Prevalence of chronic traumatic encephalopathy at death in National Football League players: retrospective population based cohort study, 2008-21

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ABSTRACT

OBJECTIVES

To determine the range of possible prevalences of chronic traumatic encephalopathy (CTE) at death among National Football League (NFL) players and examine the association between CTE severity and risk of dementia.

DESIGN

Retrospective population based cohort study.

SETTING

NFL players from the era of hard-shell helmets (post-1949) in the US, including brain donors to the UNITE (Understanding Neurologic Injury and Traumatic Encephalopathy) and UCSF ADRC (University of California, San Francisco Alzheimer's Disease Research Center) brain banks.

PARTICIPANTS

1712 former NFL players who died during 2008-21, of whom 338 donated their brains for neuropathological evaluation. Personal information and causes of death according to the National Death Index (NDI) were obtained for all NFL players who died during the study period. Neuropathologists masked to clinical and playing histories assessed postmortem CTE diagnosis and stage IV CTE. Clinicians, masked to neuropathological status, reviewed donors' medical records and informant based clinical histories, to adjudicate a dementia diagnosis.

MAIN OUTCOME MEASURES

The main outcome measures were the minimum (number of donors with CTE/total number of NFL deaths) and maximum (1-(number of donors without CTE/total number of NFL deaths)) CTE prevalence at death during the study period and the six years (2016-21) when brain donation was most frequent. To account for selection pressure of brain donation status, inverse probability weighting was used to estimate the association between stage IV CTE and study clinician diagnosed dementia.

RESULTS

Among 1712 NFL players who died, 338 (19.7%) players' brains were studied, 315 (93.2%) of whom had a diagnosis of CTE; thus, among all 1712 NFL players who died, the possible CTE prevalence at death ranged between 18.5% and 98.7%. The possible prevalence at death during 2016 to 2021, when brain donation was most frequent, ranged between 24.5% and 97.7%. Among brain donors, 104 (30.8%) had stage IV CTE, 202 (59.8%) had study clinician diagnosed dementia (dementia onset: 63.4 years, standard deviation (SD) 12.5; death: 73.1 years, SD 10.5), and 63 (18.6%) had neurodegenerative disease listed as primary cause of death. In donors, stage IV CTE was associated with study clinician diagnosed dementia (risk ratio 1.44, 95% confidence interval 1.16 to 1.78; P<0.001). Only 40.6% of donors (n=82) with study clinician diagnosed dementia had neurodegenerative disease listed as the primary or secondary cause of death.

CONCLUSIONS

At minimum, nearly a quarter of all former NFL players who died during 2016-21 had CTE neuropathology at death. Among NFL player brain donors, dementia diagnosed based on records before death was common and associated with stage IV CTE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Epidemiological studies in multiple cohorts, including NFL athletes, have shown that individuals with repetitive exposure to head impact have higher mortality from neurodegenerative disease than the general population

Similarly, multiple studies have shown a higher proportion of chronic traumatic encephalopathy (CTE) in cohorts with a history of repetitive head impacts

The extent to which CTE pathology is present in a fully enumerated cohort and the extent to which this pathology is associated with clinical symptoms, including dementia, has not been formally studied

WHAT THIS STUDY ADDS

At minimum, nearly a quarter of all former NFL players who died during 2016-21 had CTE at death, and dementia was common among donors and associated with stage IV CTE

These data provide insight into the extent to which the higher proportions of death due to neurodegenerative disease are associated with CTE pathology and provide targets for future research studies and policy recommendations

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that has been diagnosed in individuals with high exposure to repetitive head impacts.[1] Like most neurodegenerative diseases, CTE can be definitively diagnosed only based on

neuropathological evaluation after death. CTE can be reliably distinguished from other neurodegenerative diseases based on the pathognomonic lesion of CTE: the perivascular accumulation of hyperphosphorylated tau (p-tau) in neurons at the depths of the cortical sulci.[2] Because CTE can currently be diagnosed definitively only after death, the epidemiological features of CTE have been difficult to characterise. However, disease prevalence at death can be instructive, as it has been with other diseases informed by neuropathology, including neurodegenerative diseases,[3-8] cerebrovascular diseases,[9-12] and other disease processes.[13-15]

Several studies have estimated the prevalence of CTE at death in community populations. In 2018 the Framingham Heart Study reported that one of all 164 brain donors (0.6%) had CTE.[16] A study of the first 532 community dwelling brain donor members of the Kaiser Permanente health maintenance organisation identified three donors (0.6%) with CTE.[17] A study of all community members born on the left bank of the Danube between May 1925 and June 1926 found that none of the 310 donors (0%) who underwent autopsy between 2000 and 2016 had CTE.[18]

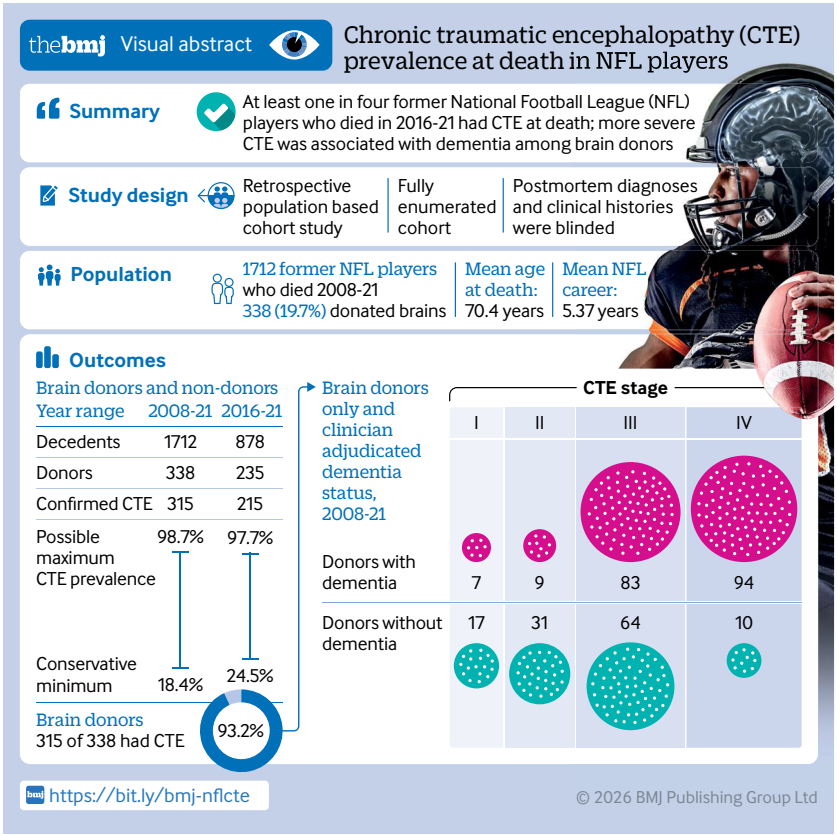
Other studies have estimated the prevalence of CTE at death in specialised cohorts. One study of donors from the Mayo Clinic Neurodegenerative Disease Brain Bank found that 21 (32%) of the 66 men with documented exposure to repetitive head impacts from contact sports had CTE, compared with none of the 198 age matched donors without such exposure documented.[19] In a study of all American football players to donate their brains to the UNITE (Understanding Neurologic Injury and Traumatic Encephalopathy) Brain Bank up to 2020, 451 of 631 donors (71.5%) had CTE.[20] Another study from the Mayo Clinic Tissue Registry, which measured exposure to repetitive head impacts based on contact sports reported in high school yearbooks and obituaries, identified CTE in 15 of the 300 donors with documented exposure to repetitive head impacts (5%), versus six of the 450 donors without documented exposure (1.3%).[21] In a study of donors to the Department of Defence Brain Bank, none of the 165 military veterans unexposed to repetitive head impacts from contact sports (0%) had CTE, whereas 10 of the 60 exposed military veterans (17%) did.[22]

In the community based cohorts discussed above that did not specifically include individuals with documented exposure to repetitive head impacts, CTE prevalences at death ranged from 0% to 1.3%. In contrast, CTE prevalence at death in specialty cohorts with exposure to repetitive head impacts from contact sports ranged from 5% to 72%. This higher prevalence is likely explained by the greater and more widespread exposure to such impacts among participants in the latter cohorts.[20] However, all these prevalence estimates may have been biased by differential selection related to brain donation, as families may have been more likely to donate the brain of an individual who had symptoms.

Additional research has sought to estimate the prevalence of CTE at death in individuals with high exposure to repetitive head impacts. National Football League (NFL) players represent a fully enumerated cohort and can provide insight into the epidemiology of CTE in individuals with such high exposure. In previous research from the Boston University CTE Center UNITE Brain Bank, of the first 111 NFL players studied after death, 110 (99%) had CTE.[23] Another study expanded on these findings by estimating the boundaries of CTE prevalence at death among former NFL players by compiling an enumerated list of all former NFL players who died during the study period; they reported that CTE prevalence among former NFL players during the study period ranged from 9.6% to 99.9%, depending on the proportion of players with CTE whose brains were donated to UNITE.[24]

The prevalence of any neurodegenerative disease has greater clinical and public health relevance if the pathology is clearly associated with clinical outcomes. Previous studies found that about 85% of donors with high severity CTE at death had dementia,[1 20 23 25] but the proportion of dementia and its relation to CTE in a fully enumerated cohort with high exposure to repetitive head impacts has not been previously reported. Additionally, extensive debate remains about the clinicopathological link between CTE and dementia.[26]

Studies using death certificate data, which is typically based on clinical report, have identified increased rates of dementia in NFL players, based on the combined report of all causes of death related to dementia and neurodegenerative disease. A study



of 3439 NFL players with at least five seasons of play between 1959 and 1988 estimated that players had more than three times the rate of death from a neurodegenerative disease compared with a matched US sample (standardised mortality ratio 3.26, 95% confidence interval (CI) 1.9 to 5.2).[27] In a subset of these NFL players, the hazard ratio for neurodegenerative death was 2.99 (95% CI 1.64 to 5.45) against a matched reference cohort of Major League Baseball players.[28] However, death certificates have been shown to underdiagnose dementia, only capturing 7% to 63% of individuals who died from the disease.[29-32]

Since a 2017 study reported CTE proportions in the UNITE Brain Bank,[23] the number of brains donated by former NFL players has tripled. We leveraged the substantial expansion of this resource to estimate the range of possible CTE prevalences in these decedents,[1 2] compare prevalences of dementia and neurodegenerative disease as determined by study clinician adjudication versus death certificates,[3] and estimate the association of stage IV CTE disease at death with dementia to examine the extent to which CTE neuropathological findings clinically manifest in individuals exposed to repetitive head impacts by leveraging a large cohort of former NFL players. We hypothesised that individuals with stage IV CTE at death would have higher a risk of a dementia diagnosis compared with those without stage IV CTE at death.

Methods

Participants

The present study limited inclusion to donors who were former American football players who played at least one game in the NFL, as these individuals represent a fully enumerated cohort and one of the most well studied subset of individuals in the world.[23 33] We further restricted analyses to those who debuted in the NFL after 1949, the year when plastic helmets became mandatory in the NFL; secondary analyses included all NFL athletes regardless of debut year. All donors were recruited from Boston University (n=333), Mount Sinai (New York; n=1), and University of California, San Francisco Alzheimer's Disease Research Center (UCSF ADRC; n=4) brain banks, which began recruitment in 2008, 2018, and 1998, respectively, and are ongoing. Recruitment and inclusion criteria for each brain bank have been detailed previously.[23 34] To be eligible for the UNITE Brain Bank through Boston University or Mount Sinai, donors must have had a history of repetitive exposure to head impacts (eg, contact sport), regardless of symptoms.

Ascertainment of NFL player deaths and professional statistics

We compiled a complete list of all former NFL players who died during the study period using methods previously reported.[33] Specifically, Pro Football Reference, formerly operated by Hidden Game Sports, maintains a comprehensive database of demographic, physical, and NFL career related information on all NFL players since the leagues conception in 1920, including years of NFL play, number of Pro Bowl Games, Hall of Fame status, primary professional position, date of birth, age at death, and date of death.[33] Additionally, we obtained death certificates from the Centers for Disease Control and Prevention National Death Index for all NFL decedents. Two clinicians (DHD, JM) independently reviewed all cause of death ICD codes and categorised them into one of eight categories. Discrepancies were resolved by discussion. These data were used to compare mortality among NFL donors and non-donors, as well as study clinician adjudicated dementia compared with those obtained from the death certificates.

Collection of clinical data and dementia assessment

Postmortem data collection from informants, as well as review of donor medical records, for the UNITE Brain Bank have been detailed previously.[34 35] Clinical history of each donor was obtained from informants double blinded to the results of neuropathological examination. Informants completed standardised assessments of the donor's function, including the Functional Activities Questionnaire, as well as cognition, including the adult version of the Behaviour Rating Inventory of Executive Function, and the Cognitive Difficulties Scale.[34] Medical records were requested for all cases and 184 were received and reviewed. At least two clinicians (MLA, RCC, DHD, BD, LG, DIK, JM, RAS) met to discuss each case and determine whether the donor had dementia based on fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and records before death.[36] Donors from the UCSF ADRC were followed in life as part of the UCSF ADRC Clinical Core (a patient care and research evaluation unit within the UCSF Memory and Aging Center), with prospective clinical assessment. Study clinicians adjudicated cause of death using all available information.

Neuropathological assessment

Neuropathologists (VEA, JFC, BRH, ACM, WWS, TDS) were masked to the participant's exposure to repetitive head impacts and clinical history, including, but not limited to, knowledge about whether a donor participated in any contact sport at any level. Neuropathologists at Boston University review cases from the combined pool of cases at the CTE Center, Veterans Affairs Amyotrophic Lateral Sclerosis Biorepository Brain Bank, Framingham Heart Study, centenarian study, Boston University Alzheimer's Disease Research Center, and all brain donors for the Veterans Affairs New England network, and they are masked to clinical and repetitive head impact histories. Neuropathologists at Mount Sinai deal with cases from its Alzheimer's Disease Research Center and Late Effects of Traumatic Brain Injury programme, and UCSF is part of the broader UCSF ADRC and thus are similarly masked to clinical history and exposure to repetitive head impacts.

Neuropathological processing and gross and microscopic examination followed previously

established methods. Twenty two sections of paraffin embedded tissue were stained for Luxol fast blue, haematoxylin and eosin, Bielschowsky silver, p-tau (AT8; pSer202, pThr205), α-synuclein, amyloid β, and phosphorylated transactive response DNA binding protein 43 kDa (pTDP-43). CTE was diagnosed using National Institutes of Health/ National Institute of Biomedical Imaging and Bioengineering neuropathological criteria, in which the minimum diagnosis threshold for CTE requires a perivascular pathognomonic lesion containing p-tau aggregates in neurons, astrocytes, and cell processes at the depths of the cortical sulci.[2 23 37-39] Supportive features for CTE diagnosis include neurofibrillary tangles and p-tau pretangles in superficial cortical layers II and III; subpial p-tau astrocytes at the glial limitans; pretangles, extracellular tangles, or neurofibrillary tangles in CA2 and CA4 of the hippocampus; and dot-like p-tau neurites.[35] Participants with a diagnosis of CTE also were assigned a CTE stage (I-IV, increasing with severity) using criteria previously developed.[37 40] Diagnosis and staging of CTE were agreed upon by consensus of at least two neuropathologists. CTE severity was further dichotomised into low severity CTE (most commonly McKee stages I and II) and high severity CTE (most commonly McKee stages III and IV); staging was additionally verified to ensure all individuals with stage I and II CTE exhibited low severity disease and all individuals with stage III and IV CTE exhibited high severity disease.[2] Well established neuropathological criteria were used to diagnose all comorbid neurodegenerative diseases.[2 20 41-50] When CTE and Alzheimer's disease were comorbid, we determined the presence of Alzheimer's disease using consensus criteria.[51] In participants meeting criteria for both CTE and Alzheimer's disease, we considered neurofibrillary tangles in CA4 and the dentate nucleus of the cerebellum to be indicative of high severity CTE; but not in the setting of advanced age and substantial burden of neurofibrillary tangles in CA1. Braak stage, used to characterise the distribution and progression of neurofibrillary tau pathology, was diagnosed according to established criteria, and moderate to severe Braak stage was considered as stages III-VI.[44]

Statistical analysis

Prevalence of CTE at death among former NFL players

We first computed the range of possible CTE prevalences at death by identifying all known cases in the donor cohort. To compute minimum prevalence at death, we divided the number of donors with CTE by all deaths in NFL players in the same time period, whereas maximum prevalence at death was computed as 1-(number of donors without CTE/total number of NFL deaths). To support the comparison of clinician adjudicated and death certificate prevalences of dementia we then generated unadjusted means and frequencies of participants' personal, American football based exposure to repetitive head impacts, functional and cognitive measures, and cause of death measures, by CTE stage and study clinician adjudicated dementia.

Association of CTE with dementia at death among former NFL players

We also estimated the association between stage IV CTE and dementia near death in all NFL players who had died. CTE data were, however, lacking for most deceased players as their brains had not been donated. If brain donation was related to both CTE and dementia through independent pathways, it is possible that the association estimated among donors differed from the association in the source population of all deceased players. Because brain donation is non-random and associated with personal and clinical factors, we used inverse probability weighting to account for unequal sampling probabilities among donors and address potential selection pressure resulting from donation. We obtained the weights for the inverse probability weighting procedures from the full source population of all NFL decedents during the study period based on their donation status. Each individual's probability of donation was based on covariates hypothesised to be associated with donor status, including age at death, race, position, Hall of Fame status, number of Pro Bowl Games, body mass index at debut game for NFL, number of years as an NFL player, and cause of death.[52] Weights were based on the inverse probability of brain donation developed by a logistic binomial model, including the aforementioned covariates, with weights equal to the inverse of the probabilities of donation status. Hence, those with low probability of being a brain donor received a higher weight, and observations with a higher probability of donation status received a lower weight. Stabilised weights were calculated, with a mean weight of 1.00 (range 0.22-8.46).

Weights were then applied to several analyses among donors. We applied robust sandwich variance estimators for all weighted regression models. Weighted modified Poisson log binomial regression was used to estimate the risk ratio of dementia at death among donors with stage IV CTE versus those without stage IV CTE, adjusting for age at death. Subsequent weighted models included additional relevant covariates, including education, age of first exposure to American tackle football, hypertension status, obstructive sleep apnoea status, position, and treatment for substance use. Weighted linear regression analyses were also conducted to estimate the relation between stage IV CTE and each informant reported clinical scale. Using these approaches, we aimed to reduce observed imbalance of covariates between donors and non-donors, such that weighted analyses better reflect the covariate distribution of the full deceased population among those whose brains were donated. However, this inverse probability weighting approach only addresses differential brain donation; it does not address differential rates of mortality.

To examine the influence of covariates, inverse probability weighting, and alternative definitions for our CTE pathology variables, we conducted several

sensitivity analyses. We examined the relation between stage IV CTE and dementia status using unweighted logistic regression adjusted for age at death. We used alternative definitions for CTE disease, including CTE presence versus absence and high severity CTE (defined as CTE stages III or IV) versus absence of high severity CTE. Covariates with missing values (range 0-25%) were imputed through predictive mean matching procedure comprising 10 rounds of multiple imputation before all analysis. Imputation using the *mice* package was used for regression analyses using Rubin's rule. All statistical analyses were completed using R Statistical Computing Package v4.4.2 (Vienna, Austria). Significance was determined at α=0.05.

Patient and public involvement

We involved patients and members of the public with lived experience of repetitive head trauma throughout the design and conduct of the study as well as in choice of outcomes and recruitment. The primary research question evaluating the prevalence of CTE was informed by their personal lived experience with long term sequalae of repeated traumatic brain injury. Lisa McHale, the director of legacy family relations at the Boston University CTE Center, was directly involved with patient recruitment and has lived experience, as her husband died with CTE.

Results

Extrapolating the prevalence of CTE at death in all NFL players

From 2008 to 2021, 1712 NFL players died, 338 (19.7%) players' brains were studied, and 315 (93.2%) donors had a diagnosis of CTE. Under the most conservative assumptions (ie, among all NFL decedents, donors with a diagnosis of CTE from the UNITE Brain Bank and the UCSF ADRC represent the only decedents with CTE), the minimum prevalence of CTE at death in NFL players during the study period would be 18.5%. Under the least conservative

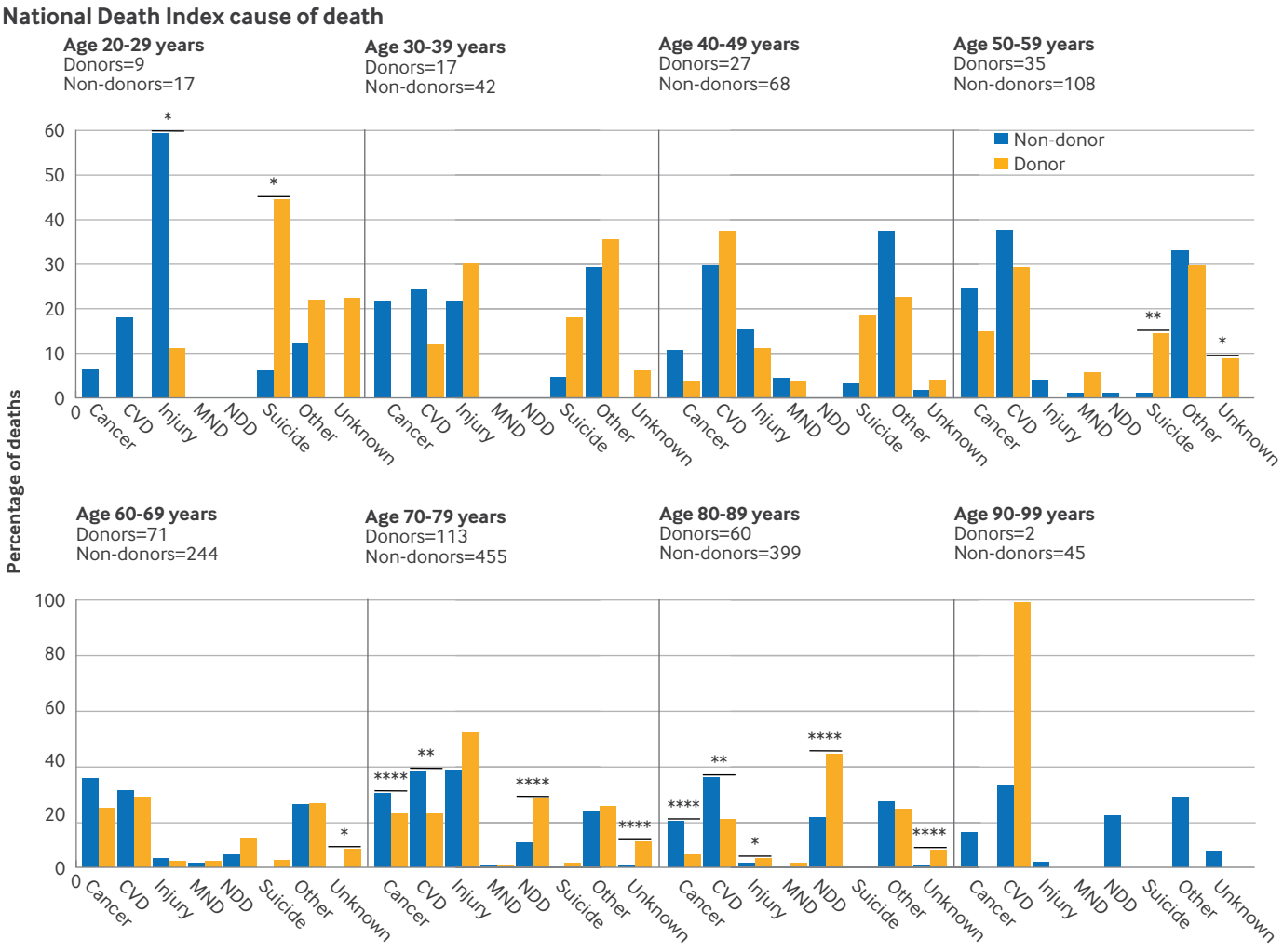


Fig 1 | Cause of death from the Centers for Disease Control and Prevention National Death Index, by National Football League player donation status and decade of death. Age bins were selected to maximise deidentification while maintaining data specificity. Significant relation between donors and non-donors within each decade of death were computed in unadjusted x^2 test: * P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. CVD=cardiovascular disease; MND=motor neuron disease; NDD=neurodegenerative disease

Table 1 | Personal and clinical characteristics of NFL brain donors by CTE stage and clinician adjudicated dementia status. Values are number (percentage) unless stated otherwise

Characteristics	CTE severity					Clinical diagnosis of dementia		All donors (n=338)
	No CTE (n=23)	Stage I (n=24)	Stage II (n=40)	Stage III (n=147)	Stage IV (n=104)	Not diagnosed (n=123)	Diagnosed (n=202)	
Mean (SD) age at death (years)	62.4 (13.7)	53.0 (17.9)	50.2 (15.9)	66.6 (13.2)	76.4 (7.15)	56.2 (15.5)	73.1 (10.5)	66.5 (15.2)
Race:								
Black	12 (52.2)	9 (37.5)	17 (42.5)	56 (38.1)	17 (16.3)	50 (40.7)	56 (27.7)	111 (32.8)
White	11 (47.8)	12 (50.0)	20 (50.0)	88 (59.9)	85 (81.7)	70 (56.9)	143 (70.8)	216 (63.9)
Other	0 (0)	3 (12.5)	3 (7.5)	3 (2.0)	2 (1.9)	3 (2.4)	3 (1.5)	11 (3.3)
Military	6 (26.1)	1 (4.2)	2 (5.0)	23 (15.6)	38 (36.5)	10 (8.1)	60 (29.7)	70 (20.7)
Mean (SD) No of years as football player	16.7 (5.56)	13.7 (3.94)	17.1 (4.31)	17.4 (4.39)	18.9 (4.68)	17.4 (4.49)	17.7 (4.79)	17.5 (4.68)
Mean (SD) No of years in NFL	6.35 (4.51)	3.64 (3.00)	5.53 (4.19)	6.84 (3.65)	8.60 (3.79)	6.24 (3.87)	7.49 (4.05)	6.98 (4.00)
Player position:								
Defensive back	3 (13.0)	2 (8.3)	6 (15.0)	19 (12.9)	13 (12.5)	17 (13.8)	25 (12.4)	43 (12.7)
Defensive line	8 (34.8)	3 (12.5)	9 (22.5)	30 (20.4)	8 (7.7)	29 (23.6)	27 (13.4)	58 (17.2)
Kicker	1 (4.3)	1 (4.2)	0 (0)	0 (0)	1 (1.0)	1 (0.8)	2 (1.0)	3 (0.9)
Linebacker	3 (13.0)	1 (4.2)	6 (15.0)	20 (13.6)	17 (16.3)	14 (11.4)	31 (15.3)	47 (13.9)
Offensive lineman	3 (13.0)	7 (29.2)	7 (17.5)	29 (19.7)	21 (20.2)	23 (18.7)	43 (21.3)	67 (19.8)
Punter	0 (0)	2 (8.3)	1 (2.5)	0 (0)	0 (0)	2 (1.6)	1 (0.5)	3 (0.9)
Quarterback	2 (8.7)	1 (4.2)	1 (2.5)	5 (3.4)	7 (6.7)	4 (3.3)	12 (5.9)	16 (4.7)
Running back	0 (0)	1 (4.2)	3 (7.5)	20 (13.6)	20 (19.2)	13 (10.6)	31 (15.3)	44 (13.0)
Tight end	1 (4.3)	1 (4.2)	2 (5.0)	7 (4.8)	7 (6.7)	8 (6.5)	10 (5.0)	18 (5.3)
Wide receiver	2 (8.7)	1 (4.2)	4 (10.0)	8 (5.4)	5 (4.8)	7 (5.7)	12 (5.9)	20 (5.9)
Other	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.5)	1 (0.3)
Study clinician adjudicated dementia diagnosis	9 (39.1)	7 (29.2)	9 (22.5)	83 (56.5)	94 (90.4)	0 (0)	202 (100)	202 (59.8)
Mean (SD) CDS total score	79.1 (46.4)	66.7 (42.8)	68.5 (37.9)	86.4 (40.2)	121 (39.5)	56.3 (32.8)	113 (36.9)	93.8 (44.6)
Mean (SD) FAQ total score	8.86 (10.6)	7.17 (9.63)	7.62 (8.42)	13.7 (10.7)	23.6 (8.73)	4.35 (5.68)	21.9 (8.70)	15.5 (11.5)
Mean (SD) BRIEF-GEC T-score	70.0 (21.2)	77.1 (20.0)	78.0 (18.2)	82.0 (17.5)	89.7 (17.6)	71.8 (19.4)	88.4 (15.7)	83.1 (18.6)
Mean (SD) BRIEF-MI T-score	69.2 (23.2)	72.3 (20.9)	76.2 (17.1)	80.2 (18.0)	91.1 (18.4)	69.1 (18.4)	88.4 (16.9)	82.2 (19.6)
Cause of death*:								
Cancer	2 (8.7)	2 (8.3)	0 (0)	21 (14.3)	11 (10.6)	20 (16.3)	16 (7.9)	36 (10.7)
Cardiovascular disease	6 (26.1)	4 (16.7)	13 (32.5)	41 (27.9)	15 (14.4)	30 (24.4)	46 (22.8)	79 (23.4)
Injury	0 (0)	1 (4.2)	5 (12.5)	7 (4.8)	8 (7.7)	10 (8.1)	11 (5.4)	21 (6.2)
Neurodegenerative	1 (4.3)	1 (4.2)	2 (5.0)	14 (9.5)	45 (43.3)	0 (0)	62 (30.7)	63 (18.6)
Neurodegenerative 1° or 2°	3 (13.0)	1 (4.2)	4 (10.0)	20 (13.6)	57 (54.8)	1 (0.8)	82 (40.6)	85 (25.1)
Suicide	3 (13.0)	4 (16.7)	5 (12.5)	9 (6.1)	0 (0)	17 (13.8)	3 (1.5)	21 (6.2)
Other	8 (34.8)	5 (20.8)	11 (27.5)	42 (28.6)	21 (20.2)	36 (29.3)	49 (24.3)	87 (25.7)
Unknown	3 (13.0)	7 (29.2)	4 (10.0)	13 (8.8)	4 (3.8)	10 (8.1)	15 (7.4)	31 (9.2)
Residential setting at death:								
Independent	12 (52.2)	12 (50.0)	23 (57.5)	56 (38.1)	8 (7.7)	90 (73.2)	21 (10.4)	111 (32.8)
Assisted living/home assistance	7 (30.4)	5 (20.8)	12 (30.0)	56 (38.1)	49 (47.1)	24 (19.5)	105 (52.0)	129 (38.2)
Memory care/nursing home	1 (4.3)	0 (0)	1 (2.5)	23 (15.6)	45 (43.3)	1 (0.8)	69 (34.2)	70 (20.7)
Unhoused	0 (0)	1 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.3)
Unknown	3 (13.0)	6 (25.0)	4 (10.0)	12 (8.2)	2 (1.9)	8 (6.5)	6 (3.0)	27 (8.0)

Percentages represent the number divided by all donors at that CTE stage and dementia status. Clinical information, including dementia diagnosis, not available for nine donors.
1°=primary; 2°=secondary; BRIEF=Behavior Rating Inventory of Executive Function (adult version); CDS=Cognitive Difficulty Scale; CTE=chronic traumatic encephalopathy; FAQ=Functional Activities Questionnaire; GEC=General Executive Composite; MI=Metacognition Index; NFL=National Football League; SD=standard deviation.
*According to Centers for Disease Control and Prevention National Death Index.

assumptions (ie, that all decedents who were not studied in the UNITE Brain Bank and the UCSF ADRC had CTE), the maximum prevalence of CTE at death during the study period would be 98.7%. Supplemental figure 1 shows the relation between minimum and maximum prevalence throughout the study period, which varies largely as a function of number of brains studied each year. Over the later six years, when brain donation was more frequent, 235 (26.8%) brains of the 878 NFL players who died were donated for analysis to the UNITE Brain Bank and the UCSF ADRC. Of those, CTE was diagnosed in 215 (91.4%), equating to a minimum prevalence of 24.5% of CTE at death for all decedents, and a maximum prevalence at death of 97.7%. Supplemental table 3 shows trends in brain donation over time, including characteristics of the donors before and after 2016. Figure 1 shows the characteristics of donors and non-donors (also see table 4).

Characteristics of donors

Table 1 shows the personal and clinical characteristics of the NFL donors. The mean age at death was 66.5 years (standard deviation (SD) 15.2 years), with age at death not associated with CTE status (P=0.28) but significantly associated with stage IV CTE (mean age at death for stage IV CTE 76.4 (SD 7.1) years; P<0.001; mean age for all other donors 62.0 (15.7) years. Total lifetime duration of American football play was not associated with CTE status (risk ratio 1.00, 95% CI 1.00 to 1.01; P=0.48) but was associated with stage IV CTE (1.07, 1.04 to 1.09; P<0.001), and high severity

Table 2 | Disease characteristics of NFL brain donors by CTE stage and clinician adjudicated dementia status. Values are number (percentage)

Characteristics	CTE severity					Clinical diagnosis of dementia		All donors
	No CTE (n=23)	Stage I (n=24)	Stage II (n=40)	Stage III (n=147)	Stage IV (n=104)	Not diagnosed (n=123)	Diagnosed (n=202)	(n=338)
Vascular disease								
Arteriolosclerosis:								
Mild	7 (30.4)	6 (25.0)	13 (32.5)	37 (25.2)	20 (19.2)	31 (25.2)	50 (24.8)	83 (24.6)
Moderate	10 (43.5)	6 (25.0)	10 (25.0)	65 (44.2)	48 (46.2)	46 (37.4)	90 (44.6)	139 (41.1)
Severe	2 (8.7)	1 (4.2)	1 (2.5)	13 (8.8)	26 (25.0)	4 (3.3)	38 (18.8)	43 (12.7)
Atherosclerosis:								
Mild	3 (13.0)	6 (25.0)	6 (15.0)	35 (23.8)	32 (30.8)	27 (22.0)	51 (25.2)	82 (24.3)
Moderate	5 (21.7)	0 (0)	2 (5.0)	19 (12.9)	24 (23.1)	7 (5.7)	42 (20.8)	50 (14.8)
Severe	3 (13.0)	0 (0)	1 (2.5)	9 (6.1)	7 (6.7)	3 (2.4)	17 (8.4)	20 (5.9)
Cerebral amyloid angiopathy:								
Mild	4 (17.4)	2 (8.3)	4 (10.0)	29 (19.7)	21 (20.2)	14 (11.4)	45 (22.3)	60 (17.8)
Moderate	4 (17.4)	1 (4.2)	2 (5.0)	15 (10.2)	19 (18.3)	5 (4.1)	34 (16.8)	41 (12.1)
Severe	1 (4.3)	0 (0)	0 (0)	5 (3.4)	11 (10.6)	1 (0.8)	16 (7.9)	17 (5.0)
Microinfarcts	5 (21.7)	1 (4.2)	1 (2.5)	24 (16.3)	21 (20.2)	14 (11.4)	37 (18.3)	52 (15.4)
Neuropathology								
Braak stage*:								
I	3 (13.0)	6 (25.0)	14 (35.0)	5 (3.4)	0 (0)	20 (16.3)	7 (3.5)	28 (8.3)
II	2 (8.7)	2 (8.3)	10 (25.0)	23 (15.6)	8 (7.7)	15 (12.2)	26 (12.9)	45 (13.3)
III	6 (26.1)	4 (16.7)	0 (0)	76 (51.7)	37 (35.6)	43 (35.0)	79 (39.1)	123 (36.4)
IV	0 (0)	1 (4.2)	0 (0)	17 (11.6)	19 (18.3)	10 (8.1)	27 (13.4)	37 (10.9)
V	2 (8.7)	0 (0)	1 (2.5)	8 (5.4)	21 (20.2)	2 (1.6)	30 (14.9)	32 (9.5)
VI	2 (8.7)	0 (0)	0 (0)	5 (3.4)	12 (11.5)	0 (0)	18 (8.9)	19 (5.6)
Diffuse plaques:								
Sparse	5 (21.7)	8 (33.3)	4 (10.0)	28 (19.0)	25 (24.0)	22 (17.9)	45 (22.3)	70 (20.7)
Moderate	5 (21.7)	1 (4.2)	1 (2.5)	26 (17.7)	26 (25.0)	10 (8.1)	46 (22.8)	59 (17.5)
Frequent	3 (13.0)	1 (4.2)	1 (2.5)	10 (6.8)	37 (35.6)	4 (3.3)	48 (23.8)	52 (15.4)
Neuritic plaques:								
Sparse	3 (13.0)	2 (8.3)	0 (0)	28 (19.0)	37 (35.6)	14 (11.4)	54 (26.7)	70 (20.7)
Moderate	2 (8.7)	0 (0)	1 (2.5)	4 (2.7)	19 (18.3)	0 (0)	26 (12.9)	26 (7.7)
Frequent	1 (4.3)	0 (0)	0 (0)	2 (1.4)	6 (5.8)	0 (0)	9 (4.5)	9 (2.7)
TDP-43	3 (13.0)	2 (8.3)	6 (15.0)	49 (33.3)	81 (77.9)	30 (24.4)	110 (54.5)	141 (41.7)
White matter rarefaction:								
Mild	4 (17.4)	8 (33.3)	24 (60.0)	55 (37.4)	22 (21.2)	48 (39.0)	60 (29.7)	113 (33.4)
Moderate	8 (34.8)	7 (29.2)	5 (12.5)	59 (40.1)	53 (51.0)	40 (32.5)	90 (44.6)	132 (39.1)
Severe	4 (17.4)	1 (4.2)	1 (2.5)	17 (11.6)	26 (25.0)	8 (6.5)	41 (20.3)	49 (14.5)
Neurodegenerative disease diagnosis								
Alzheimer's disease:								
Low	2 (8.7)	7 (29.2)	3 (7.5)	22 (15.0)	16 (15.4)	13 (10.6)	34 (16.8)	50 (14.8)
Intermediate	4 (17.4)	2 (8.3)	0 (0)	28 (19.0)	42 (40.4)	14 (11.4)	61 (30.2)	76 (22.5)
High	4 (17.4)	0 (0)	1 (2.5)	3 (2.0)	21 (20.2)	0 (0)	29 (14.4)	29 (8.6)
Frontotemporal lobar degeneration	2 (8.7)	0 (0)	1 (2.5)	5 (3.4)	15 (14.4)	2 (1.6)	21 (10.4)	23 (6.8)
Lewy body disease:								
Brainstem predominant	1 (4.3)	1 (4.2)	4 (10.0)	6 (4.1)	16 (15.4)	5 (4.1)	22 (10.9)	28 (8.3)
Limbic/neocortical	3 (13.0)	0 (0)	0 (0)	14 (9.5)	10 (9.6)	4 (3.3)	23 (11.4)	27 (8.0)
Amygdala predominant	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (0.5)	1 (0.3)
Olfactory bulb	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.8)	0 (0)	1 (0.3)
Motor neuron disease:								
TDP-43 inclusions	0 (0)	0 (0)	1 (2.5)	4 (2.7)	1 (1.0)	5 (4.1)	1 (0.5)	6 (1.8)
Other inclusions	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (0.5)	1 (0.3)
No specific inclusions	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (0.5)	1 (0.3)
Primary age related tauopathy	0 (0)	3 (12.5)	0 (0)	5 (3.4)	2 (1.9)	2 (1.6)	8 (4.0)	10 (3.0)
No other neurodegenerative disease	0 (0)	18 (75.0)	34 (85.0)	108 (73.5)	39 (37.5)	94 (76.4)	100 (49.5)	199 (58.9)

Percentages represent the number divided by all donors at that CTE stage and dementia status. Clinical information, including dementia diagnosis, not available for nine donors. Neuropathological information not available for four donors.
CTE=chronic traumatic encephalopathy; NFL=National Football League; TDP-43=TAR DNA-binding protein.
*Progressive spread of neurofibrillary tau tangles from entorhinal and transentorhinal regions (stages I-II), to limbic regions (stages III-IV), and to widespread neocortical regions (stages V-VI).

CTE (ie, CTE stages III or IV; risk ratio 1.02, 1.01 to 1.03; P<0.001) (see supplemental table 1).

Table 2 shows the disease characteristics of the NFL donors. After CTE, the most common neurodegenerative diseases were Lewy body disease (n=57, 16.9%), Alzheimer's disease (n=51, 15.1%), frontotemporal lobar degeneration (n=23, 6.8%), primary age related tauopathy (n=10, 3.0%), and motor neuron disease (n=8, 2.4%). Comorbidities were common in this cohort. The most frequent neuropathological findings were moderate to severe Braak stage (n=211, 62.4%), white matter rarefaction (n=181, 53.6%), TAR DNA-binding protein 3 (TDP-43) (n=141, 41.7%), diffuse plaques (n=111, 32.8%), and neuritic plaques (n=35,

Table 3 | Association of stage IV CTE in NFL brain donors with study clinician adjudicated dementia at death and with informant based measures of clinical impairment at death

Clinician adjudicated dementia	Estimate (95% CI)	P value
Models		
Model 1: IPD weighted adjusted for age at death and all available covariates	RR 1.44 (1.16 to 1.78)	<0.001
Model 2: IPD weighted adjusted for age at death	RR 1.45 (1.16 to 1.74)	<0.001
Model 3: log binomial adjusted for age at death	RR 1.28 (1.23 to 1.34)	<0.001
Model 4: unadjusted log binomial	RR 1.85 (1.77 to 1.94)	<0.001
Informant reported clinical scales*		
Cognitive Difficulties Scale total score:		
Model 1: IPD weighted adjusted for age at death and all available covariates	29.47 (25.23 to 33.72)	<0.001
Model 2: IPD weighted adjusted for age at death	30.87 (26.77 to 34.97)	<0.001
Model 3: linear adjusted for age at death	27.7 (24.41 to 30.99)	<0.001
Model 4: unadjusted linear	39.94 (37.02 to 42.85)	<0.001
Functional Activities Questionnaire score:		
Model 1: IPD weighted adjusted for age at death and all available covariates	6.38 (5.34 to 7.42)	<0.001
Model 2: IPD weighted adjusted for age at death	6.29 (4.99 to 7.59)	<0.001
Model 3: linear adjusted for age at death	7.11 (6.33 to 7.89)	<0.001
Model 4: unadjusted linear	11.66 (10.97 to 12.36)	<0.001
BRIEF-GEC T-score		
Model 1: IPD weighted adjusted for age at death and all available covariates	6.46 (4.3 to 8.62)	<0.001
Model 2: IPD weighted adjusted for age at death	6.84 (4.77 to 8.9)	<0.001
Model 3: linear adjusted for age at death	5.94 (4.47 to 7.41)	<0.001
Model 4: unadjusted linear	9.2 (7.88 to 10.51)	<0.001
BRIEF-MI T-score		
Model 1: IPD weighted adjusted for age at death and all available covariates	7.34 (5.18 to 9.5)	<0.001
Model 2: IPD weighted adjusted for age at death	9.22 (7.14 to 11.3)	<0.001
Model 3: linear adjusted for age at death	8.48 (6.98 to 9.98)	<0.001
Model 4: unadjusted linear	12.65 (11.3 to 14)	<0.001

Comparator: donors with stage IV CTE. Reference: donors without stage IV CTE. All available covariates included age at death, cause of death, race, body mass index, education, age at first exposure to tackle football, years of play in National Football League, proxies of fame, hypertension status, obstructive sleep apnoea status, and treatment for substance use utilising log binomial (dementia diagnosis) and linear (clinical scales) regression.
BRIEF=Behaviour Rating Inventory of Executive Function (adult version); CI=confidence interval; CTE=chronic traumatic encephalopathy; GEC=General Executive Composite; IPD=inverse probability of brain donation; MI=Metacognition Index; NFL=National Football League; RR=risk ratio.
*Values are unstandardised coefficient B (95% CI).

10.4%), and the most common vascular findings were moderate to severe arteriolosclerosis (n=183, 54.1%), atherosclerosis (n=70, 20.7%), cerebral amyloid angiopathy (n=58, 17.2%), and microinfarcts (n=52, 15.4%).

Dementia and clinical impairment underlying stage IV CTE among donors

Dementia was common among donors, with dementia diagnosed in 202 of 338 (59.8%), including nine of 23 (39.1%) of those without CTE, seven of 24 (29.2%) of those with stage I CTE, nine of 40 (22.5%) of those with stage II CTE, 83 of 147 (56.5%) of those with stage III CTE, and 94 of 104 (90.4%) of those with stage IV CTE. Using inverse probability weighting to account for potential selection pressure from donation status, adjusting for age at death, education, age of first exposure to American tackle football, hypertension status, obstructive sleep apnoea status, and treatment for substance use, stage IV CTE was associated with increased risk of dementia among donors (risk ratio 1.44, 95% CI 1.16 to 1.78; P<0.001; table 3). Secondary analyses of donors using inverse probability weighting found similar relations between stage IV CTE and dementia status adjusted only for age at death (1.45, 1.16 to 1.74; P<0.001), as did analyses without inverse probability weighting examining the relation between dementia and stage IV CTE (1.85, 1.77 to 1.94; P<0.001), and high severity CTE (2.06, 1.51 to 2.77; P<0.001), but not CTE status (1.34, 0.86 to 2.07; P=0.24). Supplemental table 2 reports results without imputation.

Of the 202 donors with a clinical diagnosis of dementia, 197 (97.5%) had neurodegenerative disease, with CTE the most common (n=193, 95.5%), followed by Alzheimer's disease (n=50, 24.8%), Lewy body disease (n=46, 22.8%), frontotemporal lobar degeneration (n=21, 10.4%), and motor neuron disease (n=3, 1.5%). There was also a high proportion of neurodegenerative comorbidities among donors with dementia, including 46 (22.8%) who had CTE and Alzheimer's disease (16 with Lewy body disease, and five with frontotemporal lobar degeneration); 40 (19.8%) who had CTE with other neurodegenerative findings besides Alzheimer's disease (28 with Lewy body disease; 15 with frontotemporal lobar degeneration; eight with primary age related tauopathy; and three with motor neuron disease); and four (2.0%) who had Alzheimer's disease without CTE findings (including two with Lewy body disease, and one with frontotemporal lobar degeneration). Of the 208 donors with CTE and no other neurodegenerative disease, 107 (53.0%) had dementia. To provide additional clinicopathological context, four example cases were randomly selected based on dementia and CTE status of donors aged 60-64 years; clinical history and disease status for these cases are included in the supplemental file.

Table 4 | Characteristics of NFL brain donors and non-donors to UNITE Brain Bank. Values are number (percentage) unless stated otherwise

Characteristics	UNITE donor status		All NFL players
	Non-donor	Donor	
No of NFL players	1378	334	1712
Mean (SD) age at death (years)	71.3 (13.9)	66.5 (15.2)	70.4 (14.3)
Race:			
Asian	1 (0.1)	1 (0.3)	2 (0.1)
Black	426 (30.9)	111 (33.2)	537 (31.4)
Hispanic	9 (0.7)	2 (0.6)	11 (0.6)
Native American	1 (0.1)	0 (0)	1 (0.1)
Pacific Islander	2 (0.1)	3 (0.9)	5 (0.3)
White	921 (66.8)	213 (63.8)	1134 (66.2)
Multiple	1 (0.1)	0 (0)	1 (0.1)
Mean (SD) measurements at NFL debut:			
Height (cm)	187.7 (5.38)	187.7 (5.66)	187.7 (5.44)
Weight (kg)	102.1 (14.4)	104.3 (14.9)	102.5 (14.5)
Body mass index	28.9 (3.22)	29.4 (3.21)	29.0 (3.23)
Years as NFL player	5.01 (3.81)	6.90 (3.99)	5.37 (3.91)
Playing position:			
Defensive back	228 (16.5)	44 (13.2)	272 (15.9)
Defensive lineman	141 (10.2)	57 (17.1)	198 (11.6)
Kicker	16 (1.2)	0 (0)	16 (0.9)
Linebacker	122 (8.9)	45 (13.5)	167 (9.8)
Offensive lineman	204 (14.8)	68 (20.4)	272 (15.9)
Punter	14 (1.0)	0 (0)	14 (0.8)
Quarterback	58 (4.2)	15 (4.5)	73 (4.3)
Running back	104 (7.5)	46 (13.8)	150 (8.8)
Tight end	39 (2.8)	19 (5.7)	58 (3.4)
Wide receiver	42 (3.0)	20 (6.0)	62 (3.6)
Multiple	410 (29.8)	20 (6.0)	430 (25.1)
Metrics of NFL fame:			
Pro Bowl player, ever	280 (20.3)	97 (29.0)	377 (22.0)
Mean (SD) No of Pro Bowl Games	0.56 (1.46)	0.94 (1.86)	0.63 (1.55)
First team Pro Bowl player, ever	115 (8.3)	40 (12.0)	155 (9.1)
Mean (SD) first team Pro Bowl Games	0.17 (0.71)	0.26 (0.87)	0.19 (0.74)
Hall of Fame	32 (2.3)	17 (5.1)	49 (2.9)
Cause of death*:			
Cancer	326 (23.7)	36 (10.8)	362 (21.1)
Cardiovascular disease	462 (33.5)	79 (23.7)	541 (31.6)
Injury	63 (4.6)	21 (6.3)	84 (4.9)
Motor neuron disease	13 (0.9)	7 (2.1)	20 (1.2)
Neurodegenerative	146 (10.6)	63 (18.9)	209 (12.2)
Neurodegenerative 1° or 2°	220 (16.0)	85 (25.1)	305 (17.8)
Suicide	9 (0.7)	21 (6.3)	30 (1.8)
Other	341(24.7)	80 (24.0)	421 (24.6)
Unknown	18 (1.3)	27 (8.1)	45 (2.6)

Percentages represent the number divided by all NFL players by donation status.
1°=primary, 2°=secondary; NFL=National Football League, SD=standard deviation, UNITE=Understanding Neurologic Injury and Traumatic Encephalopathy.
*According to Centers for Disease Control and Prevention National Index of Death.

Stage IV CTE was associated with all informant reported functional and cognitive scales among donors: each point higher on the Cognitive Difficulties Scale was associated with 1.02 higher risk (95% CI 1.01 to 1.02; P<0.001), each higher point on the Functional Activities Questionnaire was associated with 1.07 higher risk (1.06 to 1.09; P<0.001), each point on the Behavior Rating Inventory of Executive Function-General Executive Composite T-score was associated with a 1.02 higher risk of stage IV CTE (1.01 to 1.03; P<0.001), and each point on the Behavior Rating Inventory of Executive Function Metacognition Index T-score was associated with a 1.03 higher risk of stage IV CTE (1.02 to 1.03; P<0.001).

Table 1 also reports the relation between the donors' cause of death reported on death certificates and study clinician adjudicated dementia. Notably, death certificates reflected a primary dementia or neurodegenerative cause of death in 62 (30.7%) of the donors with study clinician adjudicated dementia; when combining both primary and secondary causes of death, 82 (40.6%) death certificates identified donors with study clinician adjudicated dementia. Notably, dementia was clinically diagnosed in 58.2% of donors with cardiovascular disease listed as the cause of death on their death certificates and 52.3% of donors with injury reported, which were identified as being due to falls while in nursing homes or memory care clinics.

Analyses without debut year restriction

Primary analyses were limited to donors who debuted in the NFL after 1949, because before this the use of plastic helmets was not mandatory in the NFL. After implementation of plastic helmets, the style of play in the NFL substantially changed. However, secondary analyses included all NFL athletes regardless of debut year. Of the 347 donors who died across all years, 24 (6.9%) had stage I CTE, 41 (11.8%) had stage II CTE, 149 (42.9%) had stage III CTE, 110 (31.7%) had stage IV CTE, and 23 (6.6%) did not have CTE. When including all athletes independent of debut year, from 2008 to 2021, 2079 NFL players died. Under the most conservative assumptions (ie, among all NFL decedents, donors with a diagnosis of CTE from the UNITE Brain Bank and the UCSF ADRC represent the only decedents with CTE), the minimum prevalence of CTE at death in NFL players during the study period was 16.6%. Under the least conservative assumptions (ie, that all decedents who were not studied in the UNITE Brain Bank and the UCSF ADRC had CTE), the maximum prevalence of CTE at death during the study period was 98.9%. Supplemental table 4 describes the differences between UNITE Brain Bank donors and non-donors regardless of debut year.

Differences in informant reported cause of death in donors with stage IV CTE compared with all other donors were significant, as those with a neurodegenerative cause of death had 4.53 higher risk of stage IV CTE (95% CI 3.24 to 6.33; P<0.001) and 1.42 higher risk of high severity CTE (1.28 to 1.58; P<0.001). No significant differences were observed for race by CTE status (P=0.23), but significant difference were observed for race by stage IV CTE (P<0.001), such that those with stage IV CTE were more likely to be white (82.7% *v* 57.1%; P<00.001) and Native American (0.9% *v* 0%; P<0.001), and less likely to be black (16.4% *v* 40.3%; P<0.001). Of donors, 76 (21.9%) served in the military; military service was not associated with CTE status (P=0.41), but those with stage IV CTE were more likely to serve in the military (37.3% *v* 150.0%; P<0.001). Position was not associated with CTE status (P=0.18), but there were significant differences in playing position by stage IV CTE (P=0.03), such that those with stage IV CTE were more likely to be running backs (20.9% *v* 10.3%, P=0.01) and less likely to be defensive linemen (7.3% *v* 21.5%; P=0.002).

Discussion

This study analysed the prevalence at death of neuropathologically confirmed CTE in a fully enumerated cohort with high exposure to repetitive head impacts from contact sports, including 19.7% of all former NFL players who died during the study period, and 26.8% of all who died in the last six years when brain donation was more frequent. Leveraging publicly available personal, athletic, and cause of death data from all deceased NFL players from 2008 to 2021, we calculated that former NFL players had an 18.5% to 98.7% possible prevalence of CTE at death. Evaluating the same data from 2016 to 2021, when a greater proportion of deceased players were evaluated, the possible prevalence of CTE at death was between 24.5% and 97.7%. Furthermore, these data showed that CTE was the most common disease in this cohort (93.5%), often in the absence of other neurodegenerative disease findings (58.9%).

CTE was associated with clinical impairment in this cohort. Among donors, more severe CTE pathology was associated with informant reported impairment in cognition and function and higher risk of dementia, including stage IV CTE associated with a 1.44 greater risk of dementia. CTE was often the only neurodegenerative disease found in donors with dementia (53.0%); although neuropathological comorbidities were common. This is similar to the extent to which comorbid pathology has been observed in other neurodegenerative diseases.[53] Vascular comorbidities were also frequently found in the present cohort. Previous work observed that multiple pathologies co-occurred more frequently in individuals with repeated exposure to traumatic brain injuries than could occur due to random chance, and that several of these pathologies were associated with dementia, suggesting that the presence of one pathology may predispose to additional pathologies.[54] These findings are further consistent with several past studies showing a dose-response relation between the presence and severity of CTE pathology and clinical outcomes.[25] Taken together, there is evidence that CTE pathology has clinically significant manifestations, showing the importance of understanding CTE prevalence.

Comparison with other studies

Past studies have used death certificate data to estimate neurodegenerative disease rates in NFL players. Although these studies showed increased rates for NFL players, they also indicated that deaths with neurodegenerative disease account for a small fraction of total deaths.[27 28] Past studies found that neurodegeneration as a cause of death is under-ascertained on death certificates.[29-31] We found a similar phenomenon among the NFL brain donors, with 69.3% of dementia cases not reported on death certificates, suggesting that previous reports relying on death certificates underestimated dementia.

Although duration of play was associated with stage IV CTE and high severity CTE, it was not associated with CTE status. This result contrasts with findings from brain donors with a wider range of exposures, where duration and cumulative exposure to repetitive head impacts are associated not only with CTE severity for those with CTE, but also with CTE status.[20 52] The present study only included those with the highest levels of exposure—namely, those who played American style football at the professional level. The discrepancy between these and previous findings may suggest that, for those exceeding a certain threshold of exposure to repetitive head impacts, other factors (eg, genetic, environmental) may play a larger role in whether CTE develops. However, even in this cohort

with extensive exposure to repetitive head impacts, additional exposure appeared to play a role in disease severity of CTE.

This study also compared the characteristics of deceased NFL brain donors with those of non-donors, offering potential sources of selection pressure into the UNITE Brain Bank. Compared with non-donors, donors had played professional American football for longer, played in more Pro Bowls games, and were more commonly inducted into the NFL's Hall of Fame. Donors' longer careers with more exposure to repetitive head impacts may have resulted in more clinical symptoms motivating families to donate. It is also possible that donation was related to public visibility, how quickly the media reported a death, a player's connection with the NFL community, or other factors related to identity or public persona.

Strengths and limitations of this study

This study has several limitations. Firstly, other brain banks beyond UNITE Brain Bank have reported neuropathological results from professional American football players who died. Specifically, at least 11 cases of CTE in NFL players who died during the study period have been reported in the literature or by family members of the donors.[55 56] These cases were not incorporated into the present study to maintain a consistent methodology. At least an additional 12 former NFL players who died during the study period were suspected of having CTE but were not evaluated after death, as well as 215 non-donors with neurodegenerative cause of death listed on their death certificate[56]; the presence of non-donors with symptoms further underscores the likelihood that not all cases of CTE were studied neuropathologically. These limitations would increase the lower bound of CTE prevalence reported here.

The reported prevalence of CTE in the current study is based on the total number of former NFL players known to have died during the study period. It is possible that some former NFL athletes who died were not identified and thereby not included, which would artificially decrease the denominator and bias towards an increased minimum observed prevalence of CTE in this cohort. However, all donors in the present study were part of the cohort denominator identified a priori; even if a larger theoretical cohort exists containing missing NFL decedents, this study identified the boundaries of the present cohort of NFL players.

A possibility exists that informants may have overemphasised or have biased recall of symptoms, as informants were not masked to the purpose of the study. Recall bias could alter the measurement of informant based measures of dementia but not the diagnosis of CTE. The directionality of this bias is, however, unclear. For example, it is plausible that knowledge about and suspicion of CTE before death might mean that the informant was more attuned to the donor's cognitive status and behaviours, whereas less knowledge about and suspicion of CTE might mean that informants were less consistently attuned to dementia related symptoms. If the sensitivity of dementia detection was lower in informants of individuals without CTE, we would expect an upward bias (overestimate of the effects of CTE on dementia related outcomes) based on informant data. It is reassuring, however, that the associations of stage IV CTE with cognition and behaviours based on validated informant questionnaires are consistent with the association of stage IV CTE with dementia status that was clinically adjudicated and masked to CTE status. Additionally, even if recall of symptoms was biased, this source of bias would not explain the observed relation between reported burden of symptoms and neuropathological findings, as all informants and study clinicians were both masked to disease status. This study did not have access to information about the athletic exposure of non-donors beyond playing position at the professional level, nor environmental or other risk factors. More work is needed to identify other potential risk factors of CTE status and severity.

Currently, it is not possible to definitively identify or diagnose CTE in living people. The clinical symptoms of CTE may manifest long before death, but we do not know until death whether the symptoms are associated with CTE or another neuropathological process. As such, we are limited to determining the prevalence of CTE only at death. Although the conditional proportion reported has limitations and is not equivalent to the prevalence of CTE among living football players if it could be assessed, the prevalence of CTE at death indexes both disease burden and concomitant quality of life towards the end of life. This is of interest and of value to individuals at risk, along with their care partners and family members.

Additionally, the estimation of prevalence was reliant on data from brain donors, which is subject to potential selection bias motivated by donation status; however, we aimed to mitigate these effects by using inverse probability weighting. The lack of a definitive diagnosis until death and brain donation is a common and well known problem of neurodegenerative and neuropathological processes for which multiple possible pathological explanations exist for the same clinical presentations.[3-15] A similar quantity has been estimated for the prevalence of Alzheimer's disease,[57] which has been referenced by researchers, clinicians, and policymakers working in the areas of both prevention and end of life care. Also, because CTE can only be definitively diagnosed at death, and dementia is inherently a condition of living individuals, assessing each after death restricted the study population to deceased NFL players and introduced potential selection bias from differential mortality. A potential also exists for collider stratification bias (see supplemental figure 2). Firstly, because neuropathological assessment requires brain donation, all analyses are necessarily restricted to donors, thereby conditioning on a variable that is plausibly influenced by both CTE pathology and dementia status. Secondly, all analyses condition on death, an event that was probably more likely among players who had more CTE pathology and dementia.

This conditioning may induce non-causal pathways between the exposure and outcome that was not addressed with our application of inverse probability weighting. If both CTE pathology and dementia increase the likelihood of death and of donation, the resulting bias would be expected to result in an underestimation of the association between CTE and dementia.

The measured variables between donors and non-donors used to calculate the inverse probability weighting point estimate of CTE prevalence at death were hypothesised to account for the selection factors of brain donation; therefore, future models that robustly account for selection are needed. The cohort selected for this study, NFL players, all experienced substantial exposure to head impacts during their athletic careers, likely increasing their CTE risk. As a result, these findings cannot necessarily be generalised to the American football community.

Conclusions

Together, these findings indicate that NFL players have a higher prevalence of CTE at death than has been previously shown in multiple community based studies. Furthermore, these data indicate that CTE severity at death is significantly associated with dementia in NFL player brain donors, and that dementia is common in these donors. Additional work is needed to further clarify the nature of this relation, particularly in other populations, with high lifetime exposure to repetitive head impacts.

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