Published in final edited form as:

Alzheimers Dement. 2020 June ; 16(6): 883–895. doi:10.1002/alz.12087.

Cerebrospinal fluid biomarkers of neurodegeneration, synaptic dysfunction, and axonal injury relate to atrophy in structural brain regions specific to Alzheimer's disease

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Abstract

Introduction: Patterns of atrophy can distinguish normal cognition from Alzheimer's disease (AD), but neuropathological drivers of this pattern are unknown. This study examined associations

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SUPPORTING INFORMATION

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

CONFLICTS OF INTEREST

The other authors declare no competing financial interests.

between cerebrospinal fluid biomarkers of AD pathology, synaptic dysfunction, and neuroaxonal injury with two AD imaging signatures.

Methods: Signatures were calculated using published guidelines. Linear regressions related each biomarker to both signatures, adjusting for demographic factors. Boot-strapped analyses tested if associations were stronger with one signature versus the other.

Results: Increased phosphorylated tau (p-tau), total tau, and neurofilament light (P -values $<.045$) related to smaller signatures (indicating greater atrophy). Diagnosis and sex modified associations between p-tau and neurogranin (P -values $<.05$) and signatures, such that associations were stronger among participants with mild cognitive impairment and female participants. The strength of associations did not differ between signatures.

Discussion: Increased evidence of neurodegeneration, axonopathy, and tau phosphorylation relate to greater AD-related atrophy. Tau phosphorylation and synaptic dysfunction may be more prominent in AD-affected regions in females.

Keywords

AD signature; cerebrospinal fluid; cortical thickness; sex differences

1 | INTRODUCTION

Alzheimer's disease (AD) is traditionally considered a disease of gray matter neurodegeneration, resulting from the accumulation of aggregates of amyloid beta ($A\beta$) and phosphorylated tau (p-tau).¹ As pathology evolves, atrophy occurs in a regionally specific pattern beginning in the temporal lobe and hippocampus² and spreading in concentric circles to the surrounding cortices. Recent efforts have identified magnetic resonance imaging (MRI) patterns of neurodegeneration that are specific to AD-related changes. Two identified patterns (the Schwarz AD signature³ and the McEvoy AD signature⁴) reliably distinguish individuals with normal cognition from clinical AD. However, the neuropathological drivers of this regionally specific atrophy remain uncharacterized.

Prior work has found that neurodegeneration within AD signature regions relates to amyloid deposition,⁵ in vivo cerebrospinal fluid (CSF) measurements of p-tau and total tau (t-tau),⁶ and tau burden at autopsy.³ However, beyond core AD pathology, it is unknown how concomitant pathways to neurodegeneration, such as synaptic dysfunction or axonal injury, relate to atrophy in signature regions. Previous work has implicated neurogranin (reflecting synaptic degeneration when elevated⁷) and neurofilament light (NFL, a marker of neuroaxonal injury when elevated⁸) in AD, and each is associated with smaller hippocampal volumes.^{8,9} Thus, these biomarkers may indicate pathologies that contribute to atrophy detected in the AD signatures. In addition, evidence suggests that AD risk factors, such as female sex,¹⁰ apolipoprotein E (*APOE*) $\epsilon 4$ status,¹¹ and older age,¹² may lead to heterogeneity in AD-related atrophy and must be considered when examining neuropathologic correlates of atrophy. To optimize the diagnostic and prognostic utility of AD signatures, associations of co-occurring pathologies, as well as sex-specific, genetic, and normal aging contributions, to clinically relevant atrophy must be elucidated. It is important to note that examining the molecular drivers of longitudinal change in these regions will

provide critical information regarding how these regions reliably separate individuals with normal cognition (NC) from AD.

The aim of this study is to investigate associations between CSF biomarkers of core AD pathology ($A\beta$, p-tau, and t-tau), synaptic dysfunction (neurogranin), and neuroaxonal degeneration (NFL) with two publicly available AD neuroimaging signatures among older adults.^{3,4} We hypothesize that increased CSF evidence of core AD and concomitant pathologies will relate to cortical thinning in signature regions, consistent with prior work.^{6,13} Given that the imaging signature can differentiate individuals with and without cognitive impairment^{3,4} and the known modifying effects of sex,¹⁰ *APOE* $\epsilon 4$ status,¹¹ and age¹² on neurodegeneration, associations will be tested for interactions with diagnosis, sex, *APOE* $\epsilon 4$ carrier status, and age. We hypothesize that associations between CSF biomarkers and the signature will be stronger in mild cognitive impairment (MCI) participants,⁶ female participants,¹⁰ *APOE* $\epsilon 4$ carriers,¹¹ and older adults (>73).¹² Finally, we formally tested if the pattern of neurodegeneration associated with each CSF biomarker was more strongly related to one AD signature versus the other.

2 | MATERIALS and METHODS

2.1 | Study cohort

The Vanderbilt Memory & Aging Project (VMAP) is a longitudinal observational study investigating vascular health and brain aging,¹⁴ enriched with older adults with MCI. Inclusion required participants be ≥ 60 years, speak English, have adequate auditory and visual acuity, and have a reliable study partner. As part of a comprehensive screening, participants were excluded for a cognitive diagnosis of dementia,^{15,16} magnetic resonance imaging (MRI) contraindication, history of neurological disease (eg, multiple sclerosis, stroke), heart failure, major psychiatric illness, head injury with loss of consciousness >5 minutes, or a systemic or terminal illness affecting follow-up participation. NC was defined as (1) Clinical Dementia Rating (CDR) = 0 (no dementia), (2) no deficits in activities of daily living directly attributable to cognitive impairment, and (3) no evidence of neuropsychological impairment defined as standard scores falling within 1.5 standard deviations (SD) of the age-adjusted normative mean. Early MCI (eMCI) was defined as (1) CDR = 0.5 (reflecting mild severity of impairment), (2) no deficits in activities of daily living attributable to cognitive issues, and (3) no neuropsychological impairment defined as standard scores falling within 1.5 SD of the age-adjusted normative mean.¹⁵ Finally, MCI was defined as (1) CDR = 0 or 0.5 (reflecting mild severity of impairment); (2) relatively spared activities of daily living; (3) neuropsychological impairment within at least one cognitive domain (ie, performances falling >1.5 SD outside the age-adjusted normative mean or pre-morbid level of functioning); (4) concern of a cognitive change by the participant, informant, or clinician; and (5) absence of a dementing syndrome.¹⁶ All but one participant with MCI had an amnesic profile. At enrollment, participants completed a comprehensive examination, including (but not limited to) fasting blood draw, physical examination, clinical interview, medication review, echocardiography, cardiac magnetic resonance, multi-modal brain MRI, and optional lumbar puncture. Participants were excluded from the current study for missing usable CSF, brain MRI, or covariate data. See

Supplementary Figure 1 for inclusion/exclusion details. Serial brain MRI was performed at 18-month, 3-year, and 5-year follow-up (data collection is ongoing for the latter time point). The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained from participants prior to data collection.

2.2 | Lumbar puncture and biochemical analysis

A subset of participants completed an optional fasting lumbar puncture at enrollment (n = 153, Supplementary Figure 1). To minimize adverse events,¹⁷ CSF was collected with polypropylene syringes using a Sprotte 25-gauge spinal needle in an intervertebral lumbar space. Samples were immediately mixed and centrifuged. Supernatants were aliquoted in 0.5 mL polypropylene tubes and stored at -80°C . Samples were analyzed in a single batch using a commercially available enzyme-linked immunosorbent assays (ELISA; Fujirebio, Ghent, Belgium) to measure CSF concentrations of $\text{A}\beta_{42}$ (INNOTEST β -AMYLOID₍₁₋₄₂₎), p-tau (INNOTEST PHOSPHO-TAU_(181P)), and t-tau (INNOTEST hTAU). Additional ELISAs measured CSF neurogranin¹⁸ and CSF NFL (UmanDiagnostics, Umeå, Sweden) concentrations. Board-certified laboratory technicians processed data while blinded to clinical information. Intra-assay coefficients of variation were $<10\%$.¹⁸

2.3 | Brain MRI acquisition and post-processing

VMAP participants were scanned at the Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva system (Best, The Netherlands) using an eight-channel Sensitivity Encoding reception coil array at baseline and 18-month and 3-year follow-up. A 32-channel coil was used for part of 3-year and all of 5-year data collection to date. T1-weighted images (repetition time = 8.9 ms, echo time = 4.6 ms, spatial resolution = $1\times 1\times 1\text{ mm}^3$) were acquired as part of a larger multi-modal protocol and post-processed using FreeSurfer version 5.1.0 (<http://surfer.nmr.mgh.harvard.edu/>).¹⁹ T1-weighted images were registered to Montreal Neurological Institute (MNI) space, intensity corrected, and skull stripped. Subcortical structures, cortical structures, and white matter were segmented, and white and gray matter surfaces were constructed for each hemisphere. These surfaces were used to calculate cortical thickness and inflated for visualization. Surfaces were manually inspected and corrected for registration, topological, and segmentation defects. After manual correction, images were reprocessed to update the transformation template and segmentation information. The Schwarz signature was calculated by summing bilateral cortical thickness measurements from regions shown to distinguish individuals with AD from normal cognition, including the entorhinal cortex, middle temporal cortex, inferior parietal cortex, fusiform gyrus, and precuneus.³ The McEvoy signature was calculated by a weighted sum of volumes and cortical thickness measurements from regions shown to predict conversion to AD, including the hippocampus, entorhinal cortex, middle temporal cortex, superior temporal cortex, cingulate gyrus, and orbitofrontal gyrus.⁴ Consistent with prior literature, contributions of intracranial volume were regressed out of the hippocampal volume term and contributions of age and sex were regressed out of the McEvoy signature.⁴ For both signatures, lower values indicate greater AD-related cortical thinning and atrophy.

2.4 | Experimental design and statistical analyses

APOE $\epsilon 4$ status was defined as carrier ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) or non-carrier ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 3$). For cross-sectional analyses, linear regression models with ordinary least-squares estimates cross-sectionally related baseline continuous CSF measures of $A\beta$, p-tau, t-tau, neurogranin, and NFL concentrations (pg/mL) to each signature value at baseline, adjusting for baseline age, sex, race/ethnicity, education, *APOE* $\epsilon 4$ status, and cognitive diagnosis. Models examining the McEvoy signature also adjusted for intracranial volume to fully account for the hippocampal volume term. Linear regression models also related those CSF biomarkers with significant associations to either signature as competing predictors using identical covariates. This competitive model approach assessed the extent to which variance accounted for by an individual biomarker was unique or overlapping with another biomarker. Secondary models evaluated *CSF biomarker* $\times$ *cognitive diagnosis* (excluding participants with eMCI), *CSF biomarker* $\times$ *sex*, *CSF biomarker* $\times$ *APOE* $\epsilon 4$ status, and *CSF biomarker* $\times$ *age* interactions on the AD signatures. Models were repeated stratified by diagnosis (NC, MCI), sex (male, female), *APOE* $\epsilon 4$ status (carrier, non-carrier), and age group based on the sample median (<73 , ≥ 73). For all cross-sectional models, follow-up bootstrapped analyses of partial correlations tested if the pattern of neurodegeneration associated with each CSF biomarker was more strongly related to one signature versus the other. Post hoc analyses examined biomarker associations in groups stratified by AD biomarker status, within the entire sample and within each diagnostic group (NC and MCI). Amyloid positive was defined as $A\beta_{42} \geq 530$ pg/mL.²⁰ Tau positive was defined as t-tau ≥ 400 pg/mL.²¹

In longitudinal models, linear mixed-effects regressions with random intercepts and slopes and a follow-up time interaction related baseline CSF biomarkers to AD signature trajectory. Models adjusted for baseline age, sex, race/ethnicity, education, diagnosis, *APOE* $\epsilon 4$ status, and follow-up time. Models examining the McEvoy signature also adjusted for baseline intracranial volume to fully account for the hippocampal volume term. Secondary models evaluated *CSF biomarker* $\times$ *cognitive diagnosis*, *CSF biomarker* $\times$ *sex*, *CSF biomarker* $\times$ *APOE* $\epsilon 4$ status, and *CSF biomarker* $\times$ *age* interactions on the trajectory of the AD signatures. Longitudinal models were repeated stratified by diagnosis (NC, MCI), sex (male, female), *APOE* $\epsilon 4$ status (carrier, non-carrier), and age group based on the sample median (<73 , ≥ 73).

Post hoc power calculations for the *CSF biomarker* $\times$ *sex* interaction models and models stratified by sex were conducted using an F distribution based on increased R^2 for a model that included the predictor plus covariates. Based on the available sample sizes for each comparison and type I error of 0.05, we calculated the minimum increased R^2 we were able to detect with 80% power given the total R^2 accounted for across models. Multiple comparison correction was performed using a false discovery rate. The threshold for statistical significance was set *a priori* at $P < .05$. For all significant models, sensitivity analyses were performed repeating models excluding participants with predictor or outcome values >4 SD from the group mean. Analyses were conducted using R version 3.5.2 (www.r-project.org).

3 | RESULTS

3.1 | Participant characteristics

Participants included 153 adults ages 60 to 92 (mean age $\pm$ SD 72 ± 6 years, 67% male, 93% non-Hispanic White, 33% *APOE* $\epsilon 4$ carriers). The mean follow-up time was 3.4 years and 17% of MCI participants with a CDR of 0.5 at baseline converted over the follow-up period. The average time between baseline MRI and baseline CSF acquisition was 37 days. See Table 1 for participant characteristics for the entire sample and stratified by diagnosis. See Supplementary Table 1 for participants characteristics stratified by sex.

3.2 | CSF biomarkers and the AD signatures

Among all participants, higher CSF t-tau ($\beta = -0.0001$, $P = .005$) and NFL concentrations ($\beta = -0.0001$, $P = .001$) were associated with smaller Schwarz signature values, indicating thinner cortices. Higher CSF p-tau ($\beta = -0.0159$, $P = .05$), t-tau ($\beta = -0.0027$, $P = .003$), and NFL concentrations ($\beta = -0.0014$, $P < .001$) were associated with smaller McEvoy signature values. See Table 2 and Figure 1 for details. Sensitivity models excluding outliers yielded similar results (data not shown). In bootstrapped analyses, the variance explained by CSF p-tau (95% confidence interval [CI] -0.03 , 0.03), t-tau (95% CI -0.04 , 0.03), and NFL (95% CI -0.05 , 0.02) on the Schwarz signature was not statistically different from the variance explained for the McEvoy signature for each biomarker. See Supplementary Table 2 for details.

In longitudinal models, lower CSF A β ($\beta = 0.0006$, $P < .001$), higher CSF p-tau ($\beta = -0.0034$, $P = .04$), and higher t-tau levels ($\beta = -0.0005$, $P = .01$) at baseline were associated with a greater rate of cortical thinning in the McEvoy AD signature. See Supplementary Table 3 for details.

3.3 | CSF biomarkers as competing predictors of atrophy in AD signature regions

To determine whether the CSF biomarkers represent a common pathological pathway to atrophy in AD signature regions, a linear regression model was fit including all statistically significant CSF biomarker predictors for each signature. For the Schwarz signature, higher CSF NFL remained associated with lower Schwarz signature values ($\beta = -0.00005$, $P = .01$), whereas the association with CSF t-tau was slightly attenuated ($\beta = -0.0001$, $P = .09$). See Supplementary Table 4 for details. The addition of CSF NFL to the model contributed 5.6% of variance beyond covariates and the addition of CSF t-tau contributed 3.6% of variance beyond covariates. Together, CSF NFL and t-tau contributed 6.4% of variance beyond covariates.

For the McEvoy signature, higher CSF NFL ($\beta = -0.0009$, $P = .02$) remained associated with lower McEvoy signature values in a combined model with t-tau. Similarly, when CSF NFL was combined with p-tau, only NFL remained associated with McEvoy signature values ($\beta = -0.0011$, $P = .006$). See Supplementary Table 4 for details. The addition of CSF NFL to the model contributed 4.6% of variance beyond covariates, the addition of CSF t-tau contributed 4.0% of variance beyond covariates, and the addition of CSF p-tau contributed

1.1% of variance beyond covariates. Together, CSF NFL, t-tau, and p-tau contributed 13.6% of variance beyond covariates.

3.4 | CSF biomarkers × cognitive diagnosis interactions and the AD signatures

CSF p-tau ($P = .002$), t-tau ($P = .003$), and neurogranin ($P = .03$) interacted with cognitive diagnosis on the Schwarz signature. In stratified analyses, higher CSF p-tau ($\beta = -0.0016$, $P = .009$), t-tau ($\beta = -0.0002$, $P = .002$), and NFL ($\beta = -0.0001$, $P = .001$) were associated with smaller Schwarz signature values among MCI participants only. p-tau ($P < 0.001$), t-tau ($P < .001$), and neurogranin ($P = .03$) interacted with cognitive diagnosis on the McEvoy signature. Similarly, stratified analyses revealed that higher CSF p-tau ($\beta = -0.0323$, $P = .01$), t-tau ($\beta = -0.0042$, $P = .002$), and NFL ($\beta = -0.0014$, $P = .007$) were associated with smaller McEvoy AD signature values among MCI participants only. See Table 3 for details. Sensitivity models excluding outliers yielded similar results (data not shown). In bootstrapped analyses, associations did not substantially differ in variance explained between the two signatures. See Supplementary Table 2 for details.

In longitudinal analyses, no CSF biomarker interacted with diagnosis on either AD signature trajectory. In stratified analyses, higher CSF t-tau ($\beta = -0.0006$, $P = .04$) at baseline related to a greater rate of cortical thinning in the McEvoy signature in individuals with MCI only. See Supplementary Table 5 for details. All stratified analyses restricted to MCI participants were repeated excluding the participant with non-amnesic MCI, yielding similar results (data not shown).

3.5 | CSF biomarkers × sex interactions and the AD signatures

CSF p-tau ($P = .05$) and neurogranin ($P = .04$) interacted with sex on the Schwarz AD signature. Stratified models revealed that higher CSF p-tau ($\beta = -0.0011$, $P = .04$) and t-tau ($\beta = -0.0001$, $P = .01$) related to lower Schwarz signature values in female participants only, whereas the association with neurogranin approached significance ($\beta = -0.0005$, $P = .06$). CSF neurogranin interacted with sex on the McEvoy signature ($P = .05$), such that associations were driven by female participants only ($\beta = -0.0067$, $P = .11$). Stratified analyses also revealed that higher CSF t-tau ($\beta = -0.0028$, $P = .03$) related to lower McEvoy AD signature values in female participants only. See Table 4 and Figure 2 for details. Sensitivity models excluding outliers yielded similar results (data not shown). In bootstrapped analyses, associations did not substantially differ in variance explained between the two signatures. See Supplementary Table 2 for details.

Using a threshold of $R^2 = 0.2$ for the interaction models, $R^2 = 0.4$ for the female stratified group, and $R^2 = 0.1$ for the male stratified group, calculations suggest we had 80% power to detect an increased R^2 in each AD signature outcome of 0.042–0.043 in the interaction models, 0.099–0.105 in female participants only, and 0.070–0.071 in male participants only. As an example, we had 80% power to detect 4.2% of the variance in the AD signatures explained by the CSF p-tau × sex interaction term given a total model R^2 estimate of 0.2. Variance of 4.2% in the AD signatures is relatively small, suggesting that we were powered to detect an interaction effect. In females only, we had 80% power to detect 9.9% of the variance in the AD signatures explained by CSF p-tau given a total model R^2 estimate of

0.4. Variance of 9.9% in the AD signatures is a large effect size, suggesting that we were underpowered to detect more robust female-specific effects.

In longitudinal analyses, no CSF biomarker interacted with sex on either AD signature trajectory. In stratified analyses, increased CSF p-tau ($\beta = -0.0055$, $P = .02$) and CSF t-tau ($\beta = -0.0006$, $P = .02$) at baseline related to a greater rate of cortical thinning in the McEvoy signature in female participants only. Lower baseline CSF A β related to a greater rate of cortical thinning in the McEvoy signature in both male ($\beta = 0.0005$, $P = .02$) participants. See Supplementary Table 6 for details.

3.6 | CSF biomarkers $\times$ *APOE* $\epsilon 4$ status interactions and the AD signatures

No CSF biomarker interacted with *APOE* $\epsilon 4$ status on either AD signature (P -values $> .18$). In models stratified by *APOE* $\epsilon 4$ status, higher CSF t-tau ($\beta = -0.0001$, $P = .02$) and NFL ($\beta = -0.0001$, $P = .006$) related to smaller Schwarz signature values among *APOE* $\epsilon 4$ non-carriers. CSF NFL ($\beta = -0.0014$, $P = .0001$) also related to smaller McEvoy signature values among *APOE* $\epsilon 4$ non-carriers. See Supplementary Table 7 for details. Sensitivity models excluding outliers yielded similar results (data not shown). In bootstrapped analyses, associations did not differ in variance explained between the two signatures. See Supplementary Table 2 for details.

In longitudinal models, baseline CSF p-tau (Schwarz $\beta = -0.0005$, $P = .002$; McEvoy $\beta = -0.0073$, $P = .02$), CSF t-tau (Schwarz $\beta = -0.0001$, $P = .001$; McEvoy $\beta = -0.0009$, $P = .01$), CSF neurogranin (Schwarz $\beta = -0.0002$, $P = .007$; McEvoy $\beta = -0.0026$, $P = .03$), and CSF NFL (Schwarz $\beta = -0.00002$, $P = .03$; McEvoy $\beta = -0.0004$, $P = .04$) interacted with *APOE* $\epsilon 4$ status on both AD signatures. CSF A β also interacted with the Schwarz AD signature ($\beta = 0.0001$, $P = .008$) and the McEvoy AD signature ($\beta = 0.0009$, $p = 0.05$). In stratified models, lower CSF A β (Schwarz $\beta = 0.0001$, $P = .05$; McEvoy $\beta = 0.0010$, $P = .05$) and higher CSF p-tau (Schwarz $\beta = -0.0004$, $P = .02$; McEvoy $\beta = -0.0063$, $p = 0.05$), CSF t-tau (Schwarz $\beta = -0.00004$, $P = .02$; McEvoy $\beta = -0.0007$, $P = .02$), and CSF neurogranin (Schwarz $\beta = -0.0001$, $P = .05$) related to a greater rate of cortical thinning in the AD signatures in *APOE* $\epsilon 4$ carriers only. Higher CSF NFL at baseline related to less cortical thinning in the Schwarz AD signature in *APOE* $\epsilon 4$ non-carriers only ($\beta = 0.00001$, $P = .04$). See Supplementary Table 8 for details.

3.7 | CSF biomarkers $\times$ age interactions and the AD signatures

No CSF biomarker interacted with age on either AD signature (P -values $> .10$). However, stratified analyses revealed that higher CSF t-tau ($\beta = -0.0001$, $P = .04$) and NFL ($\beta = -0.0001$, $P = .02$) related to lower Schwarz signature values among individuals over age 73. Similarly, higher CSF t-tau ($\beta = -0.0031$, $P = .02$) and NFL ($\beta = -0.0013$, $P = .004$) related to lower McEvoy signature values among individuals over age 73. See Supplementary Table 9 for details. Sensitivity models excluding outliers yielded similar results (data not shown). In bootstrapped analyses, associations did not differ in variance explained between the two signatures. See Supplementary Table 2 for details.

In longitudinal models, no CSF biomarker interacted with age on either AD signature (P -values $> .37$). However, in stratified models, increased CSF t-tau at baseline related to a

greater rate of cortical thinning in the McEvoy signature in individuals under 73 ($\beta = -0.0005$, $P = .04$). Lower baseline CSF A β also related to a greater rate of cortical thinning in the McEvoy signature in individuals both younger ($\beta = 0.0006$, $P = .03$) and older than 73 ($\beta = 0.0006$, $P = .02$). See Supplementary Table 10 for details.

3.8 | CSF biomarkers and AD signatures, stratified by biomarker status

Among amyloid-positive individuals, higher CSF t-tau ($\beta = -0.0002$, $P = .008$) and CSF NFL ($\beta = -0.0001$, $P = .03$) related to lower Schwarz signature values. Higher CSF p-tau ($\beta = -0.0285$, $P = .02$) and CSF t-tau ($\beta = -0.0036$, $P = .006$) related to lower McEvoy signature values. Among amyloid-negative individuals, higher CSF NFL related to lower Schwarz ($\beta = -0.00004$, $P = .05$) and McEvoy ($\beta = -0.0011$, $P = .008$) signature values. Among tau-positive individuals, higher CSF t-tau ($\beta = -0.0001$, $P = .05$) and CSF NFL ($\beta = -0.0001$, $P = .007$) related to smaller Schwarz signature values. Higher CSF NFL related to smaller McEvoy signature values ($\beta = -0.0016$, $P = .007$). Among tau-negative individuals, higher CSF NFL related to smaller Schwarz ($\beta = -0.0005$, $P = .04$) and McEvoy ($\beta = -0.0012$, $P = .01$) signature values. See Supplementary Tables 11 and 12 for details. Results stratified by biomarker status within each diagnostic group are presented in Supplementary Tables 13–16.

4 | DISCUSSION

Among community-dwelling older adults, higher concentrations of CSF p-tau, t-tau, and NFL were associated with lower AD signature values, indicating greater atrophy in gray matter regions affected by AD pathology. As expected, cognitive diagnosis modified the associations between CSF p-tau, t-tau, and neurogranin and AD signature values, such that associations were stronger among participants with MCI. Sex also modified associations between CSF p-tau and neurogranin and AD signature values, such that associations were stronger in females. Collectively, results suggest that CSF biomarkers of p-tau, t-tau, synaptic dysfunction, and neuroaxonal injury are associated with AD-related atrophy measured on MRI, and p-tau and synaptic dysfunction associations may be more prominent in AD-specific regions in females.

This study is among the first to show associations linking in vivo molecular biomarkers, indicating greater core AD and concomitant pathologies, with atrophy in AD-specific regions. As expected, higher levels of CSF p-tau and t-tau are associated with cross-sectional and longitudinal atrophy in the AD signatures among participants both with NC and MCI, extending prior cross-sectional work focusing only on individuals with MCI.^{3,6} As tau becomes more phosphorylated, it is no longer able to bind to microtubules within the axon,²² compromising its ability to maintain cell structure and leading to cell death.²³ In addition, it is well established that tau tangles first develop in anatomical regions included in the AD signatures.²⁴ Thus, increased levels of CSF p-tau and t-tau may indicate clinically relevant atrophy in AD-specific regions. Despite that previous work demonstrating A β relates to cortical thinning in AD signature regions,⁵ we did not detect an association between CSF A β and AD-related atrophy. It is notable that this prior study included individuals with clinical

AD, suggesting that $A\beta$ may not contribute to neurodegeneration in these regions until later disease states.

We also found an association between CSF NFL, a biomarker of neuroaxonal degeneration,²⁵ and AD-related atrophy. It is important to note that CSF NFL explained variance in the AD signatures beyond that of CSF p-tau or t-tau, suggesting that neuroaxonal injury uniquely contributes to atrophy in these regions. NFL is a support protein within large axons²⁶ that is released into the CSF in a variety of pathological states, including vascular disease,²⁷ inflammation,²⁸ and neurodegeneration.⁸ Regions included in the AD signatures, such as the entorhinal cortex and hippocampus, are vulnerable to ischemic small vessel disease²⁹ and chronic inflammation,^{30,31} possibly contributing to axonopathy in these regions. Although increased CSF NFL is not specific to AD, as supported by the null longitudinal findings, neuroaxonal degeneration does cross-sectionally contribute to AD-related atrophy, highlighting the importance of pathologies other than $A\beta$ and tau in the development of AD-related atrophy and neuroaxonal injury as a potential therapeutic target in AD.

Results suggest that diagnosis modifies CSF p-tau, t-tau, and neurogranin associations with the AD signatures, such that associations are only present in participants with MCI. These findings are consistent with prior work showing that CSF p-tau, t-tau,³² and neurogranin³³ are elevated in individuals with MCI, likely leading to greater MRI evidence of neurodegeneration in AD-specific regions. Notably, although neurogranin was not associated with either AD signature among the entire sample, the diagnostic interaction and stratified results suggest that increased CSF neurogranin has a greater contribution to AD-related atrophy in MCI compared to NC participants. Neurogranin is a post-synaptic protein prominent in the hippocampus³⁴ critical for long-term potentiation and synaptic plasticity.³⁵ In early stages of AD, synapses become disrupted and misfire, leading to neurogranin degradation in the tissue and increased leakage or secretion into the CSF.³⁶ As synaptic dysfunction begins prior to overt tau tangle formation,³³ apoptotic cascades are initiated,³⁷ followed by neurodegeneration and cognitive impairment.³⁸ Given the importance and relative overexpression of neurogranin in regions vulnerable to AD pathology,^{36,39} synaptic dysfunction in MCI, indicated by increased CSF neurogranin, may be an etiology underlying AD-related atrophy. CSF neurogranin is also elevated in conditions other than AD, such as stroke,⁴⁰ suggesting synaptic dysfunction may serve as an alternative pathway by which vascular disease contributes to AD-related atrophy.

We found that sex modifies CSF p-tau and neurogranin associations with the AD signatures, such that cross-sectional and longitudinal associations are more prominent in females. Although the interaction is not statistically significant, stratified results suggest that associations between CSF t-tau and the AD signatures are also female specific. This observation is consistent with prior work showing that the association between CSF t-tau and hippocampal volume is stronger in females.¹⁰ Although others have shown that atrophy in AD signature regions distinguishes NC from AD in both males and females,^{3,4} our results suggest that the underlying pathology may differ. Estrogen is protective of tau hyperphosphorylation⁴¹ and modulates dendritic spine density in the hippocampus,^{42,43} so the decline in estrogen in aging females may lead to increased p-tau, synaptic dysfunction,

and subsequent neurodegeneration. In addition, women generally have fewer synapses in the temporal lobe,⁴⁴ suggesting that a given degree of synaptic dysfunction in aging in the temporal lobe may exert a much greater effect on neuronal health in women compared to men. Thus, p-tau and synaptic dysfunction may be more prominent etiologies of AD-related atrophy in women, adding to the growing body of literature showing sex differences in pathology and structural brain changes in AD.^{10,45} Notably, sex-specific findings were still present for the McEvoy signature despite regressing out the statistical effects of sex when deriving this variable, highlighting the importance of critically examining sex differences in future work. Of interest, CSF NFL did not interact with sex on either AD signature, despite men having higher concentrations. It is possible that the effect of axonal injury on atrophy is more robust than other pathologies,³⁸ such that any sex-specific drivers of neuroaxonal injury are not strong enough to alter the association with atrophy. Future work is needed to better understand the mechanisms underlying sex-specific associations reported here and elsewhere.^{10,45,46}

APOE $\epsilon 4$ status did not modify cross-sectional associations but did modify longitudinal associations between CSF biomarkers and the AD signatures. *A β* , p-tau, and t-tau related to greater rates of cortical thinning in AD signature regions in *APOE* $\epsilon 4$ carriers only. *APOE* $\epsilon 4$ is implicated in synaptic dysfunction, possibly conferring tissue vulnerability such that the tissue is less resistant to the neurodegenerative effects of pathology over time. More work is needed to explore how *APOE* $\epsilon 4$ leads to neurodegeneration in AD. In addition, age did not modify any of the cross-sectional or longitudinal associations. Similarly, stratified results suggest that CSF *A β* and t-tau are associated with greater cortical thinning in individuals younger than 73 years. Although older individuals likely have greater pathological burden, older individuals also likely have more age-related processes contributing to widespread neurodegeneration, possibly obscuring associations between CSF biomarkers of pathology and cortical thinning in AD signature regions.

Finally, one observation worth noting is that none of the associations reported here were significantly different between the Schwarz³ and McEvoy⁴ signatures. Despite the McEvoy signature including hippocampal volume and cortical thickness measurements that differ from the brain regions in the Schwarz signature, the two measures do not provide different information regarding the CSF biomarkers assessed here. That is, one signature is not more sensitive to detecting atrophy associated with AD pathology, synaptic dysfunction, or axonopathy compared to the other. Future research is needed to further delineate differences in the two signatures (and others not examined here^{47–49}) and determine if specific regions within the signatures are more or less vulnerable to certain pathologies.

The current study has several strengths, including a clinically well-characterized cohort with excellent methods for quantifying cortical thickness and CSF biomarkers of AD and concomitant pathology. Additional strengths include comprehensive ascertainment of potential confounders, a comprehensive investigation of concomitant pathways to neurodegeneration beyond primary AD pathology, and the use of core laboratories using quality control procedures to analyze all CSF and brain MRI measurements in batch with technicians blinded to participant clinical information. However, limitations include the cross-sectional methods, which cannot address causality. Longitudinal studies are needed to

understand how AD pathology, synaptic dysfunction, and axonal injury affect AD-related neurodegeneration over time. When a false discovery rate was applied to correct for multiple comparisons, some of our observations did not persist, raising the possibility of a false-positive finding and emphasizing the need for replication. In addition, the cohort was older and predominantly non-Hispanic white, thus limiting generalizability to other races, ethnicities, and age groups.

This study demonstrates novel associations linking CSF biomarkers of AD pathology and axonopathy with atrophy in regions vulnerable to AD-related neurodegeneration. In addition, sex-modified associations, such that p-tau, t-tau, and neurogranin were associated with AD-related atrophy in females only. These findings suggest that synaptic dysfunction driving AD-related neurodegeneration and neuronal death may be more prominent in these regions in females. Future research is needed to better understand how these pathologies regionally interact to precipitate cognitive decline and sex-specific etiologies of neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors would like to thank the dedicated Vanderbilt Memory & Aging Project participants, their loved ones, and the devoted staff and trainees who contributed to recruitment, screening, and enrollment of the baseline cohort. The authors would also like to thank the dedicated and skilled laboratory technicians at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Sweden, who performed all the CSF analyses.

FUNDING INFORMATION

This research was supported by Alzheimer's Association IIRG-08-88733 (ALJ); National Institutes of Health, Grant/Award Numbers: R01-AG034962 (ALJ), R01-NS100980 (ALJ), R01-AG056534 (ALJ), T32-AG058524 (ALJ), K24-AG046373 (ALJ), R21-AG059941 (TJH), Paul B. Beeson Career Development Award in Aging K23-AG045966 (KAG), K23-AG030962 (ALJ), K01-AG049164 (TJH), F30-AG064847 (EEM), T32-GM007347 (EEM), UL1-TR000445 (Vanderbilt Clinical Translational Science Award), S10-OD023680 (Vanderbilt's High-Performance Computer Cluster for Biomedical Research); and the Vanderbilt Memory & Alzheimer's Center. KB holds the Torsten Söderberg Professorship in Medicine at the Royal Swedish Academy of Sciences, and is supported by the Swedish Research Council (2017-00915, 2018-02532), the Swedish Alzheimer Foundation (AF-742881), Hjärfonden, Sweden (#FO2017-0243), and a grant (#ALFGBG-715986) from the Swedish state under the agreement between the Swedish government and the County Councils, Grant/Award Numbers: ALFGBG-715986, ALFGBG-720931, the ALF-agreement. HZ is a Wallenberg Academy Fellow supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (681712), the Swedish State Support for Clinical Research (#ALFGBG-720931), and the UK Dementia Research Institute at UCL; UK Dementia Research Institute at UCL; Hjärfonden Sweden, Grant/Award Number: FO2017-0243.

KB has served as a consultant or at advisory boards for Alector, Biogen, CogRx, Lilly, MagQu, Novartis, and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. HZ has served at scientific advisory boards for Roche Diagnostics, Samumed, CogRx, and Wave; has given lectures in symposia sponsored by Biogen and Alzecure; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg.

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HIGHLIGHTS

- Cerebrospinal fluid (CSF) tau and neurofilament light relate to atrophy in AD-affected regions
- Phosphorylated tau and neurogranin relate to AD-specific atrophy in females only
- Neuronal dysfunction may be more prominent in AD-affected regions in females

RESEARCH IN CONTEXT

1. **Systematic Review:** The authors used PubMed to review literature related to Alzheimer's disease (AD) neuroimaging signatures. Prior work has identified certain patterns of brain atrophy on magnetic resonance imaging (MRI) that distinguish individuals with normal cognition from clinical AD, but the neuropathological drivers of this atrophy pattern are unknown.
2. **Interpretation:** Cerebrospinal fluid (CSF) biomarkers of phosphorylated tau, total tau, and neuroaxonal injury relate to atrophy in AD signature regions. Sex modifies phosphorylated tau and neurogranin associations with the AD signatures. Results suggest that neuronal dysfunction may be more prominent in these regions susceptible to AD-related neurodegeneration among females.
3. **Future Directions:** Understanding pathologies underlying AD-related atrophy and sex differences in these pathologies will help optimize the diagnostic and prognostic utility of the AD neuroimaging signatures. Future research is needed to better understand how these pathologies regionally interact to precipitate cognitive decline and sex-specific etiologies of neurodegeneration.

FIGURE 1.

CSF Biomarker Associations with the AD Signature. Solid lines reflect values of the AD signature corresponding to CSF biomarkers. Shading reflects 95% confidence interval. (A) Associations between CSF p-tau and the AD signatures; (B) associations between CSF t-tau and the AD signatures; (C) associations between CSF NFL and the AD signatures. AD, Alzheimer's disease; CSF, cerebrospinal fluid; NFL, neurofilament light; p-tau, phosphorylated tau; t-tau, total tau

FIGURE 2.

CSF Biomarker $\times$ Sex Interactions with the AD Signatures. Lines reflect values of the AD signatures corresponding to CSF biomarkers. Shading reflects 95% confidence interval. (A) Associations between CSF p-tau and the Schwarz AD signature, stratified by sex; male $\beta = -0.0004$, $P = .44$; female $\beta = -0.0011$, $P = .04$. (B) Associations between CSF neurogranin and the Schwarz AD signature, stratified by sex; male $\beta = -0.00002$, $P = .91$; female $\beta = -0.0004$, $P = .06$. (C) Associations between CSF neurogranin and the McEvoy AD

signature, stratified by sex; male $\beta = -0.0009$, $P = .78$; female $\beta = -0.0073$; $P = .04$; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau

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Participant characteristics

TABLE 1

Demographic characteristics	Total n = 153	NC n = 82	eMCI n = 15	MCI n = 56	P-value
Age, years	72 ± 6	72 ± 7	73 ± 6	73 ± 6	.90
Sex, % male	67	70	80	61	.30
Race, % non-Hispanic white	93	94	93	91	.82
Education, years	16 ± 3	17 ± 2	16 ± 3	15 ± 3	.002*
APOE ε4, % carrier	33	28	13	45	.03
Schwarz AD signature, mm ²	2.3 ± 0.13	2.3 ± 0.12	2.3 ± 0.09	2.2 ± 0.14	<.001, [†]
McEvoy AD signature	-0.85 ± 2.6	-0.09 ± 2.1	-0.76 ± 2.4	-1.99 ± 2.9	<.001, [†]
Time between MRI and CSF acquisition, days	37 ± 41	35 ± 42	31 ± 23	40 ± 43	.67
CSF biomarkers, pg/mL					
Aβ	718 ± 245	765 ± 226	817 ± 282	622 ± 234	<.001, [†]
p-tau	61 ± 26	56 ± 22	63 ± 17	67 ± 31	.06
t-tau	425 ± 227	373 ± 175	429 ± 125	500 ± 290	.02*
Neurogranin	196 ± 77	185 ± 74	213 ± 73	206 ± 82	.21
Neurofilament light	1070 ± 582	939 ± 453	1088 ± 465	1250 ± 718	.004*

Note. Values denoted as mean ± standard deviation or frequency. P-values were generated using a Kruskal-Wallis test for continuous variables and a Pearson test for categorical variables.

AD, Alzheimer's disease; APOE, apolipoprotein E gene; Aβ, amyloid beta; CSF, cerebrospinal fluid; eMCI, early MCI; MCI, mild cognitive impairment; NC, normal cognition; p-tau, phosphorylated tau; t-tau, total tau.

* NC is different than MCI.

[†] eMCI is different than MCI.

TABLE 2

CSF Biomarker associations with the AD signatures

	β	95% Confidence intervals	P-value
Schwarz AD signature			
A β	0.00004	−0.00005, 0.0001	.36
p-tau	−0.0008	−0.0015, 0.00003	.06
t-tau	−0.0001	−0.0002, −0.00004	.005 [*]
Neurogranin	−0.0002	−0.0004, 0.0001	.23
NFL	−0.00006	−0.0001, −0.00002	.001 [*]
McEvoy AD signature			
A β	0.0013	−0.0008, 0.0033	.22
p-tau	−0.0159	−0.0316, −0.0002	.05
t-tau	−0.0027	−0.0045, −0.0010	.003 [*]
Neurogranin	−0.0037	−0.0086, 0.0013	.14
NFL	−0.0014	−0.0021, −0.0006	<.001 [*]

Note. Models were adjusted for age, sex, education, race/ethnicity, diagnosis, and *APOE* ϵ 4 status. Models examining the McEvoy AD signature were also covaried for intracranial volume. An additional five participants were excluded from the CSF NFL analyses. β Indicates the degree of change in volume of AD signature per 1 pg/mL increase in each CSF biomarker.

AD, Alzheimer's disease; *APOE*, apolipoprotein E gene; A β , amyloid beta; NFL, neurofilament light; p-tau, phosphorylated tau; t-tau, total tau.

^{*} Indicates P-values that would survive a false discovery rate correction for multiple comparisons.

TABLE 3

CSF biomarker $\times$ diagnosis interactions on the AD signatures

	CSF biomarker $\times$ diagnosis interaction n = 138 ^d				NC n = 82 ^b				MCI n = 56 ^b			
	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
Schwarz AD signature												
A β	0.0002	-0.00003, 0.0003	.10	0.00004	-0.0001, 0.0002	.53	0.0001	-0.0001, 0.0003	.47	0.0001	-0.0001, 0.0003	.47
p-tau	-0.0025	-0.0041, -0.0009	.002 *	0.0004	-0.0008, 0.0016	.51	-0.0016	-0.0027, -0.0004	.009 *	-0.0016	-0.0027, -0.0004	.009 *
t-tau	-0.0003	-0.0005, 0.0001	.003 *	0.00003	-0.0001, 0.0002	.73	-0.0002	-0.0003, 0.0001	.002 *	-0.0002	-0.0003, 0.0001	.002 *
Neurogranin	-0.0006	-0.0011, -0.0001	.03 *	0.0001	-0.0003, 0.0004	.63	-0.0003	-0.0008, 0.0002	.19	-0.0003	-0.0008, 0.0002	.19
NFL	-0.0001	-0.0001, 0.00001	.11	-0.00001	-0.0001, 0.0001	.74	-0.0001	-0.0001, -0.00003	.001 *	-0.0001	-0.0001, -0.00003	.001 *
CSF biomarker $\times$ diagnosis interaction n = 138 ^d												
McEvoy AD signature												
A β	0.0035	-0.0002, 0.0072	.06	0.0013	-0.0011, 0.0038	.29	0.0029	-0.0016, 0.0074	.21	0.0029	-0.0016, 0.0074	.21
P-tau	-0.0541	-0.0851, -0.0231	.001 *	0.0102	-0.0119, 0.0323	.36	-0.0323	-0.0574, -0.0071	.01 *	-0.0323	-0.0574, -0.0071	.01 *
T-tau	-0.006	-0.0010, -0.0027	.001 *	0.0009	-0.0019, 0.0037	.52	-0.0042	-0.0068, -0.0016	.002 *	-0.0042	-0.0068, -0.0016	.002 *
Neurogranin	-0.0111	-0.0213, -0.0010	.03 *	0.0006	-0.0057, 0.0070	.84	-0.0057	-0.0154, 0.0040	.24	-0.0057	-0.0154, 0.0040	.24
NFL	-0.0086	-0.0024, 0.0007	.27	-0.0006	-0.0019, 0.0007	.34	-0.0015	-0.0025, -0.0004	.007 *	-0.0015	-0.0025, -0.0004	.007 *

AD, Alzheimer's disease; A β , amyloid beta; APOE, apolipoprotein E gene; CI, confidence interval; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NC, normal cognition; NFL, neurofilament light; p-tau, phosphorylated tau; t-tau, total tau.

^aNote: Models were adjusted for age, sex, education, race/ethnicity, diagnosis, and APOE ϵ 4 status.

^bModels were adjusted for age, sex, education, race/ethnicity, and APOE ϵ 4 status. Models examining the McEvoy AD signature were also covaried for intracranial volume. An additional five participants were excluded from the CSF NFL analyses. β Indicates the degree of change in volume per 1 pg/mL increase in each CSF biomarkers.

* Indicates P-values that would survive a false discovery rate correction for multiple comparisons.

TABLE 4

CSF biomarker $\times$ sex interactions on the AD signatures

	CSF biomarker $\times$ sex interaction n = 153 ^a				Female n = 50 ^b				Male n = 103 ^b			
	β	95% CI	P-value		β	95% CI	P-value		β	95% CI	P-value	
Schwarz AD signature												
A β	0.0001	-0.00005, 0.0003	.14		0.00003	-0.0001, 0.0002	.73		0.00007	-0.00005, 0.0002	.26	
p-tau	-0.0015	-0.0030, -0.000001	.05		-0.0011	-0.0022, -0.0001	.04		-0.0004	-0.0015, 0.0007	.44	
t-tau	-0.0001	-0.0003, 0.00002	.08		-0.0001	-0.0003, -0.00003	.01		-0.0001	-0.0002, 0.00004	.16	
Neurogranin	-0.0005	-0.0011, -0.00003	.04		-0.0004	-0.0008, 0.00002	.06		-0.00003	-0.0003, 0.0003	.99	
NFL	-0.00004	-0.0001, 0.00003	.26		-0.0001	-0.0001, -0.00001	.02		-0.0001	-0.0001, -0.00002	.005*	
CSF biomarker $\times$ sex interaction n = 153 ^a												
McEvoy AD signature												
A β	0.0030	-0.0004, 0.0071	.05		0.0004	-0.0042, 0.0050	.86		0.0018	-0.0005, 0.0041	.13	
p-tau	-0.0281	-0.0579, 0.0018	.06		-0.0210	-0.0438, 0.0019	.07		-0.0100	-0.0304, 0.0119	.39	
t-tau	-0.0030	-0.0064, 0.0003	.08		-0.0028	-0.0052, -0.0003	.03*		-0.0019	-0.0046, 0.0007	.14	
Neurogranin	-0.0098	-0.0200, -0.0001	.05		-0.0067	-0.0149, -0.0016	.11		-0.0007	-0.0070, 0.0056	.82	
NFL	-0.0007	-0.0021, 0.0008	.36		-0.0015	-0.0028, -0.0001	.04*		-0.0014	-0.0022, 0.0005	.001*	

AD, Alzheimer's disease; A β , amyloid beta; APOE, apolipoprotein E gene; CI, confidence interval; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NFL, neurofilament light; p-tau, phosphorylated tau; t-tau, total tau.

^aNote: Models were adjusted for age, sex, education, race/ethnicity, diagnosis, and APOE ϵ 4 status.

^bModels were adjusted for age, education, race/ethnicity, diagnosis, and APOE ϵ 4 status. Models examining the McEvoy AD signature were also covaried for intracranial volume. An additional five participants were excluded from the CSF NFL analyses, indicates the degree of change in volume per 1 pg/mL increase in each CSF biomarkers.

* Indicates *P*-values that would survive a false discovery rate correction for multiple comparisons.