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Authors

Ly, Monica
Tuz-Zahra, Fatima
Tripodis, Yorghos
et al.

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Association of Vascular Risk Factors and CSF and Imaging Biomarkers With White Matter Hyperintensities in Former American Football Players

Monica T. Ly, PhD, Fatima Tuz-Zahra, MS, Yorghos Tripodis, PhD, Charles H. Adler, MD, PhD, Laura J. Balcer, MD, MSCE, Charles Bernick, MD, MPH, Henrik Zetterberg, MD, PhD, Kaj Blennow, MD, PhD, Elaine R. Peskind, MD, Rhoda Au, PhD, Sarah J. Banks, PhD, William B. Barr, PhD, Jennifer V. Wethe, PhD, Mark W. Bondi, PhD, Lisa M. Delano-Wood, PhD, Robert C. Cantu, MD, Michael J. Coleman, MA, David W. Dodick, MD, Michael D. McClean, ScD, Jesse B. Mez, MD, MS, Joseph Palmisano, MA, MPH, Brett Martin, MS, Kaitlin Hartlage, MPH, Alexander P. Lin, PhD, Inga K. Koerte, MD, PhD, Jeffrey L. Cummings, MD, ScD, Eric M. Reiman, MD, Martha E. Shenton, PhD, Robert A. Stern, PhD, Sylvain Bouix, PhD, and Michael L. Alosco, PhD, for DIAGNOSE CTE Research Project

Correspondence

Dr. Alosco
malosco@bu.edu

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Abstract

Background and Objectives

Recent data link exposure to repetitive head impacts (RHIs) from American football with increased white matter hyperintensity (WMH) burden. WMH might have unique characteristics in the context of RHI beyond vascular risk and normal aging processes. We evaluated biological correlates of WMH in former American football players, including markers of amyloid, tau, inflammation, axonal injury, neurodegeneration, and vascular health.

Methods

Participants underwent clinical interviews, MRI, and lumbar puncture as part of the Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy Research Project. Structural equation modeling tested direct and indirect effects between log-transformed total fluid-attenuated inversion recovery (FLAIR) lesion volumes (TLV) and the revised Framingham stroke risk profile (rFSRP), MRI-derived global metrics of cortical thickness and fractional anisotropy (FA), and CSF levels of amyloid β_{1-42} , p-tau₁₈₁, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), and neurofilament light. Covariates included age, race, education, body mass index, APOE $\epsilon 4$ carrier status, and evaluation site. Models were performed separately for former football players and a control group of asymptomatic men unexposed to RHI.

Results

In 180 former football players (mean age = 57.2, 36% Black), higher log(TLV) had direct associations with the following: higher rFSRP score ($B = 0.26$, 95% CI 0.07–0.40), higher

From the VA San Diego Healthcare System (M.T.L., M.W.B., L.M.D.-W.), CA; Department of Psychiatry (M.T.L., S.J.B., M.W.B., L.M.D.-W.), University of California San Diego Health, La Jolla; Departments of Biostatistics (F.T.-Z., Y.T.), Epidemiology (R.A.), Environmental Health (M.D.M.), Biostatistics and Epidemiology Data Analytics Center (J.P., B.M., K.H.), Boston University School of Public Health, MA; Boston University Alzheimer's Disease Research Center (Y.T., J.B.M., M.L.A., R.A., R.C.C., R.A.S.), Boston University CTE Center; Department of Neurology, Boston University Chobanian & Avedisian School of Medicine; Departments of Neurology (C.H.A., D.W.D.) and Psychiatry and Psychology (J.V.W.), Mayo Clinic School of Medicine, Mayo Clinic Arizona, Scottsdale; Departments of Neurology (L.J.B.), Population Health and Ophthalmology, (L.J.B.), and Neurology (W.B.B.), NYU Grossman School of Medicine; Cleveland Clinic Lou Ruvo Center for Brain Health (C.B.), Las Vegas, NV; Department of Neurology (C.B.), University of Washington, Seattle; Department of Neurodegenerative Disease (H.Z.), and UK Dementia Research Institute (H.Z.), University College London Institute of Neurology, UK; Hong Kong Center for Neurodegenerative Diseases (H.Z.), China; Wisconsin Alzheimer's Disease Research Center (H.Z.), University of Wisconsin-Madison; Clinical Neurochemistry Laboratory (H.Z., K.B.), Sahlgrenska University Hospital, Gothenburg; Department of Psychiatry and Neurochemistry (K.B.), Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden; VA Northwest Mental Illness Research, Education, and Clinical Center (E.R.P.), Seattle, WA; Department of Psychiatry and Behavioral Sciences (E.R.P.), University of Washington School of Medicine, Seattle; Framingham Heart Study (R.A., J.B.M.); Slone Epidemiology Center (R.A.), Boston University, MA; Department of Neurosciences (S.J.B.), University of California San Diego; Psychiatry Neuroimaging Laboratory (M.J.C., A.P.L., I.K.K., M.E.S., S.B.), Departments of Psychiatry Radiology (M.E.S.), and Center for Clinical Spectroscopy (A.P.L.), Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; cBRAIN (I.K.K.), Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Ludwigs-Maximilians-Universität, Munich, Germany; Chambers-Grundy Center for Transformative Neuroscience (J.L.C.), Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas; Banner Alzheimer's Institute (E.M.R.), Phoenix; Department of Psychiatry (E.M.R.), University of Arizona, Phoenix; Arizona State University (E.M.R.), Phoenix; Translational Genomics Research Institute (E.M.R.), Phoenix; Arizona Alzheimer's Consortium (E.M.R.), Phoenix; and Department of Software Engineering and Information Technology (S.B.), École de technologie supérieure, Université du Québec, Montréal, Canada.

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Coinvestigators are listed at links.lww.com/WNL/D289.

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Glossary

$A\beta_{1-42}$ = β -amyloid (1–42); AD = Alzheimer disease; ADRD = AD-related dementia; AUDIT = alcohol use disorders identification test; BMI = body mass index; CFI = comparative fit index; CTE = chronic traumatic encephalopathy; DIAGNOSE CTE = Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy; dMRI = diffusion MRI; FA = fractional anisotropy; FLAIR = fluid-attenuated inversion recovery; FTLD = frontotemporal lobar degeneration; LGA = lesion growth algorithm; LPA = lesion prediction algorithm; NFL = neurofilament light; p-tau₁₈₁ = phosphorylated tau 181; rFSRP = revised Framingham stroke risk profile; RHI = repetitive head impact; RMSEA = root mean square error of approximation; SEM = structural equation modeling; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; TBI = traumatic brain injury; TE = echo time; TES = traumatic encephalopathy syndrome; TI = inversion time; TLV = total lesion volume; TR = repetition time; WMH = white matter hyperintensity.

p-tau₁₈₁ (B = 0.17, 95% CI 0.01–0.43), lower FA (B = –0.28, 95% CI –0.42 to –0.13), and reduced cortical thickness (B = –0.25, 95% CI –0.45 to –0.08). In 60 asymptomatic unexposed men (mean age = 59.3, 40% Black), there were no direct effects on log(TLV) (rFSRP: B = –0.03, 95% CI –0.48 to 0.57; p-tau₁₈₁: B = –0.30, 95% CI –1.14 to 0.37; FA: B = –0.07, 95% CI –0.48 to 0.42; or cortical thickness: B = –0.28, 95% CI –0.64 to 0.10). The former football players showed stronger associations between log(TLV) and rFSRP (1,069% difference in estimates), p-tau₁₈₁ (158%), and FA (287%) than the unexposed men.

Discussion

Risk factors and biological correlates of WMH differed between former American football players and asymptomatic unexposed men. In addition to vascular health, p-tau₁₈₁ and diffusion tensor imaging indices of white matter integrity showed stronger associations with WMH in the former football players. FLAIR WMH may have specific risk factors and pathologic underpinnings in RHI-exposed individuals.

Introduction

White matter hyperintensities (WMHs) are bright spots visualized on T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI sequences.¹ WMH are associated with an increased risk of stroke, cognitive decline, dementia, and death.^{2,3} Elucidating the risk factors and pathologic correlates of WMH is a high priority for informing prevention and intervention strategies.

WMH are typically presumed to reflect cerebral small vessel disease from aging and cerebrovascular risk factors (e.g., hypertension, cardiovascular disease).^{1,4} Research in Alzheimer disease (AD) and AD-related dementias (ADRDs) has uncovered the multifaceted roles and causes of WMH in the setting of neurodegenerative diseases.^{5,6} CSF β -amyloid (1–42) ($A\beta_{1-42}$), CSF hyperphosphorylated tau 181 (p-tau₁₈₁), and cortical atrophy are biomarkers of AD that have been associated with WMH.^{7,8} Postmortem studies show that the pathologic composition of WMH differs in individuals with AD compared with nondemented controls.^{6,9} WMH in AD, particularly in parietal regions, may be associated with degeneration triggered by cortical AD pathology, whereas WMH in controls are generally due to ischemia.^{6,9} The spatial distribution of WMH has also been linked to pathologies and patterns of cortical atrophy specific to AD or frontotemporal lobar degeneration (FTLD).^{5,8,10,11} Thus, in these neurodegenerative diseases, WMH stem not only from small vessel disease, but they may also initiate and/or be driven by disease-specific pathologies. The various pathways leading to and

from WMH, including amyloid, tau, neurodegeneration, and other pathologies, remain unclear and under debate.

Recent research suggests that WMH might be a late consequence from pathologies associated with exposure to repetitive head impacts (RHIs). RHI refers to the cumulative exposure to forces or blows to the head regardless of whether there was a diagnosed traumatic brain injury (TBI). Therefore, RHI can result from both symptomatic concussions and the more frequent asymptomatic subconcussions. RHI is typically measured by proxies derived from years or seasons of contact sport play and position played.¹² Exposure to RHI has been associated with cognitive and neuropsychiatric symptoms in former American football players.^{12,13} Importantly, RHI is considered the primary risk factor for chronic traumatic encephalopathy (CTE), a progressive neurodegenerative disease characterized by aggregates of perivascular p-tau in neurons at the depths of cortical sulci, and its clinical syndrome, traumatic encephalopathy syndrome (TES). TES is a set of research diagnostic criteria that includes cognitive impairment and/or neurobehavioral dysregulation as core clinical features.^{14,15} While several studies have linked RHI and neurodegenerative disease-based pathologies (e.g., p-tau, cerebral amyloid angiopathy, Lewy body disease),^{14,16,17} evolving data also show white matter injury as a prominent acute and late pathology associated with RHI.^{18–22} With this premise, FLAIR WMH have been investigated in former football players. Findings showed that WMH burden is greater in former football players compared with age-matched

asymptomatic men, and WMH are associated with cognitive impairment and greater functional decline.²⁰⁻²³

We hypothesize that WMH have specific risk factors and potential etiologies in the context of exposure to RHI. Our autopsy study supports this hypothesis because antemortem WMH were associated with greater white matter rarefaction, arteriolosclerosis, and dorsolateral prefrontal p-tau, but not amyloid, in 75 brain donors exposed to RHI.²⁰ However, risk factors and biological correlates of WMH after exposure to RHI are unclear, and the multiple pathways to WMH have yet to be elucidated in a model simultaneously examining fluid biomarkers, neuroimaging, and vascular risk factors. The objective of this study was to examine risk factors and biomarker correlates of FLAIR WMH among former elite American football players. We tested associations between FLAIR WMH and biomarkers of amyloid, p-tau, neuroinflammation, axonal injury, neurodegeneration, and vascular health. We also examined these associations in a group of asymptomatic men unexposed to RHI to determine the specificity of the relationships observed in the former football players.

Methods

Participants and Study Design

Participants were from the Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project.²⁴ The goals of this multisite study include, but are not limited to, examining risk factors and biomarkers for CTE. A detailed overview of the DIAGNOSE CTE Research Project including eligibility criteria has been described elsewhere.²⁴ This study was not an aim of DIAGNOSE CTE and represents secondary analyses of this data set. Inclusion criteria for former college football players included at least 6 years of football play with at least 3 at the college level. Former professional football players must have played at least 12 years of organized football with at least 3 in college and 4 or more seasons professionally. Exclusion criteria for the unexposed group included no reported diagnosed history of TBI at study screening and no participation in activities associated with RHI. They were required to have no reported history of formal diagnosis or treatment for psychiatric illness or cognitive impairment and no reported history of cognitive or psychiatric symptoms. They had to have a body mass index (BMI) of 24 or higher. Exclusion criteria for all participants included history of clinical stroke or significant neurologic condition, severe vision or hearing impairment, and clinically significant infectious disease, endocrine or metabolic disease, pulmonary, kidney or liver impairment, or cancer.

Participants completed clinical interviews, self-report questionnaires, MRI, lumbar puncture for CSF biomarkers, blood draw for DNA extraction, and other procedures not pertinent to this study including neuropsychological testing.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided written informed consent to be evaluated for this research study. All sites involved in the DIAGNOSE CTE Research Project received approval by their respective institutional review boards.

MRI

MRI was acquired on Siemens 3T MAGNETOM Skyra (Erlangen, Germany; software version VE11) across all 4 sites. Neuroimaging protocols included T1, T2, and diffusion MRI (dMRI). Harmonization and quality control procedures have been described.²⁴ All structural sequences were acquired at high resolution ($1 \times 1 \times 1 \text{ mm}^3$, 176 slices, $256 \times 256 \text{ cm}^2$ field of view) in the sagittal plane, including T1 magnetization-prepared rapid acquisition gradient echo (repetition time [TR] = 2,530 milliseconds, echo time [TE] = 3.36 milliseconds, inversion time [TI] = 1,100 milliseconds) and T2-weighted FLAIR (TR = 5,000 milliseconds, TE = 388 milliseconds, TI = 1,800 milliseconds). The dMRI sequence had a multishell design with 73 acquisitions spread over 5 shells (4 b = 0, 3 b = 200, 6 b = 500, 30 b = 1,000, and 30 b = 2,500 s/mm^2 ; $2 \times 2 \times 2 \text{ mm}^3$ resolution; 73 slices). The following variables were derived for analyses in this study:

WMH

WMH were estimated from FLAIR sequences using the automated lesion prediction algorithm (LPA) pipeline from the Lesion Segmentation Toolbox version 3.0.0 for SPM in MATLAB (SPM12, MATLAB version R2020a; MathWorks, Natick, MA). The LPA was selected over the lesion growth algorithm (LGA) because it does not require T1 images or user-set parameters, it runs faster, and it has been shown to outperform the LGA.²⁵ After calculating the probability of lesion presence for each voxel, lesions were segmented into new images to produce lesion probability maps. For quality control, each lesion probability map (thresholded at $\kappa = 0.5$, the default LPA recommendation) was visually inspected and compared with the FLAIR images. Three participants were excluded at this stage because of erroneous lesion classification likely due to image artifacts. Total lesion volume (TLV) was calculated (in milliliters) and then log transformed to normalize its distribution.

Cortical Thickness

Brain masking was performed using a technique based on multiatlas brain segmentation.²⁶ Preprocessing (motion correction and average, automated Talairach transformation, intensity normalization), cortical reconstruction, and volumetric segmentation were performed using the freely available FreeSurfer image analysis suite (version 7.1).²⁷ Cortical thickness was calculated as the measure of the distance (in millimeters) between the gray/white matter boundary to the gray matter/CSF boundary at each vertex on the cortical surface. Average cortical thickness was calculated as the sum of the mean left hemisphere cortical thickness and mean right hemisphere cortical thickness. This cortical thickness composite served as our global measure of neurodegeneration. Decreased cortical thickness has been associated with greater

Table 1 Participant Characteristics

	n	Former college football players	n	Former professional football players	n	Former football players (college + professional)	n	Asymptomatic unexposed men	p Value
Demographics									
Age, y, mean (SD)	60	53.45 (7.66)	120	59.09 (7.83)	180	57.21 (8.20)	60	59.27 (8.26)	0.10
Education, y, mean (SD)	60	18.10 (1.13)	120	17.83 (1.21)	180	17.92 (1.19)	60	18.08 (1.63)	0.48
Race, n (%)	60		120		180		60		0.25
Black or African American		11 (18.33)		52 (43.33)		63 (35.0)		24 (40.0)	
Native Hawaiian or other Pacific Islander		0		0		0		1 (1.67)	
White		48 (80.00)		66 (55.00)		114 (63.33)		35 (58.33)	
Multiple races		1 (1.67)		2 (1.67)		3 (1.67)		0	
Ethnicity: Hispanic or Latino, n (%)	60	0	120	3 (2.5)	180	3 (1.7)	60	0	0.74
Athletics									
Duration of football play, y, mean (SD)	60	11.51 (2.54)	120	18.02 (3.34)	180	15.85 (4.36)			
Age of first exposure, y, mean (SD)	60	10.17 (2.64)	120	11.54 (2.81)	180	11.08 (2.82)			
Position group at highest level of play, n (%)	60		120		180				
Offensive linemen		22 (36.67)		22 (18.33)		44 (24.44)			
Offensive backs and receivers		14 (23.33)		36 (30.00)		50 (27.78)			
Defensive linemen		5 (8.33)		14 (11.67)		19 (10.56)			
Linebackers		7 (11.67)		21 (17.50)		28 (15.56)			
Defensive backs		12 (20.00)		23 (19.17)		35 (19.44)			
Special teams		0		4 (3.33)		4 (2.22)			
Participation in organized hockey, n (%)	60	0	119	3 (2.52)	179	3 (1.68)			
Duration of hockey play, y, mean (range)			3	6.67 (4–10)	3	6.67 (4–10)			
Participation in boxing, n (%)	59	4 (6.78)	119	6 (5.04)	178	10 (5.62)			
Duration of boxing, years, mean (range)	4	3.75 (1–9)	6	4.17 (1–13)	10	4 (1–13)			
Participation in soccer, n (%)	60	2 (3.33)	120	1 (0.83)	180	3 (1.67)			
Duration of soccer, y, mean (range)	2	6.5 (5–8)	1	2	3	5 (2–8)			
Self-reported no. of concussions, median (IQR)	60	26 (88)	119	30 (100.5)	179	30 (88)			
APOE ε4 carrier, n (%)	59	20 (33.90)	115	33 (28.70)	174	53 (30.46)	56	11 (19.64)	0.16
Vascular risk factors									
rFSRP, mean (SD)	54	0.02 (0.03)	117	0.03 (0.04)	171	0.03 (0.03)	58	0.05 (0.04)	0.009

Continued

Table 1 Participant Characteristics (continued)

	n	Former college football players	n	Former professional football players	n	Former football players (college + professional)	n	Asymptomatic unexposed men	p Value
Body mass index, mean (SD)	60	33.81 (4.81)	120	31.99 (4.46)	180	32.59 (4.65)	60	30.78 (4.52)	0.009
Systolic blood pressure, mm Hg, mean (SD)	60	129.85 (13.80)	120	124.75 (11.17)	180	126.45 (12.31)	60	133.85 (13.32)	<0.001
Diastolic blood pressure, mm Hg, mean (SD)	60	80.43 (9.02)	120	77.87 (8.67)	180	78.72 (8.85)	60	81.65 (8.53)	0.02
History of hypertension, n (%)	60	25 (41.67)	118	53 (44.92)	178	78 (43.82)	59	26 (44.07)	1
History of high cholesterol, n (%)	60	19 (31.67)	118	48 (40.68)	178	67 (37.64)	60	26 (43.33)	0.53
History of diabetes, n (%)	60	3 (5.00)	118	9 (7.63)	178	12 (6.74)	60	7 (11.67)	0.35
History of sleep apnea, n (%)	58	18 (31.03)	119	44 (36.97)	177	62 (35.03)	59	10 (16.95)	0.01
History of coronary artery disease, n (%)	58	3 (5.17)	120	10 (8.33)	178	13 (7.30)	60	2 (3.33)	0.43
Lifetime smoker >100 cigarettes, n (%)	60	9 (15.00)	120	16 (13.33)	180	25 (13.89)	60	17 (28.33)	0.02
AUDIT total score, mean (SD)	60	5.63 (6.06)	120	4.80 (5.55)	180	5.08 (5.72)	60	3.00 (3.26)	<0.001
WMH									
TLV, mL, mean (SD)	55	1.22 (2.66)	110	2.34 (5.37)	165	1.96 (4.67)	59	1.07 (1.28)	0.03
log(TLV), mL, mean (SD)	55	-0.86 (1.53)	110	-0.32 (1.61)	165	-0.50 (1.60)	59	-0.75 (1.53)	0.30
CSF p-tau₁₈₁, pg/mL, mean (SD)	40	32.22 (11.00)	100	39.06 (19.08)	140	37.10 (17.40)	46	37.33 (16.85)	0.94
CSF Aβ₁₋₄₂, pg/mL, mean (SD)	40	863.50 (291.82)	100	790.09 (322.64)	140	811.06 (314.87)	46	942.09 (374.63)	0.04
CSF sTREM2, pg/mL, mean (SD)	40	2,683.75 (1,208.04)	98	2,397.61 (1,060.40)	138	2,480.55 (1,108.41)	46	2,736.30 (1,364.62)	0.25
CSF NfL, pg/mL, mean (SD)	40	735.91 (596.83)	100	780.57 (506.17)	140	767.81 (531.82)	46	736.97 (576.40)	0.75
Average FA	58	0.49 (0.02)	114	0.49 (0.02)	172	0.49 (0.02)	57	0.48 (0.02)	0.03
Average cortical thickness, mm	56	4.86 (0.15)	115	4.82 (0.16)	171	4.84 (0.16)	58	4.84 (0.16)	0.81

Abbreviations: AUDIT = alcohol use disorders identification test; FA = fractional anisotropy; NfL = neurofilament light; rFSRP = revised Framingham stroke risk profile; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; TLV = total lesion volume; WMH = white matter hyperintensity. *p* values indicate simple differences in values between the former football players (college and professional pooled) and the asymptomatic unexposed participants by *t* tests or χ^2 tests, without covariates.

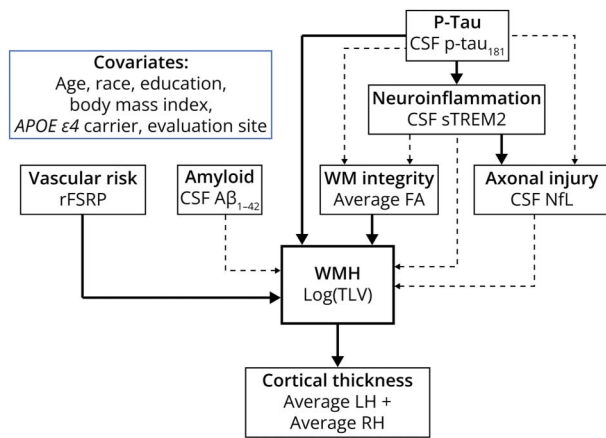
WMH burden and has been found to mediate the relationship between WMH and cognition.²⁸

White Matter Integrity

dMRI images were preprocessed using a custom pipeline.²⁹ Images were first brain-masked using a deep learning-based tool, then corrected for geometric distortions because of participant motion and eddy currents as well as susceptibility artifacts because of echo planar imaging acquisition. Corrected and brain-masked dMRI data were then processed using a custom

implementation of the ENIGMA-DTI tract-based spatial statistics,³⁰ resulting in average fractional anisotropy (FA), mean diffusivity, radial diffusivity, and axial diffusivity estimates in 46 major white matter tracts. FA is a measure of the degree of diffusion directionality that can reflect disruptions in white matter microstructure. Proxies of exposure to RHI (e.g., age of first exposure to football) in former professional football players have been associated with lower FA.³¹ Average FA across all major white matter tracts was used as a summary measure because of its high correlation with FA of individual tracts.

Figure 1 SEM of Direct and Indirect Effects on WMH



Bolded lines indicate significant associations, and dashed lines indicate non-significant associations in the former football players. FA = fractional anisotropy; LH = left hemisphere; NFL = neurofilament light; rFSRP = revised Framingham stroke risk profile; RH = right hemisphere; SEM = structural equation modeling; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; TLV = total lesion volume; WMH = white matter hyperintensity.

CSF Biomarkers

All sites used uniform methods and prefabricated sample collection kits for CSF collection.²⁴ CSF measurements included p-tau₁₈₁, Aβ₁₋₄₂, neurofilament light (NFL), and soluble triggering receptor expressed on myeloid cells 2 (sTREM2). CSF Aβ₁₋₄₂ and p-tau₁₈₁ were measured using Lumipulse technology (Fujirebio, Ghent, Belgium) as previously described.³² We also had a priori rationale for inclusion of NFL, measured using an in-house ELISA,³³ and sTREM2, measured using an in-house electrochemiluminescence assay.³⁴

CSF Aβ₁₋₄₂ and p-tau₁₈₁ are biomarkers of hallmark AD neuropathologic changes, where decreased CSF Aβ₁₋₄₂ reflects increased Aβ deposition in the brain, and increased CSF p-tau₁₈₁ reflects pathologic changes in tau.⁷ CSF NFL is a non-specific marker of axonal degeneration and injury that has been associated with WMH in cognitively normal older adults.³⁵ CSF sTREM2 is a marker of neuroinflammation and microglial activation associated with tau-related neurodegeneration.³⁶ Previous research in former professional football players also supports the inclusion of CSF sTREM2 here.³⁷

Vascular Risk

The revised Framingham Stroke Risk Profile score (rFSRP) served as a summary composite for vascular risk. The specific rFSRP algorithm has been described.³⁸ It is based on systolic blood pressure, use of antihypertensive medications, prevalent cardiovascular disease, current smoking status, current or previous atrial fibrillation, and diabetes.

Demographic, Athletic, Clinical, and Genetic Characteristics

Semistructured interviews and online questionnaires were used to collect demographic data, medical and psychiatric history, and athletic history, as well as other variables not

relevant to this study. Systolic blood pressure and diastolic blood pressure were measured on-site at the time of participation. *APOE* genotyping was conducted using standard methodology as described elsewhere.²⁴ For the purposes of this study, participants were categorized as being an *APOE* ε4 carrier or noncarrier. Race and ethnicity were self-reported. All racial groups are presented in Table 1.

Statistical Analyses

Differences in participant characteristics between former football players (college and professional pooled) and asymptomatic unexposed men were assessed using t-tests and chi-square tests. The effects of evaluation site on neuroimaging variables (e.g., log(TLV), FA, and cortical thickness) were assessed using analysis of variances for the former football players and asymptomatic unexposed men, separately. Structural equation modeling (SEM) tested direct and indirect effects between rFSRP, CSF Aβ₁₋₄₂, CSF p-tau₁₈₁, CSF NFL, CSF sTREM2, average FA, and average cortical thickness with log(TLV) (Figure 1). These variables were selected, and the directionality of pathways was hypothesized based on past research.^{6-8,35,37} Pathways between variables (e.g., CSF Aβ₁₋₄₂ and CSF p-tau₁₈₁, rFSRP and CSF Aβ₁₋₄₂) were not included for model parsimony. A priori covariates included in the model were age, race, education, *APOE* ε4 carrier status, BMI, and evaluation site. Each continuous variable was mean-centered and scaled by standard deviation. Categorical variables with more than 2 categories (e.g., site) were dummy-coded. Owing to the low numbers of participants reporting races other than White or Black/African American, race was dichotomized as White vs non-White. Missing data were addressed using full information maximum likelihood. Statistical significance was assessed using bootstrapped 95% CIs. Models were fit separately for the 180 former football players (college and professional pooled) and the 60 asymptomatic unexposed men. Secondary analyses applied the same model to the former football players stratified by college (n = 60) and professional (n = 120) level of play, which served as a proxy for RHI exposure. Model goodness of fit was assessed using the comparative fit index (CFI), where the model fit is compared with fit of a null model, and higher values (e.g., >0.90) indicate good fit, and the root mean square error of approximation (RMSEA), a parsimony-adjusted index where lower values (e.g., <0.08) indicate good fit. Between-group differences were assessed using percentage differences in the SEM coefficient estimates.

Data Availability

Investigators may request access to the deidentified data used in this study through a data sharing portal for the DIAGNOSE CTE Research Project (diagnosecte.com).

Results

Sample Characteristics

The study enrolled 240 male participants between ages 45 and 74 years, including 120 former professional football players, 60 former college football players, and 60 asymptomatic men

without a history of RHI or TBI. The former football players spanned the symptom continuum from asymptomatic to mild dementia. Participant sociodemographic, athletic histories, and relevant medical information are detailed in Table 1. There were no significant differences in any demographic variable or *APOE* $\epsilon 4$ carrier status between the former football players and asymptomatic unexposed men (all p 's > 0.05). The asymptomatic unexposed men had higher rFSRP scores, on average, because of higher systolic and diastolic blood pressure, and a greater proportion were lifetime smokers. However, the former football players had higher BMI and were more likely to have been diagnosed with sleep apnea. In the former football players, neuroimaging variables did not differ by evaluation site (log(TLV): $p = 0.55$, cortical thickness: $p = 0.09$, or FA: $p = 0.21$). In the asymptomatic unexposed men, log(TLV) differed by evaluation site ($p = 0.03$) but cortical thickness ($p = 0.29$) and FA ($p = 0.07$) did not.

Risk Factor and Biomarker Correlates in Former Football Players

Direct pathway statistics for the former football players are shown in Figure 1 and Table 2. Model fit was adequate (CFI = 0.90, RMSEA = 0.12). In the former football players, greater log(TLV) was associated with older age ($B = 0.20$, 95% CI 0.01–0.40), but not with race, education, *APOE* $\epsilon 4$ carrier status, or BMI. SEM showed that greater log(TLV) was associated with higher rFSRP score, higher CSF p-tau₁₈₁, lower FA, and reduced cortical thickness (Table 2; Figure 2). log(TLV) was not associated with $A\beta_{1-42}$, sTREM2, or NfL. There were no statistically significant indirect effects on WMH (p-tau₁₈₁ to sTREM2 to WMH: $B = 0.06$, 95% CI –0.02 to 0.15; p-tau₁₈₁ to FA to WMH: $B = 0.01$, 95% CI –0.06 to 0.06; p-tau₁₈₁ to NfL to WMH: $B = -0.03$, 95% CI –0.08 to 0.01). Regarding other model findings, higher CSF p-tau₁₈₁ was associated with higher sTREM2, which was in turn associated with higher NfL (i.e., sTREM2 levels mediated the effect of p-tau₁₈₁ on NfL) (Table 2). Sensitivity analyses tested the direct effect of WMH on p-tau₁₈₁ (i.e., reversing the direction of the pathway shown in Figure 1), which was not significant ($B = 0.07$, 95% CI –0.12 to 0.30).

Former Football Players vs Asymptomatic Unexposed Participants

Direct pathway statistics for the asymptomatic unexposed men are shown in Table 2. Model fit in the unexposed men was inferior to the model in the former football players (CFI = 0.66, RMSEA = 0.21). In the asymptomatic unexposed men, greater log(TLV) was associated with older age ($B = 0.50$, 95% CI 0.01–1.01), but not with any of the other model covariates (Table 2). Comparison of the estimates revealed substantial differences between the former football players and asymptomatic unexposed men in their associations between log(TLV) and rFSRP, FA, and CSF p-tau₁₈₁ (Table 2; Figure 2). In the former football players, rFSRP and CSF p-tau₁₈₁ showed a strong positive association and FA showed a stronger negative association with log(TLV) compared with

the unexposed men. The effect of log(TLV) on cortical thickness was similar between the 2 groups (Figure 2).

Differences by Level of Football Play

When the former football players were stratified by level of play, there were no direct associations between log(TLV) and any of the risk factor and biomarker measures in the former college football players, but the model fit was still good (CFI = 0.93, RMSEA = 0.08; Table 2). Model fit was also adequate when only the former professional football players were included (CFI = 0.91, RMSEA = 0.13), and greater log(TLV) was associated with lower FA and lower cortical thickness (Table 2). Comparison of the estimates between asymptomatic unexposed men, former college football players, and former professional football players revealed that the association between greater log(TLV) and lower FA was stronger with increasing levels of football play (college vs unexposed: 86% difference, professional vs unexposed: 319% difference). Associations between log(TLV) and cortical thickness were similar across groups (college vs unexposed: 24% difference, professional vs unexposed: 0.2% difference).

Discussion

Among former college football players and former professional football players from the DIAGNOSE CTE Research Project, FLAIR WMH were associated with greater vascular risk, higher CSF p-tau₁₈₁, lower FA, and reduced cortical thickness. FLAIR WMH were not associated with CSF $A\beta_{1-42}$ or fluid biomarkers of neuroinflammation (sTREM2) or axonal injury (NfL). Compared with asymptomatic unexposed men, the magnitudes of associations between WMH and vascular risk, p-tau₁₈₁, and FA were stronger in the former football players. In fact, aside from age, there were no significant risk factor or biomarker associations in the asymptomatic unexposed men. These associations also differed by level of football play (e.g., college vs professional), such that the former professional players showed the strongest associations between WMH and lower FA, while estimate effects between WMH and cortical thickness were similar between all 3 groups. The current findings suggest that WMH may have specific risk factor and biologic correlates in former football players.

As expected, greater vascular risk was associated with elevated WMH burden. This association was more pronounced in the former football player group, suggesting that vascular risk factors are particularly important for former elite football players, independent of BMI. In this study sample, the former football players demonstrated lower overall vascular risk compared with the asymptomatic unexposed men because of their lower systolic and diastolic blood pressure measurements, although the 2 groups showed similar rates of hypertension, diabetes, and high cholesterol. However, the former football players were significantly more likely to have higher BMI, diagnosis of sleep apnea, and unhealthy alcohol use.

Table 2 SEM Results for Former Football Players and Asymptomatic Unexposed Participants

Response	Independent	Former college football players (N = 60)		Former professional football players (N = 120)		Former football players (college + professional) (N = 180)		Asymptomatic unexposed men (N = 60)		% Diff. in estimates
		Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI	
log(TLV)	rFSRP	0.31	-0.81 to 1.35	0.23	-0.01 to 0.40	0.26 ^a	0.07 to 0.40 ^a	-0.03	-0.48 to 0.57	-1,069
log(TLV)	CSF p-tau ₁₈₁	0.23	-1.50 to 1.53	0.15	-0.07 to 0.55	0.17 ^a	0.01 to 0.43 ^a	-0.30	-1.14 to 0.37	-158
log(TLV)	CSF Aβ ₁₋₄₂	-0.18	-1.22 to 1.03	-0.06	-0.39 to 0.25	-0.17	-0.39 to 0.04	0.30	-0.04 to 0.86	-157
log(TLV)	CSF sTREM2	0.34	-0.16 to 0.95	-0.01	-0.40 to 0.34	0.17	-0.05 to 0.36	-0.02	-0.64 to 0.49	-1,073
log(TLV)	CSF NfL	-0.23	-0.73 to 0.67	-0.02	-0.29 to 0.44	-0.13	-0.29 to 0.06	0.24	-0.37 to 0.72	-156
log(TLV)	Average FA	-0.13	-0.65 to 0.42	-0.30 ^a	-0.49 to -0.09 ^a	-0.28 ^a	-0.42 to -0.13 ^a	-0.07	-0.48 to 0.42	287
Average cortical thickness	log(TLV)	-0.21	-0.61 to 0.14	-0.28 ^a	-0.53 to -0.05 ^a	-0.25 ^a	-0.45 to -0.08 ^a	-0.28	-0.64 to 0.10	-12
Average FA	CSF p-tau ₁₈₁	-0.24	-1.31 to 0.48	0.00	-0.20 to 0.24	-0.02	-0.19 to 0.20	-0.04	-0.82 to 0.69	-46
CSF sTREM2	CSF p-tau ₁₈₁	0.82 ^a	0.19 to 1.44 ^a	0.30 ^a	0.15 to 0.52 ^a	0.34 ^a	0.19 to 0.58 ^a	0.87 ^a	0.39 to 1.21 ^a	-61
CSF NfL	CSF p-tau ₁₈₁	0.29	-0.36 to 1.29	0.18	-0.04 to 0.38	0.21	-0.02 to 0.40	0.14	-0.62 to 0.69	50
CSF NfL	CSF sTREM2	0.23	-0.30 to 0.70	0.48 ^a	0.10 to 0.87 ^a	0.38 ^a	0.08 to 0.67 ^a	0.19	-0.28 to 0.52	101
Average FA	CSF sTREM2	-0.07	-0.53 to 0.43	0.16	-0.14 to 0.47	0.04	-0.17 to 0.26	0.04	-0.45 to 0.55	-1

Abbreviations: Est. = estimate; FA = fractional anisotropy; NfL = neurofilament light; rFSRP = revised Framingham stroke risk profile; SEM = structural equation modeling; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; TLV = total lesion volume.

The % difference in estimates indicates differences between the former football players (college and professional pooled) and the asymptomatic unexposed men. Sample sizes (Ns) reflect the full sample for each group; missingness in individual variables is reflected in Table 1 and was addressed using full information maximum likelihood in the SEM.

^a Statistically significant pathways according to boot-strapped 95% CIs.

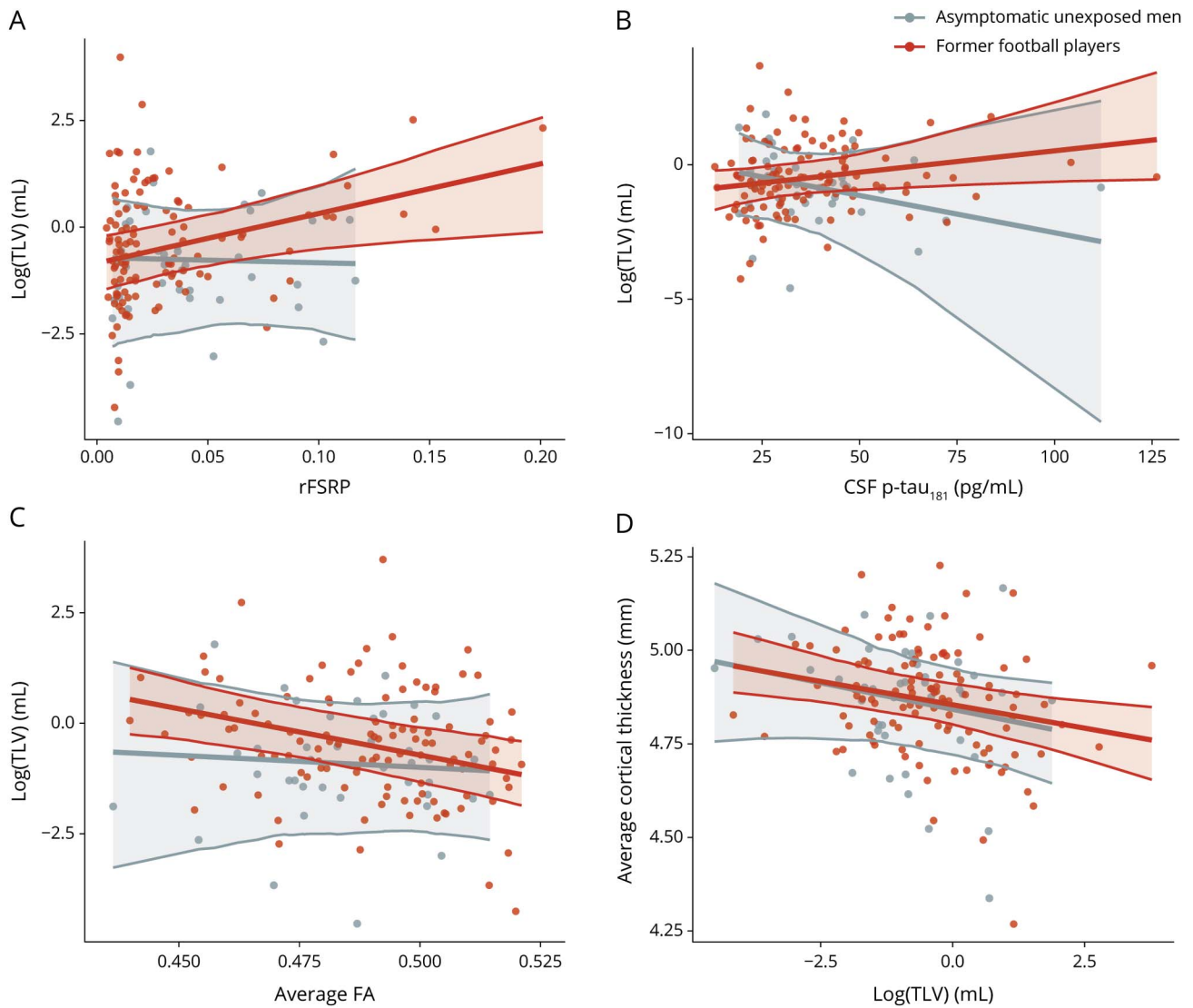
Sleep apnea and heavy alcohol use are more prevalent in former elite athletes and are associated with greater WMH burden.³⁹⁻⁴¹ Although our group previously found that the former football players in this DIAGNOSE CTE sample still have elevated WMH burden after controlling for sleep apnea, alcohol use, and high cholesterol,²¹ these risk factors remain important modifiable factors for consideration in the treatment of former football players because of their effects on cognitive and neuropsychiatric symptoms and their relationships with elevated WMH burden.

WMH were associated with CSF p-tau₁₈₁ but not CSF Aβ₁₋₄₂ in the former football players, whereas WMH were not associated with either p-tau₁₈₁ or Aβ₁₋₄₂ in the asymptomatic unexposed men. This suggests that WMH might track with p-tau in people exposed to RHI from football. An imaging-pathologic study of individuals exposed to RHI similarly found associations between antemortem FLAIR WMH and postmortem dorsolateral prefrontal p-tau severity and CTE stage.²⁰ While it is not known whether CTE p-tau pathology is present in this sample, these former football players are at risk for CTE based on their histories of exposure to RHI.⁴² In other neurodegenerative diseases, WMH burden corresponds with the distribution of their characteristic pathologies (e.g., Aβ and p-tau in AD and TDP-43 in FTLT).^{8,10,11} The absence of an association between WMH and CSF Aβ₁₋₄₂ is

consistent with past research showing no association between antemortem WMH and postmortem Aβ neuritic plaques in individuals exposed to RHI.²⁰ It also supports research that while Aβ deposition can occur in CTE, it is not a consistent early pathologic feature of CTE, in contrast to AD.^{14,15} These results are in contrast to other CSF biomarker studies in cognitively normal, preclinical AD, and AD groups that have shown no significant associations between WMH and CSF p-tau₁₈₁ but did show associations between greater WMH and lower CSF Aβ₁₋₄₂.^{7,35}

WMH were associated with lower whole brain average FA, a measure of white matter integrity, and this relationship was observed most prominently in the former professional football players. Mild TBI, especially repetitive mild TBI, causes multifocal axonal injury (e.g., shearing and tearing) accompanied by neuroinflammation.⁴³ Lower FA in several white matter tracts has been reported in athletes after subconcussive impacts.⁴⁴ Exposure to RHI might lead to axonal injury that persists or worsens with age. Proxies of exposure to RHI (e.g., age of first exposure, years of football play, and a quantitative measure based on football history and helmet accelerometer studies) have been associated with altered corpus callosum microstructure in former professional football players and greater white matter rarefaction in autopsy-confirmed CTE.^{31,45} Autopsies of brain donors with CTE show

Figure 2 Associations Between WMHs (log[TLV]) and (A) rFSRP; (B) CSF p-tau₁₈₁; (C) Average FA; and (D) Average Cortical Thickness



x-Axes show the predictor variable and y-axes the response variable according to hypothesized SEM pathways shown in Figure 1. Bands show 95% CIs. FA = fractional anisotropy; rFSRP = revised Framingham stroke risk profile; SEM = structural equation modeling; TLV = total lesion volume; WMH = white matter hyperintensity.

multifocal axonal varicosities, axonal loss, and reduced oligodendrocytes in the white matter.⁴⁶ Lower FA has been associated with not only greater WMH burden but also greater risk of conversion from normal white matter to WMH, suggesting that disrupted diffusion may be an early feature of white matter pathology.⁴⁷ Thus, WMH may capture the late effects of axonal injury resulting from RHI.

WMH were associated with neurodegeneration as measured by the MRI-derived metric of global cortical thickness, and the strength of this association was similar between the former football players and the asymptomatic men unexposed to RHI. WMH have been linked to global atrophy as well as disease-specific regional patterns of atrophy in AD and FTLT.^{8,11} Thus, WMH may be an intermediate marker to

neurodegeneration across normal aging and multiple disease processes. In autopsy-confirmed CTE, p-tau severity was associated with frontal-temporal atrophy,⁴⁸ so it is possible that there are distinct pathways from p-tau to WMH to neurodegeneration after exposure to RHI. These pathways are likely bidirectional because neurodegeneration may conversely lead to WMH, and WMH can promote tau pathology. However, on secondary analyses, we did not find that WMH predicted p-tau₁₈₁ (i.e., the direct pathway was no longer significant when the direction was reversed).

WMH were not associated with measures of neuroinflammation (CSF sTREM2) or axonal injury (CSF NfL) in the former football players or the asymptomatic unexposed men. Although several studies have shown increased serum

NfL levels in patients with mild TBI or concussion, findings are not as clear with CSF NfL or in the context of head impacts that may not meet criteria for mild TBI or concussion.⁴⁹ Hence, CSF NfL may not be as sensitive to RHI as other markers of axonal injury (e.g., FA). P-tau₁₈₁ was associated with sTREM2 in both groups, consistent with past research,³⁶ and sTREM2 was associated with NfL in the former football group. The pathway between p-tau and neuroinflammation in exposure to RHI should be explored in future research.

This study has several limitations. First, the study sample was composed of self-identified volunteers, which may have led to a biased sample. The RHI exposed group was composed only of men who are former elite American football players, and thus, the generalizability of these findings to women, to other athlete populations, and to other sources of RHI is limited. Although there were no enrollment criteria for the presence or severity of symptoms in the former football players, the control group in DIAGNOSE CTE was specifically recruited to be asymptomatic men with no history of RHI or TBI. This study did not focus on clinical outcomes, which were examined in this sample elsewhere,²¹ but it is possible that the differences in WMH associations between the former football players and the control group could be biased because of differences in symptom status at time of recruitment.

DIAGNOSE CTE was not powered for SEM analyses, and this study represents secondary analyses. The small sample size of the asymptomatic unexposed group likely contributed to suboptimal model fit and reduced statistical power, particularly in relation to the larger group of former football players. The restricted presence of pathology, particularly of WMH burden, in the asymptomatic unexposed men limited potential correlations with WMH. Further research contrasting WMH correlates in individuals with exposure to RHI compared with other clinical populations (e.g., AD, FTLD) is needed to better determine the specificity of these results.

Other methodological limitations include unbalanced sample sizes between the former college and professional football players and differences in log(TLV) by evaluation site for the asymptomatic unexposed group. It remains unclear whether CSF p-tau₁₈₁ is a valid marker of CTE p-tau, and other variants of p-tau were not examined. In MRI processing, the calculation of FA did not account for or remove voxels that may have been parts of WMH.

Another limitation is the cross-sectional nature of the data, where results cannot directly elucidate causal pathways between markers and many, if not all, of the depicted pathways likely have bidirectional effects. Hence, it remains unclear to what extent WMH represent late-stage or downstream effects of other pathologies vs an independent pathology with wide-reaching interactions. WMH are also nonspecific and tend to increase with age regardless of the presence of neurodegenerative disorders such as AD.⁴ Therefore, they are not

considered a biomarker of any specific disease pathology, but rather an informative and quantifiable measurement to understand white matter pathology.

This study did not examine other proxies of RHI such as total years of football play or age of first exposure to football or TBI-specific characteristics. Our group previously investigated associations between WMH and proxies of RHI exposure in this DIAGNOSE CTE sample. Total years of football play was not associated with WMH burden, while age of first exposure to football was associated with greater WMH only in the older (i.e., 60 years and older) football players.²¹ Given these mixed results and concern for overfitting, this study stratified former football players only by their level of play (college or professional) to maintain model parsimony and interpretability. Future research should examine the relationship between WMH and years of football play across all levels of play because our sample over-represented former athletes with long histories of football play (i.e., average of 15.85 years), limiting our ability to perform a full-dose response analysis.

This study lays the groundwork for future research to examine the clinical implications of WMH in the context of RHI. In this sample of former football players, our group previously found that WMH were associated with cognition,²¹ but intermediary pathways connecting WMH to cognition (e.g., through neurodegeneration) have yet to be explored. It will be important to disentangle the extent to which white matter injury, as measured by WMH on FLAIR MRI, contributes to TES. The causes of the heterogenous symptom profiles seen in TES are unclear and are likely to include both tau and non-tau pathologies with accumulating evidence for the role of white matter degeneration.⁵⁰ Increased understanding of the biological correlates of TES, including white matter injury, will inform future iterations of the TES diagnostic criteria.

In the context of RHI, WMH likely have multifactorial etiologies that may differ from normal aging and other neurodegenerative diseases. Associations between WMH and neurodegeneration seem transdiagnostic, while associations with disease-characteristic pathologies (e.g., p-tau) seem to be distinct and suggest multiple pathways through which exposure to RHI may lead to neurodegeneration and functional decline. FLAIR WMH findings are a promising indicator to detect the late effects of RHI by capturing tau and non-tau pathologies.

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Committee; Vice President, National Operating Committee on Standards for Athletic Equipment; and Chair, Scientific Advisory Committee, Co-Founder, and Medical Director, Concussion Legacy Foundation. He is a member of the Medical Science Committee for the National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation, and he receives royalties for published books from Houghton Mifflin Harcourt. M.J. Coleman reports no disclosures relevant to the manuscript. D.W. Dodick served as consultant for: Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, Perfood, Praxis, AYYA Biosciences, and Revance, received honoraria from: Vector psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, and Cambridge University Press, holds stock options/shareholder/patents/board of directors in: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board), AYYA Biosciences (Options), Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis, and received research support from: Department of Defense, NIH, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). M.D. McClean, J. Mez, J.N. Palmisano, B. Martin, and K. Hartlage report no disclosures relevant to the manuscript. A.P. Lin is a paid consultant to Agios Pharmaceuticals (Cambridge, MA), Biomarin Pharmaceuticals (Novato, CA), and Moncton MRI (Moncton, Canada). He is the co-founder of BrainSpec, Inc. I.K. Koerte reports no disclosures relevant to the manuscript. J.L. Cummings has provided consultation to Acadia, Alkahest, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, Grifols, Janssen, Jazz, Karuna, Merck, Novo Nordisk, Otsuka, ReMYND, Resverlogix, Roche, Samumed, Samus, Signant Health, Sunovion, Suven, United Neuroscience, and Unlearn AI pharmaceutical and assessment companies. He owns the copyright of the Neuropsychiatric Inventory. E.M. Reiman is a compensated scientific advisor for Alkahest, Alzheon, Aural Analytics, Denali, Green Valley, Retromer Therapeutics, and Vaxxinity, and a co-founder of ALZPath. M.E. Shenton reports no disclosures relevant to the manuscript. R.A. Stern is a member of the Board of Directors of King-Devick Technologies, Inc. (Chicago, IL), and he receives royalties for published neuropsychological tests from Psychological Assessment Resources, Inc. (Lutz, FL). S. Bouix and M.L. Alosco report no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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Appendix 1 Authors

Name	Location	Contribution
Monica T. Ly, PhD	VA San Diego Healthcare System; Department of Psychiatry, University of California San Diego Health	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Fatima Tuz-Zahra, MS	Department of Biostatistics, Boston University School of Public Health	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Yorghos Tripodis, PhD	Department of Biostatistics, Boston University School of Public Health; Boston University Alzheimer's Disease Research Center, Boston University CTE Center, Department of Neurology, Boston University Chobanian & Avedisian School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Charles H. Adler, MD, PhD	Department of Neurology, Mayo Clinic School of Medicine, Mayo Clinic Arizona	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Laura J. Balcer, MD, MSCE	Departments of Neurology, Population Health and Ophthalmology, NYU Grossman School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Charles Bernick, MD, MPH	Cleveland Clinic Lou Ruvo Center for Brain Health; Department of Neurology, University of Washington	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Henrik Zetterberg, MD, PhD	Department of Neurodegenerative Disease, and UK Dementia Research Institute, University College London Institute of Neurology; Hong Kong Center for Neurodegenerative Diseases; Wisconsin Alzheimer's Disease Research Center, University of Wisconsin-Madison; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Kaj Blennow, MD, PhD	Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital; Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data

Appendix 1 (continued)

Name	Location	Contribution
Elaine R. Peskind, MD	VA Northwest Mental Illness Research, Education, and Clinical Center; Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Rhoda Au, PhD	Boston University CTE Center, Boston University Alzheimer's Disease Research Center, Department of Neurology, Boston University Chobanian & Avedisian School of Medicine; Framingham Heart Study; Slone Epidemiology Center, Boston University; Department of Anatomy & Neurobiology and Medicine, Boston University Chobanian & Avedisian School of Medicine; Department of Epidemiology, Boston University School of Public Health	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Sarah J. Banks, PhD	Department of Psychiatry, University of California San Diego Health; Department of Neurosciences, University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
William B. Barr, PhD	Department of Neurology, New York University Grossman School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jennifer V. Wethe, PhD	Department of Psychiatry and Psychology, Mayo Clinic School of Medicine, Mayo Clinic Arizona	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mark W. Bondi, PhD	VA San Diego Healthcare System; Department of Psychiatry, University of California San Diego Health	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Lisa M. Delano-Wood, PhD	VA San Diego Healthcare System; Department of Psychiatry, University of California San Diego Health	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Robert C. Cantu, MD	Boston University CTE Center, Boston University Alzheimer's Disease Research Center, Department of Neurology, Boston University Chobanian & Avedisian School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Michael J. Coleman, MA	Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Appendix 1 (continued)

Name	Location	Contribution
David W. Dodick, MD	Department of Neurology, Mayo Clinic School of Medicine, Mayo Clinic Arizona	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Michael D. McClean, ScD	Department of Environmental Health, Boston University School of Public Health	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Jesse B. Mez, MD, MS	Boston University Alzheimer's Disease Research Center, Boston University CTE Center, Department of Neurology, Boston University Chobanian & Avedisian School of Medicine; Framingham Heart Study	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Joseph Palmisano, MA, MPH	Biostatistics and Epidemiology Data Analytics Center, Boston University School of Public Health	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Brett Martin, MS	Biostatistics and Epidemiology Data Analytics Center, Boston University School of Public Health	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Kaitlin Hartlage, MPH	Biostatistics and Epidemiology Data Analytics Center, Boston University School of Public Health	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Alexander P. Lin, PhD	Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital; Center for Clinical Spectroscopy, Department of Radiology, Brigham and Women's Hospital	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Inga K. Koerte, MD, PhD	Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital; cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Ludwigs-Maximilians-Universität	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Jeffrey L. Cummings, MD, ScD	Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Eric M. Reiman, MD	Banner Alzheimer's Institute; Department of Psychiatry, University of Arizona; Arizona State University; Translational Genomics Research Institute; Arizona Alzheimer's Consortium	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix 1 (continued)

Name	Location	Contribution
Martha E. Shenton, PhD	Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital; Department of Radiology, Brigham and Women's Hospital	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Robert A. Stern, PhD	Boston University CTE Center, Boston University Alzheimer's Disease Research Center, Department of Neurology, Boston University Chobanian & Avedisian School of Medicine; Department of Anatomy & Neurobiology and Medicine, Boston University Chobanian & Avedisian School of Medicine; Department of Neurosurgery, Boston University Chobanian & Avedisian School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Sylvain Bouix, PhD	Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital; Department of Software Engineering and Information Technology, École de technologie supérieure, Université du Québec	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Michael L. Alosco, PhD	Boston University Alzheimer's Disease Research Center, Boston University CTE Center, Department of Neurology, Boston University Chobanian & Avedisian School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/D289.

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