Spatially distinct atrophy is linked to β-amyloid and tau in preclinical Alzheimer disease

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ABSTRACT

Objectives: To determine whether an MRI-based Alzheimer disease (AD) signature biomarker can detect tau-related neurodegeneration in preclinical AD, and to assess whether AD signature cortical thinning is associated with cognitive changes in cognitively normal (CN) older individuals.

Methods: In a large cohort of CN individuals (n = 188), we measured the hippocampal volume and cortical thickness within independently defined AD signature regions. We cross-sectionally assessed the associations between AD signature cortical thinning or hippocampal atrophy with CSF biomarkers of tau (increased tau) and β-amyloid (Aβ) (decreased Aβ42). We also examined the impact of AD signature cortical thinning or other biomarker changes (i.e., hippocampal atrophy, reduced CSF Aβ42, or increased CSF tau) on cognitive performance in CN individuals.

Results: Elevated CSF tau was associated with AD signature cortical thinning but not hippocampal atrophy. In contrast, decreased CSF Aβ42 was associated with hippocampal loss but not AD signature cortical thinning. In addition, AD signature cortical thinning was associated with lower visuospatial performance. Reduced CSF Aβ42 was related to poorer performance on episodic memory.

Conclusions: Spatially distinct neurodegeneration is associated with Aβ and tau pathology in preclinical AD. Aβ deposition and AD signature cortical atrophy independently affect cognition in CN older individuals. ***Neurology*® 2015;84:1254–1260**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CN** = cognitively normal.

Isolated amyloidosis is the earliest stage of preclinical Alzheimer disease (AD), followed by neurodegeneration and then subtle cognitive decline.[1] However, recent work has observed that some cognitively normal (CN) individuals have neurodegeneration (e.g., AD-like brain atrophy on structural MRI) independent of amyloidosis.[2–4] These observations motivate the investigation of tau-related neurodegenerative process in preclinical AD. In addition, discrepant data exist regarding the relationships between amyloidosis or neurodegeneration and cognitive decline in preclinical AD.[3,5]

Neurodegeneration can be measured using the hippocampal volume or cortical thickness within the topography affected by AD (i.e., "AD signature").[6,7] The AD signature has been shown to predict prognosis in individuals without dementia,[8] although an important gap remains. Specifically, the AD topography has been derived primarily as a function of clinical assessment and not biomarkers. Many supposed CN older persons may have biomarker evidence of AD pathology.[9] Some individuals with clinically defined AD do not have biomarker evidence of AD pathology.[10]

Here, we refined the AD signature using a cohort of clinical and biomarker-confirmed CN and symptomatic AD individuals. In a separate group of CN individuals (n = 188), we investigated whether abnormal CSF biomarker of tau pathology was associated with

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neurodegenerative changes (AD signature cortical thinning or hippocampal atrophy) in preclinical AD. We also examined whether amyloidosis (reduced CSF β-amyloid [Aβ] 42) mediated the effects of tau on neurodegeneration. We assessed the impact of neurodegeneration or amyloidosis on cognition in CN individuals.

METHODS

Participants. Participants were research volunteers enrolled in longitudinal studies of memory and aging at the Knight Alzheimer's Disease Research Center at Washington University in Saint Louis. Recruitment procedures have been previously published.[11] Inclusion criteria were as follows: (1) age 65 years or older, (2) brain MRI and CSF collection completed within 12 months of clinical assessment, and (3) normal cognition or mild dementia due to AD, indicated by a Clinical Dementia Rating (CDR) of 0 and 1, respectively,[12] assessed at the time closest to MRI scanning and CSF collection. Participants (n = 308) were divided into 2 cohorts. Cohort 1 was used for definition of the topography of AD signature while cohort 2 was used for analyzing the relationships among MRI-based biomarkers (cortical thickness within AD signature and hippocampal volume), CSF biomarkers (Aβ42 and tau), and cognitive measures.

Standard protocol approvals, registrations, and patient consents. The Human Research Protection Office at Washington University in Saint Louis School of Medicine approved this study. Written informed consent was obtained from each participant. The guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology[13] were followed if applicable.

Clinical and neuropsychological assessments. The participant and a collateral source underwent separate semistructured interviews conducted by experienced clinicians. The presence or absence of dementia was determined by clinicians according to the principle of intraindividual decline relative to prior functional level.[14] A diagnosis of dementia due to AD was made according to standard criteria.[14]

All participants completed a neuropsychological battery that assessed the following domains: episodic memory, executive function, visuospatial ability, and semantic. For each domain, a composite score was formed by averaging *z* scores of individual tests (appendix e-1 on the *Neurology*® Web site at Neurology.org). This assessment was performed within 2 months of clinical evaluation.

CSF collection and *APOE* genotyping. After an overnight fast, CSF (20–30 mL) was obtained and analyzed for Aβ42, tau, and phosphorylated tau_{181} by plate-based ELISA (INNOTEST; Innogenetics, Ghent, Belgium).[15] Genotyping for *APOE* was conducted using procedures previously reported.[16]

Structural MRI acquisition and preprocessing. Participants were scanned on either Siemens 3T Trio (n = 110 in cohort 1 or n = 155 in cohort 2) or 1.5T Vision (n = 10 in cohort 1 or n = 33 in cohort 2) scanner (Siemens Medical Systems, Erlangen, Germany). High-resolution structural scans were obtained with a T1-weighted magnetization-prepared rapid gradient echo sequence. Images were processed with FreeSurfer (version 5.10) (http://surfer.nmr.mgh.harvard.edu) (appendix e-2).

Definition of the topography of AD signature. The topography of AD signature was identified in cohort 1 comprising participants with mild AD (CDR 1, n = 20) and a portion of CN participants (CDR 0, n = 100). The CN participants were randomly chosen from CN individuals who were negative for CSF Aβ42 (>500 pg/mL) and CSF tau (<500 pg/mL).[17] All participants with mild AD had either reduced CSF Aβ42 (≤500 pg/mL) or elevated Pittsburgh compound B binding (mean cortical binding potential ≥0.18).[17] Demographics and biomarker data for cohort 1 are provided in table 1.

For each participant in cohort 1, following the preprocessing of structural MRI data, the cortical surface representing the gray-white boundary was inflated into a sphere.[18] The inflated spheres were registered to a common spherical coordinate system that aligned cortical folding patterns across participants.[19] The surface maps of cortical thickness were compared between the mild AD and CN participants using a general linear model with adjustment for age, sex, the presence of *APOE* ε4 allele, and scanner type (3T Trio vs 1.5T Vision). The group difference map was thresholded at a vertex-wise $p < 0.001$ and cluster size ≥100 mm^2. The participants with mild AD exhibited cortical thinning in the entorhinal cortex, fusiform gyrus, inferior, middle and superior temporal gyri, superior and inferior parietal lobules, posterior cingulate gyrus, and precuneus (figure 1). These regions hereafter are collectively referred to as the AD signature.

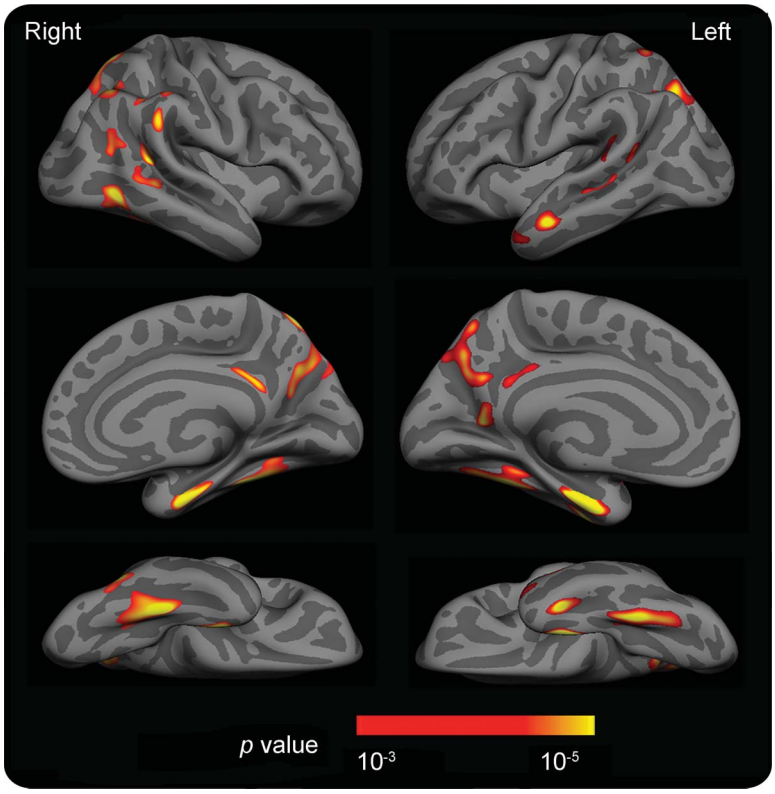
Measurements of AD signature cortical thickness and hippocampal volume in CN individuals. Demographics and biomarker data for cohort 2 (n = 188) are provided in table 2. For each participant included in cohort 2, AD signature regions, as identified above, were mapped back to this participant's individual space. Thickness values were obtained from each region

Table 1 Demographic characteristics of the cohorts used for definition of AD signature regions

	CN	AD
No.	100	20
Mean age (SD), y	71 (9)	76 (6)
Age range, y	65-90	69-87
Sex, % male	50	52
Mean education (SD), y	15 (3)	14 (2)
APOE genotype, % ε4+	26	75
Clinical status		
Mean MMSE score (SD)	29 (1)	23 (3)
CDR, no. of 0/1	100/0	0/20
Biomarker profiles		
Mean CSF $Aβ_{42}$ (SD), pg/mL	782 (205)	315 (75)[a]
Mean CSF tau (SD), pg/mL	236 (70)	665 (338)[a]
Mean PiB MCBP (SD)	NA	0.78 (0.23)[b]

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; CDR = Clinical Dementia Rating; CN = cognitively normal; MCBP = mean cortical binding potential; MMSE = Mini-Mental State Examination; NA = not applicable; PiB = Pittsburgh compound B.
CDR score of 0 indicates no dementia and 1 mild dementia. MMSE scores range from 30 (best) to 0 (worst).
[a] Data available from 13 participants.
[b] Data available from 7 participants.

Figure 1 Topography of AD signature



Surface maps of cortical thickness were compared between cognitively normal (CN) individuals (n = 100) who were negative for CSF Aβ42 (>500 pg/mL) and CSF tau (<500 pg/mL) and individuals with Alzheimer disease (AD) (n = 20) who were positive for either CSF $A\beta_{42}$ (≤500 pg/mL) or amyloid imaging with Pittsburgh compound B (mean cortical binding potential ≥0.18) using a general linear model. A group difference map (AD < CN) was thresholded at a vertex-level $p < 0.001$ and cluster size >100 mm^2 after adjustment for age, sex, presence of *APOE* ε4 allele, and scanner type (3T Trio vs 1.5T Vision). The map is displayed on the semi-inflated cortical surface of the FreeSurfer average brain with light gray regions representing gyri and dark gray regions representing sulci.

and averaged across all AD signature regions to form a composite score. In addition, hippocampal volumes were measured using FreeSurfer's subcortical stream.[20] The details of FreeSurfer's subcortical stream have been previously documented.[20] Briefly, the hippocampus was segmented using automated procedures that examined variations in voxel intensities and spatial relationships to classify subcortical regions.[20] Hippocampal volume was calculated for each participant as the product of the voxel volume and the number of voxels. Hippocampal volumes were then averaged across hemispheres and adjusted for intracranial volume. For each of the samples scanned with 3T Trio (n = 155) or 1.5T Vision (n = 33) scanner, individual composite scores of AD signature cortical thickness and adjusted hippocampal volumes were transformed to *z* scores using corresponding mean and SD derived from this sample.

Statistical analysis. The present statistical approach was informed by existing studies, which have found that (1) the relationship between CSF Aβ42 and brain atrophy differs in Aβ42-positive vs Aβ42-negative individuals (i.e., an interaction between the continuous and categorical measures of CSF Aβ42),[21,22] (2) the interaction between CSF Aβ42 and CSF phosphorylated tau_{181} is related to brain atrophy,[23] and (3) Aβ mediates the effect of tau on neurodegeneration (autopsy data).[24]

Table 2 Demographic characteristics of cognitively normal participants

No.	**188**
Mean age (SD), y	73 (6)
Age range, y	65–92
Sex, % male	41
Mean education (SD), y	16 (3)
***APOE* genotype, % ε4+**	36
Mean MMSE score (SD)	29 (1)
Mean cognitive composite *z* score (SD)	
Episodic memory	0.14 (0.97)
Executive function	0.16 (0.60)
Visuospatial	0.25 (0.76)
Semantic	0.09 (0.70)
CSF biomarker	
Mean Aβ42 (SD), pg/mL	565 (269)
Mean tau (SD), pg/mL	376 (206)

Abbreviations: Aβ = β-amyloid; MMSE = Mini-Mental State Examination.
Raw scores of neuropsychological tests were standardized to *z* scores using a sample of individuals (age = 74.5 ± 8.6 years; education = 14.8 ± 3.2 years, n = 310) from the Knight Alzheimer's Disease Research Center who were enrolled as Clinical Dementia Rating (CDR) 0 and never progressed to CDR >0 on subsequent annual follow-up. For each cognitive domain, composite *z* score was obtained by averaging the *z* scores across individual tests included in this domain. MMSE scores range from 30 (best) to 0 (worst).

Thus, we analyzed the associations of AD-associated atrophy with CSF biomarkers using equation 1, which includes the interactions between the continuous and categorical measures of CSF Aβ42, between the continuous and categorical measures of CSF tau, between CSF Aβ42 (categorical) and CSF tau (categorical), and between CSF Aβ42 (categorical) and CSF tau (continuous):

$$\begin{aligned} AD-associated\ \ atrophy = {} & \beta_0 + \beta_1(CSF\_A\beta 42) \\ & + \beta_2(A\beta\_status) \\ & + \beta_3(A\beta\_status \times CSF\_A\beta 42) \\ & + \beta_4(CSF\_tau) + \beta_5(tau\_status) \\ & + \beta_6(tau\_status \times CSF\_tau) \\ & + \beta_7(tau\_status \times A\beta\_status) \\ & + \beta_8(CSF\_tau \times A\beta\_status) \\ & + \beta_{covariates}(Age, Sex, APOE4) + \varepsilon \end{aligned}$$

Equation 1

Here, AD-associated atrophy denotes the *z* scores of AD signature cortical thickness or hippocampal volume. *CSF_Aβ42* and *CSF_tau* denote the continuous measures of CSF Aβ42 and CSF tau, respectively. *Aβ_status* and *tau_status* were categorical-defined as positive if CSF Aβ42 ≤500 pg/mL and CSF tau ≥500 pg/mL, respectively, and negative if CSF Aβ42 >500 pg/mL and CSF tau <500 pg/mL, respectively.[17] Age, sex, and *APOE* genotype (the presence vs absence of ε4 allele) were used as covariates. The interactions were first tested and reported if confirmed. After any detected interaction involving *Aβ_status* or *tau_status*, relationships between AD-associated atrophy and

CSF biomarker were assessed separately within individuals who were positive or negative for the involved biomarker using equation 2:

$$AD-associated\ \ atrophy = \beta_0 + \beta_1(CSV\_A\beta42) + \beta_2(CSF\_tau) + \beta_{covariates}(Age, Sex, APOE4) + \varepsilon \quad \text{Equation 2}$$

Multiple regression models were used to assess whether cognitive measures were associated with AD signature cortical thickness, hippocampal volume, CSF Aβ42, and CSF tau in CN individuals. Specifically, composite scores of each cognitive measure (i.e., episodic memory, executive function, visuospatial, and semantic) were used as dependent variables separately. For each model, AD signature cortical thickness, hippocampal volume, CSF Aβ42, and CSF tau were analyzed individually to determine which of them explained a significant portion of the variance (i.e., R^2). Furthermore, the 4 independent variables were examined recursively to determine which one explained a significant additional portion of the variance (i.e., increase in R^2 or ΔR^2) after accounting for the other 3. All models included age, sex, education, and *APOE* genotype (the presence vs absence of ε4 allele) as covariates. Analyses were implemented using SPSS (version 21.0; IBM Corp., Armonk, NY) with a statistical threshold for significance of $p < 0.05$, corrected for multiple comparisons for equation 1.

RESULTS

Associations of AD signature cortical thickness with CSF Aβ42 and CSF tau in CN individuals. Analyses of cohort 2 using equation 1 found interactions between CSF Aβ42 (continuous) and Aβ status (categorical) ($p = 0.02$), and between CSF tau (continuous) and tau status (categorical) ($p = 0.01$), but not between Aβ status and tau status ($p = 0.84$), and not between CSF tau and Aβ status ($p = 0.53$) regarding AD signature cortical thickness (figure e-1A). Since observed interactions suggested that the relationship between AD signature and CSF Aβ42 (continuous) was different regarding Aβ status and that the relationship between AD signature and CSF tau (continuous) was distinct regarding tau status, AD signature–CSF biomarker relationships were analyzed separately within biomarker-negative or -positive group using equation 2. Within the CSF Aβ42-positive (≤500 pg/mL, n = 104) and CSF Aβ42-negative (>500 pg/mL, n = 84) groups, the relationship between CSF Aβ42 and AD signature cortical thickness was not found (both $p \geq 0.13$) after adjusting for age, sex, *APOE* ε4, and CSF tau. An inverse relationship was observed between CSF tau and AD signature cortical thickness in the CSF tau-positive group (≥500 pg/mL, n = 46) (partial $\eta^2 = 0.15$, $p = 0.01$), but no relationship was seen in the CSF tau-negative group (<500 pg/mL, n = 142) ($p = 0.84$) after adjusting for age, sex, *APOE* ε4, and CSF Aβ42 (table e-1).

Associations of hippocampal volume with CSF Aβ42 and CSF tau in CN individuals. Analyses of cohort 2 using equation 1 revealed an interaction between CSF Aβ42 and Aβ status ($p = 0.01$), but not between Aβ status and tau status and not between Aβ status and CSF tau (both $p \geq 0.71$) regarding the hippocampal volume. Neither main effects of CSF tau or tau status nor the interaction between them was observed (all $p \geq 0.30$) for the hippocampal volume (figure e-1B). Since hippocampal volume was differentially associated with CSF Aβ42 (continuous) according to Aβ status, as indicated by the presence of CSF Aβ42–Aβ status interaction, we analyzed the hippocampal–CSF Aβ42 association separately within the CSF Aβ42-negative or -positive group using equation 2. A positive relationship was seen between CSF Aβ42 and hippocampal volume in the CSF Aβ42-positive group (≤500 pg/mL) (partial $\eta^2 = 0.07$, $p = 0.009$), but not in the CSF Aβ42-negative group (>500 pg/mL) ($p = 0.79$) after adjusting for age, sex, *APOE* ε4, and CSF tau (table e-2). Results are presented in appendix e-3 regarding evaluation of the choice of CSF biomarker cutoffs for studied relationships.

Associations of cognitive performance with AD signature cortical thickness, hippocampal volume, CSF Aβ42, and CSF tau in CN individuals. AD signature cortical thickness, hippocampal volume, CSF Aβ42, and CSF tau were first analyzed individually regarding each cognitive composite (episodic memory, executive function, visuospatial, and semantic) after controlling for age, sex, education, and *APOE* ε4. Hippocampal volume or CSF Aβ42 explained a portion of the variance in episodic memory ($R^2 = 0.02$, $p = 0.03$, and $R^2 = 0.03$, $p = 0.02$, respectively). After accounting for each other, AD signature cortical thickness, and CSF tau, CSF Aβ42 explained an additional portion of the variance in episodic memory ($\Delta R^2 = 0.02$, $p = 0.03$) while hippocampal volume was not noteworthy ($\Delta R^2 = 0.02$, $p = 0.07$). Episodic memory had no relationship with AD signature cortical thickness or CSF tau (both $p \geq 0.58$). AD signature cortical thickness explained some of the variance in visuospatial performance ($R^2 = 0.02$, $p = 0.03$) and continued to account for the same amount of variance after controlling for hippocampal volume, CSF Aβ42, and CSF tau. Visuospatial performance had no association with hippocampal volume, CSF Aβ42, or CSF tau (all $p \geq 0.25$). Neither executive nor semantic composite scores had any notable relationship with AD signature cortical thickness, hippocampal volume, CSF Aβ42, or CSF tau (all $p \geq 0.10$).

DISCUSSION

Our work demonstrates that increased CSF tau was related to AD signature cortical thinning but not reduced hippocampal volume in CN individuals with higher CSF tau levels. In contrast, decreased

CSF Aβ42 was associated with reduced hippocampal volume but not AD signature cortical thinning in CN individuals with lower CSF Aβ42 levels. In particular, the effect of increased CSF tau or decreased CSF Aβ42 was not attributed to age, sex, and *APOE* genotype. In addition, AD signature cortical thinning was associated with lower visuospatial performance. Reduced CSF Aβ42 was related to poorer performance on episodic memory.

AD-like brain atrophy parallels amyloidosis in preclinical AD.[2–4] However, the pathophysiologic correlates of Aβ-independent atrophy remain unclear. Our work shows that AD-like neurodegeneration (i.e., AD signature cortical thinning) has a direct relationship with abnormal biomarker of tau pathology. Moreover, the topography of AD signature largely parallels the initiation (entorhinal) and early progression (posterior cingulate and temporal neocortex) of neurofibrillary tangles.[25] This topographic correspondence suggests that the observed CSF tau–cortical atrophy association may reflect tangle-related neurodegeneration in the brain. This finding also indicates that the refined AD signature can detect early neurodegeneration in preclinical AD.

Studies of autopsy[24] and transgenic mice[26] postulate that Aβ mediates the effect of tau on neurodegeneration, with tau-related neurodegeneration more prevalent in individuals with higher Aβ burden than in those with lower Aβ burden. We assessed this theory within the entire cohort but found no significant difference in the association of CSF tau and AD signature cortical thickness with respect to Aβ status (i.e., CSF Aβ42-positive vs CSF Aβ42-negative). A secondary analysis within the CSF tau-positive group showed that a significant association of CSF tau with AD signature cortical thickness was seen in CSF Aβ42-positive but not CSF Aβ42-negative individuals (data not shown). However, the difference in the CSF tau–AD signature association remained nonsignificant regarding Aβ status within the CSF tau-positive group. The present observation may provide some preliminary evidence in support of the view that cortical neurodegeneration results from the synergistic effect of Aβ and tau.[23,24,27] Further work assessing this view with more sensitive and specific measure of tau pathology (e.g., tau imaging tracer) is needed.

Longitudinal studies have observed an accelerating decline in visuospatial ability in CN individuals who subsequently developed AD dementia compared with those who remained cognitively unimpaired.[28] The present result suggests a pathophysiologic correlate for the previous observation by showing that visuospatial decline is explained by subtle cortical neurodegeneration that at least is partly linked to tau pathology. In addition, we observed that lower performance on episodic memory is related to Aβ deposition or hippocampal atrophy, the former consistent with several recent reports[29,30] but not others.[3] Notably, after accounting for each other, the effect of Aβ on memory remained significant while the relationship with hippocampal atrophy was marginal. This result suggests that the impact of Aβ on memory may be independent of its effects on neurodegeneration in CN individuals. The mechanisms underlying observed Aβ-related lower memory performance remain to be explored.

Overall, our data suggest that Aβ and tau are preferentially associated with spatially distinct neurodegeneration during the preclinical phase of AD. Specifically, Aβ deposition alone may be sufficient for the atrophy in the hippocampus but not AD signature regions, which instead is related to tau pathology, or likely the mediation of Aβ on tau. These results not only agree with the emerging view of existence of "Aβ-dependent" and "Aβ-independent" pathways to preclinical AD,[2–4,31–33] but also stress that the spatial distribution of the different pathways needs to be considered. In addition, our work demonstrates that memory and nonmemory domains may be differentially affected by Aβ and neurodegeneration. This result explains several recent observations[27,34] that the joint presence of amyloidosis and neurodegeneration may be required for the emergence of clinical symptoms of AD.

Our work has limitations. We observed the association between higher CSF tau and AD signature cortical thinning after adjusting for age (and other confounders). However, age adjustment may be unable to completely remove the aging effect that is associated with tau pathology and cortical atrophy. Longitudinal studies are needed to estimate the extent to which observed CSF tau-related AD signature atrophy is specific to AD.

AUTHOR CONTRIBUTIONS

L.W.: study concept and design, analysis and interpretation, critical revision of manuscript. T.L.B.: analysis and interpretation, collection of data, study supervision. J.H.: analysis and interpretation, critical revision of manuscript. T.B.: analysis and interpretation. C.O.: analysis and interpretation. J.L.: analysis and interpretation. A.M.F.: analysis and interpretation, collection of data, critical revision of manuscript. J.C.M.: critical revision of manuscript, study supervision. B.M.A.: analysis and interpretation, collection of data, critical revision of manuscript, study supervision.

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DISCLOSURE

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