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Association of CSF Aβ, amyloid PET, and cognition in cognitively unimpaired elderly adults

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Abstract

Objective

To compare CSF β-amyloid (Aβ) and florbetapir PET measurements in cognitively unimpaired (CU) elderly adults in order to detect the earliest abnormalities and compare their predictive effect for cognitive decline.

Methods

A total of 259 CU individuals were categorized as abnormal (+) or normal (−) on CSF $A\beta_{1\text{-}42}$/$A\beta_{1\text{-}40}$ analyzed with mass spectrometry and Aβ PET measured with ^{18}F-florbetapir. Simultaneous longitudinal measurements of CSF and PET were compared for 39 individuals who were unambiguously Aβ-negative at baseline (CSF−/PET−). We also examined the relationship between baseline CSF/PET group membership and longitudinal changes in CSF Aβ, Aβ PET, and cognition.

Results

The proportions of individuals in each discordant group were similar (8.1% CSF+/PET− and 7.7% CSF−/PET+). Among baseline Aβ-negative (CSF−/PET−) individuals with longitudinal CSF and PET measurements, a larger proportion subsequently worsened on CSF Aβ (odds ratio 4 [95% confidence interval (CI) 1.1, 22.1], $p = 0.035$) than Aβ PET over 3.5 ± 1.0 years. Compared to CSF−/PET− individuals, CSF+/PET− individuals had faster (estimate 0.009 [95% CI 0.005, 0.013], $p < 0.001$) rates of Aβ PET accumulation over 4.4 ± 1.7 years, while CSF−/PET+ individuals had faster (estimate −0.492 [95% CI −0.861, −0.123], $p = 0.01$) rates of cognitive decline over 4.5 ± 1.9 years.

Conclusions

The proportions of discordant PET and CSF Aβ-positive individuals were similar cross-sectionally. However, unambiguously Aβ-negative (CSF−/PET−) individuals are more likely to show subsequent worsening on CSF than PET, supporting the idea that CSF detects the earliest Aβ changes. In discordant cases, only PET abnormality predicted cognitive decline, suggesting that abnormal Aβ PET changes are a later phenomenon in cognitively normal individuals.

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Alzheimer's Disease Neuroimaging Initiative coinvestigators are listed in appendix 2 at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CI** = confidence interval; **CU** = cognitively unimpaired; **FCSRT** = Free and Cued Selective Reminding Test; **LME** = linear mixed effects; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **PACC** = Preclinical Alzheimer Cognitive Composite; **SUVR** = standardized uptake value ratio.

Amyloid plaques have been regarded as the earliest detectable change in the Alzheimer disease (AD) pathway.[1] Approximately 30% of cognitively unimpaired (CU) adults over age 70 have biomarker evidence of abnormal β-amyloid (Aβ) pathology[2] as measured by CSF Aβ ($Aβ_{1-42}$[3–5] or the $Aβ_{1-42}$/$Aβ_{1-40}$ ratio[4–11]) and Aβ PET imaging.[12–15]

Although agreement between CSF Aβ and Aβ PET classified as abnormal/normal (+/−) measured cross-sectionally is relatively high,[3,4,16–18] many discordant cases have been reported across samples,[3–5,8,9,17,19–26] particularly in CU cohorts.[4,19–21,24] Use of the CSF $Aβ_{1-42}$/$Aβ_{1-40}$ ratio may compensate for interindividual variations in total Aβ production and thereby more precisely identify AD-related $Aβ_{1-42}$ reduction.[4–11] However, the proportion of CSF−/PET+ individuals was not influenced by the use of the $Aβ_{1-42}$/$Aβ_{1-40}$ ratio,[5–8] suggesting that Aβ PET abnormality in the absence of CSF abnormality is not due to measurement error and Aβ PET may indeed be observed first. Simultaneous longitudinal CSF and PET trajectories have never been examined to verify which measurement shows the earliest detectable abnormal changes in Aβ. To this end, we investigated relationships between cross-sectional and longitudinal CSF $Aβ_{1-42}$/$Aβ_{1-40}$ and ^{18}F-florbetapir PET in CU elderly adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We also examined the extent to which CSF Aβ and Aβ PET contribute different information to prediction of cognitive change[18–21,27,28] by investigating their associations with longitudinal cognitive change.

Methods

Participants

The data were obtained from the ADNI database (ida.loni.usc.edu). The participants in this study were CU individuals at baseline who had the following concurrent (interval <1 year) measurements available: florbetapir PET scan, structural MRI, and CSF $Aβ_{1-42}$ and $Aβ_{1-40}$ assessed with mass spectrometry. All the participants had ≥2 subsequent longitudinal cognitive tests. We classified CU individuals into 4 CSF/PET groups based on CSF+/− and PET+/− using thresholds of CSF $Aβ_{1-42}$/$Aβ_{1-40}$ and florbetapir standardized uptake value ratio (SUVR).

Standard protocol approvals, registrations, and patient consents

The ADNI study was approved by institutional review boards of all participating centers, and written informed consent was obtained from all participants or their authorized representatives.

Florbetapir PET

Details on florbetapir image acquisition are given elsewhere (adni-info.org). Baseline and follow-up florbetapir scans were coregistered to baseline structural MRI scans. Cortical retention in 34 Freesurfer-defined regions of interest was calculated using Freesurfer (V5.3.0) as described previously.[29] Florbetapir SUVRs were calculated as a ratio of regional florbetapir to that in the whole cerebellum. The SUVRs from a composite cortical area (made up of frontal, cingulate, parietal, and temporal regions)[29] were averaged to create a cortical summary SUVR. Aβ PET positivity was defined as composite SUVR ≥1.11.[30] The longitudinal SUVR slope was calculated using SUVRs that referred to a composite reference region (made up of brainstem, whole cerebellum, and eroded white matter) because this region has shown superior stability in longitudinal analyses.[29] A linear mixed effects (LME) model was used to estimate longitudinal florbetapir SUVR change (SUVR unit per year) over time including the following independent variables: time, *APOE* ε4 status, age at baseline, and sex, and a random slope and intercept for each participant.

CSF biomarkers

The CSF $Aβ_{1-42}$/$Aβ_{1-40}$ ratio was calculated using CSF $Aβ_{1-42}$ and $Aβ_{1-40}$ analyzed by the ADNI Biomarker core laboratory via 2D-UPLC-tandem mass spectrometry, as described in a previous report.[31] The threshold of CSF $Aβ_{1-42}$/$Aβ_{1-40}$ positivity was set as ≤0.138, which corresponds to the intersection of low and high distributions estimated by a Gaussian mixture model based on all 762 ADNI participants with CSF $Aβ_{1-42}$/$Aβ_{1-40}$ mass spectrometry measurements.[32] An LME model was used to estimate longitudinal CSF $Aβ_{1-42}$/$Aβ_{1-40}$ change (CSF $Aβ_{1-42}$/$Aβ_{1-40}$ per year) over time including the following independent variables: time, *APOE* ε4 status, age at baseline, and sex, and a random slope and intercept for each participant.

Longitudinal worsening of CSF Aβ and Aβ PET from CSF−/PET− individuals

Based on the design of ADNI, which obtains CSF and PET measurements at essentially the same timepoint, longitudinal worsening of CSF $Aβ_{1-42}$/$Aβ_{1-40}$ ratio and florbetapir SUVR in CSF−/PET− was determined by examining simultaneous baseline and follow-up CSF $Aβ_{1-42}$/$Aβ_{1-40}$ ratios and florbetapir SUVRs at the same time points. In order to determine the direction of change in CSF $Aβ_{1-42}$/$Aβ_{1-40}$ and florbetapir SUVR during the same period, we also used LME models (adjusting for *APOE* ε4 status, age at baseline, and sex, and including a random slope and intercept for each participant) to calculate annual rates of CSF $Aβ_{1-42}$/$Aβ_{1-40}$ and florbetapir SUVR using 2 or 3 CSF and PET measurements acquired at

approximately 2-year intervals, for a mean follow-up duration of 3.5 ± 1.0 years. The number of CSF and PET measurements was matched for each participant depending on the data available (see Results). For CSF $A\beta_{1-42}/A\beta_{1-40}$, we defined worsening as a negative slope, and for florbetapir PET SUVRs, we defined worsening as a positive slope. We used a 2-tailed McNemar χ^2 test to compare the proportion of worsening cases. Participants were then assigned to 1 of the 4 categories depending on whether 1, both, or neither biomarker showed worsening.

Cognitive tests

The previously validated Preclinical Alzheimer Cognitive Composite (PACC) score was used in this study.[33] The PACC composite score was calculated by combining *z* scores of several cognitive tests, including the total recall score from the Free and Cued Selective Reminding Test (FCSRT), the delayed recall score on the logical memory IIa subtest from the Wechsler Memory Scale, the digit symbol substitution test score from the Wechsler Adult Intelligence Scale–Revised, and the Mini-Mental State Examination (MMSE) total score. FCSRT is not used in ADNI, so the delayed recall portion of the Alzheimer's Disease Assessment Scale is used as a proxy. An LME model was used to estimate longitudinal PACC change (PACC per year) over time including the following independent variables: time, *APOE* ε4 status, age at baseline, sex, and education, and a random slope and intercept for each participant.

Influence of CSF Aβ and Aβ PET discordance on hypothetical therapeutic trials

Two possible schemes for recruiting Aβ-positive CU older adults into hypothetical anti-Aβ drug trials were compared: using CSF+ and using PET+. We calculated the sample sizes needed to detect a treatment effect in a hypothetical 4-year placebo-controlled clinical anti-AD drug trial with 80% power and a 2-tailed $\alpha = 0.05$ for these recruiting schemes.

Statistical analysis

Normality of distributions was tested using the Shapiro-Wilk test and visual inspection of data histograms. Data are presented as mean ± SD. Given a normal distribution of variables, a 2-tailed *t* test at the significance level of $p < 0.05$ was applied to compare demographic characteristics at baseline in different CSF/PET groups if not otherwise noted. A false discovery rate of 0.05 using the Benjamini-Hochberg approach[34] was employed for multiple comparisons correction. We assessed categorical differences using the Fisher exact test.

LME models were used to investigate longitudinal changes of CSF $A\beta_{1-42}/A\beta_{1-40}$ ratio and florbetapir SUVR over time in different CSF/PET groups of all the participants (regardless of simultaneous baseline and follow-up or not) with longitudinal CSF and PET data including the following independent variables: time, CSF/PET groups, CSF/PET groups × time, *APOE* ε4 status, age at baseline, and sex. LME models were also used to investigate how *APOE* ε4 status and sex affect longitudinal changes of CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR in all participants with longitudinal CSF and PET data, controlling for age at baseline. We subsequently used LME models to investigate longitudinal change of PACC decline over time in different CSF/PET groups of all the participants with longitudinal PACC data, controlling for *APOE* ε4 status, age at baseline, sex, and education. In addition, we used LME models to investigate the relationship with continuous CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR and PACC decline over time independently, controlling for the same covariates above. All the LME models included a random slope and intercept for each participant.

We examined the sequential associations between baseline CSF $A\beta_{1-42}/A\beta_{1-40}$, florbetapir SUVR, and PACC slope in a serial mediation model using the Lavaan package,[35] adjusting for *APOE* ε4 status, age at baseline, sex, and education. Total, direct, and indirect associations were calculated via a 5,000-iteration bootstrapping procedure. Note that CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR were standardized, and that the sign of CSF $A\beta_{1-42}/A\beta_{1-40}$ was changed to facilitate the comparison between CSF Aβ and Aβ PET in the mediation model and the LME models. All statistical analysis was employed in statistical program *R* (v3.6.1, The R Foundation for Statistical Computing).

Data availability

All data are available in the ADNI database (ida.loni.usc.edu). Derived data are available from the corresponding author on request by any qualified investigator.

Results

Demographic characteristics of participants in different CSF/PET groups

As shown in table 1 and figure 1, of the 259 CU participants, the majority were CSF−/PET− (58.3%), with the second largest group CSF+/PET+ (25.9%), and almost equal numbers of CSF+/PET− (8.1%) and CSF−/PET+ participants (7.9%). The baseline demographic characteristics can be found in table 1. Compared to CSF−/PET− participants, PET+ groups had significantly higher percentages of female participants, CSF+ groups had significantly higher percentages of *APOE* ε4 carriers, CSF+/PET− participants had significantly higher SUVR, and CSF−/PET+ participants had significantly lower CSF $A\beta_{1-42}/A\beta_{1-40}$. Overall, participants had cognitive follow-up of 4.5 ± 1.9 years and those with longitudinal CSF Aβ and Aβ PET data had 3.5 ± 1.1 and 4.4 ± 1.7 years of follow-up (table 1).

The longitudinal worsening directions of longitudinal CSF Aβ and Aβ PET from CSF−/PET− individuals

We examined simultaneous longitudinal CSF and PET measurements in individuals who were unambiguously Aβ-negative (CSF−/PET−) at baseline in order to determine whether these individuals were more likely to show abnormal CSF or abnormal PET changes during follow-up. Out of 151 CSF−/

Table 1 Demographic characteristics of participants in different CSF/PET groups

CSF/PET groups	CSF−/PET−	CSF+/PET−	CSF−/PET+	CSF+/PET+
259 ADNI cognitively unimpaired participants				
Participants, n (%)	151 (58.3)	21 (8.1)	20 (7.7)	67 (25.9)
Age at baseline, y	72.65 ± 6.54	75.25 ± 6.60	71.83 ± 5.42	75.94 ± 5.51[a]
Education, y	16.91 ± 2.57	16.24 ± 2.02	15.95 ± 3.03	16.19 ± 2.52
Sex, male/female	84/64	10/11	4/16[b]	21/46[b]
***APOE* ε4, %**	16.56	38.10[c]	25.00	52.24[d]
CSF $A\beta_{1-42}/A\beta_{1-40}$	0.202 ± 0.027	0.115 ± 0.022	0.180 ± 0.03[e]	0.100 ± 0.027[f]
SUVR	1.01 ± 0.05	1.05 ± 0.06[g]	1.19 ± 0.09[g]	1.37 ± 0.17[h]
PACC score	0.40 ± 2.81	−0.64 ± 2.60	−0.45 ± 2.70	−0.18 ± 2.86
No. of PACC scores	4.9 ± 1.2	5.3 ± 1.6	4.7 ± 1.6	5.0 ± 1.4
Cognitive follow-up, y	4.5 ± 1.8	5.1 ± 2.0	4.7 ± 2.0	4.4 ± 2.0
69 Participants with longitudinal CSF data				
Sample size ≥2 CSF	41	4	3	21
No. of CSF visits	2.7 ± 0.5	2.5 ± 0.6	2.7 ± 0.6	2.9 ± 0.5
Follow-up of CSF, y	3.4 ± 1.2	3.0 ± 1.2	3.1 ± 1.2	3.8 ± 0.8
226 Participants with longitudinal florbetapir PET data				
Sample size of ≥2 PET	133	19	18	56
Number of PET visits	3.0 ± 0.8	3.4 ± 1.0	2.9 ± 0.8	2.9 ± 0.8
Follow-up of PET, y	4.6 ± 1.7	5.2 ± 1.7	4.4 ± 1.8	4.1 ± 1.7

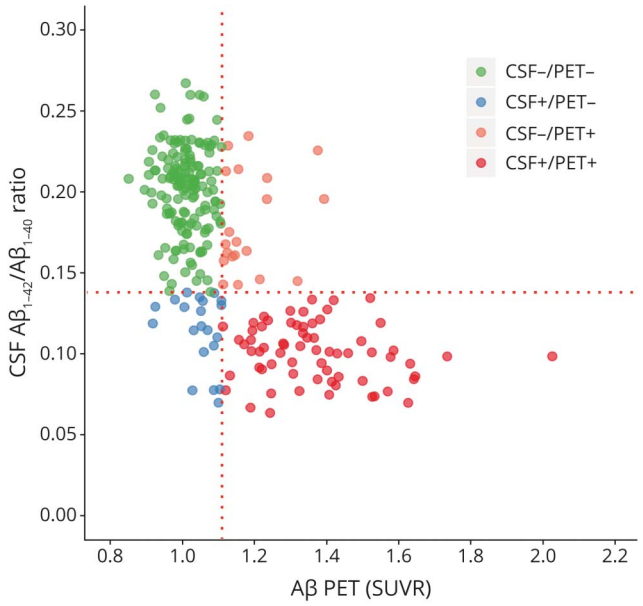
Abbreviations: Aβ = β-amyloid; ADNI = Alzheimer's Disease Neuroimaging Initiative; CI = confidence interval; PACC = Preclinical Alzheimer Cognitive Composite; SUVR = standardized uptake value ratio.
Values are mean ± SD unless indicated otherwise. Multiple comparisons correction was employed (false discovery rate < 0.05).
[a] Age: CSF+/PET+ − CSF−/PET−: estimate 3.29 [95% CI: 1.59, 4.99], $p = 0.001$; CSF+/PET+ > CSF−/PET+: estimate = 4.10 [95% CI: 1.28, 6.93], $p = 0.017$, two-sample t test.
[b] Percentage female: CSF−/PET+ > CSF−/PET−: odds ratio 4.97 [95% CI 1.51, 21.39], $p = 0.004$; CSF+/PET+ > CSF−/PET−: odds ratio 2.73 [95% CI 1.44, 5.32], $p = 0.001$, Fisher exact test.
[c] Percentage *APOE*-ε4: CSF+/PET− > CSF−/PET−: odds ratio 3.07 [95% CI 1.00 ~ 9.03], $p = 0.034$.
[d] Percentage *APOE*-ε4: CSF+/PET+ > CSF−/PET−: odds ratio 5.46 [95% CI 2.76 ~ 11.03], $p < 0.001$, Fisher exact test.
[e] CSF $A\beta_{1-42}/A\beta_{1-40}$: CSF−/PET+ < CSF−/PET−: Estimate −0.023 [95% CI: −0.039, −0.006], $p = 0.006$.
[f] CSF+/PET+< CSF+/PET−: CSF Aβ1-42/Aβ1-40: CSF+/PET+< CSF+/PET−: Estimate = −0.016 [95% CI: −0.027, −0.006], $p = 0.004$, Mann-Whitney test.
[g] SUVR: CSF+/PET− > CSF−/PET−: Estimate = 0.043 [95% CI: 0.019, 0.067], $p = 0.003$.
[h] SUVR: CSF+/PET+ > CSF−/PET+: Estimate = 0.173 [95% CI: 0.101, 0.234], $p < 0.001$, Mann-Whitney test.

PET− individuals, 39 had concurrent baseline and longitudinal CSF and PET measurements at the same time points (PET scan and lumbar puncture were conducted within ≤3 months of one another). Of this group, 13 individuals had 2 measurements (baseline and 2-year follow-up) and 26 individuals had 3 measurements (baseline, 2-year, and 4-year follow-up) for a total duration of 3.5 ± 1.0 years of follow-up. As shown in figure 2, 5 worsened (e.g., CSF slope decreased or PET slope increased) on neither, 12 worsened on CSF $A\beta_{1-42}/A\beta_{1-40}$, 3 worsened on florbetapir SUVR, and 19 worsened on both, demonstrating that CSF−/PET− individuals were more likely to worsen on CSF $A\beta_{1-42}/A\beta_{1-40}$ (odds ratio [OR] 4 [95% confidence interval (CI) 1.1, 22.1], $p = 0.035$, McNemar χ^2 test) than on florbetapir SUVR. The result was substantially the same (OR 5 [95% CI 1.1, 46.9], $p = 0.04$) when only individuals with 3 longitudinal measurements were used (4 worsened on neither, 10 worsened on CSF $A\beta_{1-42}/A\beta_{1-40}$, 2 worsened on florbetapir SUVR, and 10 worsened on both).

Longitudinal biomarker changes in different CSF/PET groups and by *APOE* ε4 status and sex

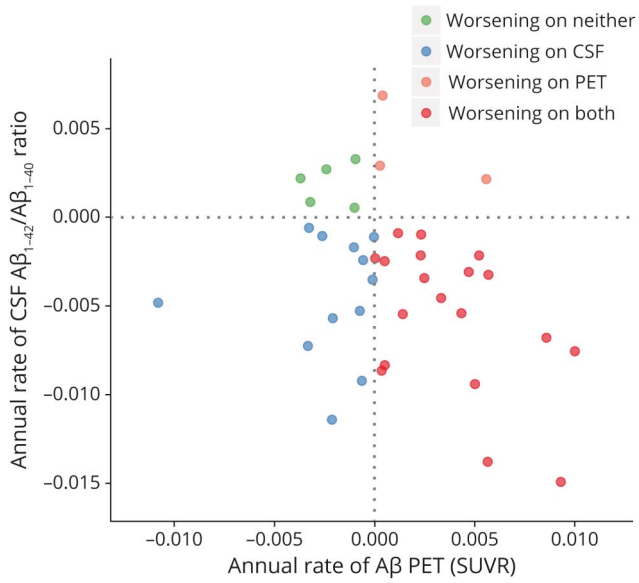
We used LME models to investigate how CSF/PET groups, *APOE* ε4 status, and sex affect longitudinal changes of CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR in all the participants with longitudinal CSF and PET data. As shown in figure 3, A and C, CSF−/PET− and CSF−/PET+ but not CSF+/PET− and CSF+/PET+ participants had significant decreases in CSF $A\beta_{1-42}/A\beta_{1-40}$. In addition, CSF−/PET+ participants had

Figure 1 Scatterplot of CSF/PET groups categorized by CSF β-amyloid (Aβ) and Aβ PET



Horizontal and vertical red dash lines denote the corresponding thresholds of CSF $A\beta_{1-42}/A\beta_{1-40}$ ratio (0.138) and florbetapir standardized uptake value ratio (SUVR) (1.11), respectively.

Figure 2 Longitudinal worsening directions of CSF β-amyloid (Aβ) and Aβ PET from CSF−/PET− individuals



Annual rates of CSF $A\beta_{1-42}/A\beta_{1-40}$ ratio and florbetapir standardized uptake value ratio (SUVR) were calculated in 39 CSF−/PET− individuals with simultaneous baseline and longitudinal CSF Aβ and Aβ PET measurements at the same time points.

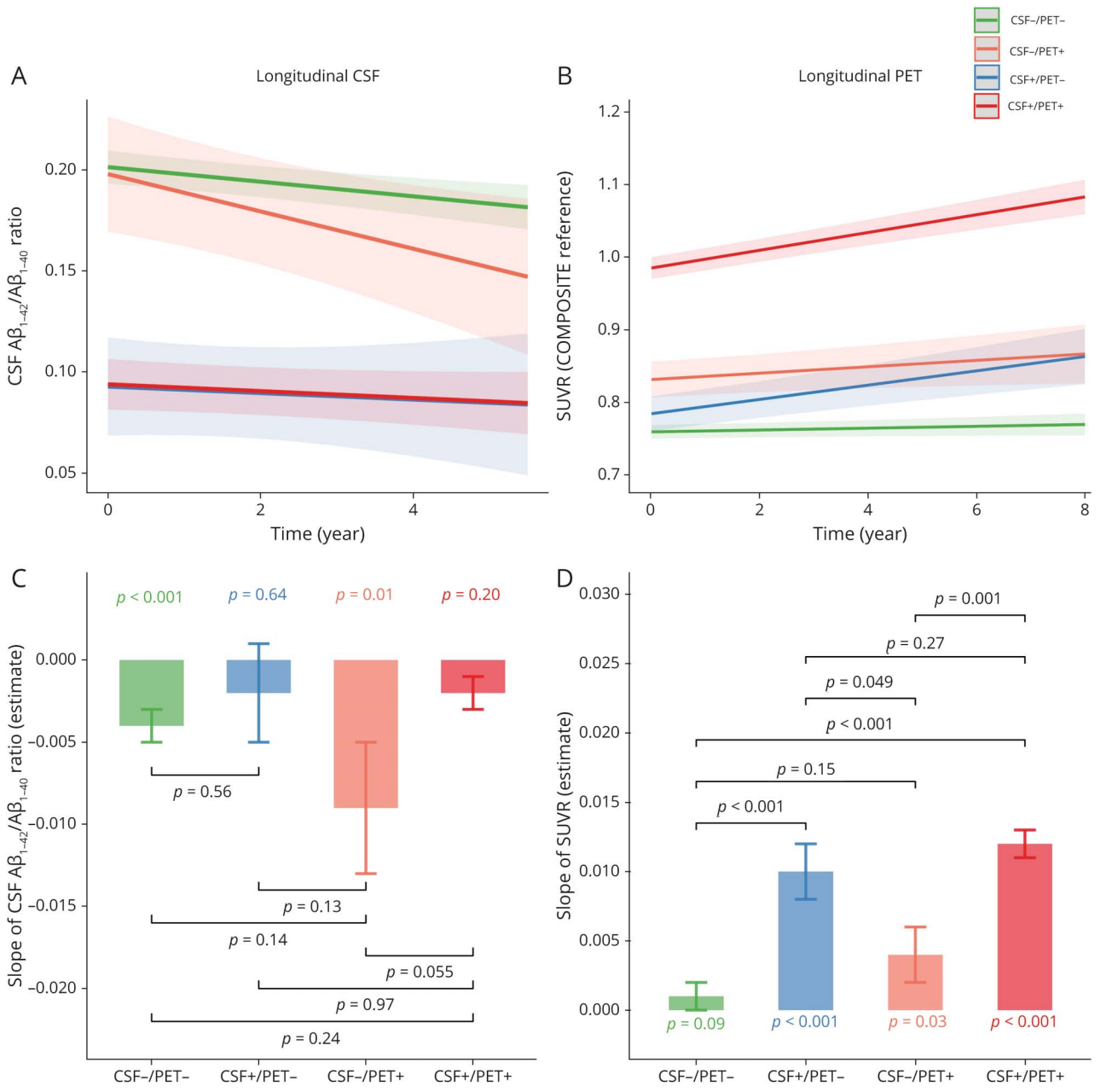
a steeper (not significant) slope of CSF $A\beta_{1-42}/A\beta_{1-40}$ decrease than CSF−/PET−, CSF+/PET−, and CSF+/PET+ participants. It is important to note that only 4 CSF+/PET− and 3 CSF−/PET+ participants had longitudinal CSF $A\beta_{1-42}/A\beta_{1-40}$, while the concordant groups had larger samples sizes (41 CSF−/PET− and 21 CSF+/PET+). We included the longitudinal CSF data as a counterpart to the longitudinal PET analyses but our ability to interpret longitudinal CSF slopes in the discordant groups is limited due to the small sample sizes. *APOE* ε4 carriers (n = 15) had lower baseline CSF $A\beta_{1-42}/A\beta_{1-40}$ (estimate −0.059 [95% CI −0.088, −0.030], $p < 0.001$) than noncarriers (n = 54), but no significant difference was found in CSF $A\beta_{1-42}/A\beta_{1-40}$ slope. Female participants (n = 36) also had lower baseline CSF $A\beta_{1-42}/A\beta_{1-40}$ (estimate −0.033 [95% CI −0.058, −0.007], $p = 0.013$) than male participants (n = 33), but no significant difference was found in CSF $A\beta_{1-42}/A\beta_{1-40}$ slope.

SUVR significantly increased in CSF+/PET−, CSF−/PET+, and CSF+/PET+ groups but not the CSF−/PET− group (figure 3, B and D). SUVR slopes of the CSF+/PET− and CSF+/PET+ but not CSF−/PET+ participants were significantly greater than in the CSF−/PET− participants, while CSF+/PET− and CSF+/PET+ participants also had significantly faster slopes of SUVR increase than CSF−/PET+ participants. In addition, we found that *APOE* ε4 carriers (n = 66) had higher baseline florbetapir SUVR (estimate 0.084 [95% CI 0.053, 0.114], $p < 0.001$) and faster slopes of florbetapir SUVR increase (estimate 0.003 [95% CI 0.0001, 0.006], $p = 0.04$) than noncarriers (n = 160), while female participants (n = 120) had higher baseline florbetapir SUVR (estimate 0.060 [95% CI 0.032, 0.089], $p < 0.001$) but not significantly faster slopes of florbetapir SUVR increase (estimate 0.002 [95% CI −0.0004, 0.005], $p = 0.096$) than male participants (n = 106).

Comparison of longitudinal cognitive decline in different CSF/PET groups

In order to understand how these biomarkers predict longitudinal cognitive decline, we used LME models to compare subsequent PACC score changes in different CSF/PET groups. CSF−/PET+ (estimate [PACC slope] = −0.506 [95% CI −0.851, −0.160]) and CSF+/PET+ (estimate −0.665 [95% CI −0.861, −0.467]) but not CSF−/PET− (estimate −0.013 [95% CI −0.142, 0.116]) or CSF+/PET− (estimate −0.095 [95% CI −0.420, 0.231]) groups had significant cognitive decline over 4.5 ± 1.9 years of mean follow-up (figure 4). CSF+/PET+ participants had significantly faster longitudinal PACC decline than CSF−/PET− (estimate [difference of PACC slope from the CSF+/PET+ group] = −0.652 [95% CI −0.887, −0.417]) and CSF+/PET− (estimate −0.570 [95% CI −0.949, −0.192]) participants but not significantly faster than CSF−/PET+ (estimate −0.160 [95% CI −0.557, 0.238]) participants. CSF−/PET+ participants (estimate [difference of PACC slope from the CSF−/PET− group] = −0.492 [95% CI −0.861, −0.123]) also had a significantly faster PACC decline than CSF−/PET− participants, whereas no significant difference was found between CSF+/PET− (estimate −0.082 [95% CI −0.430, 0.267]) and CSF−/PET− participants (figure 4B). In order to avoid conclusions based on borderline cases, we carried out the same analyses excluding individuals within ±5% of thresholds of CSF $A\beta_{1-42}/A\beta_{1-40}$ and SUVR. The results

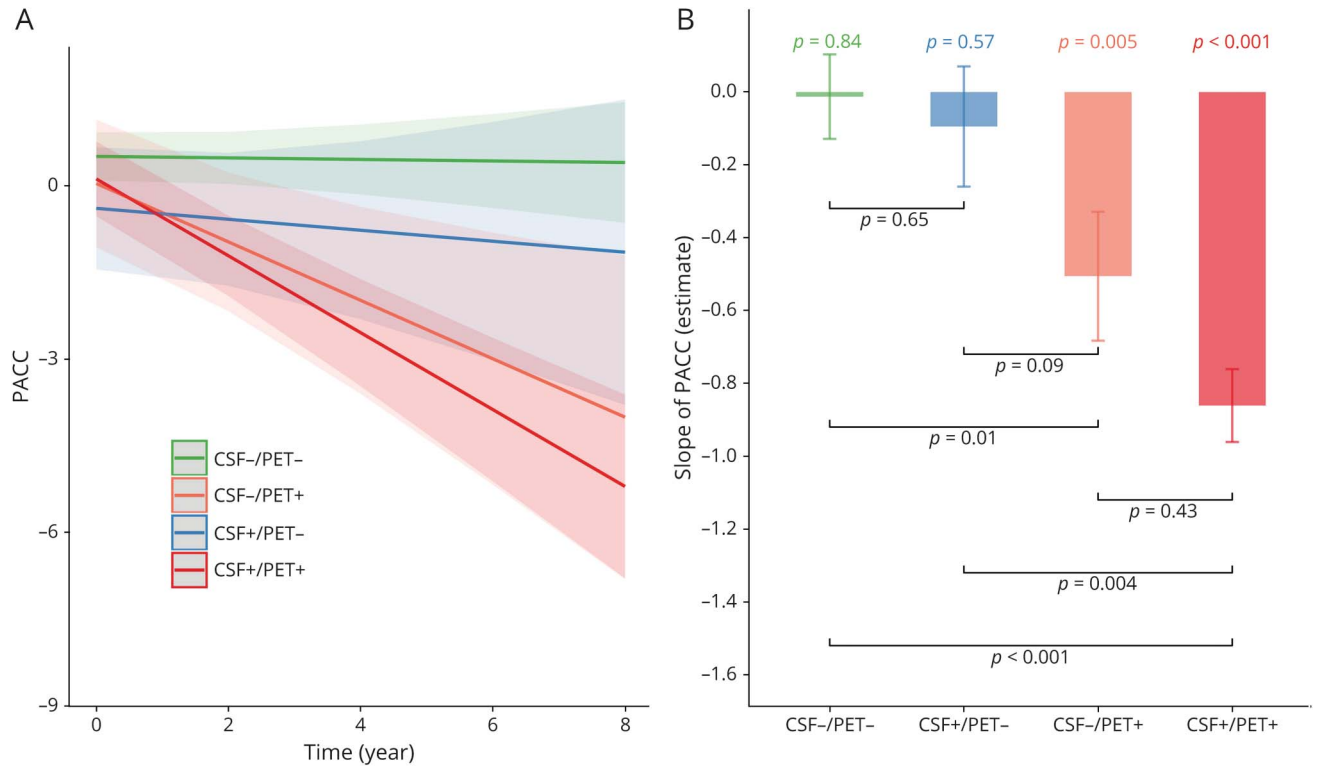
Figure 3 Longitudinal changes of CSF β-amyloid $(Aβ)_{1-42}/Aβ_{1-40}$ and florbetapir standardized uptake value ratio (SUVR) in different CSF/PET groups



Longitudinal changes of (A) CSF $Aβ_{1-42}/Aβ_{1-40}$ and (B) florbetapir SUVR over time. Comparisons of (C) CSF $Aβ_{1-42}/Aβ_{1-40}$ slopes and (D) florbetapir SUVR slopes between different CSF/PET groups. *p* Values in colored text reflect the comparison between slopes and zero. The error bars indicate standard error of the estimate of slopes. The estimates of CSF $Aβ_{1-42}/Aβ_{1-40}$ slope: CSF−/PET− (estimate −0.004 [95% confidence interval (CI) −0.006, −0.002]), CSF−/PET+ (estimate −0.009 [95% CI −0.016, −0.002]), CSF−/PET− (estimate −0.013 [95% CI −0.142, 0.116]), and CSF+/PET− (estimate −0.095 [95% CI −0.419, −229]). The estimates of difference of CSF $Aβ_{1-42}/Aβ_{1-40}$ slope from the CSF−/PET+ group: CSF−/PET− (estimate −0.006 [95% CI −0.013, 0.002]), CSF+/PET− (estimate −0.008 [95% CI −0.017, 0.002]), and CSF+/PET+ (estimate −0.007 [95% CI −0.015, 0.000]). Estimates of SUVR slope: CSF−/PET− group (estimate 0.001 [95% CI −0.0002, 0.003]), CSF+/PET− (estimate 0.010 [95% CI 0.006, 0.014]), CSF−/PET+ (estimate 0.004 [95% CI 0.0004, 0.008]), and CSF+/PET+ (estimate 0.012 [95% CI 0.010, 0.015]). Estimates of difference of SUVR slope from the CSF−/PET− group: CSF+/PET− (estimate = 0.009 [95% CI 0.005, 0.013]), CSF−/PET+ (estimate 0.003 [95% CI −0.001, 0.007]), and CSF+/PET+ (estimate 0.011 [95% CI 0.008, 0.014]). The estimates of difference of SUVR slope from the CSF−/PET+ group: CSF+/PET− (estimate 0.005 [95% CI 0, 0.011]) and CSF+/PET+ (estimate 0.008 [95% CI 0.003, 0.0012]).

were similar: both CSF−/PET+ (n = 7, estimate −1.170 [95% CI −1.1733, −0.606], $p < 0.001$) and CSF+/PET+ participants (n = 60, estimate −0.728 [95% CI −0.986, −0.469], $p < 0.001$) had greater PACC declines than the CSF−/PET− participants (n = 118), and the slope of PACC decline in the CSF+/PET− participants (n = 7, estimate −0.295 [95% CI −0.861, 0.271], $p = 0.31$) was not significantly faster than in the CSF−/PET− participants but was slower than in the CSF−/PET+ participants (estimate 0.874 [95% CI 0.105, 1.644], $p = 0.03$), while no other significant difference was found.

Figure 4 Longitudinal changes of cognition over time in different CSF/PET groups



(A) Longitudinal changes of Preclinical Alzheimer Cognitive Composite (PACC) score over time and (B) comparisons of slopes of PACC score between different CSF/PET groups. The *p* values in colored text above the bar reflect the comparison between slopes of PACC score and zero. Error bar indicates standard error of the estimate of slope of PACC.

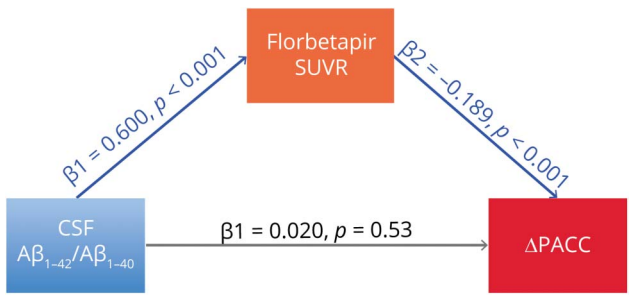
Predictive effect for cognitive decline of continuous CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR

In order to avoid the possibility that using dichotomous measures omits useful information, we also used LME models to investigate the predictive effect of continuous CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR for cognitive decline. Baseline CSF $A\beta_{1-42}/A\beta_{1-40}$ (β = −0.202 [95% CI −0.304, −0.100], $p < 0.001$) and florbetapir SUVR (β = −0.320 [95% CI −0.418, −0.222], $p < 0.001$) independently predicted subsequent longitudinal PACC decline in separate LME models over 4.5 ± 1.9 years of mean follow-up, although we note that the model with florbetapir SUVR had a lower Akaike information criterion value (6,195 vs 6,220) and higher marginal fixed effect[36] ($R^2 = 0.16$) than the model with CSF $A\beta_{1-42}/A\beta_{1-40}$ ($R^2 = 0.13$). However, the mediation model demonstrated that florbetapir SUVR significantly mediated the predictive effect of contemporaneous CSF $A\beta_{1-42}/A\beta_{1-40}$ on subsequent PACC decline (figure 5). In the mediation model, CSF $A\beta_{1-42}/A\beta_{1-40}$ (*z* score) was cross-sectionally associated (β = 0.600 [95% CI 0.486, 0.720], SE = 0.059) with florbetapir SUVR (*z* score), while florbetapir SUVR (*z* score) was associated (β = −0.189 [95% CI −0.285, −0.106], SE = 0.046) with subsequent longitudinal PACC change. This pathway (indirect effect −0.113 [95% CI −0.178, −0.064], SE = 0.028) explained 120% of the association (total effect −0.094 [95% CI −0.161, −0.030], SE = 0.033) between CSF $A\beta_{1-42}/A\beta_{1-40}$ and longitudinal PACC decline. The direct association of CSF $A\beta_{1-42}/A\beta_{1-40}$ and longitudinal PACC decline was not significant after including the florbetapir SUVR, changing the β value from −0.094 to 0.020.

Influences of discordance of CSF Aβ and Aβ PET in hypothetical drug trials

We compared the sample sizes determined by CSF and PET in a hypothetical clinical trial selecting participants based on Aβ

Figure 5 Sequential associations between CSF β-amyloid (Aβ), Aβ PET, and longitudinal cognitive change



The blue lines denote the significant pathway from CSF $A\beta_{1-42}/A\beta_{1-40}$ to longitudinal Preclinical Alzheimer Cognitive Composite (PACC) change (ΔPACC). Gray lines denote alternative pathways that were not significant.

positivity with 4 years PACC change as the outcome. Of 259 CU participants, 88 (21 CSF+/PET− and 67 CSF+/PET+) could potentially be selected as clinical trial participants if CSF $A\beta_{1-42}/A\beta_{1-40}$ was used to assess amyloid status, while 87 participants (20 CSF−/PET+ and 67 CSF+/PET+) would be selected using florbetapir SUVR to define Aβ positivity.

Table 2 summarizes the sample size per arm needed to detect a treatment effect of a drug that attenuates rate of PACC decline using rates derived from the data in a 4-year trial. A 4-year anti-AD trial was simulated because (1) the rates of PACC decline were calculated over more than 4 years of mean follow-up and (2) recent data suggest that it may take 4 years to see effects of amyloid positivity on cognition.[37] Using CSF to recruit targets for drug trial would increase the sample size to treat by 17% as compared to using PET.

Table 2 Estimate of the number of participants needed per arm to detect a β-amyloid–modifying treatment effect with cognitive decline as the primary outcome in a clinical trial with 80% power and 2-tailed α = 0.05

Sample size per arm needed to detect	Recruiting schemes of anti-AD drug trial	
	CSF	PET
25% Attenuation of PACC decline rate	530 (95% CI 402, 730)	456 (95% CI 346, 630)
50% Attenuation of PACC decline rate	133 (95% CI 101, 183)	115 (95% CI 87, 158)
100% Attenuation of PACC decline rate	34 (95% CI 26, 47)	29 (95% CI 23, 40)

Abbreviations: AD = Alzheimer disease; CI = confidence interval; PACC = Preclinical Alzheimer Cognitive Composite.

Discussion

In this study, we used contemporaneous baseline and longitudinal CSF $A\beta_{1-42}/A\beta_{1-40}$ assessed with mass spectrometry and florbetapir PET in CU individuals in order to identify the earliest abnormalities in CSF and PET and determine their associations with cognition. We replicated the well-recognized finding that CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR may be discordant in the early amyloidosis stage. We observed similar proportions of CSF Aβ+ only individuals and PET Aβ+ only individuals. However, whereas other studies have relied on primarily cross-sectional data to make inferences about CSF and PET trajectories, we were able to examine simultaneous longitudinal CSF and PET measurements in unambiguously Aβ-negative CU ADNI participants in order to detect the earliest abnormal changes. Although most of these CSF−/PET− individuals remained negative on both biomarkers during follow-up, examination of their slopes indicated that they were more likely to worsen (e.g., show longitudinal change in an abnormal direction) on CSF Aβ than on Aβ PET. This observation is consistent with the suggestion that abnormal CSF changes often precede abnormal PET changes. Importantly, however, our cross-sectional and longitudinal data also show that the opposite pattern (PET abnormality preceding CSF abnormality) is present as well, but is less frequent.

Whereas CSF+/PET− and CSF−/PET+ may reflect an earlier amyloidosis stage than CSF+/PET+, PET positivity was the strongest predictor of cognitive decline over more than 4 years of mean follow-up. When analyzed continuously in separate models, both CSF $A\beta_{1-42}/A\beta_{1-40}$ and Aβ PET independently predicted longitudinal PACC decline, but the predictive effect of cognitive decline of CSF $A\beta_{1-42}/A\beta_{1-40}$ disappeared after adding Aβ PET into the mediation model, suggesting that cognitive decline is preferentially associated with fibrillar cortical Aβ. The association between Aβ PET and cognitive change, a relatively late event in the AD pathway, provides further support for the observation that Aβ PET abnormality often occurs later than CSF abnormality.

CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR were discordant in 15.8% of participants, which was consistent with previous studies in normal individuals.[4–11] Unlike some studies,[4,5,7–9] however, we found the proportion of CSF+/PET− individuals was not higher than that of CSF−/PET+ individuals. Even after excluding those near the border, the proportions of the 2 discrepant groups remained similar, as was found in other studies.[6,10] Differences between studies in the proportions of CSF/PET discrepant participants may be due to differences in cohort, proportion of cognitively normal individuals, PET tracers, thresholds of Aβ positivity, and CSF analytic techniques. CSF Aβ and Aβ PET measure different features of Aβ pathology,[38] which may explain why discordance may be amplified in the early amyloidosis stage.

There were several methodologic features of the study that were designed to reduce noise and optimize longitudinal contemporaneous CSF and PET measurements acquired in ADNI. Notably, 67% of the sample had 3 longitudinal CSF and PET time points. Furthermore, use of the $A\beta_{1-42}/A\beta_{1-40}$ ratio has been shown recently to reduce noise, likely due to individual variability in CSF production compared with $A\beta_{1-42}$ alone,[4–11] and mass spectrometry serves as the gold standard for CSF standardization.[39] Finally, a reference region was used for florbetapir-PET that is optimized for reducing noise longitudinally.[29]

Using all of these methods to detect CSF and PET trajectories in unambiguously Aβ-negative individuals, we found that CSF−/PET− individuals were more likely to worsen on CSF Aβ than on Aβ PET, supporting the interpretation that soluble CSF Aβ change may be detectable before cortical fibrillar Aβ change. Whereas our cross-sectional data did not indicate that CSF Aβ abnormality is disproportionately more likely, other cross-sectional studies have interpreted a higher proportion of CSF+/PET− discordant participants as supporting the idea that CSF becomes abnormal first.[4,5,8,9,19,20,24,40]

In addition, we found that florbetapir SUVR increases in CSF+/PET− participants more than in CSF−/PET− participants, implying that abnormal CSF $A\beta_{1-42}/A\beta_{1-40}$ reflects an earlier stage of brain Aβ accumulation. Consistent with our finding, Palmqvist et al.[40] also found faster annual rate of SUVR increase in CSF+/PET− than CSF−/PET− in an asymptomatic ADNI cohort. By contrast, Toledo et al.[20] did not observe faster annual rates of SUVR increase in CSF+/PET− vs CSF−/PET− across a spectrum of AD in ADNI cohort. The observation that the relationship between CSF Aβ and Aβ PET varies at different amyloidosis stages[20,41] may explain these discrepancies. However, we did find that PET abnormality precedes CSF abnormality in some individuals in both cross-sectional and longitudinal analyses. In addition, we observed that CSF−/PET+ participants had a significant decrease in CSF $A\beta_{1-42}/A\beta_{1-40}$, faster than in other groups, although the discordant CSF/PET groups had very small (CSF+/PET−: n = 4, CSF−/PET+: n = 3) longitudinal sample sizes, limiting our ability to draw conclusions about these data. Nonetheless, despite the limited longitudinal CSF sample, our cross-sectional and longitudinal results together suggest that there are 2 different sequences of Aβ accumulation detected by CSF Aβ and Aβ PET. Notably, the CSF+/PET− group (but not the CSF−PET+ group) had more *APOE* ε4 carriers than the CSF−/PET− group, and *APOE* ε4 carriers tend to become abnormal on CSF Aβ earlier than on Aβ PET.[42] Consistent with previous literature,[43–45] we also observed that *APOE* ε4 carriers had significantly faster florbetapir SUVR increase than noncarriers. The CSF+/PET− participants with a high proportion of *APOE* ε4 carriers are probably at an earlier stage of amyloidosis, accumulating Aβ burden in the brain. In addition, we noticed that the CSF−/PET+ group rather than CSF+/PET− had more female participants than the CSF−/PET− group, and female participants had significantly higher baseline Aβ PET and steeper (p = 0.096) slope of Aβ PET increase than male participants. These results and previous studies[46–48] suggest that higher baseline Aβ PET observed in the CSF−/PET+ group might be associated with the high proportion of female participants.

Another finding consistent with the interpretation that discordant cases reflect earlier amyloidosis stages is that the levels of Aβ pathology (CSF $A\beta_{1-42}/A\beta_{1-40}$ ratios or florbetapir SUVRs) were most severe in the CSF+/PET+ group. However, cognitive decline in the CSF−/PET+ group did not differ from the CSF+/PET+ group, and progressed faster than in the CSF+/PET− group based on comparisons with the CSF−/PET− group. These results were substantially the same after excluding those individuals within the border zone. This observation may have 2 explanations. First, Aβ PET reflects the net accumulation of fibrillar Aβ burden, while reduced CSF Aβ indicates the current status of Aβ production vs clearance. It seems likely that brain deposits of fibrillar Aβ burden may be more important in defining pathologic brain changes than a more dynamic measure that reflects kinetic behavior of the protein.[18–21,27,28] Second, although CSF+/PET− individuals may have ongoing cortical fibrillar Aβ accumulation in the brain, CSF+/PET− likely reflects an earlier amyloidosis stage than CSF−/PET+, and may therefore require longer observation to see cognitive decline. Consistent with our findings, 2 previous studies[19,40] also failed to find significant cognitive decline in CSF+/PET− individuals, although they used CSF $A\beta_{1-42}$ to define Aβ status, which may be less reliable than CSF $A\beta_{1-42}/A\beta_{1-40}$ used in this study. In contrast with our findings, Mattsson et al.[19] did not find longitudinal cognitive decline in ADNI CSF−/PET+ CU individuals, which could reflect different cognitive tests, sample size, and shorter duration of cognitive follow-up in that study. We also investigated the predictive effect on cognitive decline of continuous CSF $A\beta_{1-42}/A\beta_{1-40}$ and florbetapir SUVR in a CU elderly cohort. The predictive effect of CSF $A\beta_{1-42}/A\beta_{1-40}$ was mediated by florbetapir SUVR in the mediation model (figure 5), also supporting the idea that cortical fibrillar Aβ deposition is more related to cognitive decline than soluble CSF Aβ burden. In contrast, Krance et al.[49] found that CSF Aβ42 (but not Aβ PET) was associated with longitudinal MMSE changes in ADNI CU participants over 2 years but not over 4 years. The discrepancy could be related to the use of different tools for measuring cognition; PACC scores used in the present study are likely more sensitive to early cognitive decline.[50]

Our findings have implications for anti-amyloid clinical trials that use either CSF biomarkers or amyloid PET imaging to identify CU participants. Discrepancies in the proportion of participants assessed with CSF vs amyloid PET at baseline to determine amyloid status influences the ability to detect longitudinal decline. Specifically, the inclusion of nonprogressing individuals, more likely to be found among abnormal CSF− screened than abnormal PET− screened participants, increases the sample size needed to detect a treatment effect. These results imply that CSF may not outperform PET when screening potential participants for anti-amyloid clinical trials, because Aβ PET imaging would confer slightly more statistical power in a therapeutic clinical trial with a cognitive change primary endpoint than CSF Aβ.

This study has several limitations. First, the ADNI participants overall are a highly selected sample, recruited to reflect the exclusionary criteria and types of individuals likely to participate in clinical trials. Second, our analyses were limited to CSF measured with mass spectrometry and PET measured with florbetapir, which may need to be replicated using other PET ligands and CSF analytical techniques. Third, because of the high level of agreement between PET and CSF measurements, the sample sizes of the discordant CSF/PET groups and CSF−/PET− individuals with longitudinal CSF biomarkers and amyloid PET imaging were relatively small, which may limit the ability to make generalizations about the findings of these groups.

Our cross-sectional and longitudinal data suggest that either CSF $A\beta_{1-42}/A\beta_{1-40}$ or Aβ PET may become abnormal first. Although most studies examining CSF and PET discordance have relied on cross-sectional data to make inferences about

longitudinal trajectories, the simultaneous longitudinal PET and CSF measurement in this study suggest that the earliest Aβ changes are more likely to be observed with CSF $A\beta_{1-42}/A\beta_{1-40}$ measurements than with Aβ PET. Probably because PET reflects brain Aβ accumulation at a later stage, it is a more robust predictor of cognitive decline. Our findings may provide insight into the variable sequential changes in CSF Aβ and Aβ PET during Aβ accumulation, and provide a meaningful reference for planning amyloid-lowering interventions in the asymptomatic stage of AD.

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Disclosure

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Appendix 1 Authors

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Leslie M. Shaw, PhD	University of Pennsylvania	Acquiring data, interpretation of results, obtaining funding, editing the manuscript
John Q. Trojanowski, MD, PhD	University of Pennsylvania	Acquiring data, interpretation of results, obtaining funding, editing the manuscript
William J. Jagust, MD	University of California, Berkeley	Acquiring data, interpretation of results, obtaining funding, editing the manuscript, study supervision
Susan M. Landau, PhD	University of California, Berkeley	Acquiring data, interpretation of results, obtaining funding, editing the manuscript, study supervision

Appendix 2 Coinvestigators

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Arthur W. Toga, PhD	University of Southern California, Los Angeles	Site investigator	Coordinated informatics core
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