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RESEARCH ARTICLE

White matter hyperintensities in former American football players

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Abstract

Introduction: The presentation, risk factors, and etiologies of white matter hyperintensities (WMH) in people exposed to repetitive head impacts are unknown. We examined the burden and distribution of WMH, and their association with years of play, age of first exposure, and clinical function in former American football players.

Methods: A total of 149 former football players and 53 asymptomatic unexposed participants (all men, 45–74 years) completed fluid-attenuated inversion recovery magnetic resonance imaging, neuropsychological testing, and self-report neuropsychiatric measures. Lesion Segmentation Toolbox estimated WMH. Analyses were performed in the total sample and stratified by age 60.

Results: In older but not younger participants, former football players had greater total, frontal, temporal, and parietal log-WMH compared to asymptomatic unexposed men. In older but not younger former football players, greater log-WMH was associated with younger age of first exposure to football and worse executive function.

Discussion: In older former football players, WMH may have unique presentations, risk factors, and etiologies.

KEYWORDS
aging, cerebrovascular disease, concussion, fluid-attenuated inversion recovery, football, microvascular disease, neurodegenerative disease, repetitive head impacts, subconcussion, white matter hyperintensities, white matter injury

Highlights

- Older but not younger former football players had greater total, frontal, temporal, and parietal lobe white matter hyperintensities (WMH) compared to same-age asymptomatic unexposed men.
- Younger age of first exposure to football was associated with greater WMH in older but not younger former American football players.
- In former football players, greater WMH was associated with worse executive function and verbal memory.

1 | INTRODUCTION

Traumatic brain injury (TBI) has long been considered a risk factor for Alzheimer's disease (AD) dementia.[1] Previous research has linked TBI with the amyloid beta pathology of AD[2] through in vivo biomarker and *post mortem* neuropathology studies.[3–6] However, there is growing research that fails to show an association between TBI and AD neuropathology.[7–11] The heterogeneity in the associations between TBI and AD might in part be due to differences in TBI severity and frequency. Different types of TBIs might trigger distinct neurodegenerative diseases and associated cognitive and neuropsychiatric decline. Repetitive head impacts (RHI) from American football and other sources have been associated with long-term neurobehavioral disturbances and chronic traumatic encephalopathy (CTE).[12–17] Symptomatic former American football players tend to not have neuritic amyloid plaques consistent with AD at autopsy or on amyloid positron emission tomography (PET) imaging.[18,19] Risk factors for long-term neurological disorders associated with RHI are still being elucidated. Years of playing football is one risk determinant for later-life neurological disorders.[12] Age of first exposure (AFE) to football might increase susceptibility to neurological consequences,[20–25] but the literature on AFE is inconsistent.[26–30] Pathway(s) that RHI lead to later life clinical symptoms are unclear. Phosphorylated tau (p-tau) is one contributor.[15] RHI are associated with an array of other neuropathologies[13,31–33] and focusing primarily on p-tau would neglect opportunities for intervention.

Ex vivo studies show white matter (WM) degeneration and microvascular injury are late pathologies of RHI.[31,34,35] In vivo diffusion tensor imaging (DTI) studies show an association between RHI and WM alterations;[21,36–39] yet, inconsistencies exist.[40] DTI is sensitive to subtle WM injury but is laborious and interpretation at the individual level is challenging. White matter hyperintensities (WMH)

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed the literature using PubMed and references of research articles. Ex vivo studies show white matter degeneration and microvascular injury are late neuropathologies in those exposed to repetitive head impacts (RHIs) through participation in contact sports including football. White matter hyperintensities (WMH) on clinically routine fluid-attenuated inversion recovery magnetic resonance imaging sequences may therefore be a practical tool to study and to detect the late effects of repetitive head impacts. The burden and distribution, however, in addition to risk factors and clinical correlates of WMH in people exposed to RHI are unknown.
2. **Interpretation**: In older former American football players, WMH may have a distinct presentation and capture unique white matter neuropathologies.
3. **Future Directions**: Future studies are needed to clarify the etiologies of WMH in the setting of repetitive head impacts.

on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) might be a practical tool to detect the late effects of RHI on WM. WMH have long been studied in AD[41–50] where their etiologies are interpreted as small vessel disease due to vascular risk factors (VRF)[46–48,51,52] and/or axonal degeneration from AD.[49,50] WMH might capture pathologies from RHI, like myelin loss and neuroinflammation. Hart et al. found greater WMH in 10 older (mean age = 66.6) cognitively impaired former National Football League (NFL) players compared to age-matched participants.[53] In a separate study of 86 symptomatic former NFL players, greater WM hypo-intensities ("hypo" used because T1 scans were used, not FLAIR) were associated with RHI.[54] An imaging–pathological correlation study of 75 deceased donors exposed to RHI linked WMH with total years of football play, WM rarefaction, p-tau, and arteriolosclerosis.[55] Findings suggested a multifactorial etiology of WMH that include RHI and non-RHI pathologies.[56,57]

WMH might have a unique presentation and associated risk factors and etiologies in people exposed to RHI. Existing studies of WMH in older individuals exposed to RHI are scarce and limited by small samples of former professional football players and have not examined spatial distribution. Here, we examined the burden and spatial distribution of FLAIR WMH in male former college and professional American football players. Total and lobar WMH were calculated and compared between the former football players and same-age asymptomatic men without a history of RHI or traumatic brain injury (TBI). Associations between WMH and total years of football play and AFE were tested, as were associations between WMH and measures of cognitive and neuropsychiatric function.

2 | METHODS

2.1 | Participants

Participants were from the Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project.[58] Objectives of DIAGNOSE CTE are to develop in vivo biomarkers for CTE, characterize its clinical presentation, and refine clinical research diagnostic criteria. The study enrolled 120 former professional football players, 60 former collegiate football players, and 60 asymptomatic men without RHI/TBI; all men between 45 and 74 years. Baseline evaluations were completed in February 2020. Eligibility criteria are provided elsewhere[58] and summarized in Methods A.1 in supporting information. At one of four US sites, participants underwent a 2-day study visit that consisted of neuropsychological testing, self-report measures of neuropsychiatric functioning, MRI, and other procedures. All sites received approval by their institutional review board. Participants provided written informed consent.

2.2 | MRI acquisition

MRIs across the four sites were conducted on a 3T MRI (MAGNETOM Skyra, Siemens Healthineers). Neuroimaging protocols included T1-, T2-, diffusion, and resting state functional MRI. We acquired all images at high resolution (1×1×1 mm^3, 176 slices, 256×256 cm^2 field of view) in the sagittal plane using 3D sequences: MPRAGE (TR = 2530 ms, TE = 3.36 ms, TI = 1100 ms), T2-weighted FLAIR (TR = 5000 ms, TE = 388 ms, TI = 1800 ms), and T2-weighted SPACE (TR = 3200 ms, TE = 412 ms). Imaging calibration and quality control were completed for sites prior to enrollment (Methods A.2 in supporting information).

2.3 | White matter hyperintensities

2.3.1 | Total volume of WMH

FLAIR sequences were analyzed to derive volume of WMH using the automated lesion prediction algorithm (LPA) pipeline from the Lesion Segmentation Toolbox (LST) v.3.0.0 (www.statistical-modelling.de/lst.html) for SPM in MATLAB (SPM12, MATLAB v.R2020a; MathWorks).[59,60] The LPA was developed to improve on the Lesion Growth Algorithm (LGA) as T1 images are not required for the LPA, and the LPA does not require the user to set parameters and it is faster.[59–61] The LPA has also been shown to outperform the LGA.[60] After calculating the probability of lesion presence for each voxel, lesions were segmented in new images to produce lesion probability maps (Figure 1). These maps were thresholded at a kappa of 0.5 (default LPA recommendation) and total volume of WMH in milliliters was extracted. For quality control, each lesion probability map was visually inspected in Slicer (threshold at 0.5) and compared to the FLAIR. Three were excluded due to erroneous lesion classification

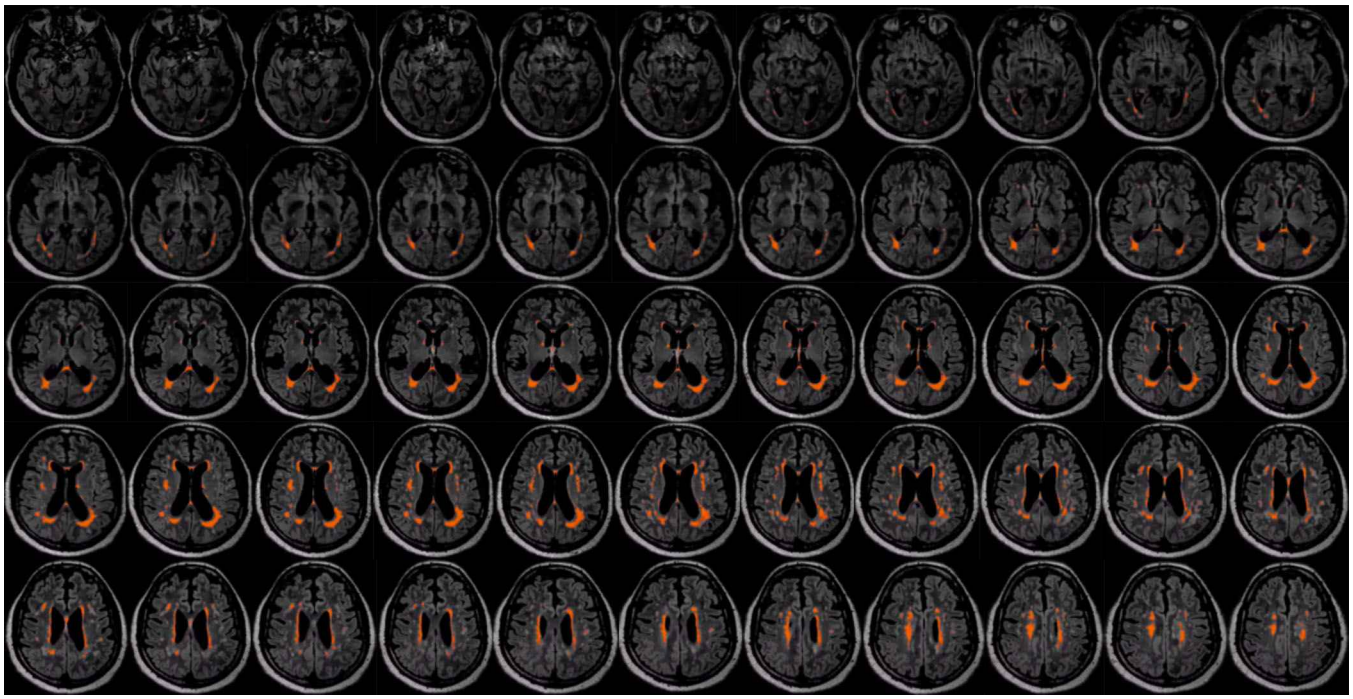

FIGURE 1 Example of lesion segmentation from the Lesion Prediction Algorithm (LPA) of the Lesion Segmentation Toolbox. This is a fluid-attenuated inversion recovery (FLAIR) scan of a former American football player. The LPA segments lesions in new images by providing an estimate for the lesion probability for each voxel. Total lesion volume (TLV) in milliliters is extracted by thresholding derived lesion probability maps at a threshold kappa of 0.5 (default LPA recommendation) and only lesions with volume >0.015 milliliters are counted. Figure shows lesion probability maps overlaid on the FLAIR with intensity threshold at 0.5 (to be similar as the LPA threshold) using Slicer

on the probability maps that appeared to be related to scan acquisition issues and resulting artifact (e.g., ghosting) and/or technical processing errors. For example, one of the scans had minimal WMH but significant lesions were marked on the lesion probability map.

2.3.2 | Regional WMH

Brain masking was performed for all FLAIR, T1w, and T2w scans using tools developed by the Psychiatry Neuroimaging Laboratory.[62–64] Masked T1w and T2w scans were processed with FreeSurfer (version 7.1) to generate gray matter and WM segmentations. WM regions were labeled based on their distance to the nearest FreeSurfer-generated cortical surface label as defined by the Desikan–Killiany atlas.[65–68] The FreeSurfer WM labels (i.e., the wmparc file)[69] were aligned to the FLAIR by registering the masked T1w from FreeSurfer (brain.mgz) to the participant's masked FLAIR image using Advanced Normalization Tools (ANTs) version 2.3 (http://stnava.github.io/ANTs/; rigid body transformation, mutual information similarity metric). The resulting transform was applied to the wmparc file to bring the WM parcellation into FLAIR space where WMH were identified. The sum of voxels with WMH for each WM region in wmparc was extracted. Total number of voxels with WMH (in microliters) in the frontal, temporal, parietal and occipital lobes was computed by taking the summary of WMH voxels in regions that comprise their respective lobe. Lobe mapping (Table A.1 in supporting information) followed FreeSurfer recommendations.[70]

2.4 | Repetitive head impact exposure

Total years of football play was the sum of years played at each level (youth, high school, college, professional [if applicable]) as self-reported by the participant. AFE to football was based on the participants response to the question, "At what age did you start playing football?"

2.5 | Neuropsychological and neuropsychiatric measures

A priori tests selected included clinically routine measures of domains negatively impacted by RHI,[14,71,72] and have been associated with WMH in former football players[54] and other populations.[44,73–75] Tests included: (1) Neuropsychological Assessment Battery (NAB) List Learning Long Delay Recall, (2) Trail Making Test Parts A and B – the difference between Trails A and B (i.e., Trails A – B) was computed and used as a measure of executive function (more negative scores reflected worse performance), (3) Symbol Digit Modalities, (4) Controlled Oral Word Association Test (FAS), (5) Golden Stroop

Color-Word Interference, (6) Behavior Rating Inventory of Executive Function–Adult version [BRIEF-A] behavioral regulation index (BRI; participant version), and (7) Beck Depression Inventory-II (BDI-II). A description of all tests has been provided elsewhere.[58] Raw scores were used. Raw scores were also converted to T-scores using normative data accounting for age, sex, and/or education (Table A.2 in supporting information).

2.6 | Sample characteristics

Semi-structured interviews were performed, supplemented by online questionnaires, to collect data on demographics, medical history, and athletic history. Reporting race and ethnicity in this study was mandated by the National Institutes of Health, consistent with its inclusion of women, minorities, and children policy. Race and ethnicity were self-reported by participants. Participants were asked the following by a research assistant, "what do you consider your race?" Participants were read the following: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. Participants were asked, "Do you consider yourself to be either Hispanic or Latino?" Options included Hispanic or Latino, or Not Hispanic or Latino. Participants were allowed to select more than one option for race and ethnicity. Coding options for race and ethnicity included not reported, unknown, and refused. Revised Framingham Stroke Risk Profile (rFSRP)[76] and body mass index (BMI) were calculated. An aliquot of whole blood was used for apolipoprotein E (*APOE*) genotyping to determine ε4 carrier status. Additional relevant variables included diagnostic history of sleep apnea and high cholesterol and the Alcohol Use Disorders Identification Test (AUDIT). The AUDIT has 10 questions (scores range from 0 to 40) that assess problematic alcohol use behaviors and likelihood of alcohol dependence.[77]

2.7 | Sample size

Figure A.1 in supporting information provides a flowchart of sample derivation. The sample for total and lobar WMH was 202 (149 former football players, 53 asymptomatic unexposed) and 195 (144 former football players, 51 asymptomatic unexposed), respectively. The sample was reduced to 139 former football players for neuropsychological and neuropsychiatric outcomes, after exclusion of missing data and participants who had evidence of suboptimal effort during testing, defined by a Test of Memory Malingering Trial 2 score less than the recommended cutoff. The sample size was 137 for Stroop Color-Word Interference due to missing data.

2.8 | Statistical analyses

Former college and professional football players were combined into a single group to increase statistical power and to reduce number of analyses. Sensitivity analyses found no differences between former professional and college football players on WMH outcomes (see the Results section). The distribution of total WMH was positively skewed and four participants had zero values; this was more pronounced for frontal, temporal, parietal, and occipital WMH. Total and regional WMH were natural log-transformed. Zero values were replaced with the minimum non-zero WMH value minus 0.01 so a log-transformation could be applied across the entire data set (Figure A.2 in supporting information).

Total and regional log-WMH served as outcomes. Because log-WMH values clustered at the lower end of the distribution, tobit regression analyses were used when WMH served as the outcome. Methods A.3 in supporting information provides an overview of tobit regression. Tobit regressions were used to: (1) compare the former football players and the asymptomatic unexposed on total, frontal, temporal, parietal, and occipital log-WMH and (2) examine the association between total years of football play and AFE on total log-WMH in the former football players. A separate tobit regression model was performed for each independent and dependent variable. Among former football players, multivariable linear regression analyses tested the association between total log-WMH, and neuropsychological test scores, BDI-II, and BRIEF-A BRI. Analytic models were performed in the entire sample and stratified by age 60. WMH are strongly associated with age[78-80] and this was observed here (Figure A.3 in supporting information). WMH are prevalent in people 60 or older, representing a common lower limit age cutoff in research investigating WMH in aging and neurodegenerative disease populations.[78,79,81]

As post hoc analyses, tobit regressions comparing the former football players and asymptomatic unexposed men on WMH outcomes were repeated after restricting the sample to those who were cognitively intact as defined by Trail Making Test Part B scores (T-score > 35). This was done to determine whether the symptomatic former football players accounted for effects observed given the unexposed participants were required to have no reported symptoms upon study entry and therefore differences in WMH could be attributable to differences in symptom status (additional details in Methods A.4 in supporting information).

A *P*-value ≤.05 defined statistical significance. *P*-values for models that examined group differences between total and regional log-WMH outcomes were false discovery rate-adjusted using the Benjamini–Hochberg procedure. For all models, a priori covariates included age, racial identity, rFSRP, BMI, *APOE* ε4 status, and MRI site. A majority of the sample was Black or White. There was insufficient representation of other racial groups to statistically examine them separately (Table 1). Racial groups were combined into non-White and White. Years of education was included as a covariate for models with clinical measures as outcomes. Years of football play was included as a covariate for the model that examined the association between AFE and log-WMH. Sleep apnea, high cholesterol, and alcohol abuse are common in former elite football players[56,57,82] and associated with WMH. As sensitivity analyses, we repeated group difference and exposure models that had significant effects with sleep apnea, high cholesterol, and the AUDIT score included as covariates. Sample size was reduced by four due to missingness.

TABLE 1 Sample characteristics

	Former American football players (n = 149)	Asymptomatic unexposed participants (n = 53)	*P*-value
Demographics			
Age, mean (SD) years	57.13 (8.17)	59.32 (8.51)	.099
Education, mean (SD) years	16.73 (1.49)	17.66 (3.45)	.062
Race, *n* (%)			
American Indian or Alaska Native	1 (0.7)	0	.831
Black or African American	51 (34.2)	19 (35.8)	
Native Hawaiian or other Pacific Islander	0	1 (1.9)	
White	95 (63.8)	33 (62.3)	
Multiple races	2 (1.3)	0	
Ethnicity, *n* (%)			–
Hispanic or Latino	3 (2.0)	0	
Neurodevelopment			
Attention-deficit/hyperactivity disorder, *n* (%)	11 (7.4)	1 (1.9)	.190
Learning disability, *n* (%)	4 (2.7)	0	.575
Athletics			
College, *n* (%)	47 (31.5)	–	–
Professional, *n* (%)	102 (68.5)	–	–
Age of first exposure, mean (SD) years	11.18 (2.78)	–	–
Duration of football play, mean (SD) years	15.96 (4.29)	–	–
Position group at highest level of play, *n* (%)			
Offensive line	37 (24.8)	–	–
Offensive backs and receivers	42 (28.2)	–	–
Defensive lineman	14 (9.4)	–	–
Linebackers	21 (14.1)	–	–
Defensive backs	31 (20.8)	–	–
Special teams	4 (2.7)	–	–
Cardiovascular disease and associated risk factors			
Alcohol use disorders identification test, mean (SD)	4.79 (5.45)	3.32 (3.33)	.023
Body mass index, mean (SD)	32.28 (4.56)	30.59 (4.65)	.022
Revised Framingham Stroke Risk Profile, mean (SD)[a]	0.03 (0.03)	0.04 (0.03)	.033
Systolic blood pressure, mean (SD) mmhg	126.33 (12.12)	132.62 (11.12)	.001
Diagnostic history of sleep apnea, *n* (%)	49 (33.3)	9 (17.3)	.033
Diagnosed or treated for history of high cholesterol, *n* (%)	53 (35.6)	24 (45.3)	.211
Diagnosed or treated for hypertension, *n* (%) yes	65 (43.6)	22 (41.5)	.789
Currently being treated for hypertension, *n* (%) yes	36 (55.4)	19 (86.4)	.010
Diagnosed or treated for diabetes, *n* (%) yes	10 (6.7)	3 (5.7)	1.000
Smoked > 100 cigarettes in lifetime, *n* (%) yes	21 (14.1)	15 (28.3)	.020
Last 30 days, *n* (%) yes	2 (9.5)	6 (40.0)	.046
History of myocardial infarction, *n* (%) yes	2 (1.3)	1 (1.9)	1.000
History of cardiac arrest, *n* (%) yes	0	0	–
History of coronary artery disease, *n* (%) yes	10 (6.7)	2 (3.8)	.736
History of congestive heart failure, *n* (%) yes	0	0	–
History of angina, *n* (%) yes	1 (0.7)	0	1.000

(Continues)

TABLE 1 (Continued)

	Former American football players (n = 149)	Asymptomatic unexposed participants (n = 53)	*P*-value
History of peripheral vascular disease, *n* (%) yes	2 (1.3)	1 (1.9)	1.000
History of angioplasty, *n* (%) yes	5 (3.4)	2 (3.8)	1.000
History of cardiac bypass surgery, *n* (%) yes	1 (0.7)	0	1.000
History of valvular heart disease, *n* (%) yes	1 (0.7)	1 (1.9)	.457
History of atrial fibrillation, *n* (%) yes	9 (6.0)	0	.116
***APOE* genotype**			
ε*4*, n (%) present	42 (28.2)	11 (20.8)	.291
Total estimated intracranial volume, mean (SD) mm^3	1146440.65 (134586.15)	1132713.34 (104642.97)	.510
White matter hyperintensities, median (IQR, min-max) microliters			
Total	654 (1626, 0-40465)	564 (1,270, 0-5892)	–
Frontal	2.00 (21, 0-2201)	1.00 (11, 0-204)	–
Temporal	0.00 (1, 0-479)	0.00 (0-25)	–
Parietal	2.00 (28, 0-3839)	0.00 (7, 0-125)	–
Occipital	3.50 (35, 0-487)	4.00 (25, 0-293)	–

Note: *N* = 148 former American football players for angina due missing data; *N* = 144 and 51 for former American football players and asymptomatic unexposed men, respectively, for total estimated intracranial volume due to missing data.
[a]Independent samples *t*-test compared the groups on continuous outcomes and chi-square or Fisher's exact test (for cell sizes < 10) were used for binary outcomes. Due to data distribution, race was recorded into White versus Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple races all combined. Note that two participants did not report their race and were excluded because we required complete data on all participants as race was included in all statistical models. Ethnicity was not included in statistical models and one participant did not report their ethnicity. *P*-values are not reported for white matter hyperintensities as group differences are modeled and reported in Table 2. Sample size reduced for lobar white matter hyperintensities due to poor T1 quality and/or missing T2-weighted sequence to estimate regional WMH. For table purposes, total and lobar WMH are expressed in microliters. However, in analyses, total WMH are in milliliters and lobar WMH are microliters. The total volume of WMH is based on all brain regions and not just those regions listed in Table A.1 in supporting information, which only refers to regions that made up the lobar composites. Therefore, discrepancy exists between total and lobar volume of WMH. For example, WMH were frequent around the lateral ventricles, in basal ganglia structures, and in the corpus callosum. These regions were not examined separately in this study (but did contribute to total volume of WMH) and were not necessarily included in the lobar composites.
Abbreviations: *APOE*, apolipoprotein E; IQR, interquartile range; SD, standard deviation; WMH, white matter hyperintensities.

3 | RESULTS

3.1 | Sample characteristics

Sample characteristics are in Table 1 and Table A.3 in supporting information. In the entire sample, greater total log-WMH was associated with older age ($r = 0.50$, $P < .001$) and higher rFSRP scores ($r = 0.45$, $P < .001$). Total log-WMH was not associated with education years ($P = .78$), BMI ($P = .45$), racial identity ($P = .98$), or *APOE* ε4 ($P = .78$). Log-WMH did not differ between the four MRI sites ($P = .31$).

3.2 | Former football players versus asymptomatic unexposed participants

Descriptive statistics and histograms of WMH are in Table 1 and Figure A.2, respectively. Among the 144 former football players, 83 (57.6%) had WMH in the frontal lobe, 41 (28.5%) had WMH in the temporal lobe, 79 (54.9%) had WMH in the parietal lobe, and 89 (61.8%) had WMH in the occipital lobe. WMH are shown in Figure 2. WMH were frequent in regions not separately examined in this study (but did contribute to total volume of WMH) and were not necessarily part of the lobar composites, especially around the lateral ventricles (all but four had WMH here), basal ganglia structures, and the corpus callosum.

Table 2 provides a summary of the tobit regressions. In the entire sample, former football players had greater total log-WMH compared to the asymptomatic unexposed ($P < .01$). Former football players had greater temporal ($P < .01$) and parietal ($P < .01$) log-WMH compared to the asymptomatic unexposed. There were no group differences for frontal ($P = .14$) or occipital WMH ($P = .23$) in the entire sample. There was no significant difference between the former professional and college football players on total ($P = .98$), frontal ($P = .99$), temporal ($P = .98$), parietal ($P = .99$) or occipital log-WMH ($P = .98$; see Table 2 for estimates and 95% confidence interval [CI]).

Of the sample, 58 former football players and 27 asymptomatic unexposed participants were ≥60 years of age, whereas 91 and 26 were less than 60, respectively. See Figure 3 for age-stratified group differences on WMH. Compared to the asymptomatic unexposed men who were ≥60 years, former football players ≥60 years had greater

TABLE 2 Summary of tobit regression models comparing former American football players and asymptomatic unexposed participants on total and regional log-transformed white matter hyperintensities

WMH variable	Total sample ($n = 149$ former football players, $n = 53$ asymp. unexposed)			≥60 years ($n = 58$ former football players, $n = 27$ asymp. unexposed)			<60 years ($n = 91$ former football players, $n = 26$ asymp. unexposed)		
	Est.	95% CI	FDR *P*-value	Est.	95% CI	FDR*P*-value	Est.	95% CI	FDR*P*-value
Total log-WMH	0.65	0.22–1.08	<.01	0.75	0.23–1.27	.01	0.54	−0.13–1.21	.28
Frontal log-WMH	0.85	−0.19–1.89	.14	1.63	0.33–2.92	.02	−0.01	−1.65–1.63	.99
Temporal log-WMH	2.03	0.67–3.39	<.01	2.35	0.60–4.11	.01	1.21	−0.71–3.13	.36
Parietal log-WMH	2.07	0.90–3.24	<.01	1.96	0.62–3.30	.01	1.88	−0.07–3.83	.28
Occipital log-WMH	0.53	−0.34–1.40	.23	0.35	−0.68–1.38	.50	0.63	−0.81–2.06	.49

Abbreviations: *APOE*, apolipoprotein E; Asymp., asymptomatic; BMI, body mass index; CI, confidence interval; Est., unstandardized estimate; FDR, false discovery rate; rFSRP, revised Framingham Stroke Risk Profile; WMH, white matter hyperintensities.
Note: Tobit regressions compared the former American football players and the asymptomatic unexposed group on total log-WMH, and frontal, temporal, parietal, and occipital log-WMH. Model covariates included age (years), racial identity (White vs. Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple races all combined), rFSRP, BMI, *APOE* ε4 carrier status (absent/present), and evaluation site.

total log-WMH ($P = .01$). Former football players ≥60 years had greater frontal ($P = .02$), temporal ($P = .01$), and parietal ($P = .01$) log-WMH compared to asymptomatic unexposed participants who were ≥60 years. There were no group differences for occipital WMH ($P = .50$).

There were no significant group differences when the sample was restricted to participants < 60 years for total or lobar log-WMH ($Ps > 0.10$).

The above effects remained after restricting the entire sample to those who had intact Trail Making Test B scores (Table A.4 in supporting information).

3.3 | Association with exposure to RHI in former football players

3.3.1 | Age of first exposure

There was no significant association observed between AFE and total log-WMH in the entire sample of former football players ($P = .09$). Among former football players ≥60 years, younger AFE to football was associated with greater total log-WMH (unstandardized beta = −0.13, 95% CI = −0.23, −0.02, $P = .02$). There was no effect in participants < 60 years (unstandardized beta = −0.03, 95% CI = −0.13, 0.08, $P = .61$). See Figure 4.

3.3.2 | Total years of football play

There was no significant association between years of football play and greater total log-WMH in the entire sample of football players (unstandardized beta = −0.01, 95% CI = −0.06, 0.04, $P = .76$), among former football players ≥60 years (unstandardized beta = 0.06, 95% CI = −0.01, 0.13, $P = .12$), or among former football players < 60 years (unstandardized beta = −0.04, 95% CI = −0.11, 0.02, $P = .19$).

3.4 | Association with clinical measures in former football players

In the entire sample of football players, greater total log-WMH was associated with lower Trails A – B scores (unstandardized beta = −4.32, 95% CI = −8.59, −0.05, $P = .047$) and fewer words recalled on NAB List Learning Long Delay Recall (unstandardized beta = −0.56, 95% CI = −0.93, −0.19, $P < .01$). Among former football players ≥60 ($n = 55$), greater total log-WMH was associated with lower Trails A – B scores (unstandardized beta = −7.03, 95% CI = −13.80, −0.30, $P = .04$). There was not a statistically significant association for NAB List Learning Long Delay Recall (unstandardized beta = −0.33, 95% CI = −1.06, 0.41, $P = .38$). Among former football players < 60 years ($n = 84$), greater total log-WMH was associated with fewer words recalled on NAB List Learning Long Delay Recall (unstandardized beta = −0.63, 95% CI = −1.08, −0.18, $P < .01$). There was not a statistically significant association for Trails A – B (unstandardized beta = −2.34, 95% CI = −7.74, 3.05, $P = .39$). Although there were differences in statistical significance by age group for Trails A – B and NAB List Learning Long Delay Recall, effect sizes across the age groups for these associations were not significantly different. There were no statistically significant associations for the BRI or the BDI-II ($Ps > 0.10$).

3.5 | Post hoc: Controlling for sleep apnea, high cholesterol, and alcohol use

Group differences remained significant in the entire sample (unstandardized beta = 0.65, 95% CI = 0.22, 1.08, $P = < .01$) and in the older participants (unstandardized beta = 0.62, 95% CI = 0.13, 1.10, $P = .01$). The estimate for AFE on total log-WMH in former football players ≥60 years remained similar (unstandardized beta = −0.10, 95% CI = −0.21, 0.003), but was not significant ($P = .057$) with the three new covariates (nine total) added in a sample of 58 former football players.

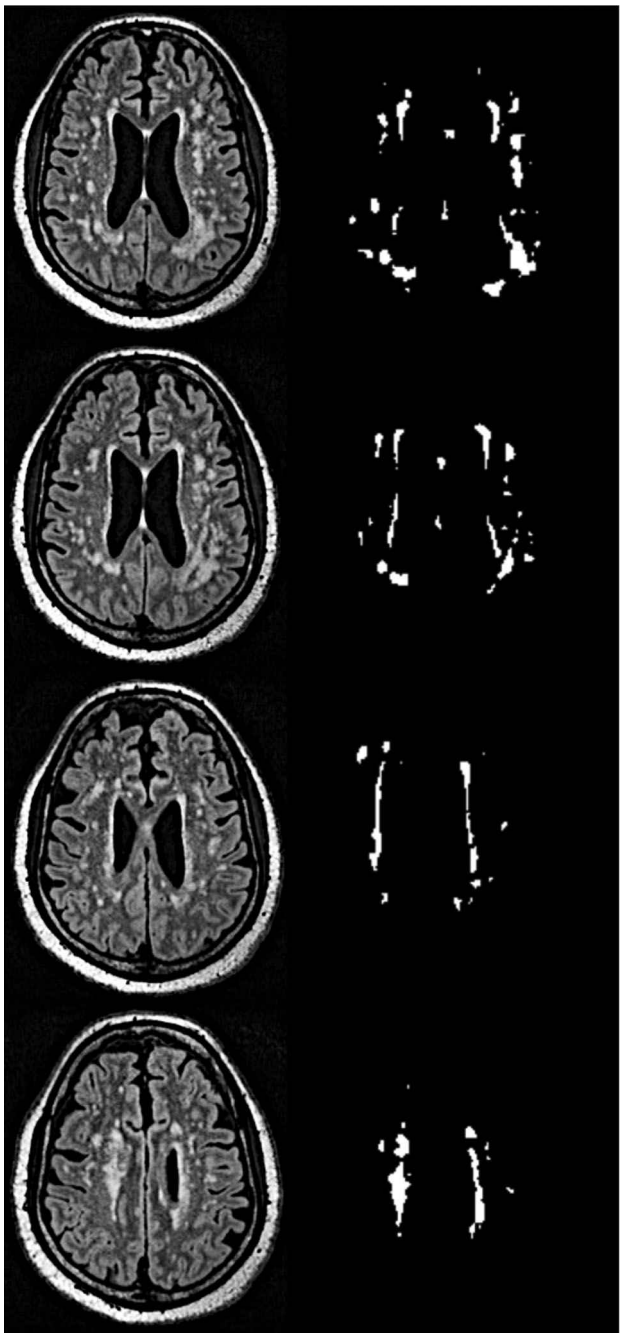

FIGURE 2 Example of regional fluid-attenuated inversion recovery (FLAIR) white matter hyperintensities (WMH) in a former American football player. Figure provides an example of the location of WMH. Left is the native FLAIR and the right is the corresponding binary lesion belief map from the Lesion Segmentation Toolbox. The binary lesion map is extracted from the Lesion Prediction Algorithm (LPA) and the threshold for computation of the lesions was 0.5 (default LPA recommendation)

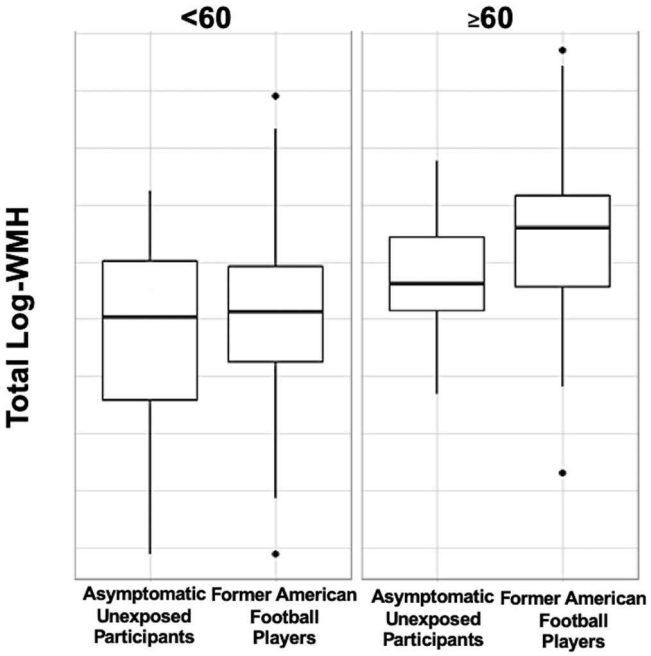

FIGURE 3 Total log-white matter hyperintensities (WMH) on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging: former American football players versus asymptomatic unexposed participants. Box plots show the differences on total volume of log-WMH, stratified by < 60 ($n = 91$ former American football players, $n = 26$ asymptomatic unexposed participants) and ≥60 years ($n = 58$ former football players, $n = 27$ unexposed participants). Group differences were statistically significant in those ≥60 years (unstandardized beta = 0.75, 95% confidence interval [CI] = 0.23–1.27) but not < 60 (unstandardized beta = 0.54, 95% CI = −0.13–1.21). Middle line in bars is median, boxes represent the interquartile range, and the whiskers represent minimum and maximum volumes

4 | DISCUSSION

Compared to same-age asymptomatic unexposed men, former college and professional football players had greater total, temporal, and parietal WMH; frontal effects were observed in older players (≥60 years). Among older and not younger former football players, greater WMH was associated with younger AFE to football. WMH were associated with worse memory and executive function in the football players. There were no significant associations between WMH and neurobehavioral dysregulation and depression symptoms. Associations were independent of *APOE ε*4 and VRF. Etiologies of WMH are multifaceted and often from aging and VRF.[46–48,51,52] Our findings suggest that WMH may have unique presentations, risk factors, and etiologies in former football players.

Compared to same-age asymptomatic unexposed men, former football players had greater volume of WMH. This is consistent with research among small samples of former professional football players.[53,54] However, Zivadinov et al. found no differences in semi-automated measured WMH between 21 retired contact sport athletes and 21 non-contact sport athletes.[40] For the first time, this study reports the spatial distribution of WMH in this population. Former football players had greater temporal and parietal WMH with frontal effects observed in the older players. There were no group differences for occipital WMH. The spatial distribution of WMH can provide insight into underlying pathophysiological and neurodegenerative

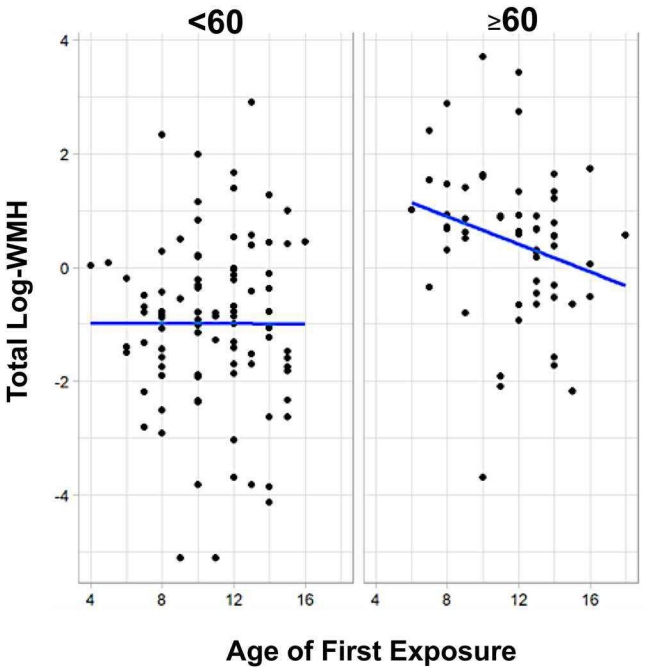

FIGURE 4 Association between age of first exposure to American football and total log-white matter hyperintensities (WMH). Scatter plots showing the association between age of first exposure to American football and total volume of log-WMH, stratified by (A) < 60 (n = 91 former American football players) and (B) ≥60 years (n = 58 former American football players). Younger age of first exposure (unstandardized beta = −0.13, 95% confidence interval = −0.23, −0.02, P = .02) to American football was associated with greater volume of log-WMH in participants who were 60 or older, controlling for age, racial identity, body mass index, revised Framingham Stroke Risk Profile, apolipoprotein E ε4 carrier status, and magnetic resonance imaging site. There were no statistically significant associations in the younger age group

disease processes.[73,83] In AD and frontotemporal dementia, the location of WMH mimic their patterns of atrophy.[73,83] Based on the neuroanatomical distribution of p-tau in CTE,[15,18,84] a frontotemporal distribution of WMH might be expected in former elite football players. An imaging–pathological correlation study of 75 donors found an association between WMH and p-tau at autopsy.[55] Experimental models also show acute TBI can trigger tau acetylation and potential axonal degeneration.[85,86] The CTE status of this sample is unknown and while lack of occipital effects are inconsistent with AD,[73,87] greater temporal and parietal WMH overlap with AD.[88,89] Frontal WMH are also observed in FTLD.[73] Overall, the spatial specificity of the present findings is unknown due to lack of a non-disease comparison group.

Exposure to football might independently contribute to WMH. It is important to note recruitment of participants was based on our predictor (elite football play) and symptom status. The asymptomatic unexposed participants were required to not have RHI and to have no reported symptoms.[58] Differences in WMH could be attributable to differences in symptom status and/or other factors related to WMH, such as VRF. However, the group differences are unlikely attributable to differences in cognitive impairment alone given group effects remained when the entire sample was restricted to those who had intact executive functions. Our analyses also accounted for VRF. The literature and current data support group differences in WMH being related to RHI. RHI from football can have lasting effects on the WM[31,34,35] that might appear on FLAIR.[48,50] In this sample, younger AFE corresponded to higher WMH in older football players; however, significance diminished (P = .057) with sleep apnea, cholesterol, and alcohol use included in models due to limited power. Younger AFE has been linked with WM alterations of the anterior corpus callosum in former NFL players.[21] Participation in football as a youth and adolescent can result in acute WM changes on DTI.[90-92] Importantly, we did not find an association between younger AFE and WMH in participants <60. Research shows no association between AFE and neurobehavioral function in young (i.e., college age) healthy amateur contact sport athletes.[26-28] AFE and clinical associations might be unique across the lifespan and more likely in aging, symptomatic populations.[22,53] Nonetheless, there is a mixed literature on this topic as null effects in older samples of former American football players exist.[29,30]

We did not observe an association between years of play and WMH. This conflicts with findings from the study of 75 donors exposed to RHI.[55] Yet, that was an autopsy study of brain donors and ≈70% had autopsy-confirmed CTE. The autopsy sample was older than this sample (average age = 61.9 vs. 57.1), nearly all were demented, and spanned the continuum of level of football play. Clinical MRIs obtained from medical records were used in that autopsy study. Years of play is a proxy for duration of exposure and other estimates of RHI might be more sensitive to WMH.[54]

WM degeneration has been shown to contribute to cognitive symptoms in former football players.[31,54] In the former football players in the current study, greater WMH were associated with worse verbal memory and executive function. A statistically significant association with verbal memory was present in younger participants, whereas a statistically significant association with executive function was observed in older participants. Despite differences in statistical significance, effect sizes across the age groups for the association between WMH and performance on tests of executive functions and memory were comparable. It was unexpected that WMH were associated with cognitive function in the younger age group given the lack of group effects on WMH in this subgroup. Because we observed the most robust effects in the entire sample, the variability in WMH and cognition that is present with all ages included likely plays an important role. Overall, the clinical significance of the WMH is uncertain due to the modest effect sizes observed, the restricted associations with clinical measures, and the sample being largely intact cognitively, on average (Table A.2). Evaluation of WMH in white matter tracts is an important future direction, as the tract location of the WMH might have key clinical implications compared to burden. We also did not find an association between WMH and behavioral dysregulation or depression, inconsistent with findings in AD/AD and related dementias.[73] CTE p-tau was recently shown to be unrelated to the reported presence of neuropsychiatric symptoms.[72] WM degeneration might be an alternative etiology for neuropsychiatric symptoms,[14,71] but granular assessments of WM might be needed to detect an association.[14]

Associations were limited to participants ≥60 years. This was expected due to the strong association between aging and WMH.[78–80]

Hart et al. also found greater WMH in older (range: 61.6–71.6) impaired former NFL players and not in the younger unimpaired players.[53] Clinically meaningful WMH in former football players are likely to manifest in older age.

5 | LIMITATIONS

Total volume of WMH in milliliters was extracted by thresholding lesion probability maps at a kappa of 0.5 (default LPA recommendation). Although there is precedence for this threshold,[60,61] low-intensity WMH might have been misclassified and false negatives were present and WMH might have been underestimated. The sample was all men and the RHI group was all former American football players. The generalizability of these findings to women and other athlete populations is limited. Racial identity was included as a covariate in the model due to literature linking race and WMH.[93] Reasons for this association are poorly understood and likely related to historical racial inequities that affect lifestyle and health conditions associated with cerebrovascular disease.[94–96] When health-care disparities are accounted for, research has found no association between racial identity and WMH.[94] Future research from this sample will model the interaction between race and social determinants on brain health outcomes. The asymptomatic unexposed men did not have a history of contact sport play; however, history of non-contact athletic history was unknown. It is possible that many participated in athletics and this could have been protective against WMH.

Last, exposure to RHI and not TBI was the focus of this study and the larger DIAGNOSE CTE Research Project. The asymptomatic men were required to have no history of RHI or TBI, or history of combat military experience. As part of the study design of the DIAGNOSE CTE Research Project, former American football players were not excluded for a history of TBI. Of the former American football players, 37 had an affirmative response to a single question that asked, "How many concussions did [participant] have outside of sports or the military?" This question was asked after the participant was read a definition of concussion that describes a concussion to be any time there is a hit to the head that results in any kind of symptoms (e.g., seeing stars, bell rung, etc.).[97] These are not diagnosed TBIs and our data on TBI external to sports are limited in scope. Post hoc analyses that excluded these 37 former football players who reported a history of TBI outside of sports or military showed that the findings remained similar. The former football players continued to demonstrate greater volume of log-WMH compared to the unexposed men (beta = 0.48, 95% CI = 0.03–0.94). The group effect was present in the older (i.e., 60 years or older; beta = 0.57, 95% CI = 0.03–1.12), but not younger (i.e., < 60 years) participants ($P = .36$).

6 | CONCLUSIONS

Older but not younger former football players had greater total, frontal, temporal, and parietal lobe WMH compared to same-age asymptomatic unexposed men. There were no group differences for occipital WMH. Greater WMH corresponded to worse neuropsychological test performance, as well as younger AFE in the older former football players. The causes of WMH are multifactorial and might have unique presentations, risk factors, and etiologies in the setting of aging and RHI exposure from football.

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CONFLICTS OF INTEREST

C.H.A. consulted for Avion, CND Life Sciences, Jazz, and Precon Health. L.J.B. is Editor-in-Chief of the *Journal of Neuro-Ophthalmology*, and is a paid consultant to Biogen (Cambridge, MA, USA). C.B. receives research support from the Ultimate Fighting Championship, Top Rank promotions, Haymon Boxing, Las Vegas Raiders, and Professional Bull Riders. He is a paid consultant for Aurora Concussion Therapy Systems, Inc. (St. Paul, MN). R.A. is a paid consultant to Biogen (Cambridge, MA, USA) and serves on the Scientific Advisory Board of Signant Health (Blue Bell, PA). W.B.B. provides expert witness testimony in legal cases involving concussion and CTE. R.C.C. is a Senior Advisor to the NFL Head Neck & Spine 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. D.W.D. reports the following conflicts within the past 12 months: consulting—Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, Perfood, Praxis, AYYA Biosciences, Revance; honoraria—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, Cambridge University Press; research support—Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI); stock options/shareholder/patents/board of directors—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. A.P.L. is a paid consultant to Agios Pharmaceuticals (Cambridge, MA, USA), Biomarin Pharmaceuticals (Novato, CA, USA), and Moncton MRI (Moncton, Canada). He is the co-founder of BrainSpec, Inc. J.L.C. 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.R is a compensated scientific advisor for Alkahest, Alzheon, Aural Analytics, Denali, Green Valley, Retromer Therapeutics, and Vaxxinity, and a co-founder of ALZPath. R.A.S. is a paid consultant to Biogen (Cambridge, MA, USA). He is a member of the Board of Directors of King-Devick Technologies, Inc. (Chicago, IL, USA), and he receives royalties for published neuropsychological tests from Psychological Assessment Resources, Inc. (Lutz, FL, USA). He is a member of the Medical Science Committee for the National Collegiate Athletic Association Student-Athlete Concussion Injury Litigation. The remaining authors have no conflicts of interest to disclose. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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