Supplementary Online Content

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eMethods 1. CTE stage classification scheme
eMethods 2. Dementia diagnostic procedures
eMethods 3. Statistical analyses
eMethods 4. Results of proportional odds and logistic regression models
eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. CTE stage classification scheme

The stage of CTE is based on location and density of p-tau, with stage I and II involving focal CTE lesions in the cerebral cortex. Stage III and IV CTE includes multiple CTE lesions and widespread cortical and subcortical NFTs, including in the medial temporal lobes. CTE stage is determined through a comprehensive evaluation of various brain regions using AT8 immunostained, 10 µm paraffin-embedded sections, including (but not limited to) the DLFC, superior temporal cortex, inferior parietal cortex, hippocampus (CA1, CA2, CA4), entorhinal cortex, and amygdala. Severity of p-tau in these regions are rated on a 0-3 scale, with 0 being no NFTs and 3 being severe NFT burden.[1,2]

eMethods 2. Dementia diagnostic procedures

A neurologist and/or neuropsychologist with expertise in neurodegenerative disorders conducted telephone clinical interviews with informants to obtain medical and clinical history, including the presence, nature, and timeline of symptoms related to cognition, behavior/mood, and daily functioning. Informants included a combination of first-degree family members, spouses/significant others, children, non-immediate family members, parents, siblings, and/or friends of the participant. Clinicians summarized the clinical presentation, and other relevant history, into a narrative and a consensus diagnosis of dementia (i.e., yes or no) at the time of death was adjudicated. The make-up of the consensus panel has evolved over time; however, since 2014, it has consistently included at least three M.D. or Ph.D. level clinicians with neurodegenerative and/or head trauma expertise in the fields of neuropsychology, behavioral neurology, psychiatry, and/or neurosurgery. All clinicians were blind to neuropathological findings and informants were unaware of the neuropathological results.

eMethods 3. Statistical analyses

A series of cumulative logit proportional odds (for ordinal outcomes) and/or logistic (for binary outcomes) regression models examined: 1) the effect of years of football play on WM rarefaction and each CBVD variable, CTE stage, and DLFC NFT burden; 2) the relationship between WM rarefaction and CBVD with dementia (yes or no); 3) the association between each WM rarefaction and each CBVD variable with CTE stage and DLFC NFT burden; and 4) the relationship between CTE stage and DLFC NFT burden with dementia. All analyses controlled for age and race. Years of play is associated with CTE stage[2,3] and was included as a covariate for analyses that had p-tau as the outcome. These proportional odds and logistic regression models were performed to guide selection of variables into a simultaneous equations regression model and determine model pathways among years of football play, WM rarefaction and CBVD, p-tau pathology, and dementia. A conservative p-value of ≤ 0.20 served as the selection criterion into the model. Simultaneous equations regression modeling is a form of structural equation modeling that simultaneously evaluates relationships and pathways among multiple predictors and outcomes.[4] The simultaneous examination of relationships and interactions among numerous variables (including confounders) in a single model reduces Type I error.

eMethods 4. Results of proportional odds and logistic regression models

Based on the proportional odds and logistic regression analyses that showed effects below the $p \leq 0.20$ threshold, the following direct effects were modeled in the simultaneous equations regression model: 1) years of football play on WM rarefaction, 2) years of football play on CTE stage and DLFC NFT burden, 3) arteriolosclerosis and WM rarefaction on dementia, and 4) DLFC NFT burden on dementia. Age and race were modeled to have direct effects on WM rarefaction, arteriolosclerosis, p-tau severity, and dementia. Note that the relationship between years of play and arteriolosclerosis did not meet the $p \leq 0.20$ threshold, nor did any of the relationships between arteriolosclerosis or WM rarefaction with CTE p-tau severity. There were no effects for microinfarcts (absence vs. presence, or when examined as a continuous summary composite).

eReferences

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