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RESEARCH ARTICLE

sTREM2 in discordant CSF Aβ_{42} and p-tau181

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Abstract

INTRODUCTION: Little is known about the factors underpinning discordant cerebrospinal fluid (CSF) amyloid beta (Aβ)$_{42}$ versus p-tau181/Aβ_{42} or CSF Aβ_{42} versus Aβ positron emission tomography (PET).

METHODS: We stratified 570 non-demented Alzheimer's Disease Neuroimaging Initiative (ADNI) participants by Aβ PET and further by CSF Aβ_{42} or p-tau181/Aβ_{42}. We used analysis of covariance testing adjusting for covariates, followed by Tukey post hoc pairwise comparisons, to compare CSF soluble triggering receptor expressed on myeloid cells-2 (sTREM2) across four participant groups: CSF+ $_{A\beta42}$ with CSF− $_{p\text{-}tau/A\beta42}$, CSF− $_{A\beta42}$ with CSF+ $_{p\text{-}tau/A\beta42}$, and concordant CSF$_{A\beta42}$/CSF$_{p\text{-}tau/A\beta42}$. We also compared sTREM2 across discordant and concordant CSF$_{A\beta42}$/PET.

RESULTS: Regardless of Aβ PET status, CSF+$_{A\beta42}$ with CSF−$_{p\text{-}tau/A\beta42}$ had lower sTREM2 than CSF−$_{A\beta42}$ with CSF+$_{p\text{-}tau/A\beta42}$. CSF sTREM2 was similarly also associated with discordant CSF Aβ42 /PET.

DISCUSSION: Our study suggests the potential roles of sTREM2 in discordant CSF Aβ_{42} and p-tau181/Aβ_{42} and discordant CSF$_{A\beta42}$/PET. Low- and high-CSF sTREM2 may affect the accuracy of p-tau181/Aβ_{42} during the clinical work-up of AD.

KEYWORDS
Alzheimer's disease (AD), amyloid-β PET, CSF$_{A\beta42}$, CSF$_{p\text{-}tau/A\beta42}$, CSF sTREM2

Highlights

- 17% of non-demented older adults had discordant CSF Aβ_{42} versus p-tau181/Aβ_{42}.
- sTREM2 differed between discordant cases of CSF Aβ_{42} versus p-tau181/Aβ_{42}.

- 20% of non-demented older adults had discordant CSF Aβ_{42} versus Aβ PET.
- sTREM2 also differed between discordant cases of CSF Aβ_{42} versus Aβ PET.
- p-tau181/Aβ_{42} may miss 6.7% of PET+ non-demented older adults with low sTREM2.

1 | BACKGROUND

Alzheimer's disease (AD) is now a biologically defined entity that follows a stereotypical "pathophysiological cascade" starting with abnormal amyloid beta (Aβ) followed by abnormal phosphorylated tau (p-tau), neurodegeneration, and clinical symptoms.[1] A recent longitudinal study demonstrated that cerebrospinal fluid (CSF) Aβ_{42} and A$\beta_{42/40}$ ratio diverged 18 and 14 years before symptom onset, respectively, between those who developed AD later and those who did not, compared to 11 years of CSF p-tau181, confirming that changes in CSF Aβ_{42} and A$\beta_{42/40}$ ratio precede p-tau181.[2] Despite the temporal differences, Aβ_{42} and p-tau181 are frequently used separately for confirming underlying AD pathology. Specifically, FDA-approved tests employ ratios of CSF Aβ_{42} and p-tau181 (ie, CSF Aβ_{42}/$_{40}$ and p-tau181/Aβ_{42}), which were shown to be superior to the individual biomarkers when compared to Aβ positron emission tomography (PET).[3] CSF Aβ_{42}/$_{40}$ and p-tau181/Aβ_{42} were equally predictive of amyloid-β PET status in participants from the Mayo Clinic Study of Aging and their associated Alzheimer's Disease Research Center.[4] However, it is not infrequent for patients to have discordant results with these CSF ratios or individual biomarkers (CSF Aβ_{42}, A$\beta_{42/40}$, p-tau181, p-tau181/Aβ_{42}).[5,6] Furthermore, some patients exhibit discordant results between CSF Aβ_{42} and Aβ PET.[7]

In this study, we investigated CSF soluble triggering receptor expressed on myeloid cells 2 (sTREM2) between discordant cases of CSF Aβ_{42} versus p-tau181/Aβ_{42} and of CSF Aβ_{42} versus Aβ PET. CSF sTREM2 is a surrogate marker for microglial activation that plays a crucial role in AD development. While the roles of TREM2 and sTREM2 in the pathophysiology of AD are complex and still a matter of active research, an emerging body of knowledge shows that increased sTREM2 is associated with slowed rates of atrophy and clinical progression.[8–11] TREM2 is crucial for microglia to compact Aβ, leading to plaques that, in turn, limit the spread of Aβ, preserve the neurites of nearby neurons, and ultimately may play a neuroprotective role.[12] sTREM2 results from the proteolytic shedding of TREM2 and is known to activate microglia, bind oligomeric Aβ_{42}, and protect against Aβ pathology in mice.[13] Recent studies suggest the roles of high sTREM2 in attenuating the decrease of CSF Aβ_{42} while simultaneously increasing p-tau181 in patients with abnormal Aβ,[8,14] pointing to the relevance of sTREM2 for the interpretation of CSF Aβ_{42} and p-tau181 in the clinical setting. The current work thus examines CSF sTREM2 in discordant CSF Aβ_{42} and p-tau181/Aβ_{42} and discordant CSF Aβ_{42} and Aβ PET in non-demented participants in ADNI. We use Aβ_{42} instead of Aβ_{42}/$_{40}$ because ADNI has limited Aβ_{40} data to calculate the ratio. Although Aβ_{42} is not used clinically for diagnosing AD, Aβ_{42} is superior to Aβ_{42}/$_{40}$ for detecting earlier changes,[2] and CSF Aβ_{42} alone has been widely used in research studies to identify AD. We use p-tau181/Aβ_{42} because it is clinically used for diagnosis of AD.

2 | METHODS

2.1 | Study participants

Data used to prepare this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, fluid biomarkers, and clinical and neuropsychological assessment could be combined to measure the progression of mild cognitive impairment (MCI) and early AD.

We included ADNI participants without dementia who were cognitively normal (CN) or had MCI. Participants were included if they also had available (1) CSF Aβ_{42} and CSF p-tau181, (2) CSF sTREM2, (3) Aβ PET, (4) demographic/medical information (age, sex, and body mass index [BMI]), and (5) the ε4 allele of the apolipoprotein E gene (*APOE4*) carrier status. CN participants had Mini-Mental State Examination (MMSE) scores between 24 and 30 and a global Clinical Dementia Rating (CDR) of 0.[15] MCI participants had MMSE scores between 24 and 30, a global CDR score of 0.5, a CDR memory score of 0.5 or greater, and objective memory impairment on the Wechsler Memory Scale – Logical Memory II test.[15] Participants were excluded if they had (1) a diagnosis of dementia documented at their baseline visit and (2) a time difference exceeding 180 days between the dates documented for Aβ PET and CSF biomarker (Aβ_{42}, sTREM2) examinations. Applying these criteria resulted in a final study population of 570 participants. Table S1 lists the data files used for biomarker variables.

Ethics approval was obtained by the ADNI investigators from the local ethics committees of all involved sites, and informed consent was obtained from all participants or legal guardian(s)/legally authorized representatives. All methods were carried out according to relevant guidelines and regulations. Per the Institutional Review Board of the University of Minnesota, this study was non-human subject research.

2.2 | AD biomarkers

CSF Aβ_{42} and p-tau181 were assessed by a fully automated Elecsys Cobas e 601 instrument by the ADNI Biomarker Core and CSF sTREM2 by Meso Scale Discovery ELISA by Christian Haass's lab.[9,16,17] ADNI

performed ^{18}F-florbetapir PET acquisition and analysis according to previous protocols.[18,19] Specifically, ADNI used a native-space structural MRI scan that was closest in time to each Aβ PET scan and first segmented and parcellated the MRI scan with Freesurfer (FS) version 7.1.1 and then coregistered to the Aβ PET imaging with statistical parametric mapping (SPM). The Aβ PET measurement reflected the tracer uptake in a cortical summary standardized uptake value ratio (SUVR) (ie, composed of frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal regions, defined by the Desikan–Killiany atlas) and captured the overall amyloid burden in the brain. ADNI normalized PET intensity using the whole cerebellum. This study used the ADNI-recommended 1.11 cutoff to determine amyloid positivity based on the upper limit of cortical uptake in whole cerebellum-normalized SUVRs in young control samples.[20]

We defined CSF Aβ_{42} positivity as <976.6 pg/mL, which was optimized for Aβ PET concordance,[21] in the primary analysis. To ensure the robustness of the study results, we used two different Aβ_{42} cut points (<880 pg/mL and <1100 pg/mL), which were not optimized for Aβ PET concordance in ADNI. Specifically, an Aβ_{42} cut point <1100 pg/mL was optimized for the BioFINDER cohort; a cut point <880 pg/mL was based on 1100 pg/mL and an adjustment factor of 0.8, which accounted for pre-analytical differences from the BioFINDER to the ADNI cohort.[21]

The CSF p-tau181/Aβ_{42} or A$\beta_{42/40}$ ratio is superior to CSF Aβ_{42} alone for identifying patients with AD, primarily due to the robustness of the ratios against the impact of pre-analytical factors and differences in the processing of amyloid precursor protein.[22] The CSF p-tau181/Aβ_{42} ratio was calculated based on the Roche Elecsys CSF p-tau181 and Aβ_{42} tests reported in their original units of ng/mL and pg/mL, respectively. A CSF p-tau181/Aβ_{42} ratio >0.023 is FDA-approved to confirm underlying AD pathology (ie, consistent with a positive Aβ PET scan result).[4] Because the Roche Elecsys CSF Aβ_{42} test has an upper reportable limit of 1700 pg/mL, we assigned a value of 1701 pg/mL to the Elecsys Aβ_{42} values >1700 pg/mL for the CSF p-tau181/Aβ_{42} calculations.[4]

2.3 | MRI scans

Prior research suggested abnormal CSF flow dynamics as an explanation for false-positive CSF Aβ_{42} but normal p-tau181/Aβ_{42} ratio[23,24] or normal Aβ PET.[25] A board-certified neurologist with a subspecialty training in behavioral/cognitive neurology (WGM) visually evaluated 41 MRI scans of PET− participants with CSF+ $_{A\beta42}$ with CSF− $_{p\text{-}tau/A\beta42}$ and 18 MRI scans of PET+ participants with CSF+ $_{A\beta42}$ with CSF− $_{p\text{-}tau/A\beta42}$ for findings of disproportionate enlargement of subarachnoid space (DESH).[26]

2.4 | Statistical analysis

ANOVA was used to compare continuous variables (eg, age, Aβ PET SUVR, CSF Aβ_{42}, CSF p-tau181/Aβ_{42}, and CSF sTREM2) and reported means and standard deviations and chi-squared tests to compare categorical variables (eg, cognitive status, sex, and *APOE4* presence) across biomarker categories and reported counts and percentages in Table 1. An analysis of covariance (ANCOVA) test with adjustment for age, sex, *APOE4* status, and cognitive status followed by Tukey post hoc pairwise comparisons was used to determine whether CSF sTREM2 between any two groups was significantly different (Tukey adjusted $p < .05$).

RESEARCH CONTEXT

1. **Systematic review**: We reviewed the literature using Google Scholar and found that despite the many existing studies of CSF sTREM2, none examined whether CSF sTREM2 underpins discordant CSF Aβ_{42} versus p-tau181/Aβ_{42} or CSF Aβ_{42} versus Aβ PET.
2. **Interpretation**: Our findings demonstrated a substantial minority of non-demented older adults had discrepant CSF results according to CSF Aβ_{42} versus p-tau181/Aβ_{42} ratio or CSF Aβ_{42} versus Aβ PET, which were associated with opposite CSF sTREM2 levels. Our results are consistent with prior work examining CSF sTREM2, Aβ_{42}, and p-tau181 and suggest low and high sTREM2 may affect the accuracy of using the p-tau181/Aβ_{42} ratio for clinical diagnosis of AD.
3. **Future directions**: We want to study the possibility of adding CSF sTREM2 to improve the diagnostic accuracy of AD biomarkers and understand the biological factors contributing to differences in CSF sTREM2.

3 | RESULTS

3.1 | Categorization of study participants based on CSF Aβ42 or p-tau181/Aβ42 and Aβ PET

We first divided the 570 non-demented ADNI participants into Aβ PET− (n = 301) and PET+ (n = 269). We used the ADNI-recommended >1.11 cutoff to determine Aβ PET positivity.[18,20] We then divided each PET group into CSF− and CSF+ based on Aβ_{42} or p-tau181/Aβ_{42}. For the CSF Aβ_{42} cut point, we used <976.6 pg/mL, determined to achieve optimal concordance with Aβ PET in ADNI.[21] For CSF p-tau181/Aβ_{42}, we used >0.023, which is approved by the FDA for identifying AD. Using the combination of CSF and PET biomarkers, we ended up with four groups (CSF−/PET−, CSF+/PET−, CSF−/PET+, CSF+/PET+) for each of the Aβ_{42} and p-tau181/Aβ_{42} CSF categorizations. Table 1 lists the demographics of four biomarker categories based on CSF Aβ_{42} and PET (left) and CSF p-tau181/Aβ_{42} and PET (right). Of 301 PET− participants, 246 and 55 were classified based on Aβ_{42} as CSF− and CSF+, respectively; 277 and 24 were classified as

TABLE 1 Demographic and data across biomarker categories based on CSF Aβ_{42} and PET (left) and CSF p-tau181/Aβ_{42} and PET (right).

		CSF Aβ42					CSF p-tau181/Aβ42				
		PET− (301)		PET+ (269)			PET− (301)		PET+ (269)		
	Total	CSF−/PET−	CSF+/PET−	CSF−/PET+	CSF+/PET+	*p* value	CSF−/PET−	CSF+/PET−	CSF−/PET+	CSF+/PET+	*p* value
N	570	246	55	57	212		277	24	47	222	
Age (year)	71.9 (7.0)	70.8 (7.0)	70.0 (7.2)	72.8 (7.1)	73.3 (6.6)	<.001	70.3 (7.0)	74.2 (6.9)	72.2 (6.4)	73.4 (6.8)	<.001
BMI (kg/m^2)	27.6 (4.8)	28.3 (4.8)	27.3 (4.9)	27.4 (5.2)	26.8 (4.5)	.0090	28.3 (4.9)	26.4 (4.4)	28.2 (5.4)	26.7 (4.5)	.0011
Sex											
Female (*n*)	266 (47%)	119 (48%)	17 (31%)	37 (65%)	93 (44%)	.0028	127 (46%)	9 (38%)	29 (62%)	101 (45%)	.1527
Male (*n*)	304 (53%)	127 (52%)	38 (69%)	20 (35%)	119 (56%)		150 (54%)	15 (62%)	18 (38%)	121 (55%)	
Cognitive status											
CN (*n*)	205 (36%)	115 (47%)	22 (40%)	21 (37%)	47 (22%)	<.001	129 (47%)	8 (33%)	22 (47%)	46 (21%)	<.001
MCI (*n*)	365 (64%)	131 (53%)	33 (60%)	36 (63%)	165 (78%)		148 (53%)	16 (67%)	25 (53%)	176 (79%)	
***APOE4* carrier status**											
No (*n*)	331 (58%)	197 (80%)	34 (62%)	37 (65%)	63 (30%)	<.001	218 (79%)	13 (54%)	33 (70%)	67 (30%)	<.001
Yes (*n*)	239 (42%)	49 (20%)	21 (38%)	20 (35%)	149 (70%)		59 (21%)	11 (46%)	14 (30%)	155 (70%)	
CSF Aβ42 (pg/mL)	1104.6 (447.9)	1513.4 (236.6)	780.0 (157.7)	1277.9 (249.6)	667.9 (176.0)	<.001	1421.2 (329.9)	897.4 (369.9)	1169.4 (375.5)	718.4 (236.5)	<.001
Amyloid PET (SUVR)	1.2 (0.2)	1.0 (0.1)	1.0 (0.1)	1.3 (0.2)	1.4 (0.2)	<.001	1.0 (0.1)	1.1 (0.1)	1.2 (0.1)	1.4 (0.2)	<.001
CSF p-tau (ng/mL)	25.0 (13.4)	19.5 (6.7)	15.4 (7.6)	32.0 (15.9)	32.1 (15.1)	<.001	17.8 (5.9)	29.5 (10.1)	18.9 (6.1)	34.9 (15.1)	<.001
CSF p-tau/Aβ42[1]	29.3 (24.9)	13.0 (4.6)	21.6 (14.2)	26.5 (15.4)	51.0 (27.2)	<.001	12.7 (3.4)	35.9 (13.6)	16.7 (4.1)	52.0 (25.8)	<.001
CSF sTREM2 (pg/mL)	3904.5 (2123.6)	3907.7 (2066.8)	2694.6 (1417.6)	5075.4 (2222.2)	3899.7 (2150.5)	<.001	3552.7 (1830.7)	5225.3 (3192.5)	4019.3 (2105.1)	4176.3 (2240.7)	<.001

Note: For continuous variables, means, standard deviations, and *p* values from ANOVAs are reported; for categorical variables, counts, percentages, and *p* from chi-squared tests are reported. CSF p-tau/Aβ42 ratio was calculated using the original unit (ie, [ng/mL]/[pg/mL]), and then the results were scaled by 1000 to avoid preceding zeros. Therefore, the FDA-approved cut point of >0.023 using the original unit (ie, [ng/mL]/[pg/mL]) should be scaled accordingly by 1000 to be >23.

Abbreviation: sTREM2, soluble triggering receptor expressed on myeloid cells 2; SUVR, standardized uptake value ratio.

TABLE 2 Demographics and data of participants who had different CSF classifications depending on $A\beta_{42}$ versus p-tau181/$A\beta_{42}$ (CSF+ $_{A\beta42}$ with CSF− $_{\text{p-tau/A}\beta42}$ and CSF− $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$).

	PET− (51/301)		PET+ (46/269)		
	CSF+ $_{A\beta42}$ with CSF− $_{\text{p-tau/A}\beta42}$	CSF− $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$	CSF+ $_{A\beta42}$ with CSF− $_{\text{p-tau/A}\beta42}$	CSF− $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$	*p* value
N	41	10	18	28	
Age (year)	68.9 (7.7)	75.9 (9.5)	76.3 (6.0)	75.9 (7.5)	<.001
BMI (kg/m2)	27.7 (4.8)	26.7 (2.6)	28.7 (4.9)	27.0 (4.6)	.7897
Sex					
Female (*n*)	12 (29%)	4 (40%)	7 (39%)	15 (54%)	.1594
Male (*n*)	29 (71%)	6 (60%)	11 (61%)	13 (46%)	
Cognitive status					
CN (*n*)	16 (39%)	2 (20%)	10 (56%)	9 (32%)	.3435
MCI (*n*)	25 (61%)	8 (80%)	8 (44%)	19 (68%)	
***APOE4* carrier Status**					
No (*n*)	27 (66%)	6 (60%)	12 (67%)	16 (57%)	.7759
Yes (*n*)	14 (34%)	4 (40%)	6 (33%)	12 (43%)	
CSF Aβ42 (pg/mL)	823.8 (123.1)	1241.2 (277.3)	783.2 (132.9)	1142.1 (153.6)	<.001
Amyloid PET (SUVR)	1.0 (0.1)	1.0 (0.1)	1.2 (0.1)	1.4 (0.2)	<.001
CSF p-tau (ng/mL)	12.1 (3.1)	35.8 (8.6)	14.1 (3.6)	42.5 (16.5)	<.001
CSF p-tau/Aβ42[1]	15.0 (4.1)	29.0 (5.0)	18.2 (4.1)	37.5 (15.0)	<.001
CSF sTREM2 (pg/mL)	2245.1 (1086.9)	6925.1 (4165.6)	3465.5 (2428.8)	5813.2 (2372.3)	<.001

Note: For continuous variables, means, standard deviations, and *p* values from ANOVAs are reported; for categorical variables, counts, percentages, and *p* from chi-squared tests are reported. CSF p-tau/Aβ42 ratio was calculated using the original unit (ie, [ng/mL]/[pg/mL]), and then the results were scaled by 1000 to avoid preceding zeros. Therefore, the FDA-approved cut point of >0.023 using the original unit (ie, [ng/mL]/[pg/mL]) should be scaled accordingly by 1000 to be >23.

Abbreviation: sTREM2, soluble triggering receptor expressed on myeloid cells 2; SUVR, standardized uptake value ratio.

CSF− and CSF+ based on p-tau181/$A\beta_{42}$, respectively. Of 269 PET+ participants, 57 and 212 were classified based on $A\beta_{42}$ as CSF− and CSF+, respectively; 47 and 222 were classified as CSF− and CSF+ based on p-tau181/$A\beta_{42}$, respectively.

Of the 570 participants, 19.6% (112/570) had CSF/PET discordant groups (ie, CSF+/PET− and CSF-/PET+) based on CSF $A\beta_{42}$, higher than 12.4% (or 71/570) of participants with CSF/PET discordant groups based on CSF p-tau181/$A\beta_{42}$. The CSF/PET concordant groups (ie, CSF−/PET− and CSF+/PET+) based on CSF $A\beta_{42}$ were similar to the CSF/PET concordant groups based on CSF p-tau181/$A\beta_{42}$ in that both age and percentage of participants with MCI gradually increased in parallel to CSF and PET positivity, with CSF−/PET− demonstrating lower and CSF+/PET+ demonstrating higher age and percentage of participants with MCI. The CSF/PET discordant groups (ie, CSF+/PET− and CSF−/PET+) based on CSF $A\beta_{42}$ were similar to the CSF/PET discordant groups based on CSF p-tau181/$A\beta_{42}$ in that there were more male in the CSF+/PET− groups than in the CSF−/PET+ groups. However, age between the discordant CSF/PET groups had reverse directions: based on CSF $A\beta_{42}$, CSF+/PET− participants were younger than CSF−/PET+ participants (70.0 [7.2] years vs 72.8 [7.1] years), whereas, based on p-tau181/$A\beta_{42}$, CSF+/PET− participants were older than CSF−/PET+ participants (74.2 [6.9] years vs 72.2 [6.4] years).

3.2 | sTREM2 in participants with discordant CSF $A\beta_{42}$ and p-tau181/$A\beta_{42}$

Table 2 summarizes the participants who had different CSF classifications depending on $A\beta_{42}$ versus p-tau181/$A\beta_{42}$, along with demographics, CSF p-tau181, and CSF sTREM2 (Table 2). Among the 301 PET− participants, 41 had CSF+ $_{A\beta42}$ with CSF− $_{\text{p-tau/A}\beta42}$. These participants had low CSF p-tau181 (mean [SD]: 12.1[3.1] pg/mL), despite low $A\beta_{42}$. Ten PET− participants had CSF− $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$. These participants had high CSF p-tau181 (35.8 [8.6] pg/mL), despite normal $A\beta_{42}$ (Figure 1A,B,C). The 41 CSF+ $_{A\beta42}$ with CSF− $_{\text{p-tau/A}\beta42}$ participants had lower sTREM2 than 10 CSF− $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$ participants (2245.1 [1086.9] vs 6925.1 [4165.6] pg/mL, Tukey adjusted *p* value < .0001, by ANCOVA test adjusting for age, sex, *APOE4* status, and cognitive status followed by Tukey post hoc pairwise group comparisons) (Table 2 and Figure 1D). CSF p-tau181/$A\beta_{42}$ classified 41 more PET− participants correctly compared to $A\beta_{42}$ but classified 10 more PET− participants incorrectly compared to $A\beta_{42}$ (Figure 1A).

Among the 269 PET+ participants, 18 had CSF+ $_{A\beta42}$ with CSF− $_{\text{p-tau/A}\beta42}$. These participants had low p-tau181 (14.1[3.6] pg/mL), despite decreased $A\beta_{42}$. Twenty-eight PET+ participants had CSF−

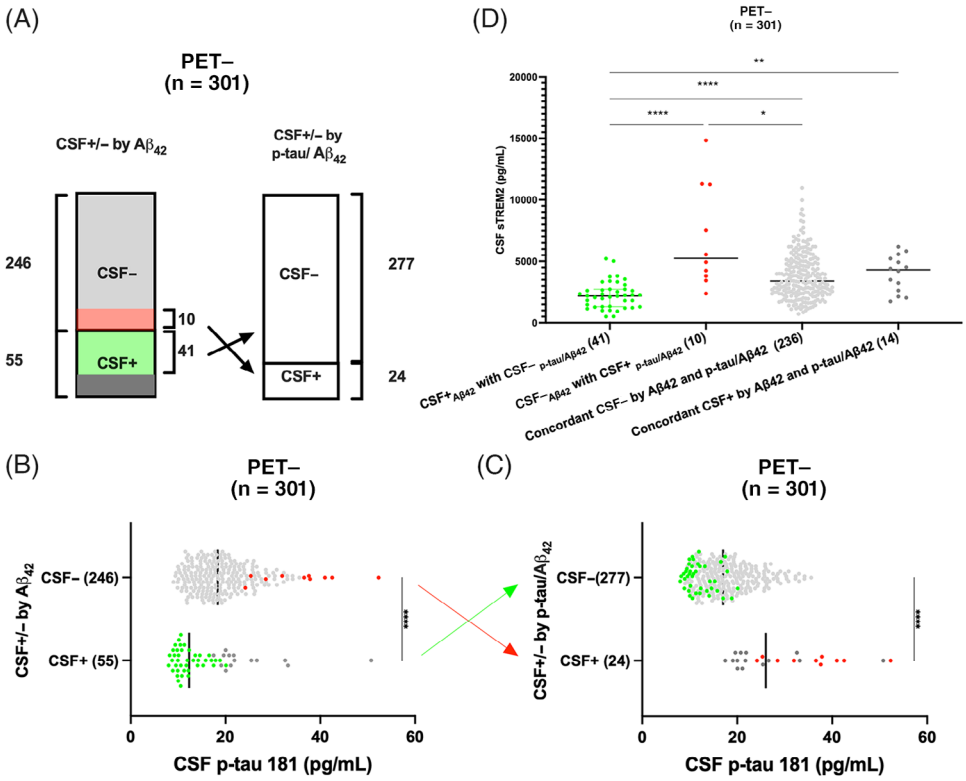

FIGURE 1 CSF p-tau181 and sTREM2 within PET– participants who had different CSF classifications depending on Aβ_{42} versus p-tau181/Aβ_{42}. (A) Illustration of PET– participants who were CSF+ $_{A\beta42}$ with CSF– $_{p\text{-}tau/A\beta42}$ (green) and CSF– $_{A\beta42}$ with CSF+ $_{p\text{-}tau/A\beta42}$ (red). (B) CSF p-tau181 concentrations of CSF– and CSF+ based on Aβ_{42}; an ANOVA test was used to determine whether p-tau181 differed between CSF– and CSF+. (C) CSF p-tau181 concentrations of CSF– and CSF+ based on p-tau181/Aβ_{42}; an ANOVA test was used to determine whether p-tau181 differed between CSF– and CSF+. (D) CSF sTREM2 concentrations of participants who were CSF+ $_{A\beta42}$ with CSF– $_{p\text{-}tau/A\beta42}$ (green), CSF– $_{A\beta42}$ with CSF+ $_{p\text{-}tau/A\beta42}$ (red), concordant CSF– by Aβ_{42} and p-tau/Aβ_{42} (light gray), and concordant CSF+ by Aβ_{42} and p-tau/Aβ_{42} (dark gray); an analysis of covariance test with adjustment for age, sex, *APOE4* status, and cognitive status followed by Tukey post hoc pairwise comparisons was used to determine whether CSF sTREM2 between any two groups was significantly different (Tukey adjusted p value < .05). *: .01 < p or Tukey adjusted p value < .05; **: .001 < p or Tukey adjusted p value < .05; ***: 0.0001 < p or Tukey adjusted p value < .001; ****: p or Tukey adjusted p value < .0001. sTREM2, soluble triggering receptor expressed on myeloid cells-2.

$_{A\beta42}$ with CSF+ $_{p\text{-}tau/A\beta42}$. These participants had high CSF p-tau181 (42.5 [16.5] pg/mL), despite normal Aβ_{42} (Figure 2A,B,C). The 18 CSF+ $_{A\beta42}$ with CSF– $_{p\text{-}tau/A\beta42}$ participants had lower sTREM2 than the 28 CSF– $_{A\beta42}$ with CSF+ $_{p\text{-}tau/A\beta42}$ participants (3465.5[2428.8] vs 5813.2 [2372.3] pg/mL, Tukey adjusted p value < .001) (Table 2 and Figure 2D). P-tau181/Aβ_{42} classified 28 more PET+ participants correctly compared to Aβ_{42}, but it classified 18 more PET+ participants incorrectly compared to Aβ_{42} (Figure 2A).

Although a decrease in CSF Aβ_{42} is the earliest pathology of AD, and CSF Aβ_{42} alone has been widely used in research studies to identify AD, there is no consensus on which CSF Aβ_{42} cut points should be used to diagnose AD. To ensure our results were robust for different CSF Aβ_{42} cut points, we used two more CSF Aβ_{42} cut points: 880 and 1100 pg/mL that were not optimized for Aβ PET concordance in ADNI. Figure S1 demonstrated that the sTREM2 results were similar when different CSF Aβ_{42} cut points were used, in that CSF+ $_{A\beta42}$ with CSF– $_{p\text{-}tau/A\beta42}$ participants had lower sTREM2 than CSF– $_{A\beta42}$ to CSF+ $_{p\text{-}tau/A\beta42}$, regardless of amyloid PET status (ie, PET– or PET+).

3.3 | sTREM2 in participants with discordant CSF Aβ_{42} and Aβ PET

In addition to discordant CSF Aβ_{42} and p-tau181/Aβ_{42}, we investigated CSF sTREM2 levels in discordant CSF Aβ_{42} and Aβ PET (left side of Table 1). Of the 570 participants, 112 had discordant CSF Aβ_{42} and Aβ PET: 55 were CSF+/PET– and 57 CSF–/PET+. The 55 CSF+/PET– participants had lower sTREM2 levels than the 57 CSF–/PET+ participants (2694.6 [1417.6] vs 5075.4 [2222.2] pg/mL, Tukey adjusted p value < .001) (Figure 3). Figure S2 demonstrates that the sTREM2 results were similar when different CSF Aβ_{42} cut points (< 880 pg/mL and < 1100 pg/mL) were used, in that CSF+/PET– participants had lower sTREM2 than CSF–/PET+ participants.

4 | DISCUSSION

We found that there were more participants with CSF/PET discordant based on CSF Aβ_{42} and PET than based on CSF p-tau181/Aβ_{42}

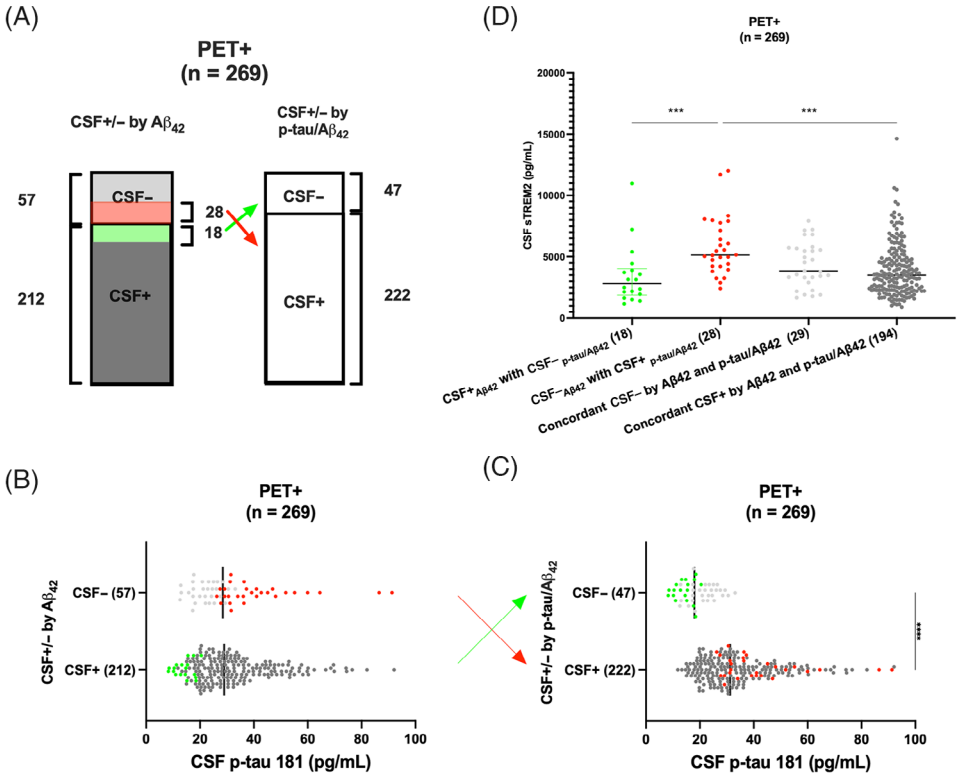

FIGURE 2 CSF p-tau181 and sTREM2 within PET+ participants who had different CSF classifications depending on $A\beta_{42}$ versus p-tau181/$A\beta_{42}$. (A) Illustration of PET+ participants who were CSF+ $_{A\beta42}$ with CSF– $_{\text{p-tau/A}\beta42}$ (green) and CSF– $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$ (red). (B) CSF p-tau181 concentrations of CSF– and CSF+ based on $A\beta_{42}$; an ANOVA test was used to determine whether p-tau181 differed between CSF– and CSF+. (C) CSF p-tau181 concentrations of CSF– and CSF+ based on p-tau181/$A\beta_{42}$; an ANOVA test was used to determine whether p-tau181 differed between CSF– and CSF+. (D) CSF sTREM2 concentrations of participants who were CSF+ $_{A\beta42}$ with CSF– $_{\text{p-tau/A}\beta42}$ (green), CSF– $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$ (red), concordant CSF– by $A\beta_{42}$ and p-tau/$A\beta_{42}$ (light gray), and concordant CSF+ by $A\beta_{42}$ and p-tau/$A\beta_{42}$ (dark gray); an analysis of covariance test with adjustment for age, sex, *APOE4* status, and cognitive status followed by Tukey post hoc pairwise comparisons was used to determine whether CSF sTREM2 between any two groups was significantly different (Tukey adjusted p value < .05). *: .01 < p or Tukey adjusted p value < .05; **: .001 < p or Tukey adjusted p value < .05; ***: .0001 < p or Tukey adjusted p value < .001; ****: p or Tukey adjusted p value < .0001. sTREM2, soluble triggering receptor expressed on myeloid cells-2.

and PET (19.6% [or 112/570] vs 12.4% [or 71/570]), consistent with previous findings that p-tau181/$A\beta_{42}$ was superior to $A\beta_{42}$ when compared to Aβ PET.[3] The study's primary finding is that a substantial minority (approximately 17%) of non-demented older adults had discrepant CSF results according to $A\beta_{42}$ versus the p-tau181/$A\beta_{42}$ ratio, which was associated with opposite CSF sTREM2 levels. Participants who were classified as positive by $A\beta_{42}$ but negative by p-tau181/$A\beta_{42}$ ratio (ie, CSF+ $_{A\beta42}$ with CSF– $_{\text{p-tau/A}\beta42}$) had lower sTREM2 than those participants who were classified as negative by $A\beta_{42}$ but positive by p-tau181/$A\beta_{42}$ (ie, CSF– $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$), regardless of Aβ PET status (ie, PET– or PET+). Similarly, approximately 20% of non-demented older adults had discordant CSF $A\beta_{42}$ and Aβ PET results, which was associated with opposite CSF sTREM2 levels, in that CSF+/PET– participants had lower sTREM2 levels than CSF–/PET+ participants. Of note, CSF sTREM2 is significantly associated with Aβ plaque-related increase in CSF p-tau181.[14,27] In addition, a longitudinal study from the Dominantly Inherited Alzheimer Network (DIAN) cohort found that in early pre-symptomatic stages of AD, an augmented annual rate of increase in sTREM2 was associated with a diminished annual rate decrease in CSF $A\beta_{42}$, consistent with a theory that microglia clustering around the smallest Aβ seeds at a very early stage of AD reduces the growth and spread of Aβ.[8] For participants with low sTREM2 and decreased CSF $A\beta_{42}$ with normal CSF p-tau181/$A\beta_{42}$, insufficient sTREM2 may be implicated in abnormal $A\beta_{42}$ without concomitant increase in p-tau181. For those with high sTREM2 with normal CSF $A\beta_{42}$ but abnormal CSF p-tau181/$A\beta_{42}$, high sTREM2 may increase Aβ-related p-tau181 while attenuating the decrease of CSF $A\beta_{42}$. Our results have implications for the clinical diagnosis of AD in that the CSF p-tau181/$A\beta_{42}$ ratio may miss the 6.7% (or 18/269) of PET+ non-demented older adults with decreased $A\beta_{42}$, low p-tau181, and low sTREM2 (ie, CSF+ $_{A\beta42}$ with CSF– $_{\text{p-tau/A}\beta42}$). In PET– participants, CSF p-tau181/$A\beta_{42}$ ratio may misclassify the 3.3% (or 10/301) of PET– non-demented older adults with normal $A\beta_{42}$, high p-tau181, and high sTREM2 (ie, CSF– $_{A\beta42}$ with CSF+ $_{\text{p-tau/A}\beta42}$).

A low CSF $A\beta_{42}$ but normal p-tau181/Aβ42 (ie, CSF+ $_{A\beta42}$ with CSF– $_{\text{p-tau/A}\beta42}$) may be due to abnormal CSF dynamics such as normal pressure hydrocephalus.[23,24] We examined the MRI scans of CSF+ $_{A\beta42}$ with CSF– $_{\text{p-tau/A}\beta42}$ participants to rule out abnormal CSF flow

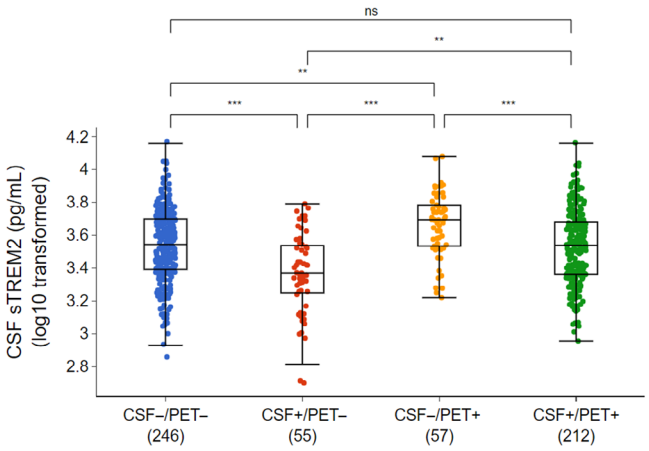

FIGURE 3 CSF sTREM2 levels across biomarker categories based on CSF Aβ_{42} (< 976.6 pg/mL) and Aβ PET. An analysis of covariance test with adjustment for age, sex, *APOE4* status, and cognitive status followed by Tukey post hoc pairwise comparisons was used to determine whether CSF sTREM2 between any two groups was significantly different (Tukey adjusted p value < .05). *Tukey adjusted p value < .05; **: .001 ≤ Tukey's adjusted p value < .01; ***: Tukey adjusted p value < .001. ns: not significant; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

dynamics. Four of the 41 CSF+ $_{A\beta42}$ with CSF− $_{p\text{-tau/A}\beta42}$ PET− participants and three of the 18 CSF+ $_{A\beta42}$ with CSF− $_{p\text{-tau/A}\beta42}$ PET+ participants had one or more radiographic features of DESH (high and tight cerebral convexity, enlarged sylvian fissures, or ventriculomegaly disproportionate to cerebral atrophy). We conducted Fisher exact tests to compare the prevalence of DESH in our study to that of Graff-Radford et al., who reported that 6.6% (or 45/684) of healthy participants had evidence of DESH per an automated MRI assessment.[28] The p values exceeded .05, suggesting that the prevalence of DESH in our study of CSF+ $_{A\beta42}$ with CSF− $_{p\text{-tau/A}\beta42}$ PET− and PET+ participants were not statistically significant from that of Graff-Radford et al.

This study's strength includes analyzing a comprehensive ADNI dataset to elucidate the role of CSF sTREM2 behind discordant CSF Aβ_{42} and p-tau181/Aβ_{42} results and discordant CSF Aβ_{42} and Aβ PET results. Due to limited CSF Aβ_{40} data availability in ADNI, we were unable to assess whether there were any discrepant participants by CSF A$\beta_{42/40}$ and p-tau181/Aβ_{42} and whether CSF sTREM2 differed between discordant CSF A$\beta_{42/40}$ and p-tau181/Aβ_{42} results. Also, we do not know the underlying factors that influence CSF sTREM2 levels, of which there are many, such as multiple sclerosis,[29] genetic variants (eg, rs7232, a missense variant in the MS4A6A gene of chromosome 11), and biological processes for regulating viruses and immune response.[30] We cannot rule out non-AD conditions that can increase p-tau181, such as vascular dementia.[31] Another limitation is that ADNI's study population differs from that of community studies. Therefore, additional studies with more representation of diverse cohorts are needed to generalize and expand upon our findings.

5 | CONCLUSIONS

This study demonstrated opposite CSF sTREM2 levels in discordant CSF Aβ_{42} and p-tau181/Aβ_{42} and discordant CSF Aβ_{42} and Aβ PET. Our results are consistent with prior work examining CSF sTREM2, Aβ_{42}, and p-tau181 and suggest low and high sTREM2 levels may affect the accuracy of the p-tau181/Aβ_{42} ratio in the clinical diagnosis of AD.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

All raw data used in this study are freely available from https://ida.loni.usc.edu.

CONSENT STATEMENT

Consent was not necessary for the study.

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SUPPORTING INFORMATION

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

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