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Associations of Neurodegeneration Biomarkers in Cerebrospinal Fluid with markers of Alzheimer's Disease and Vascular Pathology

Dror Shir[a], **Michelle M. Mielke**[b,e], **Ekaterina I. Hofrenning**[b], **Timothy G. Lesnick**[b], **David S. Knopman**[a], **Ronald C. Petersen**[a,b], **Clifford R. Jack Jr**[c], **Alicia Algeciras-Schimnich**[d], **Prashanthi Vemuri**[c], **Jonathan Graff-Radford**[a]

[a]Department of Neurology, Mayo Clinic, Rochester, Minnesota 55905, USA

[b]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota 55905, USA

[c]Department of Radiology, Mayo Clinic, Rochester, Minnesota 55905, USA

[d]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota 55905, USA

[e]Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina, 27101

Abstract

Corresponding Author: Dr. Jonathan Graff-Radford, Department of Neurology, Mayo Clinic, 200 First Street, SW, Rochester, Minnesota 55905, USA. Telephone: 507-284-2111, Graff-radford.jonathan@mayo.edu.

Conflict of Interest

M.M. Mielke served as a consultant to Brain Protection Company, Biogen, and LabCorp and receives research support from the National Institutes of Health and the Department of Defense. She is a Senior Associate Editor for Alzheimer's and Dementia: The Journal of the Alzheimer's Association. She is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

D.S. Knopman serves on a Data Safety Monitoring Board for Biogen (fee paid to institution), the DIAN-TU study (receives personal consulting fees), Agenbio (unpaid), and an endovascular carotid reconstruction study (unpaid). He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals, and the Alzheimer's Disease Cooperative Study, and receives research support from the National Institutes of Health and philanthropic funds. He is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

Drs. Knopman and Mielke are Editorial Board Members of this journal but were not involved in the peer-review process nor had access to any information regarding its peer-review.

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V. J. Lowe consults 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). A. Algeciras-Schimnich participates in advisory boards for Roche Diagnostics, Fujirebio Diagnostics and Siemens.

All other authors have no conflicts to report.

Background: The National Institute on Aging-Alzheimer's Association Research Framework proposes defining Alzheimer's disease by grouping imaging and fluid biomarkers by their respective pathologic processes. The AT(N) structure proposes several neurodegenerative fluid biomarkers (N) including total tau (t-tau), neurogranin (Ng), and neurofilament light chain (NfL). However, pathologic drivers influencing each biomarker remain unclear.

Objective: To determine whether CSF-neurodegenerative biomarkers (N) map differentially to Alzheimer's pathology measured by Aβ42 (an indicator of amyloidosis, [A]), p-tau (an indicator of tau deposition, [T]) and MRI vascular pathology indicators (measured by white-matter integrity, infarcts, and microbleeds [V]).

Methods: Participants were from Mayo Clinic Study of Aging (MCSA) with CSF measures of NfL, Ng, t-tau, Aβ42 and p-tau and available MRI brain imaging. Linear models assessed associations between CSF neurodegeneration (N) markers, amyloid markers (A), tau (T), and vascular pathology (V).

Results: Participants (n=408) had a mean age of 69.2±10.7; male, 217 (53.2%); cognitively unimpaired, 359 (88%). All three neurodegeneration biomarkers correlated with age ($p<0.001$ for NfL and t-tau, $p=0.018$ for Ng). Men had higher CSF-NfL levels; women had higher Ng ($p<0.001$). NfL and t-tau levels correlated with infarcts ($p=0.009$, $p=0.034$ respectively); no biomarkers correlated with white-matter integrity. N biomarkers correlated with p-tau levels (T, $p<0.001$). Higher Aβ42 levels associated with higher N-biomarker levels but only among cognitively unimpaired (A, $p<0.001$).

Conclusions: The influence of vascular pathology in the general population on CSF (N) biomarkers is modest, with greater influence of infarcts than white-matter disruption. Neurodegeneration markers more closely correlated with tau than amyloid markers.

Keywords

Alzheimer's; amyloid; cerebrospinal fluid; neurodegeneration; neurofilament light chain; neurogranin; total tau; white matter integrity

Introduction

The AT(N) system of the National Institute on Aging-Alzheimer's Association Research Framework [1] includes markers of neurodegeneration. By definition, these markers are non-specific to Alzheimer's disease but are a measure of severity in that they are more proximate in time and causality to cognitive decline. Multiple pathologies can impact each marker of neurodegeneration. In this study, we examined three commonly investigated fluid biomarkers of neurodegeneration (N) = total tau (t-tau), neurogranin (Ng), and neurofilament light chain (NfL). It has been shown that these three markers correlate and are elevated in Alzheimer's Disease (AD) [2, 3], suggesting that they reflect some common aspects of neurodegeneration. CSF t-tau is a marker of neurodegeneration thought to reflect the intensity of neuronal damage (N), whereas CSF p-tau, a marker of the phosphorylated tau found in neurofibrillary tangles, is an estimate of tau pathology (T). Ng is a neuronal-specific postsynaptic protein and marker of synaptic integrity and function [4]. While CSF t-tau and p-tau levels are highly correlated, t-tau has also been shown to be elevated in

non-Alzheimer's pathologies [5, 6], highlighting the need to identify different pathological influences on CSF biomarkers. Among the (N) biomarkers, t-tau and Ng, are thought to be more closely associated with AD-related synaptic and neuronal degeneration [7–10]. On the other hand, NfL, a useful neurodegeneration marker reflecting axonal degeneration and white matter disruption [11], is considered non-specific and independent of amyloid pathology [7, 12, 13].

Data on associations between N CSF biomarkers and vascular impairment vary, depending on the type of vascular pathology investigated, the disease severity, and the population analyzed [14]. Compared to other N biomarkers, NfL has been found to be more closely related to vascular risk factors, small vessel disease and stroke history [12, 15]. Previous studies demonstrated higher levels of CSF t-tau in association with vascular impairment, multiple microbleeds [16] and after acute strokes [17] but without any obvious link to white matter hyperintensities [7, 18, 19]. Although CSF Ng levels correlate with the volume of acute cerebral ischemia [20], Ng is considered a promising marker of synaptic dysfunction rather than vascular pathology [21].

Focusing on the overlap of AD and cerebrovascular disease, the objective of this study was to determine the associations between AD (A, T) and vascular pathologies (V) with different (N) markers in a community-based sample. We hypothesized that NfL levels were more influenced by vascular brain changes compared to t-tau and Ng.

Methods

The study, which was done in accord with the Helsinki Declaration of 1975, was approved by Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants.

Participants

We included participants from the Mayo Clinic Study of Aging (MCSA). The MCSA is a population-based, longitudinal study examining the epidemiology of cognitive decline and risk of mild cognitive impairment (MCI) among residents living in Olmsted County, Minnesota, which began enrolling in 2004. Details of the study and its design were previously described [22]. In short, the MCSA includes 15-month interval evaluations done by a study coordinator, a physician, and a psychometrist. Final clinical diagnoses are established by consensus using previously published criteria [23, 24]. The current study included 408 participants with available MRI data as well as cerebrospinal fluid (CSF) measures.

CSF analyses

CSF samples were collected via lumbar puncture. The collected CSF was transported to the lab in polypropylene tubes, aliquoted, and stored at −80°C without any additional freeze-thaw cycles until use. Aβ42, t-tau, and hyperphosphorylated tau- 181 (p-tau) were analyzed using Elecsys β-amyloid (1–42) CSF, Elecsys Total-Tau CSF, and Elecsys Phospho-Tau (181P) CSF electrochemiluminescence immunoassays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) [25–27]; these assays are approved for clinical

use in countries that accept the Conformité Européenne (CE) mark. These immunoassays are for investigational purposes and are not yet approved for clinical use in the United States. As previously described, the quality control process included a validation method of precision and accuracy prior to beginning the analysis, as well as using Elecsys PreciControl samples throughout the trial to monitor the quality of the results [28]. In-house developed enzyme-linked immunosorbent assays (ELISAs) were used to measure CSF NfL and Ng concentrations; assay characteristics and methods have been described elsewhere [29–31].

Imaging measures

Structural MRI was acquired using standardized magnetization-prepared, rapid-gradient echo (MPRAGE) sequences on 3-Tesla GE scanners (GE Medical Systems). FreeSurfer version 5.3 was run on the MPRAGE scans. Diffusion-tensor imaging sequences were processed and analyzed for fractional anisotropy of the genu of the corpus callosum (FA-GCC) using standardized processing that was previously published [32, 33]. In addition to its low measurement variability, the anterior part (genu) of the corpus callosum provides information about diffusion directionality and may be more sensitive to small-vessel disease as a cerebrovascular biomarker [33]. Two-dimensional FLAIR image was used to detect WMH using a semi-automated method, as explained previously [34, 35]. In short, FLAIR images were used to identify possible WMH voxels using a clustering method, and information from MPRAGE image was incorporated to reduce false positives. Total WMH estimated volume was then edited by a trained imaging analyst for accuracy and scaled as the percentage of total intracranial volume (TIV). Recognition and grading of infarcts was done as previously described [36] using FLAIR MRI co-registered to the MPRAGE scan. Cerebral microbleeds (CMB) were recognized and computed as previously described [37] in agreement to consensus criteria [38, 39] as homogeneous hypointense lesions in the gray or white matter, which are distinct from vessel flow voids on T2* GRE images. All possible infarcts and CMB were initially identified by trained image analysts and confirmed by a vascular neurologist to whom all clinical information was masked.

Assessment of vascular pathology (V)—The (V) component was based on MRI markers of cerebrovascular disease (CVD), as previously described [32]. In brief, we used a previously validated principle component analyses, with imaging assessments of CVD from T2* GRE, FLAIR, and diffusion MRI including FAGCC and WMH. As a quantitative indicator of white-matter microstructure degeneration, the PC1 variable is a weighted sum of the deep and periventricular regional WMH score and White Matter Integrity (FAGCC) score. An increase in WMH as well as a decrease in FAGCC was reflected by a higher PC1 score. The continuous number of microbleeds and continuous number of infarctions were binned into two components (PC2 and PC3). PC2 was calculated based on the total number of deep and lobar microbleeds. PC3 corresponded to the number of cortical and subcortical infarcts recognized on imaging as described above.

Statistical analyses

Continuous demographic and clinical data were summarized using means and standard deviations; categorical variables were summarized as counts and percentages. NfL measures were transformed using a natural logarithm transformation to normalize the distributions.

One outlier with an extreme CSF NfL value (>30,000 pg/mL) was excluded from the analyses. Univariate and multivariate linear models were conducted to associate outcomes with each predictor of interest (N biomarkers: t-tau, Nfl, Ng). All multivariate models were adjusted for age and sex. To address the curvature in p-tau CSF levels, quadratic terms were included as necessary in the final models to account for non-linear relationships (p-tau^2). Parsimonious models were produced through a backward-elimination process.

Results

Participants

The characteristics of the 408 participants with CSF measures and available MRI scans are shown in Table 1. The mean age was 69.19 (±10.71); there were 217 men (53.19%). A total of 359 (87.99%) participants were cognitively unimpaired, 46 (11.27%) had MCI, and three (0.74%) had dementia. There were 210 (51.4%) participants with CSF Aβ42<1026 pg/mL, and 130 (31.9%) participants with elevated CSF p-tau levels (p-tau>21 pg/mL). Sixty-four (15.69%) participants had infarcts; 50 (12.2%) had evidence on neuroimaging of cerebral microbleeds and 59 (14.46%) had high WMH burden (WMH/TIV >1.7% [40], correlative to Fazekas 3+).

Associations of CSF N markers with AD CSF biomarkers and vascular pathology

Results from univariate linear models are shown in Table 2. The associations between demographic variables and markers of amyloid (Aβ42), tau (p-tau), vascular pathology (PC1 and PC3), and CSF N biomarkers are shown in Table 3. Additional analyses, including a vascular component comprised of microbleeds (PC2), did not reveal significant associations and was therefore excluded from the presented models.

NfL

In the univariate linear models (Table 2), higher CSF NfL levels correlated with higher p-tau levels ($p<0.001$) but not with CSF Aβ42 levels. An association was observed between CSF NfL levels and the two vascular variables, PC1 and PC3 ($p<0.001$). In the multiple-regression models (Table 3), CSF NfL levels were associated with age ($\beta=0.02$, $p<0.001$, Partial $R^2=0.071$) and were higher in men than women ($\beta=0.23$, $p<0.001$, Partial $R^2=0.045$). CSF NfL levels were associated with CSF p-tau levels ($\beta=0.02$, $p<0.001$, Partial $R^2=0.071$), but no association was found with Aβ42 (Table 3). A relationship between NfL and vascular pathology was significant for infarcts (PC3, $\beta=0.09$, $p=0.009$, Partial $R^2=0.017$), but not for white-matter damage (PC1, $p=0.412$).

T-tau

In the univariate linear models (Table 2), CSF t-tau levels positively correlated with CSF Aβ42 levels ($p=0.003$), CSF p-tau ($p<0.001$), and both PC1 and PC3 ($p<0.001$, $p=0.005$ respectively). Multiple-regression models (Table 3) showed that CSF t-tau levels were associated with age ($\beta= 0.24$, $p=0.049$, Partial $R^2=0.010$). Increased CSF t-tau levels were associated with higher CSF p-tau levels (T, $\beta=1697.55$, $p<0.001$, Partial $R^2=0.95$). A weak association was observed between higher Aβ42 levels and CSF t-tau levels (A, $\beta=0.02$,

p<0.001, Partial R^2=0.14). Finally, higher CSF t-tau levels were associated with more infarcts (PC3, β=2.26, p=0.034, Partial R^2=0.011) (Table 3).

Ng

Higher Ng levels were associated with higher p-tau levels (Table 2, p<0.001) but also with higher CSF Aβ42 level (p<0.001). There was no association between Ng levels and number of infarcts (PC3, p=0.059), or other vascular variables. Subsequent multiple-regression analyses (Table 3) showed that CSF Ng levels correlated with age (β=−0.57, p=0.018, Partial R^2=0.018) and were higher in women than men (β=−14.46, p<0.001, Partial R^2=0.041). Higher CSF Ng levels were closely associated with higher CSF p-tau levels (T, β=1089.51, p<0.001, Partial R^2=0.67), but an association with higher CSF Aβ42 levels (A, β=0.02, p<0.001, Partial R^2=0.064) was also observed. No associations were found between Ng and the measures of vascular pathology (Table 3).

As shown in Table 3, significant associations for all three biomarkers survived parsimonious model analyses involving backwards elimination of predictors until only significant predictors remain. Exclusion of the three participants diagnosed with dementia from the analyses did not change the observed associations.

Predictive plots for average male and female participants

Predictive plots based on the full regression models (Table 3) according to sex are shown in Figure 1. The predicted plots of CSF N biomarkers by sex followed similar trajectories, yet at baseline males had consistently higher CSF NfL values while females had higher Ng levels. A significant interaction was observed for infarcts (PC3) as a predictor of CSF t-tau, where an increased infarct score predicted higher t-tau levels for males but not for females (p=0.035).

Associations between CSF Aβ42 and N biomarkers

To further explore the unexpected positive associations of the N markers with CSF Aβ42 levels, additional models stratified by cognitive impairment status were conducted, controlling for age (Table 4). The observed association remains in the cognitively unimpaired participants only. For cognitively impaired participants, the direction of the association between CSF AB42 levels and NfL and t-tau levels changed to negative, although this was not significant in this small subgroup.

Discussion

In the present study our aim was to determine how CSF N biomarkers, NfL, t-tau and Ng differentially associate with CSF measures of Aβ42 (A) and p-tau (T) and imaging measures of vascular pathology (V). All three biomarkers increased with age; NfL levels were higher in males whereas Ng levels were higher in females. We found that cerebrovascular pathology modestly influences NfL and t-tau levels but not Ng, with infarcts having a greater impact on neurodegeneration biomarkers in comparison to white-matter disruption. All three biomarkers were associated with p-tau levels (T). Among the

cognitively unimpaired participants, CSF N biomarkers were positively associated with CSF Aβ42 levels (A).

According to our findings, vascular pathology has a limited impact on CSF N biomarkers in this mostly cognitively unimpaired cohort. It appears that of the two components of V investigated, the first composed of white-matter hyperintensity and integrity scores (PC1) and the second of neuroimaging evidence of infarctions (PC3), infarctions drove the observed associations while there was no association with microbleeds (PC2). NfL is a sensitive but non-specific, amyloid-independent marker of white-matter integrity and axonal injury[13, 15], more closely associated with vascular risk factors, small vessel disease and history of stroke compared to other N biomarkers [12, 15]. Our results support these findings, with NfL levels showing the strongest association with neuroimaging evidence of infarctions. However, no association was observed between PC1 and NfL levels in mostly cognitively unimpaired individuals. In studies where participants are cognitively impaired or have greater burden of symptomatic cerebrovascular disease and, therefore, greater white-matter damage, there is an association between WMH and CSF NfL [13, 15, 41, 42]. These findings suggest that CSF NfL better captures vascular brain changes in populations with symptomatic cerebrovascular disease or more severe cognitive impairment. Similarly, CMB (PC2) were previously linked with cognitive impairment and dementia in patients with significant cerebrovascular disease [43–45], but our cohort of mostly cognitively unimpaired individuals showed no association with N biomarkers, suggesting a correlation may occur in a more severely affected population or a population where cerebrovascular disease is over-represented.

In previous studies, t-tau and Ng were better predictors of amyloid status than NfL[7, 46], but our results show an inverse relationship between these N biomarkers and CSF Aβ42 levels. Ng, a post synaptic protein localized in dendritic spines of association cortex neurons, was previously found to be elevated in AD patients as opposed to other neurodegenerative illnesses [46, 47], and elevated CSF t-tau was found to be relevant for AD diagnosis, severity, and prediction of disease progression [48, 49]. Our cohort consisted of mostly cognitively unimpaired individuals (88%). It appears that the inverse relationship observed between CSF Aβ42, Ng, and t-tau levels is driven by the large, cognitively unimpaired subgroup, as seen in the cognition-stratified analysis. In clinically or pathologically advanced populations, these two N biomarkers may be more accurate for predicting amyloid status.

As opposed to CSF NfL, the relationship between small-vessel disease and CSF t-tau has shown mixed results, with some studies showing that WMH burden serves as a modifier of atrophy rate and t-tau increase in patients with MCI [50] and others not finding these relationships [7, 18, 19]. Our results did not show an association between PC1 (WMH and white-matter integrity summation) and CSF t-tau ($p=0.097$), although this may reflect the low number of participants with MCI and, therefore, high Braak neurofibrillary tangle stage.

Using CSF T-tau as a marker of (N) is complicated by the fact that levels are highly correlated with CSF p- tau, a marker of (T), as previously shown [12, 51, 52]. Because CSF p-tau is considered to be specific to amyloid pathology [12], it’s possible that CSF t-tau is a

N biomarker more closely related to AD. However, additional studies with a larger number of cognitively impaired individuals with more severe vascular and amyloid pathologies are needed to further elucidate the value of CSF t-tau for diagnosis or prognosis in AD.

Growing evidence indicates that cerebrovascular and AD neuropathology risk factors vary by gender [53], affecting resilience and vulnerability, and leading to complex interactions. In most studies, CSF biomarkers are usually adjusted for sex, but only a few explored sex differences [53]. These sex-specific differences are thought to be reflected in ante-mortem measurement of CSF biomarkers, with higher NfL levels in men, thought to represent vascular burden [12, 54, 55], higher measurement of t-tau and p-tau in women[56–58], and increased Ng levels in women. Even though these differences are considered more pronounced in advance disease stages [57], our results indicate a significant interaction sex effect when PC3 (infarcts count) is used as a predictor of t-tau levels in a mostly cognitively unimpaired sample, revealing an association only in males. Sex may modulate CSF t-tau elevation influenced by vascular insults.

Limitations of the study warrant consideration. First, the MCSA is a community-based study, more likely representative of the general population than other clinic-based studies, but predominantly of European ancestry, which might limit generalizability. A second limitation is the lack of CSF measures of Aβ40; therefore, our definition of (A) is based solely on Aβ42, and not on the Aβ42/40 ratio, which was shown to be a superior estimate of brain amyloid [59, 60]. Given the exploratory nature of this study, no multiple comparison correction was applied to the models.

The CSF N measures will most likely be used as measures of disease progression than for a clinical diagnosis. Our findings suggest that the CSF N biomarker changes are associated with advanced neuropathology and clinical status. CSF NfL levels may begin to be influenced at lower levels of vascular pathology compared to other N biomarkers, specifically by infarcts, and this should be considered in the clinical evaluation. Longitudinal studies with serial CSF measures are needed to better determine the relationships between CSF N measures, CSF Ab42 (A), CSF p-tau (T), and vascular pathology (V) over time.

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Data Availability Statement

The data supporting the findings of this study are available on request from the corresponding author.

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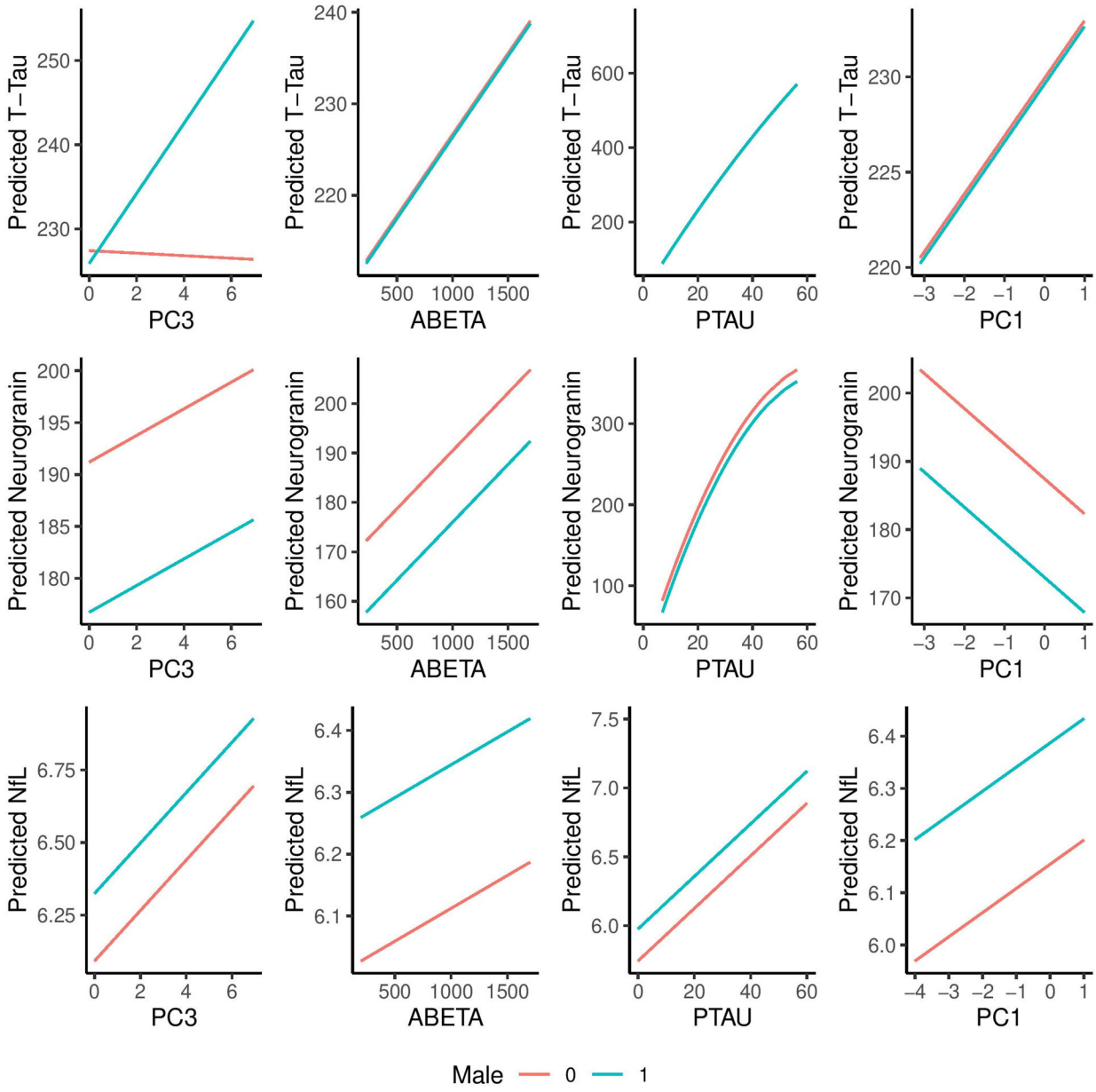

Figure 1. Predicted plots of CSF N biomarkers with sex interactions.

Prediction plots are based on the full linear higher order models. The curvature in the P-tau covariate reflects the higher order term (x^2) in the T-tau and neurogranin models. Units for t-tau, neurogranin, NfL, ABETA, p-tau are pg/mL. PC1 is a weighted sum of the WMH score and White Matter Integrity (FA-GCC) score. PC3 is based on total number of infarcts. Abbreviations: t-tau, total tau; p-tau, phosphorylated tau; NfL, neurofilament light chain

Table 1.

Participant Demographics by Cognitive Status

	Cognitively Unimpaired, N = 359	Cognitively Impaired, N = 49	P-value
Age, yrs.	68.03 (10.57)	77.45 (7.69)	<0.001
Male	191.00 (53.20%)	26.00 (53.06%)	>0.9
Education, yrs.	14.70 (2.47)	13.43 (3.56)	0.009
CSF Aβ42 (pg/mL)	1,077.46 (409.97)	839.14 (463.97)	<0.001
CSF T-tau (pg/mL)	218.11 (83.45)	275.54 (108.06)	<0.001
CSF P-tau (pg/mL)	18.89 (7.62)	24.55 (11.65)	<0.001
CSF NfL (pg/mL)	6.19 (0.63)	6.61 (0.66)	<0.001
Neurogranin (pg/mL)	175.80 (65.33)	196.08 (63.66)	0.036
Vascular measures*			
PC1	−0.87 (0.63)	−0.30 (0.55)	<0.001
PC2	−0.30 (1.39)	−0.48 (1.18)	0.12
PC3	0.28 (0.85)	0.36 (0.77)	0.2
WMH	0.01 (0.01)	0.02 (0.01)	<0.001
Any Infarction	53 (15%)	11 (22%)	0.2
Cortical Infarction	0.07 (0.41)	0.14 (0.46)	0.037
Subcortical Infarction	0.22 (0.68)	0.22 (0.51)	0.4
FA GCC	0.61 (0.04)	0.57 (0.06)	<0.001

Mean (SD); n (%)

*Vascular measures were calculated as follows: PC1 is a weighted sum of the WMH score and White Matter Integrity (FA-GCC) score; PC2 is based on total number of deep and lobar microbleeds; PC3 is based on total number of infarcts. WMH is presented as percentage of total intracranial volume (TIV).

Abbreviations: MCI, Mild Cognitive Impairment; t-tau, total tau; p-tau, phosphorylated tau; NfL, neurofilament light chain; FA GCC, Fractional anisotropy for the genu of Corpus Collosum.

Table 2.

Linear regression models of CSF neurodegenerative biomarkers predicting Alzheimer's and vascular pathology

	NfL	Neurogranin	T-Tau
Aβ42	<0.001, p =0.729	0.044, p <0.001	0.0311, p =0.003
P-Tau	0.0315, p <0.001	6.108, p <0.001	10.272, p <0.001
PC1*	0.324, p <0.001	7.107, p =0.153	34.945, p <0.001
PC3†	0.185, p <0.001	7.278, p =0.059	14.533, p =0.005

Coefficients presented are regression coefficients from univariate models.

*PC1 is a weighted sum of WMH score and White Matter Integrity (FA-GCC) score.

†PC3 is based on total number of infarcts.

Table 3.

Associations between CSF neurodegeneration biomarkers and Alzheimer's and vascular pathology biomarkers using full linear high order and parsimonious models

	NfL						Neurogranin						T-Tau					
	Full Models			*Parsimonious Models*			*Full Models*			*Parsimonious Models*			*Full Models*			*Parsimonious Models*		
Predictors	***Coefficient***	***P***	***Partial R^2***	***Coefficient***	***P***	***Partial R^2***	***Coefficient***	***P***	***Partial R^2***	***Coefficient***	***P***	***Partial R^2***	***Coefficient***	***P***	***Partial R^2***	***Coefficient***	***P***	***Partial R^2***
(Intercept)	4.27	**<0.001**		4.29	**<0.001**		196.34	**<0.001**		212.29	**<0.001**		192.01	**<0.001**		181.62	**<0.001**	
Age	0.02	**<0.001**	0.071	0.02	**<0.001**	0.12	−0.57	**0.018**	0.014	−0.76	**<0.001**	0.040	0.24	**0.049**	0.010	0.36	**<0.001**	0.033
Male	0.23	**<0.001**	0.045	0.23	**<0.001**	0.043	−14.46	**<0.001**	0.041	−13.60	**<0.001**	0.038	−0.30	0.862	<0.001			
Aβ42	0.00	0.107	0.006				0.02	**<0.001**	0.064	0.02	**<0.001**	0.071	0.02	**<0.001**	0.14	0.02	**<0.001**	0.13
PTAU	0.02	**<0.001**	0.071	0.02	**<0.001**	0.078	1089.51	**<0.001**	0.67	1090.84	**<0.001**	0.67	1697.55	**<0.001**	0.95	1696.59	**<0.001**	0.95
PTAU^2							−270.01	**<0.001**		−273.84	**<0.001**		−110.86	**<0.001**		−109.15	**<0.001**	
PC1*	0.05	0.412	0.002				−5.15	0.162	0.005				3.03	0.097	0.007			
PC3†	0.09	**0.009**	0.017	0.10	**0.002**	0.023	1.28	0.550	<0.001				2.26	**0.034**	0.011	2.50	**0.018**	0.014
PC3† Male													4.30	**0.035**	0.011			
N	408			408			408			408			408			408		
R^2	0.341			0.336			0.727			0.726			0.963			0.963		

* PC1 is a weighted sum of WMH score and White Matter Integrity (FA-GCC) score.

† PC3 is based on total number of infarcts.

Abbreviations: NfL, neurofilament light chain; t-tau, total tau. P-tau, phosphorylated tau.

Table 4.

Cognitive impairment-stratified models (Aβ42 age-adjusted)

	Neurogranin (CU)		**Neurogranin (Impaired)**		**NfL (CU)**		**NfL (Impaired)**		**T-Tau (CU)**		**T-Tau (Impaired)**	
Predictors	*Coefficient*	*P*	*Coefficient*	*P*	*Coefficient*	*P*	*Coefficient*	*P*	*Coefficient*	*P*	*Coefficient*	*P*
(Intercept)	8.06	0.730	13.72	0.890	3.85	**<0.001**	5.13	**<0.001**	−95.33	**0.001**	−75.06	0.647
Aβ42	0.06	**<0.001**	0.01	0.620	0.0003	**<0.001**	−0.0004	0.080	0.07	**<0.001**	−0.02	0.606
Age	1.48	**<0.001**	2.26	0.070	0.03	**<0.001**	0.02	0.063	3.55	**<0.001**	4.74	**0.022**
Observations	359		49		359		49		359		49	
R^2	0.182		0.070		0.256		0.159		0.265		0.128	

CU (n=359), Impaired (n=49)

Abbreviations: CU, cognitively unimpaired; NfL, neurofilament light chain; t-tau, total tau.