

Duration of Soccer Play and Chronic Traumatic Encephalopathy (CTE)

Bobak Abdolmohammadi, BA^{1,2}; Nicholas Parise, BA^{1,2}; Samantha Thevenin, BA¹; Brett Martin, MS^{1,3}; Joseph Palmisano, MA, MPH^{1,3}; Christopher Nowinski, PhD⁴; Douglas I. Katz, MD^{1,2,5}; Brigid C. Dwyer, MD^{1,2,5}; Robert C. Cantu, MD^{1,4,6-7}; Lee E. Goldstein, MD, PhD^{1,8-10}; Robert A. Stern, PhD^{1-2,11-12}; Michael L. Alosco, PhD^{1,2}; Daniel H. Daneshvar, MD, PhD¹³⁻¹⁵; Yorghos Tripodis, PhD^{1,16}; Victor E. Alvarez, MD^{1,17-18}; Thor D. Stein, MD, PhD^{1,17-19}; Ann C. McKee, MD^{1,17-19}; Jesse Mez, MD, MS¹⁻²

¹Boston University Alzheimer's Disease Research Center and CTE Center, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; ²Department of Neurology, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; ³Biostatistics and Epidemiology Data Analytics Center, Boston University School of Public Health, Boston, MA, USA; ⁴Concussion and CTE Foundation, Boston, MA, USA; ⁵Braintree Rehabilitation Hospital, Braintree, MA, USA; ⁶Department of Neurosurgery, Emerson Hospital, Concord, MA, USA; ⁷Department of Neurosurgery, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; ⁸Departments of Biomedical, Electrical & Computer Engineering, Boston University College of Engineering, Boston, MA, USA; ⁹Department of Psychiatry, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; ¹⁰Department of Radiology, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; ¹¹Department of Anatomy & Neurobiology, Boston University Chobanian & Avedisian School of Medicine, 72 East Concord St., Boston, MA 02118, USA; ¹²Department of Neurosurgery, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA; ¹³Department of Rehabilitation Medicine, Harvard Medical School, Boston, MA, USA; ¹⁴Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital, Boston, MA, USA; ¹⁵Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Boston, MA, USA; ¹⁶Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA; ¹⁷VA Boston Healthcare System, U.S. Department of Veteran Affairs, Boston, MA, USA; ¹⁸VA Bedford Healthcare System, U.S. Department of Veteran Affairs, Bedford, MA, USA; ¹⁹Department of Pathology and Laboratory Medicine, Boston University Chobanian and Avedisian School of Medicine, Boston, MA, USA

BACKGROUND

- Chronic traumatic Encephalopathy (CTE) is a progressive neurodegenerative tauopathy associated with exposure to repetitive head impacts (RHI) frequently experienced through contact sport participation.
- CTE has been predominantly described in American football, ice hockey, and rugby players, boxers, and military veterans. Over the past decade, research has suggested a robust dose-response relationship between years of American football, ice hockey, and rugby play and CTE risk.
- Soccer is the world's most popular sport, with approximately 240 million registered players across 205 member associations worldwide. CTE has also been described in some soccer players.
- While there are various descriptions of CTE in former soccer players, the mechanisms leading to CTE risk from soccer play are ill-defined.
- To our knowledge, no cohort-level studies have been conducted to assess whether RHI incurred from soccer play leads to increased risk for CTE

OBJECTIVES

- To test the hypothesis that increasing duration of soccer career play, measured in years, would be associated with a corresponding increase in CTE risk and severity.
- To test whether adjustment for potential selection bias by utilizing inverse probability weighting changes the estimated associations.
- To verify if CTE neuropathology is associated with presence of dementia and an informant-reported clinical scale measuring daily function.

METHODS

- Overview:** A case series of 69 brain donors to the UNITE Brain Bank whose primary RHI exposure came from soccer play.
- Clinical/Neuropathologic Evaluation:** A series of retrospective online surveys and telephone interviews were conducted with informants, including collection of primary position and years of soccer play. Standardized neuropathological assessments were conducted on each brain donor blinded to any clinical or demographic information (**Figure 1**).
- Statistical Analysis:** We used binary logistic regression to estimate the association of duration played with CTE diagnosis and dementia, Bayesian piecewise regression to estimate the association with cumulative ptau burden, and linear regression to estimate the association with FAQ score. To quantify conditions under which selection bias could invalidate our findings, we conducted simulation analyses for CTE diagnosis. **Figure 1: Brain Bank study methodology**

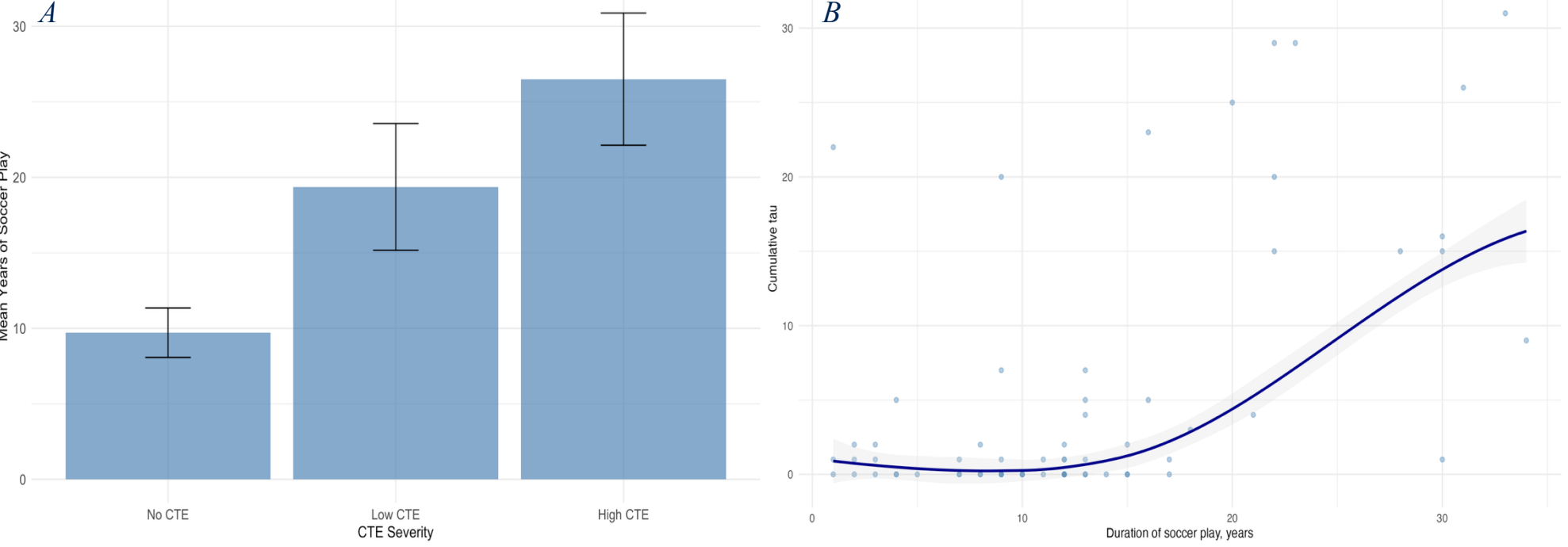


RESULTS

Table 1: Sample characteristics of 69 total brain donors

Characteristic	CTE+ (n=17)	CTE- (n=52)	Total (n=69)
Male sex (n, %)	16 (94)	41 (79)	57 (83)
Informant-reported White race (n, %)	17 (100)	51 (98)	68 (99)
Age at death (mean, SD)	55.8 (25)	37.1 (18)	41.7 (21.1)
Years of soccer play (mean, SD)	21.9 (7.3)	9.4 (5.3)	12.5 (8.0)
Age of first exposure (mean, SD)	6.8 (3.4)	7.1 (3.1)	7 (3.2)
Median concussion count (IQR)	18 (9-33)	6 (4-20)	9 (4-20)
Professional soccer play (n, %)	10 (59)	1 (2)	11 (16)
Primary position of play			
Goalkeeper (n, %)	3 (18)	12 (23)	15 (22)
Defender (n, %)	1 (6)	14 (27)	15 (22)
Midfielder/winger (n, %)	7 (41)	10 (19)	17 (25)
Forward/striker (n, %)	4 (24)	6 (12)	10 (15)
Multiple positions (n, %)	2 (12)	2 (4)	4 (6)
Unreported (n, %)	0	8 (15)	8 (12)
Primary Cause of Death			
Suicide (n, %)	4 (24)	20 (39)	24 (35)
Accidental overdose (n, %)	3 (18)	11 (21)	14 (20)
Neurodegenerative (n, %)	7 (41)	5 (10)	12 (17)
Other (n, %)	3 (18)	16 (31)	19 (28)
Clinician-adjudicated dementia (n, %)	6 (35)	7 (14)	13 (19)
Neuropathology			
Stage I CTE (n, %)	8 (47)	-	8 (12)
Stage II CTE (n, %)	3 (18)	-	3 (4)
Stage III CTE (n, %)	1 (6)	-	1 (1)
Stage IV CTE (n, %)	5 (29)	-	5 (7)
Low-stage CTE (I & II) (n, %)	11 (65)	-	11 (16)
High-stage CTE (III & IV) (n, %)	6 (35)	-	6 (9)
Alzheimer's disease (n, %)	6 (35)	2 (4)	8 (12)
Lewy body disease (n, %)	1 (6)	3 (6)	4 (6)
Motor neuron disease (n, %)	1 (6)	0	1 (1)
FTLD-tau/FTLD-TDP43 (n, %)	1 (6)	2 (4)	3 (4)
Atherosclerosis, mod-severe (n, %)	1 (6)	2 (4)	3 (4)
Arteriolosclerosis, mod-severe (n, %)	6 (35)	18 (35)	24 (35)
White matter rarefaction, mod-severe, (n, %)	8 (47)	14 (27)	22 (32)
CAA, mod-severe (n, %)	3 (18)	5 (10)	8 (12)

Figure 2: A) Distribution of duration of play by CTE severity, and B) LOESS plot depicting cumulative tau burden by duration of play



REFERENCES

- Abdolmohammadi B, Tuz-Zahra F, Uretsky M, et al. Duration of Ice Hockey Play and Chronic Traumatic Encephalopathy. *JAMA Netw Open*. 2024;7(12):e2449106.
- McKee AC, Cairns NJ, Dickson DW, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*. 2016;131(1):75-86.

RESULTS

Figure 3: Images of stage II CTE neuropathology (adapted from Abdolmohammadi et al. 2024)

Legend: Photomontage of stage II CTE shows hemispheric 50-µm tissue sections immunostained with AT8.

A) left frontal lobe. B) Anterior frontal lobe. C) pathognomonic CTE lesion (ptau neurofibrillary tangles). D) Pathognomonic CTE lesions (neurites around central vessel).

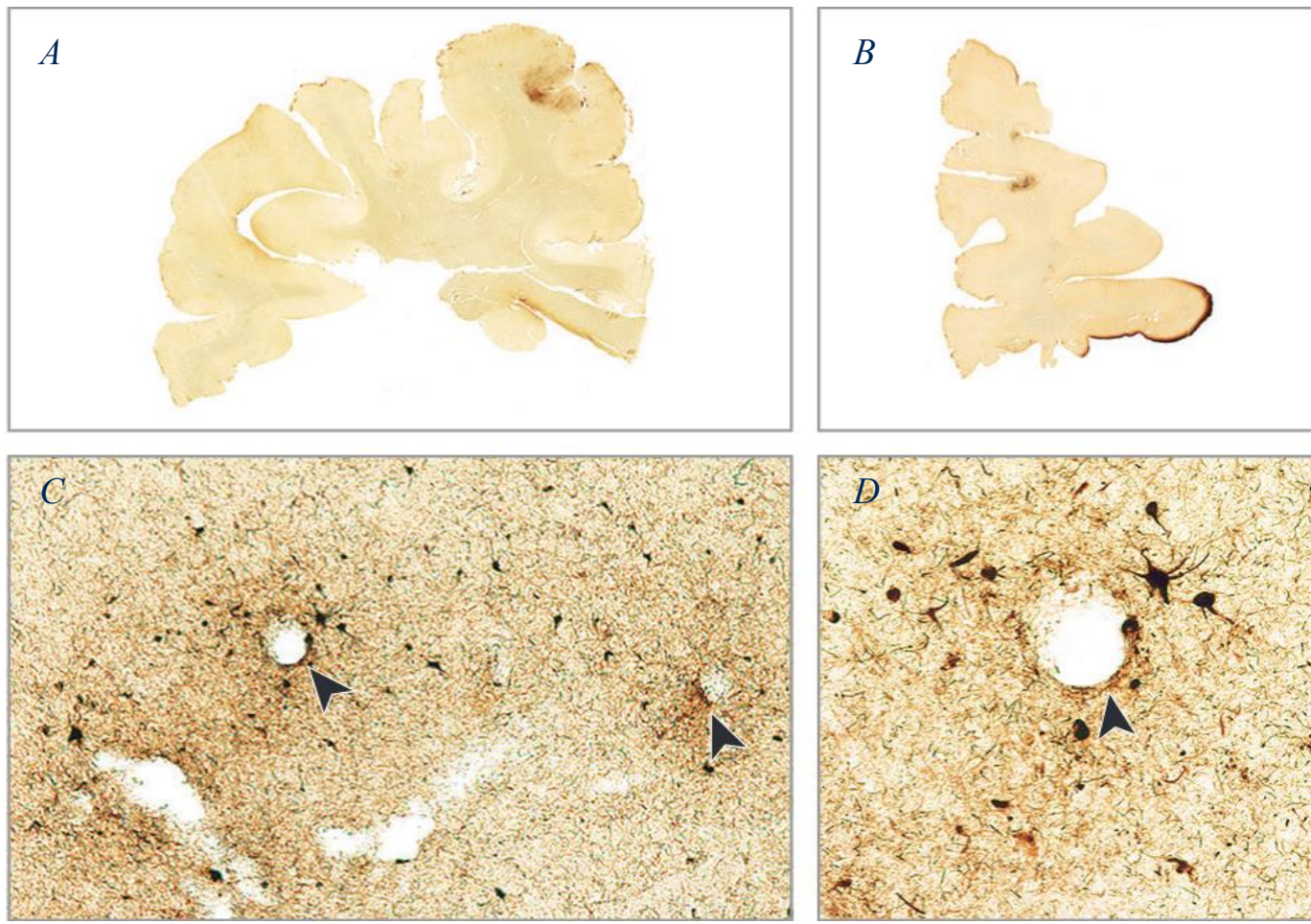


Table 2: Analyses assessing the relationship between duration played and CTE neuropathology

A) Relationship between duration played and CTE neuropathology	
Outcome	Association magnitude (95% confidence interval)
CTE diagnosis	Odds ratio of having CTE
Duration, per year	1.27 (1.11, 1.53); p=0.003
Cumulative ptau burden	Unit increase in cumulative ptau burden
Duration, per year <13.25 years	0.02 (full range; -0.04, 0.05)
Duration, per year >13.25 years	0.54 (full range; 0.50, 0.58)
B) Simulation analyses assessing the relationship between duration played and CTE neuropathology	
Outcome	Median association magnitude
CTE diagnosis	Median odds ratio of having CTE (full range)
Duration, per year	1.28 (1.19, 1.32)
C) Relationship between cumulative ptau burden with dementia diagnosis and FAQ score	
Outcome	Association magnitude (95% confidence interval)
Dementia diagnosis	Odds ratio of having dementia
Cumulative ptau burden, unit increase	1.10 (0.97, 1.24); p=0.13
FAQ score	Standardized unit increase in FAQ score
Cumulative ptau burden, unit increase	0.039 (0.013, 0.067); p=0.006

CONCLUSIONS

- Among former soccer playing brain donors, most professionals were diagnosed with CTE (10/11, 91%).
- We observed a dose-response association showing 1.27 higher odds of CTE diagnosis for each additional year of soccer play.
- Simulation analyses demonstrated that this relationship remained robust under conditions where duration of play was associated with brain bank selection across a range of scenarios.
- We found that each year of soccer play above 13.25 years corresponded with a 0.54-point increase in cumulative p-tau burden.
- Cumulative ptau burden was not associated with clinician-adjudicated dementia status but was associated with increased impairment in iADLs as measured by functional activities questionnaire (FAQ) score.
- More research is needed to better elucidate the impact more granular soccer-specific measures of RHI, such as heading, may have on CTE risk.