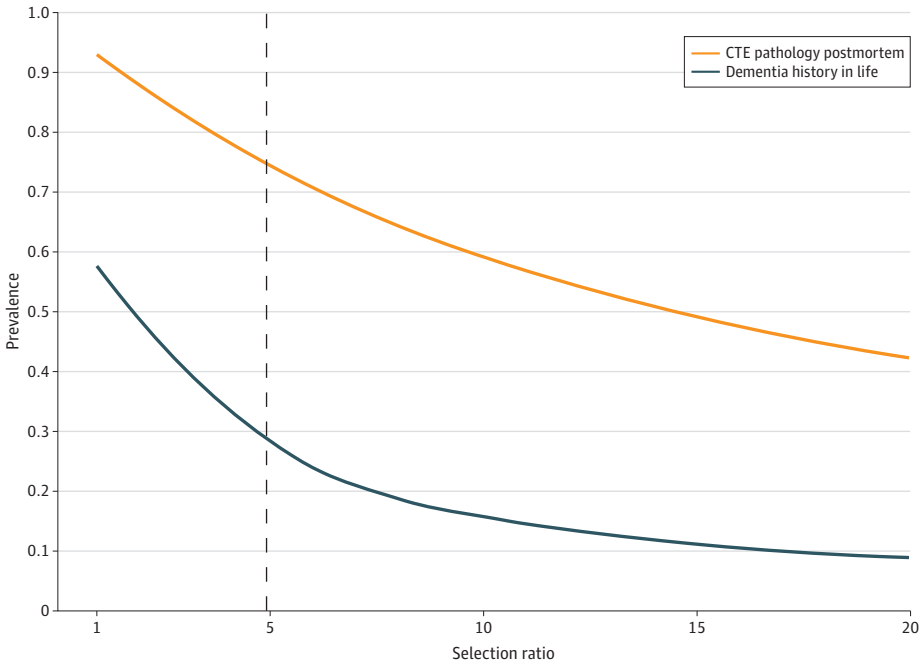

Figure displays the mathematical association between the selection ratio, CTE neuropathology at death, and dementia history in life. The dotted line marks the selection ratio estimated in these analyses, with the corresponding CTE and dementia prevalences reported. This figure is updated from the Binney et al[16] figure displaying similar results.

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that the prevalence of CTE neuropathology among former professional football players could plausibly range from approximately 10% to 100%. Our results provide a more precise estimate within this range by explicitly modeling the brain donation process and incorporating information on the cause of death and population-level estimates of MCI and dementia.

A central challenge in estimating selection bias in brain bank studies is the absence of comparable clinical information among nondonors. To address this limitation, we used dementia-related cause of death from the NDI as a proxy for clinically significant cognitive symptoms and supplemented these data using population-level estimates of MCI prevalence from the NFL-LONG study,[19] a recent study with a large sample size that reported rates of MCI and dementia in former NFL players. This approach allowed us to construct a broader category of clear cognitive symptoms, capturing both dementia and estimated MCI cases. Using this proxy, we estimated that former NFL players with clear cognitive symptoms were approximately 5 times more likely than those without such symptoms to have their brain donated. Even after accounting for differential brain donation, our findings suggest that the prevalence of CTE among deceased NFL players remains high. Sensitivity analyses using alternative assumptions about MCI prevalence and age restrictions yielded broadly similar prevalence estimates, indicating that the findings are robust to reasonable variations in the underlying assumptions. Additionally, and more broadly, this framework provides a general approach for estimating disease prevalence from autopsy-based cohorts when participation is influenced by clinical symptoms.

Limitations

Several limitations should be considered. First, the classification of clear cognitive symptoms and calculation of the selection ratio relied on dementia-related cause of death and estimated MCI prevalence as proxy for CTE status rather than direct clinical assessment for nondonors. Dementia is frequently underreported on death certificates, and some individuals with cognitive impairment may die of unrelated causes without dementia being recorded.[20] We partially addressed this limitation by expanding the cognitive symptoms category using the ratio of MCI to dementia cases because the reported ratios are likely overestimates due to survey nonresponse among individuals with dementia. However, even with this enrichment, we expect our estimates of the prevalence of clear cognitive symptoms to be undercounts. Because the selection ratio depends solely on the relative difference of cognitive impairment between donors and nondonors rather than on absolute counts, nondifferential underascertainment has substantially less impact than differential underascertainment between groups. To evaluate the sensitivity of our approach to this limitation, the sensitivity analysis which included consensus dementia or MCI history for donors used the MCI-enrichment method within nondonors and the clinical benchmark consensus dementia history and MCI history values within donors, effectively allowing for undercounting in the nondonor group and accurate counting in the donor group. This approach biases the selection ratio upwards and the corresponding prevalences downwards. This lower-bound estimate still yields a bias-adjusted prevalence of 63.7% for CTE neuropathology and 18.3% for dementia history in life. A related but distinct assumption concerns the use of cognitive symptoms as a proxy for CTE status itself. The selection ratio we estimated compares the probability of brain donation between decedents with and without clear cognitive symptoms, whereas the adjustment requires the ratio of donation probabilities between decedents with and without CTE neuropathology. To the extent that symptoms and neuropathology are imperfectly concordant, the symptom-based ratio differs from the CTE-specific selection ratio, and the adjusted prevalence estimates affect that uncertainty. Because brain donation decisions are made on the basis of a decedent's observed clinical course rather than on neuropathologic status, which cannot be ascertained during life, we regard the symptom-based ratio as the most defensible available approximation.

A second limitation is the assumption that the population-level estimates of ratios of MCI prevalence to dementia prevalence apply equally within the donor stratum and the nondonor stratum. Third, despite adjusting for several factors associated with brain donation, unmeasured

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factors related to both symptoms and donation decisions may still influence our selection ratio estimates. Fourth, the results apply specifically to deceased NFL players and do not generalize to individuals with lower levels of RHI exposure or living former NFL players. Fifth, there is limited understanding of the longitudinal progression of CTE pathology during life and its association with symptoms distinct from symptoms potentially caused by other pathologies. We were thus limited to estimating all-cause dementia prevalence as opposed to CTE-caused dementia. Sixth, we were unable to address possible differential selection into the deceased pool of NFL players because it is currently unknown whether (or by what magnitude) CTE independently increases mortality risk. This limitation further emphasizes that the CTE estimates provided in this analysis cannot be extended to currently living NFL players. Seventh, the prevalence estimate of 74.5% corresponds to all stages of CTE and does not directly estimate the symptom burden in living NFL players. Many cases may have been early stage at the time of death and possibly symptom free.

The bias-adjusted 27.2% prevalence estimate of all-cause history of dementia in our target population gives more insight into the symptom burden in living players. It should be noted that many individuals who do not develop dementia may still become cognitively impaired, although with limited data on nondementia cognitive impairment, it is difficult to estimate a prevalence at this time. This dementia estimate differs from the cross-sectional NFL-LONG dementia prevalence of 8.9% in living NFL players older than 50 years[19] for at least 2 reasons: (1) the 27.2% is an estimate of the prevalence of dementia history at the time of death whereas the NFL-LONG estimate includes many younger players who may still develop dementia before death and (2) the NFL-LONG estimate likely suffers from selection bias and underestimates dementia prevalence because those with dementia are less likely to respond to a questionnaire. Our 27.2% dementia estimate is based on the observed prevalence of dementia in the donor group, which had a mean age of death of 67.0 years, whereas nondonors had a mean age of death of 74.7 years. Therefore, the true lifetime dementia prevalence in our target population is likely higher than 27.2% because development of dementia is highly age dependent and nondonors would have more time to develop dementia before death.

Conclusions

In this cross-sectional study of 2362 deceased former NFL players, we have provided what are, to our knowledge, the first population-level estimates of CTE neuropathology prevalence among deceased former NFL players while explicitly accounting for brain donation selection bias. Importantly, the estimated prevalence of CTE neuropathology remained substantial across a wide range of assumptions regarding the brain donation process. Even if individuals with cognitive symptoms were 10 times more likely to donate their brains, the estimated prevalence would still exceed 60%. Together, these findings suggest that selection bias inflates donor-based estimates but is unlikely to account for the high burden of CTE neuropathology observed among deceased former NFL players. Estimating the prevalence of CTE in football players at lower levels of play (eg, high school or college) will be important to better define the scope of this public health concern. However, this will prove substantially more challenging due to the lack of available data (eg, causes of death or MCI rates) on nondonors at lower levels of play. There remains a continued need for research into the mechanisms, clinical manifestations, and prevention of CTE across all levels of play.

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Concept and design: Gallini, Weuve, Daneshvar, Tripodis.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Gallini, Tripodis.

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REFERENCES

1. Bieniek KF, Ross OA, Cormier KA, et al. Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathol*. 2015;130(6):877-889. doi:10.1007/s00401-015-1502-4

2. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709-735. doi:10.1097/NEN.0b013e3181a9d503

3. Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. 2017;318(4):360-370. doi:10.1001/jama.2017.8334

4. Mez J, Daneshvar DH, Abdolmohammadi B, et al. Duration of American football play and chronic traumatic encephalopathy. *Ann Neurol*. 2020;87(1):116-131. doi:10.1002/ana.25611

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5. Priemer DS, Iacono D, Rhodes CH, Olsen CH, Perl DP. Chronic traumatic encephalopathy in the brains of military personnel. *N Engl J Med*. 2022;386(23):2169-2177. doi:10.1056/NEJMoa2203199

6. Tiemensma M, Byard RW, Vink R, Affleck AJ, Blumbergs P, Buckland ME. Chronic traumatic encephalopathy (CTE) in the context of longstanding intimate partner violence. *Acta Neuropathol*. 2024;148(1):1. doi:10.1007/s00401-024-02757-3

7. Bieniek KF, Cairns NJ, Crary JF, et al; TBI/CTE Research Group. The second NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2021;80(3):210-219. doi:10.1093/jnen/nlab001

8. Daneshvar DH, Nair ES, Baucom ZH, et al. Leveraging football accelerometer data to quantify associations between repetitive head impacts and chronic traumatic encephalopathy in males. *Nat Commun*. 2023;14(1):3470. doi:10.1038/s41467-023-39183-0

9. McKee AC, Alosco ML, Huber BR. Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurg Clin N Am*. 2016;27(4):529-535. doi:10.1016/j.nec.2016.05.009

10. McKee AC, Mez J, Abdolmohammadi B, et al. Neuropathologic and clinical findings in young contact sport athletes exposed to repetitive head impacts. *JAMA Neurol*. 2023;80(10):1037-1050. doi:10.1001/jamaneurol.2023.2907

11. Mez J, Solomon TM, Daneshvar DH, et al. Assessing clinicopathological correlation in chronic traumatic encephalopathy: rationale and methods for the UNITE study. *Alzheimers Res Ther*. 2015;7(1):62. doi:10.1186/s13195-015-0148-8

12. Haneuse S, Schildcrout J, Crane P, Sonnen J, Breitner J, Larson E. Adjustment for selection bias in observational studies with application to the analysis of autopsy data. *Neuroepidemiology*. 2009;32(3):229-239. doi:10.1159/000197389

13. Ban VS, Madden CJ, Bailes JE, Hunt Batjer H, Lonser RR. The science and questions surrounding chronic traumatic encephalopathy. *Neurosurg Focus*. 2016;40(4):E15. doi:10.3171/2016.2.FOCUS15609

14. Schwab N, Hazrati LN. Assessing the limitations and biases in the current understanding of chronic traumatic encephalopathy. *J Alzheimers Dis*. 2018;64(4):1067-1076. doi:10.3233/JAD-180373

15. Iverson GL, Gardner AJ, Shultz SR, et al. Chronic traumatic encephalopathy neuropathology might not be inexorably progressive or unique to repetitive neurotrauma. *Brain*. 2019;142(12):3672-3693. doi:10.1093/brain/awz286

16. Binney ZO, Bachynski KE. Estimating the prevalence at death of CTE neuropathology among professional football players. *Neurology*. 2019;92(1):43-45. doi:10.1212/WNL.0000000000006699

17. LeClair J, Weuve J, Fox MP, et al. Relationship between level of American football playing and diagnosis of chronic traumatic encephalopathy in a selection bias analysis. *Am J Epidemiol*. 2022;191(8):1429-1443. doi:10.1093/aje/kwac075

18. Alosco ML, Kasimis AB, Stamm JM, et al. Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes. *Transl Psychiatry*. 2017;7(9):e1236. doi:10.1038/tp.2017.197

19. Walton SR, Brett BL, Chandran A, et al. Mild cognitive impairment and dementia reported by former professional football players over 50 yr of age: an NFL-LONG study. *Med Sci Sports Exerc*. 2022;54(3):424-431. doi:10.1249/MSS.0000000000002802

20. Harrison KL, Hunt LJ, Ritchie CS, Yaffe K. Dying with dementia: underrecognized and stigmatized. *J Am Geriatr Soc*. 2019;67(8):1548-1551. doi:10.1111/jgs.15895

SUPPLEMENT 1.

eTable 1. Neurodegenerative Disease International Classification of Disease (ICD) Code Mapping
eAppendix 1. NDI and UNITE Data Descriptions
eAppendix 2. Derivation of Selection Ratio
eTable 2. NFL-LONG Reported MCI and Dementia Prevalences by Age Strata
eAppendix 3. Example of MCI enrichment
eTable 3. Reclassification of MCI Individuals to Expand Dementia Cause of Death Definition to "Clear Cognitive Symptoms" (70-74 Age of Death)
eAppendix 4. MCI Expansion Methodology Modifications
eReferences

SUPPLEMENT 2.

Data Sharing Statement

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