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RESEARCH ARTICLE

A study of the longitudinal changes in multiple cerebrospinal fluid and volumetric magnetic resonance imaging biomarkers on converter and non-converter Alzheimer's disease subjects with consideration for their amyloid beta status

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Abstract

Introduction: This study aims to determine whether newly introduced biomarkers Visinin-like protein-1 (VILIP-1), chitinase-3-like protein 1 (YKL-40), synaptosomal-associated protein 25 (SNAP-25), and neurogranin (NG) in cerebrospinal fluid are useful in evaluating the asymptomatic and early symptomatic stages of Alzheimer's disease (AD). It further aims to shed new insight into the differences between stable subjects and those who progress to AD by associating cerebrospinal fluid (CSF) biomarkers and specific magnetic resonance imaging (MRI) regions with disease progression, more deeply exploring how such biomarkers relate to AD pathology.

Methods: We examined baseline and longitudinal changes over a 7-year span and the longitudinal interactions between CSF and MRI biomarkers for subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We stratified all CSF (140) and MRI (525) cohort participants into five diagnostic groups (including converters) further dichotomized by CSF amyloid beta (Aβ) status. Linear mixed models were used to compare within-person rates of change across diagnostic groups and to evaluate the association of CSF biomarkers as predictors of magnetic resonance imaging (MRI) biomarkers. CSF biomarkers and disease-prone MRI regions are assessed for CSF proteins levels and brain structural changes.

Results: VILIP-1 and SNAP-25 displayed within-person increments in early symptomatic, amyloid-positive groups. CSF amyloid-positive (Aβ+) subjects showed elevated baseline levels of total tau (tTau), phospho-tau181 (pTau), VILIP-1, and NG. YKL-40, SNAP-25, and NG are positively intercorrelated. Aβ+ subjects showed negative

MRI biomarker changes. YKL-40, tTau, pTau, and VILIP-1 are longitudinally associated with MRI biomarkers atrophy.

Discussion: Converters (CNc, MCIc) highlight the evolution of biomarkers during the disease progression. Results show that underlying amyloid pathology is associated with accelerated cognitive impairment. CSF levels of Aβ42, pTau, tTau, VILIP-1, and SNAP-25 show utility to discriminate between mild cognitive impairment (MCI) converter and control subjects (CN). Higher levels of YKL-40 in the Aβ+ group were longitudinally associated with declines in temporal pole and entorhinal thickness. Increased levels of tTau, pTau, and VILIP-1 in the Aβ+ groups were longitudinally associated with declines in hippocampal volume. These CSF biomarkers should be used in assessing the characterization of the AD progression.

KEYWORDS
Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative (ADNI), cerebrospinal fluid, longitudinal analysis, magnetic resonance imaging (MRI), neuronal injury

1 | INTRODUCTION

The fundamental mechanisms in the pathogenesis of Alzheimer's disease (AD) are yet to be fully understood,[1] given the many subtle changes in the biomarkers and the indistinct transitional phases of AD. The neuropathological basis of AD includes the accumulation of amyloid plaques containing amyloid beta (Aβ) peptides and neurofibrillary tangles (NFTs). The concentrations of the Aβ peptide (Aβ42), total tau (tTau), and phosphorylated tau181 (pTau), the most widely studied cerebrospinal fluid (CSF) biomarkers for neurodegenerative diseases such as Parkinson disease[2] and AD,[3–4] are altered in the preclinical and symptomatic stages of AD.[5–9] Moreover, increased CSF levels of synaptosomal-associated protein-25 (SNAP-25)[7] and neurogranin (NG)[10 - 11] imply synaptic damage, whereas the high level of neuronal calcium sensor protein (VILIP-1)[12 - 13] reflects neuronal injury.[14] Furthermore, secreted glycoprotein (YKL-40) is related to neuroinflammation.[15,16] Finding the associations between these CSF biomarkers and AD pathophysiology both in asymptomatic and early symptomatic stages is critical for early diagnosis of AD. In addition to the CSF biomarkers, neuroimaging techniques such as structural magnetic resonance imaging (MRI) can be used for early detection to identify those at risk of developing AD, and to provide insights into variants of AD with different clinical outcomes.[2,17,18] From a neuropathological perspective, it has been shown that regional atrophy in the medial temporal lobes and the neocortex (especially the parietal lobes) are affected very early in the course of the disease.[14,19] However, it is not clear whether the combination of MRI biomarkers along with tTau, pTau, YKL-40 (neuroinflammation), and the novel CSF neuronal injury biomarkers SNAP-25, VILIP-1, and NG would provide better information about the clinical and pre-clinical stages of AD or whether their independent analysis is sufficient for the early detection of AD.

In this study we evaluate baseline measurements and longitudinal changes in the aforementioned CSF biomarkers along with signature AD MRI-derived regional volumes. Here we aim to identify the association between biomarkers and AD pathophysiology with different clinical stages of AD. A particular focus of this study is the inclusion in the analysis of CSF and MRI biomarkers from those who progressed in cognitive impairment to either MCI or AD. Furthermore, this study encompasses the subjects with available CSF Aβ levels to investigate the patterns of intrapatient longitudinal changes while contrasting normal CSF profiles with abnormal ones. Finally, we test the association of CSF biomarkers and regional brain atrophy.

2 | METHODS

2.1 | The Alzheimer's Disease Neuroimaging Initiative (ADNI) data set

Data used in this study were obtained from the Alzheimer's Diseases Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu/methods/documents). ADNI is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD (http://adni.loni.usc.edu). The data set included participants between the ages of 55 and 90 recruited from 63 different sites across the United States and Canada. Participants underwent a series of initial tests, which were repeated at yearly or longer intervals, including clinical and cognitive assessments, brain imaging, and biochemical tests.

2.2 | Participants

In this study, we analyzed three cohorts: CSF, MRI, and CSF-MRI. Their respective inclusion criteria along with the number of subjects are depicted in Figure 1. Participants were selected from the ADNI cohort

if they met the following inclusion criteria: (a) completed at least two visits; (b) diagnoses did not revert to a previous diagnosis (e.g., if they progressed from cognitively normal [CN] to mild cognitive impairment [MCI], they did not subsequently convert back to CN); (c) had available CSF biomarker results for at least the baseline visit; and (d) had available processed longitudinal MRI and CSF data.

We considered five ADNI-defined clinical groups over a 7-year period:

1. *Stable normal (CN)*: Subjects diagnosed as cognitively normal, who remained normal at each visit.
2. *Converter normal (CNc)*: Subjects who were diagnosed as normal in a previous visit, who progressed to MCI or dementia in a future visit.
3. *Stable MCI (MCI)*: Subjects diagnosed as MCI, who remained MCI at all available visits.
4. *Converter MCI (MCIc)*: Subjects diagnosed as MCI in a previous visit who progressed to AD.
5. *AD dementia (AD)*: Subjects who were diagnosed as AD at each visit.

To form the CSF cohort, we considered all subjects for which there existed CSF data for the baseline visit and at least one additional timepoint. On the other hand, the MRI cohort was formed by all subjects who similarly had valid MRI data points for the baseline visit and at least one other one. Finally, the CSF-MRI cohort included patients who had available data points for both MRI and CSF biomarkers for the same timepoints. The CSF and CSF-MRI cohorts each included 140 individuals (41 CN, 13 CNc, 33 MCI, 37 MCIc, and 16 AD), whereas there were 525 participants in the MRI group (130 CN, 13 CNc, 177 MCI, 89 MCIc, 116 AD). These five diagnosis groups (CN, CNc, MCI, MCIc, and AD) were further stratified based on CSF Aβ status.

2.3 | CSF and MRI biomarkers

The values for the CSF biomarkers Aβ42, tTau, and pTau were measured using fully automated electrochemiluminescence Roche Elecsys immunoassays in the ADNI Biomarker Core at the University of Pennsylvania. The data was downloaded from the LONI site (UPENNBIOMK9.csv file). These immunoassays are under development by Roche Diagnostic for investigational use only and not yet commercially available. Postmortem Aβ positivity confirmed the cut-off value (<192 pg/mL) established previously by Shaw et al..[3] These CSF biomarker values were downloaded from the LONI site (UPENNBIOMK1_8.csv files).

The values used for NG, SNAP-25, and VILIP-1 were measured with microparticle-based immunoassays using Single Molecule Counting technology, originally developed for the Erenna System by Singulex and now part of EMD Millipore. YKL-40 was measured with a plate-based enzyme-linked immunoassay (MicroVue ELISA; Quidel, San Diego, CA). These biomarker values were also downloaded from the LONI site (FAGANLAB.csv files).

The following MRI biomarkers were used: entorhinal cortex thickness and volumes for the inferior parietal lobule, inferior temporal lobule, temporal pole, and hippocampus. All MRI biomarker values were averaged for the left and right hemispheres. Structural brain MRI was performed according to the ADNI protocol. T1-weighted images were acquired on a 1.5 or 3.0 Tesla scanner and the data were processed at that time using FreeSurfer 4.4.

RESEARCH IN CONTEXT

1. Systematic review: In this study the authors used traditional sources such as PubMed and Web Of Science. Previous studies mainly focused on the effect of longitudinal changes in CSF and/or MRI biomarkers on the AD progression with Amyloid-β status for the non-converter groups or only including mild cognitive impairment converter (MCIc) group. The appropriate articles have been cited in the manuscript.
2. Interpretation: Our study presents a comprehensive analysis of the CSF and MRI biomarkers with and without considering Amyloid-β status for the converter and non-converter groups. This study expands on prior research by providing our findings on the longitudinal analysis of such biomarkers for AD progression.
3. Future directions: The continuation of this study may include a) additional imaging, biofluid, and genetic biomarkers, b) validation of the study results on the larger population – based cohort.

2.4 | Statistical analysis

Baseline demographic variables and cognitive scores for a Mini–Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive 11 (ADAS11), Alzheimer's Disease Assessment Scale-cognitive 13 (ADAS13), clinical dementia rating (CDR) are summarized in Table 1 for each of the subjects in the CSF cohort and in Table 2 for participants in the MRI study, along with longitudinal cognitive changes for each of the five diagnostic groups. The baseline characteristics (mean and SD) of the CSF and MRI biomarkers for the different groups are presented in Tables 3 and 4, respectively. Extensive model assumption diagnostics were performed through normality and equal variance tests. CSF Aβ42, tTau, pTau, pTau/Aβ42, VILIP-1, SNAP-25, YKL-40, and NG values were log10-transformed, and the logarithmic values were used for between-group comparisons and longitudinal analysis. Analyses of variance (ANOVA) with Tukey multiple comparison post hoc pairwise analysis and chi-square tests were used to test for significant differences between groups for continuous and categorical measurements, respectively. Pearson correlation was used to test associations between CSF Aβ42, tTau, pTau, pTau-to-Aβ42 ratio, VILIP-1, SNAP-25, YKL–40, and NG.

Because one of this study's goals was to detect changes in significant biomarkers associated with AD, we used widely used linear

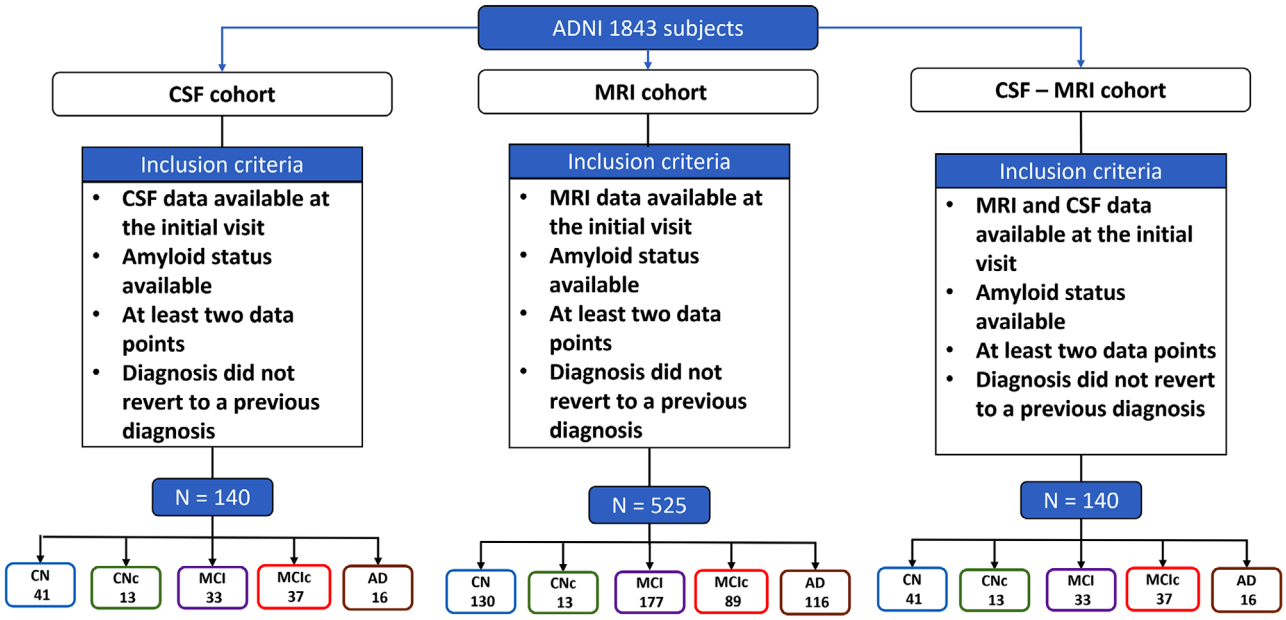

FIGURE 1 Cohort generation criteria and final breakdown for the CSF, MRI, and CSF-MRI studies

mixed-effect models to examine patterns in cognitive performance, CSF concentrations, and MRI atrophy over time.[20] All models included random slopes and intercepts at the subject level, with an unstructured covariance matrix using the maximum likelihood method over the five diagnostic groups (CN, CNc, MCI, MCIc, and AD) and 10 subgroups (CN Aβ+, CN Aβ−, CNc Aβ+, CNc Aβ−, MCI Aβ+, MCI Aβ−, MCIc Aβ+, MCIc Aβ−, AD Aβ+, and AD Aβ−). In addition to the mean intercept and slope for each group (unadjusted models), we included age (at baseline), gender, education, apolipoprotein (*APOE*) ε4 carriage, and their interaction with subject groups as covarities. The MRI biomarkers were also adjusted for intracranial volume (ICV) (see Supporting Information).

Finally, the association between CSF and MRI biomarkers was tested using linar mixed models with random intercepts and slopes at the subject level. The predictors were each CSF biomarker and its interaction by time, age at baseline, gender, education, *APOE* ε4 carriage, and ICV. Model were tested separatly for Aβ+ and Aβ− subjects. The underlying model assumptions of homoscedastic (i.e., homogeneity of variance) and linearity were both met. All analyses were performed using SAS/STAT v14.2 software with statistical significance set at alpha level of 0.05.

3 | RESULTS

3.1 | Baseline and longitudinal characteristics of demographic and cognitive performance tests for CSF study

The partipant's mean ages for the diagnostic groups ranged between 72.45 and 77.0 years, with the CNc group having the highest mean age (Table 1). The percentage of female participants was larger in the CNc (53.85%) and AD (62.50%) groups, than the CN, MCI, MCIc groups; as expected, *APOE* ε4 carriers were more frequent in the MCIc (59.46%) and AD (75.00%) groups. The number of years of education ranged from 4 to 20 years, with a mean of 15 (±1) years. The mean baseline cognitive scores are identified for each of the five groups, showing the expected significant changes from CN to AD. Among the longitudinal changes, significant annual rates of change were present for the AD and the MCIc groups (for all cognitive measures), for the MCI group (ADAS13 and ADAS11), and for the CNc group (all, except MMSE). The number of subjects per each time point is shown in Table SA3.

3.2 | Baseline and longitudinal characteristics of CSF biomarkers

The baseline levels and longitudinal changes for the CSF biomarkers for CN, CNc, MCI, MCIc, and AD are presented in Table 3, and further stratified into Aβ+ and Aβ− groups (Table SA1).

Aβ42 (Elecsys): Baseline concentration characteristics of Aβ42 using a novel Elecsys method (Roche, Basel) shows a pattern of decreasing baseline values following increasing cognitive impairment across the five groups. Levels are significantly lower in the AD group compared to CN, CNc, MCIc, and MCI groups ($P < 0.05$). Baseline levels are also lower in the MCIc group compared to CN, CNc, and MCI ($P < 0.0001$). Longitudinally, all groups show decreases in their mean levels over time, but a statistically significant decrease is present only in the AD ($P = 0.001$) and CN ($P = 0.020$) groups (Table 3). The baseline levels for all Aβ-positive groups, except CNc, are significantly lower than those of Aβ-negative groups ($P < 0.0001$). Longitudinally, the CN Aβ− rate of change is statistically significant ($P = 0.026$) (Table SA1).

tTau (Elecsys): Baseline levels of tTau are statistically lower in the CN and MCI groups than in the AD ($P < 0.05$) and MCIc ($P < 0.05$) groups.

TABLE 1 Baseline demographic measures and estimated cognitive within-person annual rate of change for CSF study

		CN	CNc	MCI	MCIc	AD
No. of subjects		41	13	33	37	16
Baseline measurements						
Age	Mean	75.98	76.69	75.74	73.06	73.43
	SD	(5.04)	(4.43)	(6.62)	(5.67)	(6.77)
Education	Mean	15.66	15.62	16.39	16.03	15.00
	SD	(3.37)	(2.66)	(2.69)	(2.65)	(2.99)
MMSE	Mean	29.15	29.46	27.15[a,b]	26.57[a,b]	22.88[a,b,c,d]
	SD	(1.11)	(0.66)	(1.39)	(1.68)	(2.87)
ADAS11	Mean	8.80	10.74	16.39[a,b]	20.47[a,b]	29.27[a,b,c,d]
	SD	(3.70)	(3.55)	(6.21)	(6.10)	(8.31)
ADAS13	Mean	5.77	6.90	9.79[a]	12.44[a,b]	19.02[a,b,c,d]
	SD	(2.69)	(2.99)	(3.96)	(4.73)	(6.86)
CDRSB	Mean	0.04	0.00	1.45[a]	1.58[a]	4.41[a,c,d]
	SD	(0.13)	(0.00)	(0.76)	(0.77)	(1.69)
Gender (F/M)	%	41.46/58.54	53.85/46.15	30.30/69.70	29.73/70.27	62.50/37.50
APOE ε4 (0/1,2)	%	78.05/21.95	79.92/23.08	54.55/45.45	40.54/59.46	25.00/75.00[a]
Estimated annual slopes						
MMSE	Slope	-0.04	-0.36	-0.36	**-1.46**	**-2.60**
	SE	(0.16)	(0.26)	(0.19)	**(0.16)**	**(0.31)**
	P-value	0.803	0.182	0.067	**<.0001**	**<.0001**
ADAS11	Slope	0.21	**1.02**	**1.00**	**2.97**	**5.03**
	SE	(0.28)	**(0.48)**	**(0.38)**	**(0.32)**	**(0.59)**
	P-value	0.468	**0.036**	**0.012**	**<.0001**	**<.0001**
ADAS13	Slope	0.36	**1.68**	**0.70**	**2.51**	**5.22**
	SE	(0.30)	**(0.50)**	**(0.36)**	**(0.30)**	**(0.67)**
	P-value	0.240	**0.001**	**0.045**	**<.0001**	**<.0001**
CDRSB	Slope	0.02	**0.44**	0.15	**1.20**	**2.46**
	SE	(0.09)	**(0.15)**	(0.11)	**(0.09)**	**(0.17)**
	P-value	0.864	**0.005**	0.142	**<.0001**	**<.0001**

Abbreviations: AD, Alzheimer's disease; ADAS13, Alzheimer's Disease Assessment Scale 13; *APOE*, apolipoprotein E gene; CDRSB, Clinical Dementia Rating score (sum of boxes); CN, normal control; CNc, converter CN; MCI, mild cognitive impairment; MCIc, converter MCI; MMSE, Mini-Mental Examination, ADAS11, Alzheimer's Disease Assessment Scale 11.

Note: Significant slope is at least $P < 0.05$, represented in bold numbers.

Note: Significance difference between groups:

[a]Significantly different from CN.

[b]Significantly different from CNc.

[c]Significantly different from MCI.

[d]Significantly different from MCIc.

[e]Significantly different from AD.

In addition, baseline levels of tTau are statistically lower in CNc than in AD ($P < 0.05$). Over time, tTau levels increase significantly in the CN ($P < 0.0001$), CNc ($P = 0.02$), MCI ($P = 0.003$), and MCIc ($P = 0.010$) groups (Table 3). Baseline characteristics of tTau show a pattern of elevated baseline values in Aβ+ when compared to the Aβ− groups. Baseline levels of tTau are statistically higher in CN Aβ− than in MCI Aβ− ($P < 0.05$) and CN Aβ− ($P < 0.05$). Moreover, baseline levels are statistically higher in the MCIc and AD groups in comparison to other groups. Longitudinally, tTau levels increase in both amyloid-positive and amyloid-negative CN ($P < 0.009$), CNc Aβ+ ($P = 0.049$), MCI Aβ+ ($P = 0.001$), and MCIc Aβ+ ($P = 0.004$) groups (Table SA1).

pTau (Elecsys): Baseline levels of pTau are statistically lower in CN compared to AD ($P < 0.05$) and MCIc ($P < 0.05$). In addition, baseline levels of pTau are statistically lower in CNc and MCI in comparison to MCIc and AD ($P < 0.05$). Over time, the pTau levels significantly increase in CN ($P < 0.0001$), whereas they decrease for AD ($P < 0.001$)

TABLE 2 Baseline demographic measures and estimated cognitive within-person annual rate of change for MRI study

		CN	CNc	MCI	MCIc	AD
No. of subjects		130	13	177	89	116
Baseline measurements						
Age	Mean	73.91	76.11	72.53	72.62	73.57
	SD	(5.73)	(6.30)	(7.24)	(7.22)	(8.20)
Education	Mean	16.27	15.54	15.71	15.92	15.18[a]
	SD	(2.72)	(2.47)	(2.89)	(3.09)	(2.81)
MMSE	Mean	29.15	28.54	27.72[a]	27.11[a]	23.27[a,b,c,d]
	SD	(1.07)	(0.97)	(1.65)	(1.90)	(1.91)
ADAS11	Mean	5.67	8.51[a]	9.24[a]	12.83[a,b,c]	18.28[a,b,c,d]
	SD	(3.08)	(2.70)	(3.87)	(4.95)	(6.60)
ADAS13	Mean	8.71	13.13[a]	15.06[a]	20.71[a,b,c]	28.45[a,b,c,d]
	SD	(4.17)	(3.56)	(5.89)	(6.31)	(7.98)
CDRSB	Mean	0.03	0.04	1.28[a]	1.86[a,c]	4.33[a,b,c,d]
	SD	(0.14)	(0.14)	(0.75)	(0.94)	(1.63)
Gender (F/M)	%	52.31/47.69	53.85/46.15	41.81/58.19	42.70/57.30	47.41/52.59
APOE (0/1,2)	%	74.62/25.38	61.54/38.46	56.50/43.50[a,b]	31.46/68.54	31.03/68.97[a,c]
Estimated annual slopes						
MMSE	Slope	-0.03	-0.51	**-0.25**	**-1.60**	**-2.15**
	SE	(0.10)	(0.34)	**(0.09)**	**(0.12)**	**(0.16)**
	P-value	0.759	0.138	**0.009**	**<.0001**	**<.0001**
ADAS11	Slope	-0.03	0.65	**0.46**	**3.25**	**4.36**
	SE	(0.18)	(0.62)	**(0.17)**	**(0.22)**	**(0.30)**
	P-value	0.849	0.291	**0.008**	**<.0001**	**<.0001**
ADAS13	Slope	-0.05	0.89	**0.74**	**4.14**	**4.85**
	SE	(0.20)	(0.69)	**(0.19)**	**(0.25)**	**(0.34)**
	P-value	0.801	0.194	**<.0001**	**<.0001**	**<.0001**
CDRSB	Slope	0.03	**0.38**	**0.22**	**1.31**	**1.24**
	SE	(0.06)	**(0.19)**	**(0.05)**	**(0.07)**	**(0.08)**
	P-value	0.634	**0.048**	**<.0001**	**<.0001**	**<.0001**

Abbreviations: AD, Alzheimer's disease; ADAS13, Alzheimer's Disease Assessment Scale 13; APIOE, apolipoprotein E gene; CDRSB, Clinical Dementia Rating score (sum of boxes); CN, normal control; CNc, converter CN; MCI, mild cognitive impairment; MCIc, converter MCI; MMSE, Mini-Mental Examination, ADAS11, Alzheimer's Disease Assessment Scale 11.

Note: Significant slope is at least $P < 0.05$, represented in bold numbers.

Note: Significance difference between groups:

[a]Significantly different from CN.

[b]Significantly different from CNc.

[c]Significantly different from MCI.

[d]Significantly different from MCIc.

[e]Significantly different from AD.

(Table 3). The baseline characteristics of pTau show a pattern of elevated baseline values in Aβ+ compared to Aβ− (Table SA1).

pTau/Aβ42 (Elecsys): The baseline levels of the ratio between pTau and Aβ42 are statistically lower in CN compared to AD ($P < 0.05$), MCIc ($P < 0.05$), and MCI ($P < 0.05$). Baseline levels of pTau and Aβ42 are statistically lower in CNc compared to AD ($P < 0.05$) and MCIc ($P < 0.05$). Furthermore, its baseline levels are statistically lower in MCIc when compared to AD ($P < 0.05$). Over time pTau/Aβ42 levels increase significantly in CN ($P < 0.001$), CNc ($P = 0.040$), and MCIc ($P = 0.048$) (Table 3). The baseline characteristics of this ratio show a pattern of elevated baseline values in Aβ+ compared to Aβ− (Table SA1).

VILIP-1: Although the baseline characteristics of VILIP-1 show a pattern of increasing baseline values following decline of cognitive performance across all five groups. The baseline levels of VILIP-1 are statistically higher in MCIc compared to CN ($P < 0.05$) and MCI ($P < 0.05$). Longitudinally, the VILIP-1 levels decrease significantly for AD ($P = 0.006$)

TABLE 3 Baseline CSF biomarkers measures and estimated within-person annual rate of change

		CN	CNc	MCI	MCIc	AD
No. of subjects		41	13	33	37	16
Baseline CSF biomarker						
Aβ42, pg/L	Mean	1168.10	1038.80	863.18[a]	663.92[a,b,c]	551.19[a,b,c,d]
	SD	(465.22)	(473.84)	(461.85)	(295.48)	(211.05)
tTau, pg/mL	Mean	241.00	271.35	288.60	326.98[a,c]	394.48[a,b,c]
	SD	(79.54)	(69.06)	(131.54)	(115.86)	(157.90)
pTau, pg/mL	Mean	22.24	25.83	28.74	32.77[a,b,c]	41.22[a,b,c]
	SD	(8.33)	(8.32)	(14.84)	(14.05)	(19.01)
pTau/ Aβ42	Mean	0.03	0.03	0.04[a]	0.06[a,b,c]	0.08[a,b,c,d]
	(SD)	(0.032)	(0.021)	(0.035)	(0.036)	(0.038)
VILIP-1, pg/mL	Mean	142.82	168.98	159.14	179.21[a,c]	179.29
	SD	(43.90)	(48.31)	(62.53)	(61.08)	(68.86)
SNAP-25, pg/mL	Mean	4.59	4.44	4.98	5.87[a,b,c]	6.14[a,b,c]
	SD	(1.49)	(1.37)	(2.06)	(1.84)	(1.68)
YKL-40, pg/mL	Mean	401.94	355.59	403.97	371.53	456.69[b,d]
	SD	(138.52)	(81.35)	(143.10)	(111.99)	(158.33)
NG, pg/mL	Mean	2243.11	2675.86	2626.12	2724.08	3291.31[a,c]
	SD	(972.72)	(1114.29)	(1521.20)	(1390.45)	(1579.80)
CSF biomarker estimated annual slopes						
Aβ42, pg/L	Slope	**-0.006**	-0.002	-0.002	-0.005	**-0.025**[a , b , c , d]
	SE	**(0.003)**	(0.004)	(0.004)	(0.003)	**(0.007)**
	P-value	**0.020**	0.571	0.605	0.136	**0.001**
tTau, pg/mL	Slope	**0.008**	**0.008**	**0.009**	**0.006**	-0.010[a,b,c,d]
	SE	**(0.002)**	**(0.004)**	**(0.003)**	**(0.002)**	(0.005)
	P-value	**<.0001**	**0.020**	**0.003**	**0.010**	0.052
pTau, pg/mL	Slope	**0.009**	0.007	0.005	0.001[a]	**-0.020**[a , b , c , d]
	SE	**(0.002)**	(0.004)	(0.003)	(0.002)	**(0.005)**
	P-value	**<.0001**	0.055	0.074	0.709	**<.0001**
pTau/Aβ42	Slope	**0.016**	**0.011**	0.009	**0.007**	0.006
	SE	**(0.003)**	**(0.005)**	(0.005)	**(0.004)**	(0.008)
	P-value	**<.0001**	**0.040**	0.050	**0.048**	0.448
VILIP-1, pg/mL	Slope	0.0001	-0.003	0.003	-0.004	**-0.017**[a , c , d]
	SE	(0.003)	(0.004)	(0.004)	(0.003)	**(0.006)**
	P-value	0.870	0.452	0.338	0.219	**0.006**
SNAP-25, pg/mL	Slope	-0.003	-0.001	0.0001	-0.004	**-0.015**[a]
	SE	(0.003)	(0.005)	(0.004)	(0.003)	**(0.007)**
	P-value	0.234	0.888	0.910	0.238	**0.028**
YKL-40, pg/mL	Slope	**0.006**	0.004	0.001	**0.010**	0.003
	SE	**(0.003)**	(0.005)	(0.004)	**(0.003)**	(0.007)
	P-value	**0.036**	0.487	0.804	**0.003**	0.699
NG, pg/mL	Slope	0.002	0.002	0.005	**-0.009**[a , c]	**-0.032**[a , b , c , d]
	SE	(0.004)	(0.006)	(0.005)	**(0.004)**	**(0.009)**
	P-value	0.513	0.784	0.315	**0.021**	**0.001**

Abbreviations: AD, Alzheimer's disease; CN, normal control; CNc, converter CN; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MCIc, converter MCI; Ng, neurogranin; pTau, phosphorylated tau181; SNAP-25, synaptosomal-associated protein-25; tTau, total tau; VILIP-1, visinin-like protein 1; YKL-40, chitinase-3-like protein 1.; Aβ42, amyloid beta.

Note: Significant slope is at least $P < 0.05$, represented in bold numbers.

[a]Significantly different from CN.

[b]Significantly different from CNc.

[c]Significantly different from MCI.

[d]Significantly different from MCIc.

[e]Significantly different from AD.

TABLE 4 Baseline MRI biomarkers measures and estimated within-person annual rate of change

		CN	CNc	MCI	MCIc	AD
No. of subjects		130	13	177	89	116
Baseline MRI biomarker						
Entorhinal thickness, mm	Mean	7.13	6.84	6.70[a]	6.00[a,b,c]	5.47[a,b,c,d]
	SD	(0.63)	(1.03)	(1.03)	(1.01)	(1.03)
Inferior parietal, mm^3	Mean	23642.3	22820.2	23824.2	21980.8[a,c]	20568.95[a,c]
	SD	(3490.83)	(3143.22)	(3513.83)	(3807.69)	(4100.79)
Inferior temporal, mm^3	Mean	19964.6	18823.85	19451.66	17966.4[a,c]	16884.94[a,c]
	SD	(3081.56)	(2164.56)	(2949.59)	(3203.37)	(3251.26)
Precuneus, mm^3	Mean	16505.28	15922.15	16663.51	15792.47	14934.10[a,c]
	SD	(2367.63)	(2117.38)	(2450.92)	(2524.93)	(2581.16)
Temporal pole, mm^3	Mean	4159.18	4061.23	4088.07	3859.19[a]	3843.47[a,c]
	SD	(693.80)	(626.00)	(643.78)	(708.71)	(703.07)
Hippocampus, mm^3	Mean	7001.35	6677.85	6472.27[a]	5802.43[a,b,c]	5499.43[a,b,c]
	SD	(879.33)	(797.45)	(1101.34)	(1084.91)	(1064.98)
MRI biomarker estimated annual slopes						
Entorhinal thickness, mm	Slope	-0.07	-0.14	-0.10[a]	-0.24[a,b,c]	-0.25[a,b,c]
	SE	(0.01)	(0.04)	(0.01)	(0.01)	(0.02)
	P-value	<.0001	<.0001	<.0001	<.0001	<.0001
Inferior parietal, mm^3	Slope	-193.13	-335.08	-302.20[a]	-625.37[a,b,c]	-693.21[a,b,c]
	SE	(32.92)	(112.75)	(31.34)	(39.74)	(57.48)
	P-value	<.0001	0.003	<.0001	<.0001	<.0001
Inferior temporal, mm^3	Slope	-205.69	-381.18	-278.61	-725.39[a,b,c]	-789.68[a,b,c]
	SE	(28.58)	(96.14)	(26.64)	(34.44)	(45.24)
	P-value	<.0001	<.0001	<.0001	<.0001	<.0001
Precuneus, mm^3	Slope	-116.94	-200.49	-187.09[a]	-331.93[a,c]	-438.69[a,b,c,d]
	SE	(22.10)	(75.97)	(21.13)	(26.69)	(39.31)
	P-value	<.0001	0.009	<.0001	<.0001	<.0001
Temporal pole, mm^3	Slope	-32.90	-102.78[a]	-77.83[a]	-195.16[a,b,c]	-205.28[a,b,c]
	SE	(8.01)	(26.81)	(7.42)	(9.65)	(12.27)
	P-value	<.0001	<.0001	<.0001	<.0001	<.0001
Hippocampus, mm^3	Slope	-64.18	-117.02	-125.49[a,b]	-222.50[a,b,c]	-207.81[a,b,c]
	SE	(8.83)	(29.46)	(8.15)	(10.63)	(13.34)
	P-value	<.0001	<.0001	<.0001	<.0001	<.0001

Abbreviations: AD, Alzheimer's disease; CN, normal control; CNc, converter CN; MCI, mild cognitive impairment; MCIc, converter MCI.
Note: Significant slope is at least $P < 0.05$.
[a]Significantly different from CN.
[b]Significantly different from CNc.
[c]Significantly different from MCI.
[d]Significantly different from MCIc.
[e]Significantly different from AD.

(Table 3). After dichotomizing groups into $A\beta+$ and $A\beta-$, CN $A\beta+$ becomes statistically higher in contrast to CN $A\beta-$ ($P < 0.05$) among others (Table SA1).

SNAP-25: Baseline levels of SNAP-25 are significantly higher in AD and MCIc as compared to CN, CNc, and MCI ($P < 0.05$) (Table 3). Longitudinally, SNAP-25 levels decrease significantly for AD ($P = 0.028$) (Table 3). Moreover, these baseline levels are statistically significant between the CN $A\beta+$ and CN $A\beta-$ ($P < 0.05$) groups as well as in other groups (Table SA1).

YKL-40: Although baseline levels of YKL-40 in CNc and MCIc are much lower than in CN and MCI, there are no significant differences between them. The YKL-40 baseline levels are statistically lower in

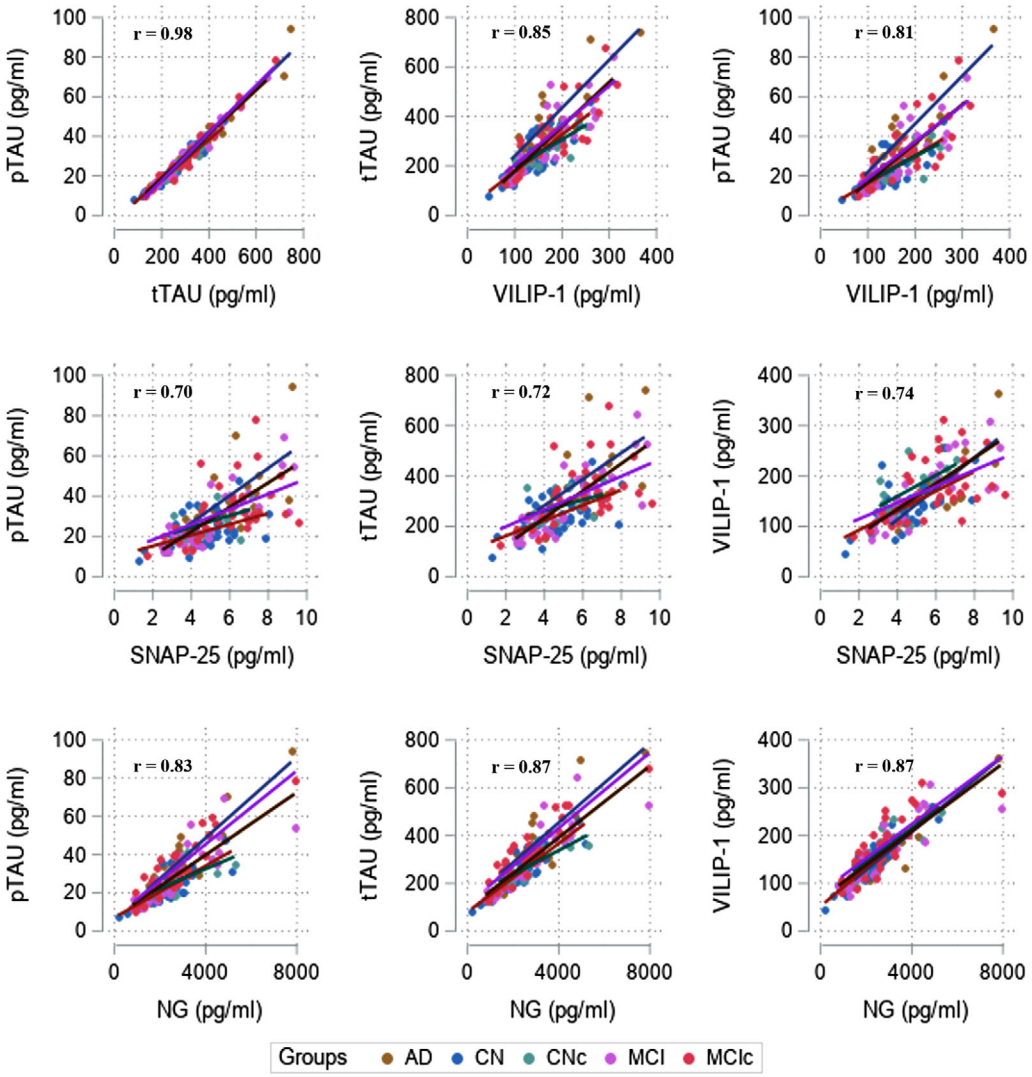

FIGURE 2 Pearson correlations (r ≥ 0.65) between CSF and neural injury biomarkers. Abbreviations: CSF, Aβ42, amyloid beta cerebrospinal fluid; Ng, neurogranin; pTau, phosphorylated tau181; SNAP-25, synaptosomal-associated protein-25; tTau, total tau; VILIP-1, visinin-like protein 1; AD, Alzheimer's disease; CN, normal control; CNc, converter CN; MCI, mild cognitive impairment; MCIc, converter MCI

CNc and MCIc than in AD ($P < 0.05$). Longitudinally, only a decrease in YKL-40 in the MCIc group shows significance ($P = 0.0003$) (Table 3). The longitudinal pattern of change of YKL-40 becomes statistically significant for CNc Aβ− after stratifying the CN group ($P = 0.018$). Finally, YKL-40 shows a significant positive slope for the MCIc Aβ+ group ($P = 0.003$) (Table SA1).

NG: It is evident that the baseline levels of NG are higher in the AD group when compared to the CN and MCI groups ($P < 0.05$). Longitudinally, the AD group displays a great decrease in mean NG levels over time as compared to other groups ($P < 0.0001$) (Table 3). Moreover, these baseline levels are statistically significant between the CN Aβ+ and CN Aβ− ($P < 0.05$), as well as others (Table SA1).

Positive correlations between biomarkers at the baseline level are the strongest between pTau and tTau with **r** = 0.98, VILIP-1 and tTau with r = 0.85, and VILIP-1 and pTau with **r** = 0.81. NG and tTau, pTau, and VILIP-1 with **r** of 0.83, 0.87, and 0.87, respectively. SNAP-25 is moderately correlated with tTau, pTau, and VILIP-1 with **r** of 0.72, 0.70, and 0.74, respectively (Figure 2). Aβ42 is significant, but weakly negatively correlated with t-tau with r = −0.22 and pTau with r = −0.32. YKL-40 is weakly positively correlated with tTau, pTau, VILIP-1, SNAP-25, and NG, with **r** in the range between 0.29 and 0.46 (Table SA4).

3.3 | Baseline and longitudinal characteristics of demographic and cognitive performance tests for MRI study

The mean age of most subgroups is ≈73-years-old (SD, ±10 months), except for CNc subjects, with a mean age of 76. The percentage of female participants in subgroup populations is higher than that of male participants in the CN and CNc groups but lower in all others. The concentration of *APOE* ε4 negatives shows a generally decreasing trend with increasing cognitive impairment. MMSE shows increases in the rate of decline, which is higher for progressively impaired

subgroups (CN < CNc < MCI < MCIc < AD). All other cognitive measures (ADAS11, ADAS13, CDRSB) show the same trend but are opposite in direction (Table 2).

3.4 | Baseline and longitudinal characteristics of MRI biomarkers

The baseline levels and longitudinal patterns of change for the MRI biomarkers of the five groups are presented in Table 4 and further stratified into Aβ+ and Aβ− (Table SA2). Moreover, baseline concentrations and longitudinal rates of change of the entorhinal thickness and the hippocampus are plotted for each of the five groups in Figure 3.

Entorhinal thickness: At baseline, entorhinal thickness decreases along with cognitive decline across all five groups. The levels are statistically lower ($P < 0.05$) in AD when compared to CN, CNc, MCI, and MCIc. Baseline levels are also statistically lower ($P < 0.05$) in MCIc compared to CN, CNc, and MCI as well as for MCI when compared to CN. Longitudinally, all groups show significant decrease ($P < 0.05$) in mean levels over time, with a steeper decline in AD (Table 4). In Aβ+ groups, baseline levels are greater than those of Aβ− subjects for CN, MCI, and AD, but lower in the converter groups. Longitudinally, all groups except CNc Aβ− and AD Aβ+ have negative rates of change of significant value ($P < 0.05$) (Table SA2).

Inferior parietal lobule: Baseline levels of the inferior parietal lobule are statistically lower ($P < 0.05$) for AD when compared to CN and MCI. These levels are also statistically lower ($P < 0.05$) in MCIc when compared to CN and MCI. Over time, all groups show significant decreases in mean levels, with the highest decrease for AD (Table 4). After dichotomizing for Aβ+ and Aβ−, longitudinal levels decrease significantly ($P < 0.05$) in the Aβ+ group as compared to the Aβ− group except for stable CN where the difference in slopes was not significant at $P < 0.05$ (Table SA2).

Inferior temporal lobule: Baseline levels of the inferior temporal gyrus are statistically lower ($P < 0.05$) for AD compared to CN and MCI. They are also statistically lower ($P < 0.05$) in MCIc compared to CN and MCI. All groups show a significant decrease ($P < 0.05$) in mean levels over time with the highest decrease for AD (Table 4). For converters with Aβ+, baseline levels are larger than those of Aβ−, but this is not visible in any of the stable groups. All Aβ+ groups have significantly steeper ($P < 0.05$) negative rates of change than their counter Aβ− groups (Table SA2)

Precuneus: The baseline volumes of the precuneus region are statistically lower ($P < 0.05$) for AD subjects when compared to CN and MCI. The annual rate of change is significantly lower ($P < 0.05$) for AD in contrast to all other groups (Table 4). On the other hand, such baseline volumes are statistically lower ($P < 0.05$) for AD Aβ+ than for CN Aβ+, CN Aβ−, MCI Aβ+, and MCI Aβ−. Longitudinally, the volumetric rates of change are statistically different ($P < 0.05$) for Aβ+ versus Aβ− only for the MCI group (Table SA2).

Temporal Pole: Baseline volumes of the temporal pole region are statistically lower for AD compared to CN and MCIs as well as for MCIc when compared to CN. The annual rate of change is significantly more negative ($P < 0.05$) for AD compared to all other groups except MCIc (Table 4). There is no statistically significant difference at $P < 0.05$ for the baseline levels of this biomarker when separating according to Aβ status. Longitudinally, the rates of change are statistically different ($P < 0.05$) for CN Aβ+ and Aβ−, CNc Aβ+ versus Aβ−, and MCI Aβ+ and Aβ− (Table SA2).

Hippocampus: As shown in Table 4, baseline levels of the hippocampal region are significantly lower ($P < 0.05$) for AD than for CN, CNc, and MCI. Longitudinally, the AD and MCIc groups show the greater decreases in mean volume. Table SA2 shows a statistically significant difference ($P < 0.05$) between AD Aβ+ and CNc Aβ− and MCI Aβ−. Longitudinally, the hippocampal biomarker for the Aβ+ groups shows a steeper decline than for the Aβ− groups.

3.5 | Association between CSF and MRI biomarkers

Based on the combination of the CSF and MRI biomarkers and Aβ pathology, there are 91 amyloid-positive and 49 amyloid-negative subjects. Longitudinal associations between CSF and MRI biomarkers are shown in Figure 4. Over time, YKL-40 was associated with a decrease in entorhinal thickness in the Aβ+ as well as in the Aβ− groups ($P = 0.025$ and $P = 0.0026$, respectively). In addition, YKL-40 was associated with temporal pole atrophy in Aβ+ ($P = 0.021$). Over time, tTau ($P = 0.036$), pTau ($P = 0.008$), and VILIP-1 ($P = 0.0267$) were associated with smaller hippocampal volumes in the Aβ+ groups.

4 | DISCUSSION

The primary goal of this study was to evaluate structural MRI and CSF biomarkers in the ADNI cohort, at baseline and longitudinally, to determine their utility for AD diagnosis and prognosis as well as to investigate the association between CSF and signature AD MRI biomarkers.

The CSF analysis yields the following findings:

1. The levels of pTau, the ratio of pTau to Aβ42, and SNAP-25 were higher in both the MCIc and AD groups compared with the CN and CN converters, whereas the levels of tTau and VILIP-1 were lower in the CN group than in the MCIc group. Of interest, the levels of YKL-40 were lower in the CN and MCI converter groups than in AD group. The NG levels were statistically higher in AD compared to the CN and MCIc groups. Our findings indicate that AD has a CSF profile consistent with AD pathology, with lower Aβ42 and higher tTau and pTau levels compared to the other groups, in alignment with prior AD studies.[22–24]
2. There was a statistically significant increase over time in the concentration of pTau for cognitively normal subjects but this lessened with increasing cognitive impairment, before decreasing rapidly to a negative slope for the AD group with statistical significance. The tTau levels displayed a trend similar to that of the pTau levels, except for the CNc, MCI, and MCIc groups, where there is a

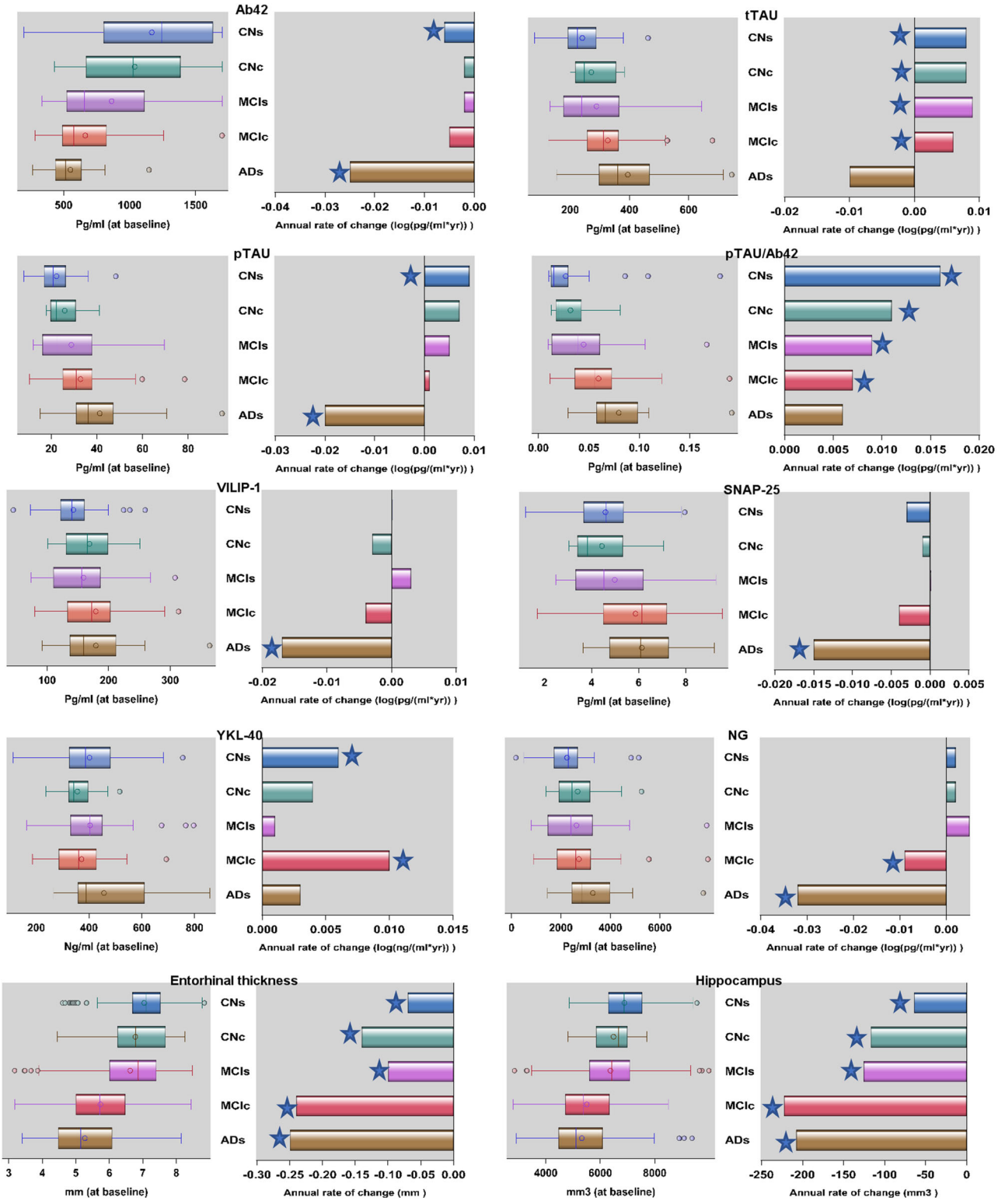

FIGURE 3 Baseline boxplots and longitudinal rate of change for the CSF and selected MRI biomarkers. Abbreviations: CSF, Aβ42, amyloid beta cerebrospinal fluid; Ng, neurogranin; pTau, phosphorylated tau181; SNAP-25, synaptosomal-associated protein-25; tTau, total tau; VILIP-1, visinin-like protein 1; YKL-40, chitinase-3-like protein 1. *Note*: Significant slope is *P*-value <0.05, represented by asterisk

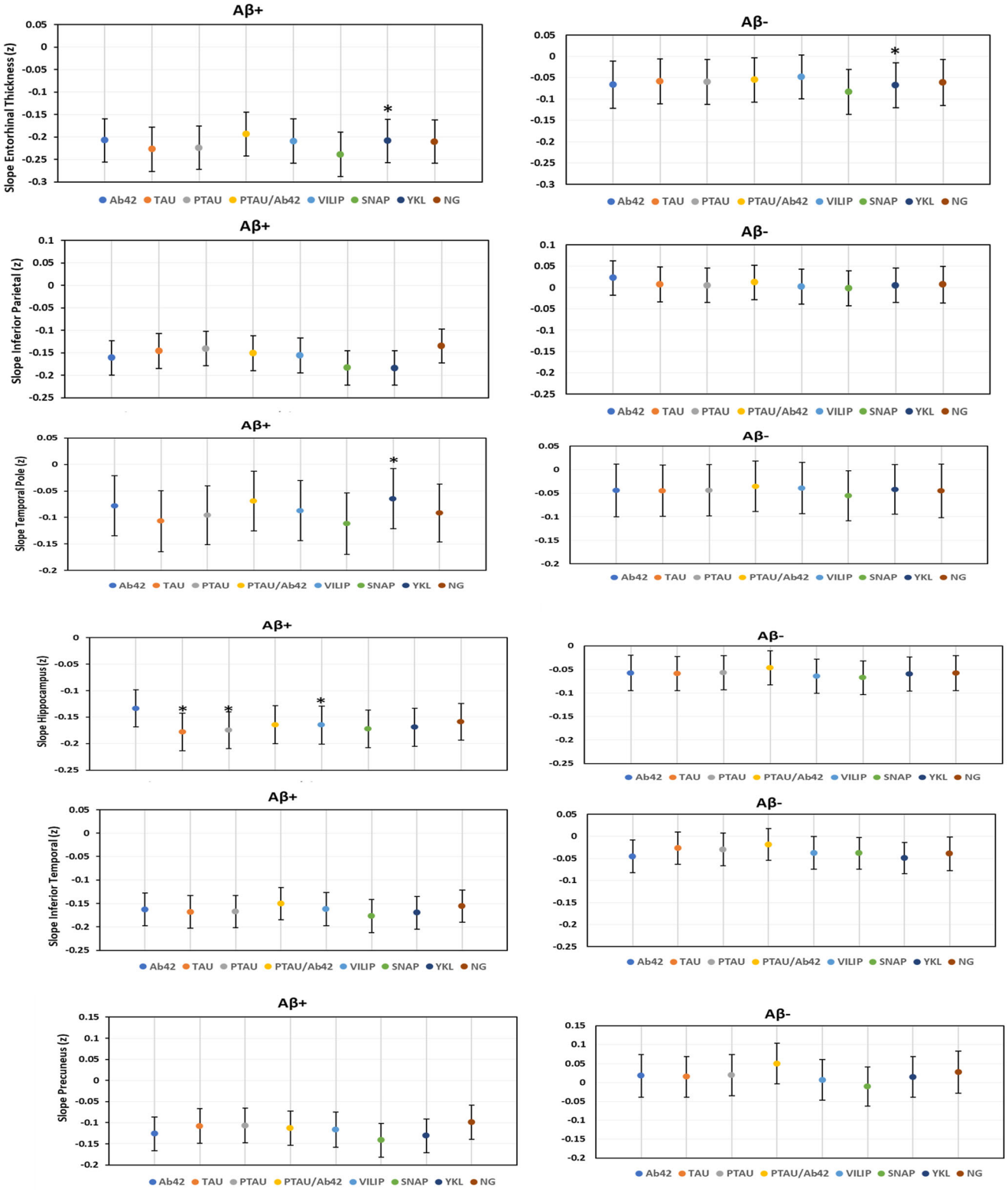

FIGURE 4 Longitudinal association between cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) biomarkers. The effects are the estimates (β coefficients) with corresponding 95% CIs from the linear mixed models, which are effects of time and the biomarker by time interactions. CSF and MRI biomarkers were z transformed to normalize the distributions and to allow for comparison to neuroimaging measures. Abbreviations: Aβ42, amyloid beta cerebrospinal fluid; Ng, neurogranin; pTau, phosphorylated tau181; SNAP-25, synaptosomal-associated protein-25; tTau, total tau; VILIP-1, visinin-like protein 1; YKL-40, chitinase-3-like protein 1; Aβ+, amyloid positive; Aβ-, amyloid negative.
Note: Effects are significant at $P < 0.05$, represented by star

statistically significant difference present. Moreover, our findings confirm some prior studies on neural injury biomarkers including VILIP-1, SNAP- 25, YKL-40, and NG.[22,25] In particular, VILIP-1, YKL-40, and NG decreased rapidly in the AD cohort, and the YKL-40 concentration increased rapidly in the MCI subjects who progressed to AD.

3. We observed a statistically difference between amyloid positive and amyloid negative within the CN and MCIc diagnostic groups for pTau, tTau, pTau/Aβ*42*, VILIP-1, and NG. SNAP-25 showed significance between amyloid groups only in the MCIc group. Such findings can assist in diagnosis, utilizing the amyloid (A), tau (T), neurodegeneration (N) research framework.[21]

Amyloid biomarkers establish the presence of AD pathology, which may or may not be the primary underlying pathology causing cognitive impairment or dementia. It is now clear that the presence of underlying amyloid pathology is associated with more rapid clinical progression of cognitive and functional impairment. Amyloid biomarkers can be used for the selection of participants with the target pathology for anti-amyloid pharmaceutical agents in clinical trials. Pre-clinical AD participants do not show any evidence of cognitive abnormalities (although they may have declined from past cognitive performance levels) and can be identified only through the use of biomarkers for secondary prevention or delay of disease trials. Cognitively normal individuals with negative amyloid or normal CSF levels of Aβ are subjects for primary prevention trials, whereas individuals with normal cognition and evidence of abnormal brain amyloid can be participants in secondary prevention trials. It is also anticipated, as it is common practice, that amyloid biomarkers will be used for the selection of patients who may receive approved anti-amyloid agents for the disease-modifying treatment of AD. The utility of biomarkers for underlying tau, neurodegeneration, and associated pathology is likely to aid the staging of the disease, predicting future course, and determining response to treatment. These biomarkers can also be used in clinical trials to determine outcomes and target engagement. Thus trials that use biomarker outcomes and consider the subject's Aβ status can be shorter, require fewer enrolled subjects necessary to show clinical benefit statistically, and are more cost effective, especially among patients with probable AD, CN to MCI converters, stable MCI, MCI to AD converters, and control participants .

The main findings of the MRI analysis are:

1. The entorhinal thickness and hippocampal volume are the primary MRI biomarkers that indicate atrophy in the early stages (CN to MCI) among analyzed regions of interest.
2. Subjects with positive amyloid deposition experienced brain atrophy at a faster rate than those without amyloid deposition.
3. There is no significant in-group variability of the baseline levels of MRI biomarkers between the different amyloid subgroups.
4. The baseline levels and longitudinal changes Entorhinal Thickness, Inferior Parietal lobule, Inferior Temporal lobule, Temporal Pole, Hippocampus could be used to predict whether MCI patients will progress to AD.

This study also shows that although all groups displayed brain atrophy over time, its rate is steeper in groups with subsequently increasing cognitive impairments. That is, CN showed the least brain atrophy rate, followed by CNc, and then by MCI, MCIc, and finally AD, which displays the steepest rate of brain atrophy. This association between amyloid accumulation and brain atrophy with AD progression has also been shown in previous studies.[26–30] Our results reflect strong evidence that amyloid positivity is associated with physiological brain changes, such as accelerated volumetric decline in multiple cortical areas across CN, CNc, MCI, and MCIc groups.

The longitudinal association between CSF and MRI biomarkers analysis revealed that:

1. Over time, YKL-40 was associated with atrophy in the temporal pole region in the amyloid-positive group and in entorhinal thickness (both in amyloid-positive groups).
2. tTau, pTau, and VILIP-1 are associated with hippocampus atrophy in the amyloid-positive group.

These results suggest that YKL-40, tTau, pTau, and VILIP-1 may respond to neurodegeneration in AD.

It is worth noting that there are limitations to our study. The relatively small sample sizes in some of the groups in this research might affect the statistical power necessary to detect significant differences. This also limits the generality of our results to wider populations, and it requires validation in larger cohorts. In future studies, we could include additional relevant biomarkers such as neurofilament light, an indicator of neuro-axonal damage,[30,31] as they were used successfully in Mielke et al.[30] to predict changes in white matter integrity but Tosun et al.[31] could not detect amyloid positivity in the participants. This suggest that more research could be performed in terms of its feasibility for AD progression assessment.

5 | CONCLUSIONS

This study produced an in-depth analysis of the baseline and longitudinal rates of change of several AD biomarkers with respect to cognitive impairment and Aβ positivity. It looked at the role played by CN and MCI converters, which has been ignored or looked over in the past. By doing so, we have provided evidence that although certain biomarkers can be used to predict which cognitively impaired individuals will progress to AD, others showed little to no significance. Furthermore, Aβ status was not significant across groups for baseline measurements of MRI volumes, whereas it did show significance for the CSF biomarkers. However, YKL-40, tTau, pTau, and VILIP-1 did show significant longitudinal changes associated with MRI biomarker atrophy. Nonetheless, Aβ status did show significance in the rate of change of MRI biomarkers.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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