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RESEARCH ARTICLE

Association between contact sports participation and chronic traumatic encephalopathy: a retrospective cohort study

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chronic traumatic encephalopathy, contact sports, football, tau, traumatic brain injuries.

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Abstract

Chronic traumatic encephalopathy is a debilitating neurodegenerative disorder associated with repetitive traumatic brain injuries often sustained through prior contact sport participation. The frequency of this disorder in a diverse population, including amateur athletes, is unknown. Primary historical obituary and yearbook records were queried for 2566 autopsy cases in the Mayo Clinic Tissue Registry resulting in identification of 300 former athletes and 450 non-athletes. In these cases, neocortical tissue was screened for tau pathology with immunohistochemistry, including pathology consistent with chronic traumatic encephalopathy, blinded to exposure or demographic information. Using research infrastructure of the Rochester Epidemiology Project, a comprehensive and established medical records-linkage system of care providers in southern Minnesota and western Wisconsin, medical diagnostic billing codes pertaining to head trauma, dementia, movement disorders, substance abuse disorders and psychiatric disorders were recorded for cases and controls in a blinded manner. A total of 42 individuals had pathology consistent with, or features of, chronic traumatic encephalopathy. It was more frequent in athletes compared to non-athletes (27 cases versus 15 cases) and was largely observed in men (except for one woman). For contact sports, American football had the highest frequency of chronic traumatic encephalopathy pathology (15% of cases) and an odds ratio of 2.62 (P-value = 0.005). Cases with chronic traumatic encephalopathy pathology had higher frequencies of antemortem clinical features of dementia, psychosis, movement disorders and alcohol abuse compared to cases without chronic traumatic encephalopathy pathology. Understanding the frequency of chronic traumatic encephalopathy pathology in a large autopsy cohort with diverse exposure backgrounds provides a baseline for future prospective studies assessing the epidemiology and public health impact of chronic traumatic encephalopathy and sports-related repetitive head trauma.

INTRODUCTION

Chronic traumatic encephalopathy (CTE) is a debilitating and enigmatic neurodegenerative disorder associated with repetitive traumatic brain injuries, often sustained through prior contact/collision sport participation or military-related exposure (3, 14, 15, 23, 24). The clinical presentation of CTE ("traumatic encephalopathy syndrome") includes a spectrum of neurological and psychiatric symptoms encompassing cognitive dysfunction, emotional dysregulation, behavioral change and motor disturbance (26). Neuropathological consensus criteria for the diagnosis of CTE define the underlying pathognomonic lesion as hyperphosphorylated tau aggregates in neurons, astrocytes and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci (13). At present, there exists ongoing debate and research regarding the threshold, progression, specificity and clinical salience of this tau pathology (6).

Given that approximately 28 million children (≤15 years old), 8 million high school athletes and 500 000 collegiate athletes participate in organized sports programs annually in the United States alone (19–21), research regarding whether playing specific sports (especially at the amateur level) is associated with an increased risk of developing CTE pathology is imperative. Previous studies attempting to address this issue have been limited by small sample sizes, lack of a robust control group and/or have involved mostly collegiate or professional American football players (1, 17). In the current study, participation in specific sports was assessed retrospectively in a large autopsy cohort using historical data from obituaries and high school yearbooks. Our objectives were first to assess associations of participation in these sports with presence of CTE, and second to compare clinical features between individuals with and without CTE.

MATERIALS AND METHODS

Study cohort

The Mayo Clinic Tissue Registry, a histological registry of all Mayo Clinic formalin-fixed and/or paraffin-embedded tissue, blocks and slides (totaling over 20 million tissue samples) in Rochester, Minnesota collected 2844 consecutive autopsy cases between 01/01/2005 and 06/18/2016 following next-of-kin consent for complete or "brain-only" postmortem examination, including research authorization (Figure 1). Individuals without available neocortical brain tissue (N = 194) and individuals <1 year of age at death (N = 84) were excluded, resulting in 2566 cases considered for study inclusion. These exclusion criteria were elected as cortical tissue was necessary for neuropathological query, and infants less than one year in age had a low probability of experiencing repetitive mild trauma that could be determined by this study's assessment methodology. Autopsy source was not exclusionary, such that medicolegal, research, physician and family requested autopsies were available. Racial background was similar for this study population (Table 1) compared to the City of Rochester and Olmsted County, Minnesota (31). This study was approved by Institutional Review Boards at Mayo Clinic and Olmsted Medical Center.

Assessment of sports participation

Sports participation assessment for each subject was based on information from obituaries and high school yearbooks. Subjects were included in the study if they (1) had both obituary and yearbook information available revealing no participation in any sports, or (2) had either obituary or yearbook information available (or both) revealing participation in at least one sport. The final study sample size was 750 subjects after applying these criteria. Several differences were observed when comparing characteristics of the 750 subjects to the 1816 patients excluded because of the lack of sufficient sports participation information (Table S1).

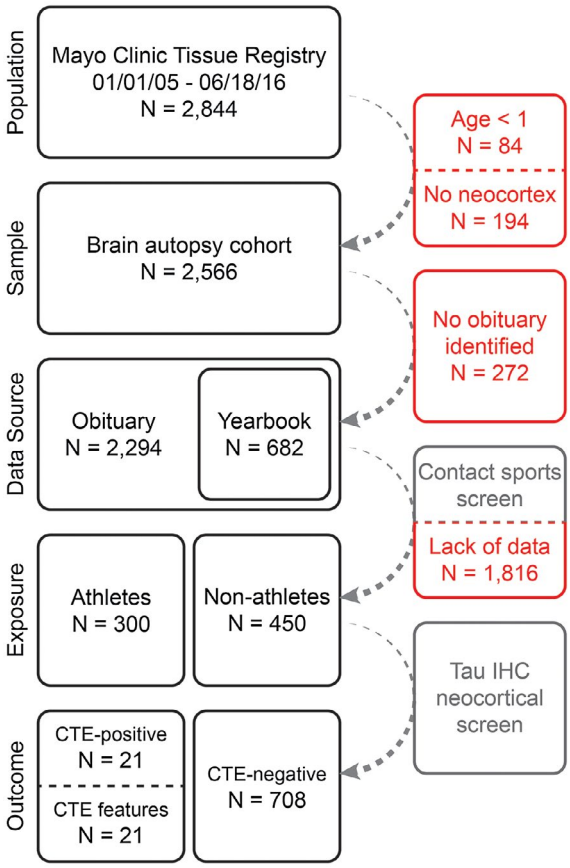

Figure 1. *Study workflow.* Obituaries were queried for all consented autopsy cases in the Mayo Clinic Tissue Registry from 2005 to 2016 (irrespective of any clinical or pathological diagnoses) with cortical brain tissue. Gray boxes denote a query while red boxes represent case exclusion. Obituary data were used to identify yearbook records. Together, contact sports participation was assessed from these historical primary sources, identifying 300 athletes (various sports) and 450 non-athletes. Subsequent assessment via tau immunohistochemistry ascertained presence or absence of CTE pathology.

Online obituaries (2294 [89%] cases identified) were searched using www.google.com for participant name, term "obituary," and year of death. Personal identity was verified using the individual's date of birth and date of death. Sports participation and education data were abstracted from obituary records, including type of sport(s) and participation age/level/duration and institutional name, city, state and year of graduation. Contact sports were defined as any organized athletic activity with the potential for frequent head impact between participants or a participant and sports-related equipment, and included baseball/softball, basketball, boxing, football, hockey, lacrosse/field hockey, soccer and wrestling. For female athlete inclusivity, participation in high school girls athletic associations was also recorded. Non-contact sports including cross-country, track and field, swimming, tennis and golf were not classified as sports participation for the purposes of this study.

Table 1. Characteristics according to sex and participation in any sports (ie, athlete or non-athlete). Abbreviations: G.A.A. = Girls Athletic Association; PTSD = post-traumatic stress disorder; AD = Alzheimer's disease; CTE = chronic traumatic encephalopathy.

Variable	Athletes (N = 300)	Non-athletes (N = 450)	Females (N = 273)	Males (N = 477)
Demographic information				
Age at death (years)	68 (7, 99)	64 (18, 100)	67 (7, 100)	66 (12, 99)
Sex (Male)	232 (77.3%)	245 (54.4%)	0 (0.0%)	477 (100.0%)
Race (white)	292 (98.0%)	439 (98.7%)	268 (99.3%)	463 (97.9%)
Years of education	14 (2, 21)	13 (8, 21)	13 (2, 21)	14 (6, 21)
Military	98 (32.7%)	115 (25.6%)	7 (2.6%)	206 (43.2%)
Athletic information				
Baseball/Softball	73 (24.3%)	0 (0.0%)	9 (3.3%)	64 (13.4%)
Youth or high school	57 (19.3%)	0 (0.0%)	9 (3.3%)	48 (10.1%)
Beyond high school	12 (4.1%)	0 (0.0%)	0 (0.0%)	12 (2.5%)
Basketball	106 (35.3%)	0 (0.0%)	14 (5.1%)	92 (19.3%)
Youth or high school	98 (33.0%)	0 (0.0%)	14 (5.1%)	85 (17.9%)
Beyond high school	4 (1.3%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Boxing	7 (2.3%)	0 (0.0%)	0 (0.0%)	7 (1.5%)
Football	142 (47.3%)	0 (0.0%)	2 (0.7%)	140 (29.4%)
Youth or high school	126 (42.1%)	0 (0.0%)	2 (0.7%)	124 (26.1%)
Beyond high school	15 (5.0%)	0 (0.0%)	0 (0.0%)	15 (3.2%)
G.A.A.	41 (13.7%)	0 (0.0%)	41 (15.0%)	0 (0.0%)
Hockey	25 (8.3%)	0 (0.0%)	5 (1.8%)	20 (4.2%)
Youth or high school	17 (5.7%)	0 (0.0%)	5 (1.8%)	12 (2.5%)
Beyond high school	7 (2.3%)	0 (0.0%)	0 (0.0%)	7 (1.5%)
Soccer	8 (2.7%)	0 (0.0%)	3 (1.1%)	5 (1.0%)
Wrestling	39 (13.0%)	0 (0.0%)	0 (0.0%)	39 (8.2%)
Youth or high school	38 (12.7%)	0 (0.0%)	0 (0.0%)	38 (8.0%)
Beyond high school	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Other*	4 (1.3%)	0 (0.0%)	0 (0.0%)	4 (0.8%)
Number of sports played				
0	2 (0.7%)	450 (100.0%)	207 (75.8%)	245 (51.4%)
1	189 (63.0%)	0 (0.0%)	59 (21.6%)	130 (27.3%)
2	76 (25.3%)	0 (0.0%)	6 (2.2%)	70 (14.7%)
3 or 4	32 (11.0%)	0 (0.0%)	1 (0.4%)	32 (6.7%)
Clinical information				
Alcoholism	50 (16.7%)	92 (20.4%)	29 (10.6%)	113 (23.7%)
Anxiety	60 (20.0%)	106 (23.6%)	82 (30.0%)	84 (17.6%)
Bipolar	44 (14.7%)	92 (20.4%)	60 (22.0%)	76 (15.9%)
Dementia	96 (32.0%)	113 (25.1%)	79 (28.9%)	130 (27.3%)
Depression	95 (31.7%)	180 (40.0%)	116 (42.5%)	159 (33.3%)
Drug abuse	12 (4.0%)	37 (8.2%)	16 (5.9%)	33 (6.9%)
Head injury	37 (12.3%)	54 (12.0%)	31 (11.4%)	60 (12.6%)
Movement disorder	45 (15.0%)	56 (12.4%)	25 (9.2%)	76 (15.9%)
Psychosis	129 (43.0%)	187 (41.6%)	116 (42.5%)	200 (41.9%)
PTSD	8 (2.7%)	11 (2.4%)	11 (4.0%)	8 (1.7%)
Schizophrenia	6 (2.0%)	3 (0.7%)	3 (1.1%)	6 (1.3%)
Suicide	18 (6.0%)	31 (6.9%)	14 (5.1%)	35 (7.3%)
Tobacco abuse	94 (31.3%)	151 (33.6%)	64 (23.4%)	181 (37.9%)
Neuropathological information				
Tau pathology	261 (87.0%)	344 (76.4%)	219 (80.2%)	386 (80.9%)
AD pathology	72 (24.0%)	105 (23.3%)	74 (27.1%)	103 (21.6%)
CTE				
CTE-negative	273 (91.0%)	435 (96.7%)	272 (99.6%)	436 (91.4%)
Features of CTE	12 (4.0%)	9 (2.0%)	1 (0.4%)	20 (4.2%)
CTE-positive	15 (5.0%)	6 (1.3%)	0 (0.0%)	21 (4.4%)

The sample median (minimum, maximum) is shown for continuous variables. Information was unavailable regarding race (N = 7), level of baseball played (N = 4), level of basketball played (N = 3), level of football played (N = 1) and level of hockey played (N = 1).

[†]Other sports included college lacrosse (N = 3 males) and amateur rodeo (N = 1 male).

Yearbook records (682 [27%] cases identified) were searched using the high school name, city, state and year of graduation primarily through www.classmates.com, with a smaller subset identified through Southeastern Minnesota local libraries. Individuals were verified using first name, and last name or maiden name. Sports

participation, as previously defined, and extracurricular activity data were abstracted for all participants in accordance with published Rochester Epidemiology Project yearbook studies (7, 29).

Medical record query

The Rochester Epidemiology Project is a comprehensive medical records-linkage system of care providers in southern Minnesota and western Wisconsin (28). As previously described (30), diagnostic codes were queried from the Rochester Epidemiology Project database for the following disorders: head trauma, dementia, movement, alcoholism, drug abuse, tobacco abuse, anxiety, depression, bipolar, post-traumatic stress, psychosis, schizophrenia and suicide. Classification for the disorders was qualified according to individual lifetime presence or absence of any corresponding diagnostic code from 01 January 1976 to 18 June 2016. Military service was qualified as present or absent based upon death certificate records linked to each case in the Rochester Epidemiology Project database.

Neuropathological evaluation

According to preliminary recommendations for restricted cortical sampling in CTE, 78% of neuropathologically diagnosed CTE cases with varying degrees of severity can be identified via examination of the frontal, parietal and temporal cortices (2). To screen for CTE pathology in this series, we aimed to evaluate previously sampled formalin-fixed, paraffin-embedded tissue from these three regions. Blocks were selected from frontal and temporal neocortices for all 750 participants. Of additionally available archived neocortical tissue blocks, tissue was included for 565/750 individuals for neuropathological evaluation including parietal (N = 318), additional frontal (N = 112) and additional temporal (N = 135) lobes, such that a maximum of three different blocks per cases were assessed. Following deparaffinization and antigen retrieval, tau immunohistochemistry was performed using monoclonal AT8 phospho-tau antibody (1:2500 dilution) and EnVision+ Mouse reagent kits on the same LabVision™ 480S autostainer. Subsequently, slides were hematoxylin counterstained, dehydrated and coverslipped.

Tau immunostained slides from all 750 cases were assessed independently by two evaluators (KFB and MMB), blinded to any personal identifier, sports participation information or clinical information. Cases were evaluated for Alzheimer-type pathology (tau-positive neuritic plaques) and aging-related tau astrogliopathy in accordance with defined consensus neuropathological criteria (5, 9). Cases with pathology consistent with all aspects of the CTE neuropathology consensus criteria, namely (A) "hyperphosphorylated tau aggregates," (B) "in neurons, astrocytes, and cell processes," (C) "around small vessels" and (D) "in an irregular pattern at the depths of the cortical sulci," were classified as "CTE-positive" (13). "Features of CTE" was used to designate cases with multiple lesions suggestive of CTE pathology without fitting all parts of the criteria verbatim, exclusive of Alzheimer-type pathology and aging-related tau astrogliopathy. Cases void of any CTE pathology were classified as "CTE-negative." Features of CTE and CTE-positive cases were jointly classified and analyzed as "combined CTE pathology," which was the primary outcome measure of the study. As a result of its rarer occurrence, CTE-positive was evaluated as a secondary outcome. All cases with tau pathology identified by either initial evaluator were also assessed by a third blinded evaluator (DWD), and a final consensus classification was determined.

Statistical analysis

Associations of participation in specific sports with occurrence of the separate outcomes of combined CTE pathology and CTE-positive were examined using unadjusted and multivariable logistic regression models, where odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. As only one female subject had features of CTE, associations were not possible to assess in females, and were therefore examined only in males. Considering commonly used guidelines regarding the number of variables that can be included in a given model (25, 32), multivariable models for the primary outcome of combined CTE pathology were adjusted for the subset of pre-specified potential CTE risk factors (age at death and documented head injury subsequent to any sports participation) that differed between male subjects with and without combined CTE pathology with a P-value < 0.10, and also for all individual contact sports that were associated with combined CTE pathology in unadjusted analysis with a P-value < 0.10. When examining associations of participation in specific contact sports with CTE-positive, multivariable models were adjusted for all contact sports that were associated with CTE-positive in unadjusted analysis with a P-value < 0.10.

Comparisons of demographic, clinical and neuropathological information between patients with and without CTE outcomes were made using a Wilcoxon rank sum test or Fisher's exact test. A Bonferroni correction for multiple testing was made for the primary analysis evaluating associations of participation in specific sports with CTE outcomes. Specifically, to account for the eight different sports examined (including "other" category), P-values < 0.00625 were considered as statistically significant. P-values < 0.05 were considered as statistically significant for all other analyses. All statistical tests were two-sided. Statistical analyses were performed using SAS (version 9.4) and R Statistical Software (version 3.2.3). The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available as information could compromise the privacy of research participants.

RESULTS

Patient characteristics

The final sample size was 750 subjects after applying study criteria. A summary of demographic, sports participation, clinical and neuropathological information is provided in Table 1

for the 477 males and 273 females as well as for subjects who participated in at least one sport ("athletes") and for non-athletes. Sixty-six (24%) females played at least one sport with girls athletic associations (15%), basketball (5%) and baseball/softball (3%) being most common. For males, 232 (49%) played at least one contact sport; football was most common (29%), followed by basketball (19%), baseball (13%) and wrestling (8%). Characteristics are shown according to specific sports played in Table S2 (males) and Table S3 (females).

Frequency of CTE and tau pathology

Twenty-one males (2.8%) were identified with tau pathology consistent with CTE consensus neuropathological criteria (Table 1). The burden of neocortical tau pathology varied from marked to mild (Figure 2). Additionally, 21 cases (2.8%, 20 males, 1 female) were identified and designated as "features of CTE." Together, combined CTE pathology was observed in 5.6% of the cohort. The median age of death for these 42 cases was 73 years (range 33–91). Tau-immunoreactive neuritic plaques, pathognomonic of Alzheimer's disease, were observed in 177 (23.6%) subjects; 15 subjects had both combined CTE pathology and Alzheimer's disease neuritic plaques. In total, 605 cases had at least one tau-immunoreactive lesion (neurite, neurofibrillary tangle, neuritic plaque, or glial inclusion), while 145 (19.4%) study cases were entirely free of tau pathology in the cortical sections evaluated.

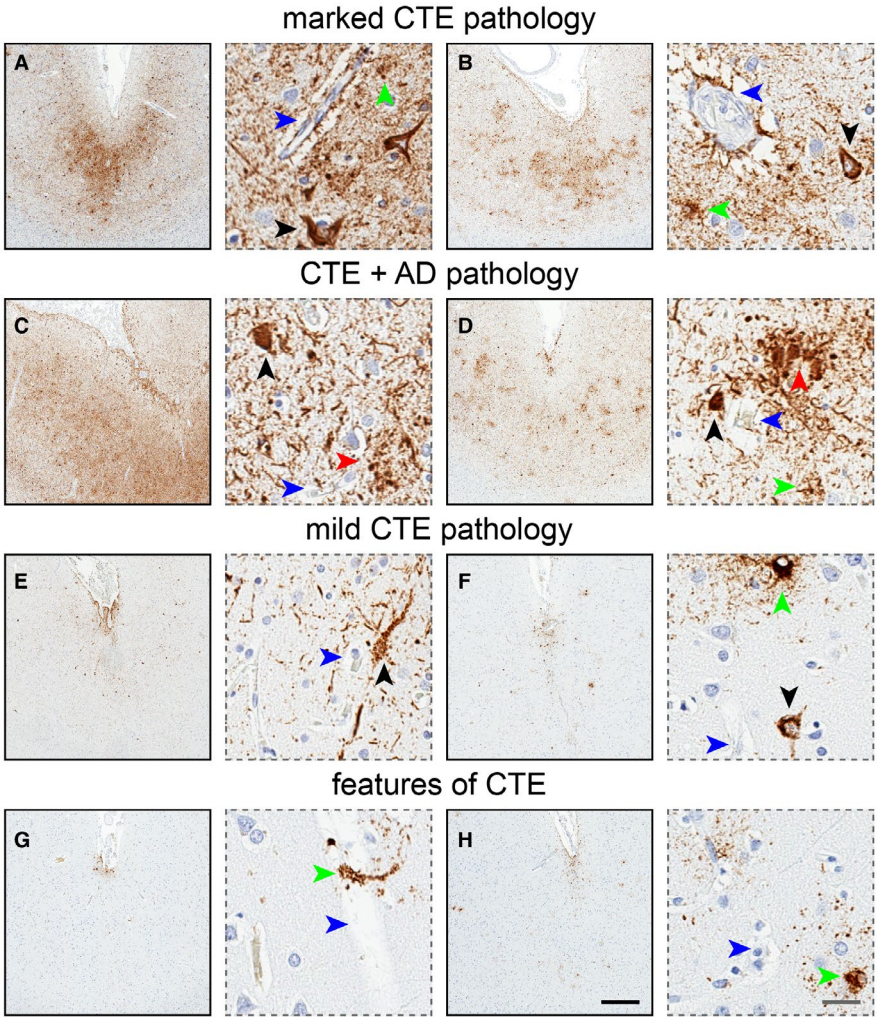

Figure 2. *Chronic traumatic encephalopathy (CTE) pathology*. CTE is characterized by focal deposition of hyperphosphorylated tau protein (brown signal) in neurons (black arrows) and astrocytes (green arrows) around penetrating blood vessels (blue arrows) at the depths of cortical sulci, as shown here in two cases (**A**,**B**). CTE pathology can be observed concomitantly with Alzheimer's disease pathology, namely tau-immunoreactive neuritic plaques (red arrows), making CTE evaluation more complicated in cases with high Alzheimer's disease burden (**C**) than cases with lower Alzheimer's disease burden (**D**). Other CTE cases may demonstrate more subtle neuropathology yet harbor all the required components of the consensus criteria (two cases; **E**,**F**). Finally, some cases show focal and patchy tau pathology reminiscent of CTE and inconsistent of other tauopathies, yet do not meet all consensus criteria (two cases; **G**,**H**). Possibly attributable to very early pathogenesis or limited restrictive sampling, "features of CTE" delineates high probability for pathological CTE yet not in accordance with all CTE consensus standards. Black bar: 500 μm, gray bar: 25 μm.

Clinical features of CTE in males

To avoid making comparisons between subjects with and without CTE pathology that are completely confounded by sex, we made such comparisons in males only (Table 2). In comparison to CTE-negative males, males with combined CTE pathology tended to be older at death ($P = 0.006$), had a lower likelihood of anxiety ($P = 0.029$), and had a higher likelihood of dementia ($P = 0.017$), movement disorders ($P = 0.024$), psychosis ($P = 0.005$) and AD neuropathology ($P = 0.027$). These results were relatively consistent when comparing CTE-negative subjects to CTE-positive subjects (Table 2). Given the differing minimum age at death between CTE-negative males (12 years) and males with combined CTE pathology (33 years), in secondary analysis, we excluded the 26 (5.5%) CTE-negative males with an age at death <30 years in order to address the possibility that this difference in minimum age at death influenced our results. The aforementioned statistically significant differences in characteristics that were observed between CTE-negative males and those with combined CTE pathology remained significant in this subset of 451 males with an age at death of at least 30 years (all $P \leq 0.033$).

Participation in contact sports and CTE outcomes in males

In multivariable analysis (Table 3, Figure S1), football was the only sport significantly associated with increased odds of combined CTE pathology in males (OR = 2.62, $P = 0.005$). Although not significant after correcting for multiple testing, CTE-positive was more common in multivariable analysis for subjects who boxed and those who played football (Table 3). A reasonable number of individuals played baseball or football beyond high school, and therefore for these two sports we performed subgroup analysis (Table 3). Playing football beyond high school was associated with a substantially increased odds of combined CTE pathology in multivariable analysis (OR = 13.23, $P < 0.001$). Findings were similar though weaker when considering CTE-positive (OR = 6.84, $P = 0.0056$). Conversely, in comparison to non-football players, odds of combined CTE pathology (OR = 1.84, $P = 0.11$) and CTE-positive (OR = 2.29, $P = 0.094$) were not significantly increased in multivariable analysis for participants of only youth or high school football (Table 3). Results of all association analyses were relatively similar when adjusting for additional variables in multivariable analysis (Tables S4-S7).

We assessed whether playing more than one sport may be associated with CTE outcomes in males (Table S8). In multivariable analysis adjusting for age at death and football, playing two or more sports was not strongly associated with combined CTE pathology (OR = 1.30, $P = 0.55$) or CTE-positive (OR = 0.96, $P = 0.94$). Conversely, the association of playing football with combined CTE pathology was consistent when adjusting for playing multiple sports in addition to age at death (OR = 2.37, $P = 0.039$), with similar results for CTE-positive (OR = 2.77, $P = 0.063$). The higher increased risk of CTE outcomes in football players regardless of other sports played is illustrated in Figure 3 (combined CTE

Table 2. Comparison of demographic, clinical and neuropathological characteristics according between subjects with and without CTE outcomes in males. Abbreviations: CTE = chronic traumatic encephalopathy; AD = Alzheimer's disease.

Variable	CTE-negative (N = 436)	Combined CTE pathology (N = 41)	*P*-value: CTE-negative vs. combined CTE pathology	CTE-positive (N = 21)	*P*-value: CTE-negative vs. CTE-positive
Demographic information					
Age at death (years)	65 (12, 99)	73 (33, 91)	0.006	75 (39, 89)	0.038
Race (white)	424 (98.1%)	39 (95.1%)	0.21	19 (90.5%)	0.068
Years of education	14 (6, 21)	16 (12, 21)	0.36	16 (12, 21)	0.41
Military	186 (42.7%)	20 (48.8%)	0.51	11 (52.4%)	0.50
Clinical information					
Alcoholism	103 (23.6%)	10 (24.4%)	0.85	4 (19.0%)	0.79
Anxiety	82 (18.8%)	2 (4.9%)	0.029	1 (4.8%)	0.15
Bipolar	69 (15.8%)	7 (17.1%)	0.82	4 (19.0%)	0.76
Dementia	112 (25.7%)	18 (43.9%)	0.017	12 (57.1%)	0.004
Depression	145 (33.3%)	14 (34.1%)	1.00	9 (42.9%)	0.35
Drug abuse	31 (7.1%)	2 (4.9%)	1.00	1 (4.8%)	1.00
Head injury	57 (13.1%)	3 (7.3%)	0.46	1 (4.8%)	0.50
Movement disorder	64 (14.7%)	12 (29.3%)	0.024	8 (38.1%)	0.010
Psychosis	174 (39.9%)	26 (63.4%)	0.005	14 (66.7%)	0.023
PTSD	7 (1.6%)	1 (2.4%)	0.52	1 (4.8%)	0.30
Schizophrenia	5 (1.1%)	1 (2.4%)	0.42	1 (4.8%)	0.24
Suicide	34 (7.8%)	1 (2.4%)	0.35	0 (0.0%)	0.39
Tobacco abuse	162 (37.2%)	19 (46.3%)	0.31	8 (38.1%)	1.00
Neuropathological information					
AD	88 (20.2%)	15 (36.6%)	0.027	10 (47.6%)	0.006

The sample median (minimum, maximum) is shown for continuous variables. *P*-values result from a Wilcoxon rank sum test or Fisher's exact test. Information was unavailable regarding race (N = 4 subjects without CTE pathology).

Table 3. Associations of exposure to individual sports with occurrence of combined CTE pathology and CTE-positive in males. Abbreviations: CTE = chronic traumatic encephalopathy; OR = odds ratio; CI = confidence interval.

		Association with combined CTE pathology					Association with CTE-positive				
		N (%) with combined	Unadjusted analysis		Adjusting for age at death, baseball, boxing and football†		N (%) with CTE-	Unadjusted analysis		Adjusting for boxing and football‡	
Sport	N	CTE	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	positive	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Primary analysis of individual sports											
Baseball											
No	413	32 (7.8%)	1.00 (reference)	N/A	1.00 (reference)	N/A	16 (3.9%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	64	9 (14.1%)	1.95 (0.88, 4.30)	0.099	1.42 (0.62, 3.27)	0.41	5 (7.8%)	2.10 (0.74, 5.95)	0.16	1.57 (0.52, 4.72)	0.43
Basketball											
No	385	30 (7.8%)	1.00 (reference)	N/A	1.00 (reference)	N/A	16 (4.2%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	92	11 (12.0%)	1.61 (0.77, 3.34)	0.20	0.95 (0.41, 2.23)	0.91	5 (5.4%)	1.33 (0.47, 3.72)	0.59	0.97 (0.32, 2.95)	0.95
Boxing											
No	470	39 (8.3%)	1.00 (reference)	N/A	1.00 (reference)	N/A	19 (4.0%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	7	2 (28.6%)	4.42 (0.83, 23.54)	0.081	3.62 (0.63, 20.79)	0.15	2 (28.6%)	9.50 (1.73, 52.12)	0.010	10.29 (1.79, 59.28)	0.009
Football											
No	337	20 (5.9%)	1.00 (reference)	N/A	1.00 (reference)	N/A	10 (3.0%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	140	21 (15.0%)	2.80 (1.46, 5.35)	0.002	2.62 (1.33, 5.15)	0.005	11 (7.9%)	2.79 (1.16, 6.73)	0.022	2.87 (1.17, 7.01)	0.021
Hockey											
No	457	39 (8.5%)	1.00 (reference)	N/A	1.00 (reference)	N/A	20 (4.4%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	20	2 (10.0%)	1.19 (0.27, 5.32)	0.82	1.27 (0.27, 5.97)	0.77	1 (5.0%)	1.15 (0.15, 9.03)	0.89	1.44 (0.18, 11.53)	0.73
Soccer§											
No	472	41 (8.7%)	1.00 (reference)	N/A	N/A	N/A	21 (4.5%)	1.00 (reference)	N/A	N/A	N/A
Yes	5	0 (0.0%)	N/A	1.00	N/A	N/A	0 (0.0%)	N/A	1.00	N/A	N/A
Wrestling											
No	438	38 (8.7%)	1.00 (reference)	N/A	1.00 (reference)	N/A	20 (4.6%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	39	3 (7.7%)	0.88 (0.26, 2.98)	0.83	0.86 (0.25, 3.05)	0.82	1 (2.6%)	0.55 (0.07, 4.21)	0.56	0.43 (0.06, 3.38)	0.42
Other†											
No	473	41 (8.7%)	1.00 (reference)	N/A	N/A	N/A	21 (4.4%)	1.00 (reference)	N/A	N/A	N/A
Yes	4	0 (0.0%)	N/A	1.00	N/A	N/A	0 (0.0%)	N/A	1.00	N/A	N/A
Subgroup analysis¶											
Baseball—youth or high school only											
No	413	32 (7.8%)	1.00 (reference)	N/A	1.00 (reference)	N/A	16 (3.9%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	48	6 (12.5%)	1.70 (0.67, 4.30)	0.26	1.11 (0.41, 3.00)	0.83	5 (10.4%)	2.89 (1.01, 8.26)	0.048	2.03 (0.66, 6.32)	0.22
Baseball—beyond high school††											
No	461	38 (8.2%)	1.00 (reference)	N/A	1.00 (reference)	N/A	21 (4.6%)	1.00 (reference)	N/A	N/A	N/A
Yes	12	3 (25.0%)	3.71 (0.96, 14.29)	0.057	3.89 (0.98, 15.44)	0.053	0 (0.0%)	N/A	1.00	N/A	1.00
Football—youth/high school only											
No	337	20 (5.9%)	1.00 (reference)	N/A	1.00 (reference)	N/A	10 (3.0%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	124	14 (11.3%)	2.02 (0.99, 4.13)	0.055	1.84 (0.87, 3.90)	0.11	8 (6.5%)	2.26 (0.87, 5.85)	0.095	2.29 (0.87, 6.03)	0.094
Football—beyond high school											

Table 3. *Continued.*

		Association with combined CTE pathology					Association with CTE-positive				
			Unadjusted analysis		Adjusting for age at death, baseball, boxing and football†			Unadjusted analysis		Adjusting for boxing and football‡	
Sport	N	N (%) with combined CTE	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	N (%) with CTE-positive	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
No	461	34 (7.4%)	1.00 (reference)	N/A	1.00 (reference)	N/A	18 (3.9%)	1.00 (reference)	N/A	1.00 (reference)	N/A
Yes	15	7 (46.7%)	10.99 (3.76, 32.13)	<0.001	13.23 (4.23, 41.36)	<0.001	3 (20.0%)	6.15 (1.60, 23.74)	0.008	6.84 (1.76, 26.66)	0.0056

ORs, 95% CIs and *P*-values result from logistic regression models. *P*-values < 0.00625 were considered as statistically significant after applying a Bonferroni adjustment for multiple testing. Information was unavailable regarding level of baseball played (N = 4) and level of football played (N = 1).

†Models involving baseball—youth or high school and baseball—beyond high school were not adjusted for baseball, and models adjusting for football—youth or high school and football—beyond high school were not adjusted for football.‡Models involving football—youth or high school and football—beyond high school were not adjusted for football.§Because of the lack of subjects who played soccer or other sports and who had combined CTE pathology or CTE-positive, logistic regression analysis was not possible; *P*-values result from Fisher's exact test and multivariable analysis was not performed.¶Only baseball and football were examined in subgroup analysis as these were the only sports for which a reasonable number of subjects played beyond high school. When comparing individuals who did and did not play a given youth or high school sport, individuals who played that sport beyond high school were excluded to avoid combining individuals who did not play a given sport and individuals who played that sport beyond high school in to the same category.††Because of the lack of subjects who played baseball beyond high school and who had CTE-positive, logistic regression analysis was not possible; *P*-values result from Fisher's exact test and multivariable analysis was not performed.

pathology) and Figure S2 (CTE-positive). All of these findings were consistent when examining the subset of 451 males with an age at death of at least 30 years (data not shown).

DISCUSSION

Understanding the incidence/prevalence of CTE through standard epidemiologic methodologies is challenging. With a heterogeneous admixture of behavioral, mood, cognitive and motor features (18), antemortem symptomatology in autopsy-confirmed CTE cases demonstrates significant interpersonal variability and clinical overlap with other neurodegenerative and psychiatric disorders, including Alzheimer's disease, frontotemporal dementias, Lewy body disorder, bipolar disorder and schizophrenia. Molecular neuroimaging and biofluid disease markers have not yet been sufficiently studied and validated on large study cohorts for routine clinical use. Autopsy cohorts are necessary for understanding the public health relevance of CTE as postmortem neuropathological assessment remains the diagnostic gold standard.

Because of differing sampling approaches and inclusion criteria, reported frequencies of CTE in autopsy cohorts has varied considerably, from 80%–99% in cohorts of predominantly experienced football players (15, 17), to 12%–32% in neurodegenerative disorder brain banks (1, 10) and to 6% in specific autopsy-confirmed disorders screened for comorbidity of CTE pathology (multiple system atrophy and amyotrophic lateral sclerosis) (8, 33). Herein, review of obituaries and yearbooks was used to ascertain contact sports exposure in an autopsy cohort of 750 individuals, and standardized tau immunohistochemistry was used to screen and evaluate pathology blinded to clinical information. Combined CTE pathology was found in 42 brains, or 5.6% of the study cohort and almost exclusively in men (8.8%). Collectively, 2.8% of subjects were CTE-positive, all of whom were male.

Importantly, we observed that participation in American football, specifically American football beyond high school, was associated with a markedly increased odds of both combined CTE pathology and CTE-positive outcomes in males; of the 15 males who played football beyond high school, seven (46.7%) had combined CTE pathology and 3 (20.0%) CTE-positive. Of particular interest in our study, though participation in football that did not extend beyond high school was associated with an approximate twofold increased risk of CTE outcomes, these findings were not statistically significant. Of note, of the 124 individuals who played youth or high school football and did not play beyond that point, 110 (88.7%) did not have CTE pathology. Therefore, although our findings do suggest that playing youth or high school football may be associated with a slightly elevated risk of CTE (larger studies are needed to confirm this), they also indicate that most players of youth or high school football do not experience CTE outcomes. Additionally, though there was some evidence of an association between participating in boxing and an elevated risk of CTE outcomes based on our findings, participation in baseball, basketball, hockey, soccer

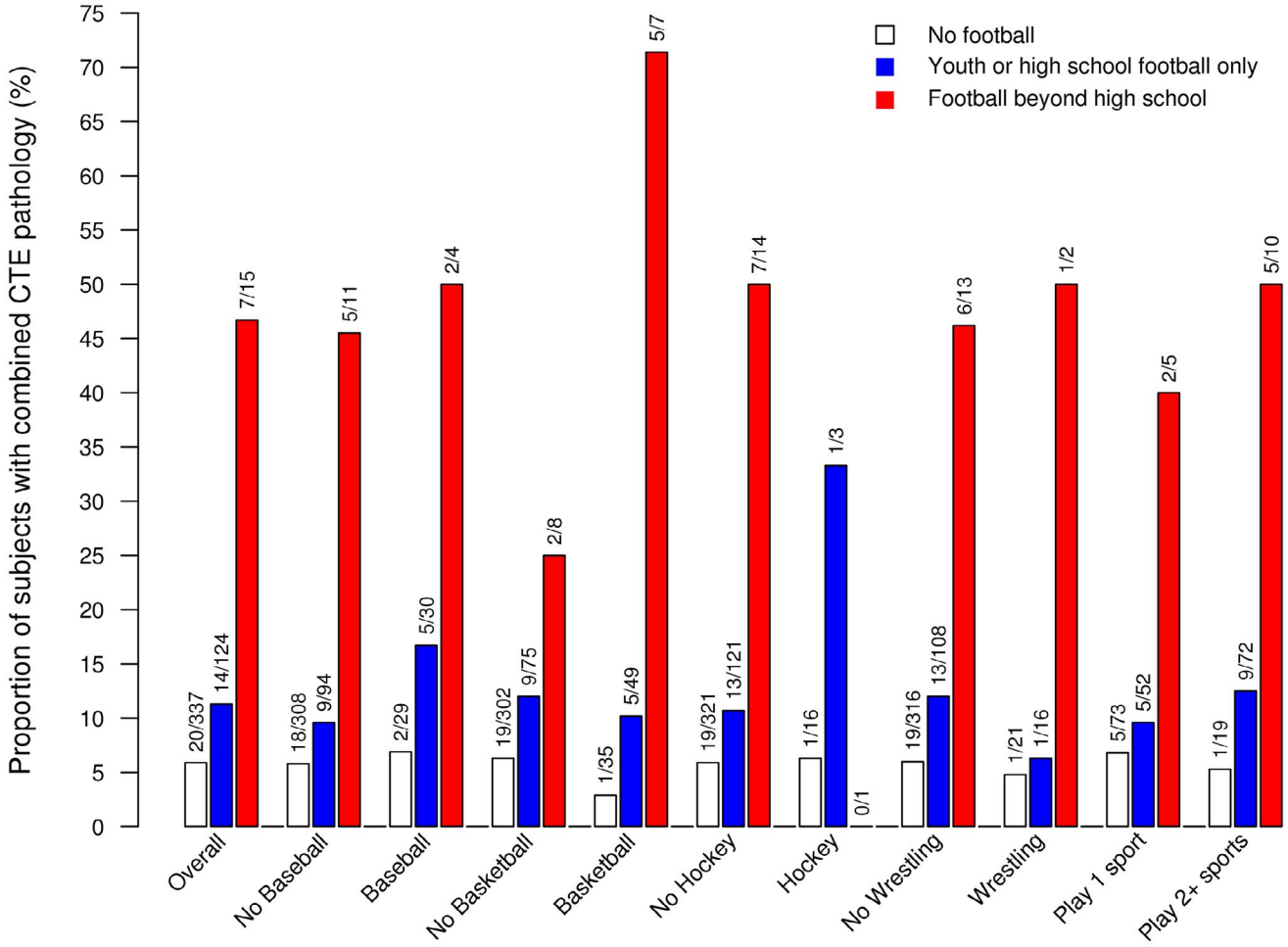

Figure 3. Proportion of males with combined CTE pathology in individuals who did not play football (white bars), who played youth or high school football only (blue bars), or who played football beyond high school (red bars) in the overall group and also in subgroups based on other sports played.

or wrestling were not strongly associated with occurrence of combined CTE pathology or CTE-positive.

Of the 42 combined CTE pathology brains, 21 were classified as CTE-positive, consistent with established consensus criteria, while 21 displayed features of CTE. The features of CTE designation recognizes neuropathological diagnostic probability of the disorder, while accounting for study limitations and limitations regarding the range of CTE pathology. Despite not meeting the consensus definition of CTE pathology, the 21 features of CTE cases were more consistent with CTE than Alzheimer's disease, pathological aging or aging-related tau astrogliopathy alone. These findings are similar to observations by Drs. Noy, Krawitz and Del Bigio who identified 34/111 autopsy cases with lesions described as "CTE-like" and "CTE Stage <I," of which 53% had a history of head trauma (22). Herein, features of CTE cases may be a product of limited sectioning (one five-micron thick section) of the tissue block and analysis of tissue from only two to three neocortical regions. More exhaustive sampling and sectioning might assist in adjudicating whether cases with features of CTE are in fact CTE-positive. Alternatively, features of CTE may represent the earliest emergence of CTE pathology, perhaps at a latent or prodromal disease state, which marks the beginning of this progressive tauopathy below the threshold of current criteria (criteria developed from evaluation of common features in cases with advanced disease) (13). Ambiguity related to the nomenclature, assessment and relevance of very early or mild perivascular tau pathology would benefit from further validation and refinement of CTE pathological criteria.

Medical diagnoses were assessed using the Rochester Epidemiology Project research infrastructure to evaluate antemortem clinical manifestations of CTE pathology. Individuals with combined CTE pathology demonstrated rates of dementia, movement disorders and psychosis that were higher than CTE-negative cases. Importantly, individuals with combined CTE pathology did not have higher rates of head trauma diagnoses compared to CTE-negative subjects, suggesting that the etiology of CTE pathology

is intrinsic to the repetitive traumatic brain injury sustained through contact sports participation and not single-incident head trauma sustained later in life. Moreover, the frequency of certain disorders previously noted to associate with CTE, including illicit drug abuse, anxiety, depression, post-traumatic stress disorder and suicide (11, 12, 24), were not observed significantly more often in subjects with combined CTE pathology compared to CTE-negative subjects.

While this study is the largest neuropathological assessment of CTE in an autopsy series to date, there are several limitations. First, assessment of sports participation in females was more restricted compared to males. Many women in the study cohort attended higher education institutions prior to enactment of the United States Patsy T. Mink Equal Opportunity in Education Act (commonly referred to as "Title IX") and were not provided opportunities to participate in the same types of athletic organizations as their male counterparts. No women athletes were classified as CTE-positive and a single non-athlete woman was assessed as features of CTE. As a result, we were unable to assess associations between participation in sports and CTE outcomes in females. The only two published cases of CTE in women to date was of a victim of domestic abuse (27) and an autistic individual with self-injury behavior (4); while there is no reason to speculate our case experienced domestic violence or self-injury, these variables are unknown. It seems reasonable to postulate that if more women had played contact sports in our cohort, the frequency of CTE would have correspondingly increased. Second, ascertainment of participation in contact sports was based on available information that was collected retrospectively from online obituaries and high school yearbooks, as opposed to prospective data collection or interviews. Next-of-kin interviews were not possible as contact information was inaccessible for this study. While interviews would be beneficial for validating exposures, these techniques are not without their own limitations including susceptibility to recall bias (16). Despite having previously demonstrated the utility of these exposure ascertainment techniques, in obituaries and yearbooks separately (1, 7, 29), we cannot rule out the possibility of sports participation in non-athletes that was omitted in obituary and yearbook sources or the possibility of repetitive head trauma sustained from other non-sport-related or non-military-related sources. This limitation is especially relevant as 15 individuals in this study (fourteen males, one female) classified as "non-athletes" were observed to have combined CTE pathology (nine features of CTE, six CTE-positive). Third, yearbook and obituary sports data was limited to sport type and sport participation level; it was not possible to uniformly assess more detailed information such as position and duration of play. Finally, while the Mayo Clinic Tissue Registry serves as a comprehensive tissue archive for numerous medical research studies (not strictly neurodegenerative disorders), brain autopsies by nature are elected by the family or physician and as such represent convenience sampling (notably, autopsy randomization sampling is infeasible in practice).

In conclusion, we identified a small, yet significant, frequency of CTE pathology in this study cohort from the Mayo Clinic Tissue Registry. In assessing a variety of contact sports, we identified specific athletic activities, such as American football, that were more strongly associated with CTE pathology compared to other sports, and within football, a dose-response relationship between exposure and CTE pathogenesis. These initial results have important implications regarding the public health relevance of CTE. As our data suggests associations between football and CTE are strongest for participation beyond high school, it may be prudent to prioritize regulatory reform mitigating head trauma at the collegiate and professional levels. Future prospective, longitudinal studies focused on specific sports positions, participation duration and sustained head impacts during participation (number, force, latency, etc.) in large population-based cohorts will help further benefit our scientific understanding of sports-related head trauma and the etiology of CTE.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site:

Table S1. Comparison of demographic and clinical characteristics between the 750 included subjects and the 1816 subjects who were excluded because of insufficient athletic information.

Table S2. Characteristics according to sports played in females.

Table S3. Characteristics according to sports played in males.

Table S4. Association between exposure to individual sports and occurrence of combined CTE pathology in males with additional multivariable adjustments.

Table S5. Association between exposure to individual sports and occurrence of CTE-positive in males with additional multivariable adjustments.

Table S6. Subgroup analysis of associations of exposure to sports and occurrence of combined CTE pathology in males with additional multivariable adjustments.

Table S7. Subgroup analysis of association between exposure to individual sports and occurrence of CTE-positive in males with additional multivariable adjustments.

Table S8. Associations of playing multiple sports with occurrence of combined CTE pathology and CTE-positive in males.

Figure S1. Proportion of males with CTE-positive in individuals who did not play football, who played youth or high school football only, or who played football beyond high school in the overall group and also in subgroups based on other sports played.

Figure S2. Odds ratios and 95% confidence intervals from multivariable analysis displaying the associations of exposure to specific sports with the separate outcomes of combined CTE pathology and CTE-positive in males. Baseball—beyond high school is not displayed for the CTE-positive outcome as none of the 12 subjects who played baseball beyond high school had CTE-positive, making estimation of an odds ratio impossible.