Journal of Alzheimer's Disease Reports 7 (2023) 1237–1246
DOI 10.3233/ADR-230073
IOS Press

Short Communication

Association of Cerebrovascular Imaging Biomarkers, Depression, and Anxiety, with Mild Cognitive Impairment

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Received 16 July 2023
Accepted 8 October 2023
Published 3 November 2023

Abstract. The study included 1,738 Mayo Clinic Study of Aging participants (≥50 years old; 1,460 cognitively unimpaired and 278 with mild cognitive impairment (MCI)) and examined the cross-sectional association between cerebrovascular (CVD) imaging biomarkers (e.g., white matter hyperintensities (WMH), infarctions) and Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI) scores, as well as their association with MCI. High (abnormal) WMH burden was significantly associated with having BDI-II>13 and BAI > 7 scores, and both (CVD imaging biomarkers and depression/anxiety) were significantly associated with MCI when included simultaneously in the model, suggesting that both were independently associated with the odds of MCI.

Keywords: Alzheimer's disease, anxiety, cerebrovascular, depression, mild cognitive impairment, neuroimaging

INTRODUCTION

Neuropsychiatric symptoms (NPS) and cerebrovascular disease (CVD) are common in older adults, and both are associated with cognitive impairment [1, 2]. In population-based studies [2, 3], nonpsychotic NPS prevalence ranges from 25% in cognitively unimpaired (CU) persons to about 50% in persons with mild cognitive impairment (MCI) [3]; persons living with dementia can present with even higher NPS frequency [2].

NPS are associated with an increased risk of MCI [4, 5] or dementia [6–10]. In addition, CVD is associated with cognitive impairment; vascular brain injury

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such as white matter hyperintensity (WMH) volume and infarctions can be identified by neuroimaging during life, which is critical as white matter integrity changes have a crucial role in vascular contributions to cognitive impairment and dementia [11, 12]. WMHs are often observed on MRI scans of older adults and have been associated with aging, cerebrovascular risk factors, and late-life depression [13]. However, research on the association between cerebral small vessel disease (e.g., WMHs, infarcts, microbleeds) and depression, anxiety, or other neuropsychiatric symptoms is still inconclusive and warrants further examination [14, 15].

The study aimed to assess the cross-sectional association between CVD imaging biomarkers (e.g., WMH, infarctions) and NPS. We sought to assess the hypothesis that CVD imaging biomarkers are associated with depression and anxiety, and both—depression/anxiety and CVD biomarkers—are independently associated with MCI.

METHODS

Study population

The Mayo Clinic Study of Aging (MCSA) [16] is a prospective population-based cohort study of cognitive aging initiated in 2004 in Olmsted County (MN, USA). The study invites participants using an age- and sex-stratified random sample of Olmsted County residents, achieved using the Rochester Epidemiology Project (REP) [17] resources.

The design and conduct of MCSA were previously reported [16]. Briefly, at each MCSA visit (baseline and every 15 months), the participants undergo a comprehensive cognitive evaluation and are classified as having MCI [18] or dementia [19] or are cognitively unimpaired (i.e., participants who perform in the normal range and do not meet the MCI or dementia criteria) by a consensus expert committee of a study coordinator, a physician, and a neuropsychologist, after reviewing all information collected for each participant.

The present study included 1,738 MCSA [16] participants ($\geq$50 years old) without dementia, with available data on cognitive diagnosis, the Beck Depression Inventory-II (BDI) (self-reported) [20], the Beck Anxiety Inventory (BAI) (self-reported) [21] and having WMH data via FLAIR-MRI [22]. We used the first visit meeting these requirements (starting in 2005).

Study approval was obtained from the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota, and participants provided written informed consent before participation. In the case of participants with cognitive impairment sufficient to interfere with capacity, assent was obtained from a legally authorized representative.

Depression and anxiety inventories

Both the BDI-II and BAI are validated and comprise 21 items. The BDI-II measures common symptoms of depression over the past two weeks, e.g., feelings of guilt or loss of interest, while the BAI measures common anxiety symptoms over the past week (e.g., nervousness or fear of losing control). An ordinal scale ranging from 0 to 3 is used to rate severity of each item (total score 0 to 63; a higher score indicates higher severity of symptoms). The study analysis used BDI-II and BAI total scores as continuous measures, as well as categorical, i.e., as BDI-II score > 13 (more than minimal symptoms, indicating clinical depression) and BAI score > 7 (more than minimal symptoms, indicating clinical anxiety).

Neuroimaging

MRI images were acquired on 3T MRI scanners (GE Healthcare, Waukesha, WI). For each individual, both the structural T1 weighted magnetization prepared rapid gradient echo (MPRAGE) image and FLAIR (fluid-attenuated inversion recovery)-MRI image were used for WMH segmentation [23]. Methods were explained in detail previously [22]. In brief, possible WMH voxels were identified through clustering via connected components using the FLAIR images. To remove nonbrain tissue and voxels that had a high likelihood of being gray matter and not likely WMH, SPM5 segmentation was used from T1 weighted image aligned to the FLAIR images and corresponding brain masks. If additional clusters occurred external to areas categorized as white matter, made up of a single isolated voxel, or had no supra-threshold FLAIR voxels after blurring, they were excluded. Then the WMH were manually edited by trained analysts to correct any incorrect WMH classifications and warrant WMH segmentation consistency across participants. Voxels were removed if they were associated with infarcts and not considered as part of the WMH measurement. The absolute burden of WMH (cm3) was normalized to total

intracranial volume (TIV; cm3). To identify individuals with high levels of WMH (i.e., cut point for abnormal WMH levels), three Gaussian mixture distributions of age versus WMH/TIV % were fit [24]. One cluster appeared to capture a significant proportion of participants with highly abnormal WMH levels and thus, a cut point of $\geq 1.7\%$ of WMH/TIV % was chosen for abnormality based on this cluster. In addition, 3D MPRAGE and FLAIR images were reviewed, and subcortical and cortical infarctions were identified and classified as previously described [25]. Trained image analysts, blinded to participant information, marked the site of possible infarcts, which were reviewed independently by a neuroradiologist and a vascular neurologist. Abnormal CVD was defined as presence of either abnormal WMH/TIV burden or infarctions.

Covariates and potential confounders

At the baseline visit, participant information collected included age, sex, education, weight, height, and Apolipoprotein E ε4 (*APOE ε4*) genotype status, which was determined using standard methods from a blood draw using [26]. The chronic disease burden was assessed for the study baseline from a modified Charlson Comorbidity Index (Charlson Index) [27] score based on electronic diagnosis codes; dementia codes were not included in the index, as MCSA assesses cognitive status. Comorbidities, including diabetes mellitus, hypertension, stroke, history of atrial fibrillation, coronary heart disease, or congestive heart failure, were ascertained using the REP medical records linkage system by expert RN abstractors. To assess the total burden of vascular/metabolic conditions, we created the vascular disease burden (VDB), by the summation of the following nine conditions (adding one point for each condition that is present): diabetes mellitus, hypertension, stroke, history of atrial fibrillation, coronary heart disease, congestive heart failure, dyslipidemia, obesity (based on current body mass index), and peripheral vascular disease; VDB total score resulted in a range of 0-9.

Statistical analysis

Descriptive statistics were calculated and presented as median and range for continuous variables or frequencies (N) with percentages (%) for categorical variables. We compared characteristics between groups using the Wilcoxon rank-sum and Chi-square tests. We ran hurdle regression models for CVD imaging biomarkers predicting BDI-II and BAI scores adjusted for age, sex, and education. Hurdle models consist of two parts: first is the hurdle portion, which is a logistic regression model for predicting positive values versus a value of zero. The second part is a model for the positive values for which we used a truncated negative binomial regression model. Rootogram plots showed that the truncated negative binomial regression model fit the data well. From the logistic portion, we obtained odds ratios (OR), 95% confidence intervals (CI), and p-values, and from the negative binomial portion, we obtained incidence rate ratios (IRR), 95% CI, and p-values. We also ran separate logistic regression models adjusted for age, sex, and education to examine the association of CVD imaging biomarkers with BDI-II>13 (versus ≤ 13) and BAI > 7 (versus ≤ 7) scores, from which we obtained ORs, 95% CI, and p-values.

We additionally ran logistic regression models adjusted for age, sex, education, and *APOE ε4* status to examine the association of BDI-II and BAI scores with MCI (versus CU). We computed ORs, 95% CI, and p-values. We ran these models for BDI-II and BAI individually and including CVD imaging biomarkers. For interpretability and comparability of coefficients, BDI-II and BAI were both z-scored for these analyses by subtracting the mean and dividing by the standard deviation. Similarly, WMH/TIV was z-scored in all models in which it appears.

Potential effect modification by WMH biomarkers in the association between BDI-II and MCI was examined using an interaction term between WMH and BDI-II in a model adjusting for age, sex, education (years), and *APOE ε4* status. No statistically significant interaction was observed (not shown in tables). All analyses were considered statistically significant at a p-value<0.05 and were performed using the SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). The hurdle models were run using version 1.5.5 of the 'pscl' package in R.

RESULTS

Study participants

Participants' characteristics at study baseline are presented in Table 1. Participants' median age (range) was 70.91 (50.20-95.33) years, 53.3% were male; 99 (5.7%) participants had BDI-II score higher than 13, and 199 (11.5%) had BAI score greater than 7. There

Table 1
Participants' characteristics at study baseline

Characteristics	Total ($N = 1,738$)
Age ()	70.91 (50.20-95.33)
Male, n (%)	927 (53.3%)
Education (years)	14.00 (0.00-20.00)
APOE ε4 carrier, n (%)	495 (28.7%) {15}
Neuropsychiatric symptoms	
Beck Depression Inventory-II total	3.00 (0.00-52.00) {1}
Beck Depression Inventory-II>13	99 (5.7%) {7}
Beck Anxiety Inventory total	1.00 (0.00-40.00) {1}
Beck Anxiety Inventory > 7	199 (11.5%) {1}
Conditions	
Mild cognitive impairment, n (%)	278 (16%)
Diabetes mellitus, n (%)	288 (16.6%) {6}
Hypertension, n (%)	1074 (62.0%) {6}
Dyslipidemia, n (%)	1371 (79.2%) {6}
Coronary artery disease, n (%)	447 (25.8%) {6}
Atrial fibrillation, n (%)	176 (10.2%) {6}
Congestive heart failure, n (%)	99 (5.7%) {6}
Vascular disease burden, n (%)*	2.00 (0.00-8.00) {22}
Charlson Comorbidity Index∼	2.00 (0.00-22.00)
Cerebrovascular biomarkers	
WMH/TIV	0.006 (0.000-0.089)
Abnormal WMH/TIV, n (%)	297 (17.1%)
Presence of Infarctions, n (%)**	263 (16.5%) {144}

Median (range) unless otherwise stated; {N}, number of participants missing data; *APOE*, Apolipoprotein E; WMH, white matter hyperintensities volume; TIV, total intracranial volume; Abnormal WMH/TIV, WMH/TIV %≥1.7%. *includes: diabetes mellitus, hypertension, stroke, history of atrial fibrillation, coronary heart disease, congestive heart failure, dyslipidemia, obesity (based on current body mass index), and peripheral vascular disease with a range of 0-9. ∼excluding dementia. **cortical and subcortical.

were 278 (16%) participants with MCI at study baseline. Ninety-eight percent of participants were White and 99% were not Hispanic or Latino.

Participants with BDI-II score > 13 had, on average, fewer years of education, higher BAI score, higher Charlson Comorbidity Index, higher total vascular disease burden, and were more likely to have MCI and abnormal WMH burden.

Association of cerebrovascular biomarkers with depression and anxiety symptoms

Higher WMH/TIV was associated with having a BDI-II>0, e.g., each one SD increase in WMH/TIV was associated with a 24% higher likelihood of having a BDI-II>0, on average (OR = 1.24, 95%CI 1.04-1.49; Table 2). Among those with a positive BDI-II score, each SD increase in WMH/TIV was associated with a 7% increase in BDI-II score (IRR = 1.07, 95%CI: 1.01-1.13). The presence of infarctions was associated with significantly higher likelihood of having a BDI-II>0 on average, and borderline significantly higher BDI-II score in those with a positive BDI-II score. Participants with abnormal WMH/TIV (versus not) had 2.25 times the odds of having a BDI-II score > 13 (OR = 2.25, 95%CI: 1.32-3.83).

Each one SD increase in WMH/TIV was associated with an 18% higher likelihood of having a BAI score > 0, on average (OR = 1.18, 95%CI: 1.04-1.33; Table 2), although among those with a positive BAI score, each SD increase in WMH/TIV was not associated with a significant increase in the score, on average (IRR = 1.08, 95%CI: 1.00-1.17). Among those with a positive BAI score, having abnormal WMH/TIV was associated with a 32% increase in BAI score (IRR = 1.32, 95%CI: 1.08-1.63). Although the presence of infarctions was not associated with a higher likelihood of having a BAI > 0 (OR = 0.98, 95%CI: 0.73-1.30), the presence of infarctions was associated with a significantly higher BAI score (IRR = 1.25, 95%CI 1.01-1.55) among those with BAI > 0.

Participants with abnormal CVD biomarkers (i.e., presence of abnormal WMH/TIV and/or infarctions) had 1.93 times the odds of having a BAI score > 7 compared to participants without abnormal CVD biomarkers (OR = 1.93, 95%CI: 1.33-2.79).

We did not adjust for vascular clinical conditions as they are in the same causal pathway as cerebrovascular injury.

Association of cerebrovascular biomarkers, depression, and anxiety symptoms with MCI

The BDI-II score was significantly associated with the odds for MCI (per 1 SD, OR: 1.40, 95%CI:1.23-1.59; Table 3). This estimate was minimally decreased (per 1 SD, OR: 1.38, 95%CI:1.21-1.57) when WMH/TIV was also included in the model, and both WMH/TIV (per 1 SD, OR: 1.20, 95%CI:1.05-1.38) and BDI-II score were significantly associated with MCI. We observed a similar pattern of associations for BAI score, as well. The presence of infarctions and higher BDI-II score (or BAI score) were also significantly associated with MCI when included in the same model.

DISCUSSION

High (abnormal) WMH burden was significantly associated with having BDI-II>13 and BAI > 7 scores, and both (CVD imaging biomarkers and depression or anxiety symptoms) were significantly

Table 2
Associations of Cerebrovascular Imaging Biomarkers with BDI-II and BAI score

	Hurdle Models						Logistic regression models		
CVD Biomarkers	OR^1	(95% CI)	p	IRR^2	(95% CI)	p	OR^^	(95% CI)	p
	BDI-II score (outcome)						BDI>13 (outcome)		
WMH/TIV	1.24	(1.04, 1.49)	0.018	1.07	(1.01, 1.13)	0.029	1.30	(1.07, 1.57)	0.007
Abnormal WMH/TIV	1.33	(0.90, 1.97)	0.150	1.24	(1.08, 1.43)	0.003	2.25	(1.32, 3.83)	0.003
Presence of infarctions	1.51	(1.02, 2.24)	0.039	1.15	(0.10, 1.33)	0.056	1.57	(0.89, 2.76)	0.121
Presence of cortical infarctions	2.66	(1.21, 5.87)	0.015	1.13	(0.91, 1.41)	0.266	1.33	(0.55, 3.22)	0.522
Presence of subcortical infarctions	1.33	(0.88, 2.02)	0.172	1.10	(0.94, 1.29)	0.224	1.45	(0.79, 2.66)	0.234
Abnormal CVD	1.52	(1.08, 2.14)	0.018	1.21	(1.06, 1.39)	0.005	2.00	(1.18, 3.40)	0.011
	BAI score (outcome)						BAI>7 (outcome)		
WMH/TIV	1.18	(1.04, 1.33)	0.011	1.08	(1.00, 1.17)	0.065	1.13	(0.97, 1.32)	0.115
Abnormal WMH/TIV	1.41	(1.05, 1.88)	0.022	1.32	(1.08, 1.63)	0.007	1.97	(1.33, 2.91)	0.001
Presence of infarctions	0.98	(0.73, 1.30)	0.867	1.25	(1.01, 1.55)	0.037	1.53	(1.03, 2.28)	0.035
Presence of cortical infarctions	1.18	(0.75, 1.86)	0.475	1.28	(0.93, 1.78)	0.131	1.79	(1.01, 3.17)	0.045
Presence of subcortical infarctions	0.97	(0.72, 1.32)	0.866	1.19	(0.94, 1.49)	0.142	1.28	(0.83, 1.98)	0.262
Abnormal CVD	1.20	(0.92, 1.56)	0.173	1.29	(1.07, 1.57)	0.009	1.93	(1.33, 2.79)	0.001

CVD, cerebrovascular; BDI-II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; WMH, white matter hyperintensities; TIV, total intracranial volume; Abnormal WMH/TIV, WMH/TIV %≥1.7%; Abnormal CVD, presence of either abnormal WMH burden or infarctions. ^1,2 retained from (1) the logistic regression portion of the hurdle model for predicting positive values versus 0 and (2) the negative binomial model for predicting the positive values, adjusted for age, sex, education. For example, the first estimate from the logistic regression portion of the hurdle model suggests that each one SD increase in WMH / TIV is associated with a 24% higher likelihood of having a BDI-II score greater than zero, on average; and the IRR of 1.07 suggests that amongst those with a positive BDI score, each one SD increase in WMH / TIV is associated with a 7% increase in BDI score, on average. ^^ retained from a logistic regression model adjusted for age, sex, and education.

Table 3
Associations of Cerebrovascular Imaging Biomarkers, BDI-II and BAI score with MCI

Independent variables OR^	Total/with MCI (95% CI)	Mild cognitive impairment (outcome)		
		p		
BDI-II score	1717/278	1.40	(1.23 1.59)	<0.001
WMH/TIV[1]	1717/278	1.20	(1.05, 1.38)	0.008
BDI-II score[1]		1.38	(1.21, 1.57)	<0.001
Abnormal WMH/TIV[2]	1717/278	1.76	(1.26, 2.46)	0.001
BDI-II score[2]		1.38	(1.21, 1.57)	<0.001
Presence of infarctions[3]	1573/173	1.66	(1.12, 2.43)	0.010
BDI-II score[3]		1.40	(1.21, 1.61)	<0.001
BAI score	1722/278	1.31	(1.16, 1.49)	<0.001
WMH/TIV[4]	1722/278	1.21	(1.06, 1.38)	0.006
BAI score[4]		1.30	(1.14, 1.47)	<0.001
Abnormal WMH/TIV[5]	1722/278	1.77	(1.27, 2.47)	0.001
BAI score[5]		1.29	(1.14, 1.46)	<0.001
Presence of infarctions[6]	1578/173	1.69	(1.14, 2.49)	0.008
BAI score[6]		1.40	(1.23, 1.60)	<0.001

BDI-II, Beck Depression Inventory II; BAI, Beck Anxiety Inventory; MCI, mild cognitive impairment; WMH, white matter hyperintensities; TIV, total intracranial volume; Abnormal WMH/TIV, WMH/TIV %≥1.7%; Abnormal CVD, presence of either abnormal WMH burden or infarctions. [1,2,3,4,5,6] imaging biomarker and BDI-II or BAI score simultaneously included in the model if they have the same superscript number. ^ retained from a logistic regression model additionally adjusted for age, sex, education and *APOE* ε4 status; for interpretability and comparability of coefficients, BDI-II and BAI were both z-scored for these analyses.

associated with MCI when included simultaneously in the model, suggesting that both were independently associated with the odds of MCI. We additionally observed that having higher WMH/TIV and/or abnormal WMH/TIV were associated with having a higher than zero BDI-II and BAI score, with higher score in those with positive BDI-II and BAI scores, as well as, with having more (versus less) than minimal depression and anxiety symptoms. Brain infarctions were also associated with having a higher than zero BDI-II (but not BAI) score, higher BAI score in those with higher than zero BAI score, and with more than minimal anxiety symptoms.

The present study findings are consistent with previous reports [28] suggesting that NPS and CVD imaging biomarkers are independently associated with greater odds of MCI. NPS and vascular brain injury (i.e., WMH burden and brain infarcts) have been associated with an increased risk of cognitive impairment [4–10, 29]. Cerebrovascular disease, e.g., stroke, is associated with NPS (including depression and anxiety) and cognitive dysfunction, suggesting that depressive symptoms in that setting could be associated with inflammatory processes, genetic and epigenetic variations, white matter disease, cerebrovascular deregulation, among others as additional pertinent causal factors [30].

WMHs are often observed on MRI scans of older adults and have been associated with aging, cerebrovascular risk factors, and late-life depression [13]. However, research on the association between WMHs, depression, anxiety, or other neuropsychiatric symptoms is still inconclusive [14]. Cross-sectional [31–33] and longitudinal [14, 34, 35] studies have supported a positive association between WMHs and depression in cognitively impaired or unimpaired older adults. Similarly, previous studies [13, 36, 37] have supported an association between WMH with anxiety. However, not all studies agree [38, 39], and these associations require further investigation [15]. In addition, manifestations of vascular disease could differ depending on vascular injury location. For example, a recent meta-analysis suggested that in the post-acute stroke phase, depression was associated with frontal and basal ganglia infarcts [40]. Small basal ganglia lesions and large cerebral cortical white matter lesions have been associated with persistent depressive symptoms [41, 42] while a meta-analysis of 16 longitudinal studies[43] suggested that deep WMHs were associated with increased dementia risk, but not the perivascular WMHs. Thus, future studies need to address the potential differential effects of CVD lesion location on depression and other NPS [41].

In this cross-sectional study, we did not investigate mechanisms of action, and it is hard to speculate whether any differences we observed in the CVD imaging biomarkers associations with BDI-II and BAI outcomes underlie a differential impact of the CVD biomarkers on depression and anxiety

symptomatology. However, in the past, we proposed [44] four possible mechanisms linking NPS and Alzheimer's disease pathology in predicting cognitive outcomes, which may be relevant to this study as well. For example, a synergistic interaction between vascular brain injury and NPS (e.g., depression) may lead to cognitive impairment. It is also conceivable that reverse causation could account for the findings, i.e., a person who starts struggling with cognitive impairment may feel discouraged and feel depressed over the evolving loss of cognitive function due to an underlying Alzheimer's pathology and comorbid CVD as defined by the 2018 NIA-AA research framework [45]. Yet another potential explanation could be the vascular depression hypothesis of old age or "etiologic pathways," e.g., aging related vascular brain injury may lead to NPS (e.g., depression) that in turn leads to deleterious impact on hippocampus and other pertinent structures thereby leading to cognitive impairment. Finally, a shared pathway, i.e., an underlying AD pathology and comorbid CVD, may lead to both depression and cognitive impairment [46]. We hasten to add that these and other possible mechanisms are not mutually exclusive, and additional mechanisms could exist waiting to be discovered.

Our study also adds to growing knowledge on the association of cerebral small vessel disease, depression, and anxiety symptoms, in a large community-based study. This area of research needs further investigation [15], and our team will continue elucidating these associations and undertake a longitudinal investigation in the future.

Strengths of the study are the large sample size, the comprehensive cognitive evaluation, and access to a state-of-the-art neuroimaging dataset. However, findings need to be also considered in light of the study's limitations. The cross-sectional study design limits our ability to make causal inferences. In addition, participants volunteering to undergo imaging studies might be different in some characteristics (e.g., with fewer comorbidities) than participants who did not select imaging studies [47]. Ninety-eight percent of participants were White, and 99% were not Hispanic or Latino, thus, investigation of these associations in more diverse populations is needed.

ACKNOWLEDGMENTS

This work was funded by grants from the National Institutes of Health (NIH) (R01 AG57708). The Mayo Clinic Study of Aging was supported by the NIH (U01 AG006786, P30 AG062677, R37 AG011378, R01 AG041851, R01 NS097495), the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic, GHR Foundation, Mayo Foundation for Medical Education and Research, the Liston Award, the Schuler Foundation and used the resources of the Rochester Epidemiology Project (REP) medical records linkage system, which is supported by the National Institute on Aging (AG 058738), by the Mayo Clinic Research Committee, and by fees paid annually by REP users. The content of this article is solely the responsibility of the authors and does not represent the official views of the NIH or the Mayo Clinic. The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CONFLICT OF INTEREST

Maria Vassilaki has received research funding from F. Hoffmann-La Roche Ltd and Biogen and consulted for F. Hoffmann-La Roche Ltd; currently, she receives research funding from NIH; she has equity ownership in Johnson and Johnson, Medtronic, Merck, and Amgen.

Jonathan Graff-Radford receives support from the NIH, serves on the DSMB for StrokeNET, and is an investigator in clinical trials sponsored by Esai and the Alzheimer's Treatment and Research Institute at USC.

Prashanthi Vemuri receives NIH funding.

Eugene L Scharf is a consultant for Boston Scientific but receives no compensation.

Mary M. Machulda receives NIH funding.

Julie A. Fields serves as a consultant for Medtronic, Inc. and receives research support from the NIH.

Walter K. Kremers receives research support from the NIH.

Val J. Lowe serves as a consultant for Bayer Schering Pharma, Piramal Life Sciences, Life Molecular Imaging, Eisai Inc., AVID Radiopharmaceuticals, and Merck Research, and receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals, and the NIH (NIA, NCI).

Clifford R. Jack Jr. has no financial conflicts to disclose; he receives research support from NIH and the Alexander Family Alzheimer's Disease Research

Professorship of the Mayo Clinic.

David S. Knopman serves on a Data Safety Monitoring Board for the Dominantly Inherited Alzheimer Network Treatment Unit study. He served on a Data Safety monitoring Board for a tau therapeutic for Biogen (until 2021) but received no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Magellan Health, Biovie and Alzeca Biosciences but receives no personal compensation. He attended an Eisai advisory board meeting for lecanemab on December 2, 2022, but received no compensation. He receives funding from the NIH.

Ronald C. Petersen serves as a consultant for Roche, Inc., Eisai, Inc., Genentech, Inc. Eli Lilly, Inc., and Nestle, Inc., served on a DSMB for Genentech, receives royalties from Oxford University Press and UpToDate, and receives NIH funding.

Yonas E. Geda receives funding from NIH and the BARROW Neurological Foundation.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The Mayo Clinic Study of Aging makes data available to qualified researchers upon reasonable request.

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