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Nonlinear Association Between Cerebrospinal Fluid and Florbetapir F-18 β-Amyloid Measures Across the Spectrum of Alzheimer Disease

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Abstract

IMPORTANCE—Cerebrospinal fluid (CSF) and positron emission tomographic (PET) amyloid biomarkers have been proposed for the detection of Alzheimer disease (AD) pathology in living patients and for the tracking of longitudinal changes, but the relation between biomarkers needs further study.

OBJECTIVE—To determine the association between CSF and PET amyloid biomarkers (cross-sectional and longitudinal measures) and compare the cutoffs for these measures.

DESIGN, SETTING, AND PARTICIPANTS—Longitudinal clinical cohort study from 2005 to 2014 including 820 participants with at least 1 florbetapir F-18 (hereafter referred to as simply florbetapir)–PET scan and at least 1 CSF β-amyloid 1–42 (Aβ1–42) sample obtained within 30 days of each other (501 participants had a second PET scan after 2 years, including 150 participants with CSF Aβ1–42 measurements). Data were obtained from the Alzheimer's Disease Neuroimaging Initiative database.

MAIN OUTCOMES AND MEASURES—Four different PET scans processing pipelines from 2 different laboratories were compared. The PET cutoff values were established using a mixture-modeling approach, and different mathematical models were applied to define the association between CSF and PET amyloid measures.

RESULTS—The values of the CSF Aβ1–42 samples and florbetapir-PET scans showed a nonlinear association (R^2 = 0.48–0.66), with the strongest association for values in the middle range. The presence of a larger dynamic range of florbetapir-PET scan values in the higher range compared with the CSF Aβ1–42 plateau explained the differences in correlation with cognition (R^2 = 0.36 and R^2 = 0.25, respectively). The *APOE* genotype significantly modified the association between both biomarkers. The PET cutoff values derived from an unsupervised classifier converged with previous PET cutoff values and the established CSF Aβ1–42 cutoff levels. There was no association between longitudinal Aβ1–42 levels and standardized uptake value ratios during follow-up.

CONCLUSIONS AND RELEVANCE—The association between both biomarkers is limited to a middle range of values, is modified by the *APOE* genotype, and is absent for longitudinal changes; 4 different approaches in 2 different platforms converge on similar pathological Aβ cutoff levels; and different pipelines to process PET scans showed correlated but not identical results. Our findings suggest that both biomarkers measure different aspects of AD Aβ pathology.

Alzheimer disease (AD) pathology is defined by the deposition of extracellular β-amyloid (Aβ) plaques and intracellular tau neurofibrillary tangles in the brain.[1] These deposits correlate with Aβ positron emission tomographic (PET) radiotracer retention[2–4] and cerebrospinal fluid (CSF) Aβ levels.[5–7] As expected, the CSF Aβ1–42 levels and the standardized uptake value ratios (SUVRs) of the different PET Aβ ligands are associated[8–19] and show similar classification accuracy and diagnostic agreement. Conversely, plasma Aβ levels show a weak association with these biomarkers[8,18] and cannot predict the clinical diagnosis.[20] Whereas recent larger studies have noted a nonlinear association between CSF and PET measures of Aβ pathology, which was less obvious in smaller cohorts,[15,16] most studies have centered on diagnostic utility or have assumed a linear association and applied

parametric models without a value transformation. The goal of our study was to (1) assess the presence of nonlinear associations between CSF Aβ1–42 samples and florbetapir F-18 (hereafter referred to as simply florbetapir)–PET scans processed using different pipelines, (2) compare amyloid cutoffs across platforms, and (3) study the association between longitudinal measures of both amyloid biomarkers in a large longitudinal cohort study.

Methods

Participants

A total of 820 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants with CSF Aβ1–42 and florbetapir-PET Aβ imaging measurement values obtained with in 30 days were included in our study (Table 1). Florbetapir was not available at the baseline ADNI 1 visit, and therefore some of these participants had their first florbetapir-PET scan performed during subsequent visits. The number of visits in which PET scans were performed were 739 at baseline, 23 at 24 months, 3 at 36 months, 25 at 48 months, 25 at 60 months, and 5 at 72 months. For the CSF Aβ1–42 mixture model analysis, 1005 participants with a CSF Aβ1–42 measurement were included (ie, all participants with at least 1 CSF Aβ1–42 measurement to estimate the CSF Aβ1–42 cutoff level). Data were downloaded on September 12, 2014. A total of 501 participants had a second PET amyloid scan performed within 2 years, and a total of 150 participants also had CSF samples obtained within 30 days of the second PET scan. The CSF Aβ1–42 data used in the preparation of this article were obtained from UPENNBIOMK and UPENNBIOMK5–7 data generated by the ADNI Biomarker Core.

The ADNI (http://www.adni-info.org) was launched in 2004 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the US Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, and has been extensively reviewed elsewhere[21] (eAppendix in the Supplement). A diagnosis of mild cognitive impairment or AD was established based on the criteria by Petersen et al[22,23] for mild cognitive impairment and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[24] for probable AD. Protocols were submitted to institutional review boards for each participating location and their written unconditional approval obtained and submitted to Regulatory Affairs at the ADNI Coordinating Center (ADNI-CC) prior to commencement of the study. Written informed consent for the study was obtained from all participants and/or authorized representatives.

CSF Collection and Aβ1–42 Measurement

The CSF samples were obtained in the morning after an overnight fast and processed as previously described[25,26] (eAppendix in the Supplement). The Aβ1–42 level was measured using the multiplex xMAP Luminex platform (Luminex Corp) with Innogenetics (INNO-BIA AlzBio3, for research use–only reagents) immunoassay kit–based reagents. The capture and detection antibodies for Aβ1–42 were 4D7A3 and 3D6, respectively.[26] All longitudinal CSF samples belonging to the same participant were measured in the same plate to avoid assay-to-assay variation.

Florbetapir-PET Scan Processing

Florbetapir image data were acquired from a variety of PET scanners at ADNI sites nationwide. Image data were acquired in four 5-minute frames 50 to 70 minutes after injection of approximately 10 mCi, and the 4 frames were coregistered to each other, averaged, interpolated to a uniform image (160 × 106 × 96) and voxel size (1.5 mm^3), and smoothed to a uniform resolution (8-mm full width at half-maximum) to account for differences between scanners.[27]

We included florbetapir SUVRs developed in 2 different laboratories (the University of Utah in Salt Lake City and the University of California, Berkeley), each including 2 different measures obtained using a different reference (eAppendix in the Supplement). Both laboratories used the same scans that were preprocessed as already detailed. From the University of Utah analysis, we included averaged regional values from medial and lateral frontal, temporal, and parietal cortices that were normalized either using the cerebellar region (the average cerebellum) or the white matter (the average white matter) as reference region. Two summary measures were obtained at the University of California, Berkeley using Aβ deposition in frontal, cingulate, lateral parietal, and temporal cortices and either the whole cerebellum as reference (the summary cerebellum) or the whole cerebellum, brainstem/pons, and eroded subcortical white matter (the summary composite) as reference region. There were 450 and 501 participants who had 2 PET scans obtained within 2 years at the University of Utah and University of California, Berkeley laboratories, respectively.

Statistical Analysis

For univariate group comparisons, analysis of variance and χ^2 tests were applied for quantitative and qualitative variables. Power transformations were applied to normalize distributions in the analyses performed for the demographic variables included in Table 1. We used 5 different models to test which one better explained the association between CSF Aβ1–42 levels and PET SUVRs: lineal, polynomial, exponential, hyperbolic, and multivariate adaptive regression splines (MARSs). An MARS creates piecewise regression models (hinges) for each variable in the model, and these models are separated by knots to capture changes in the association according to different ranges of the measures, using a data-driven approach. To test the models, the sample was divided into a training set and a test set, which included two-thirds and one-third of the participants, respectively. Each participant was only included once in this analysis. The different statistical models were developed in the training set using a 10-fold cross-validation and afterward applied to the test set. The coefficient of determination (R^2) is reported to summarize the goodness of fit of each model. Cutoffs for amyloid biomarkers were obtained using a previously reported strategy that uses finite mixture models (eTable 1 and eFigure 1 in the Supplement).[28,29]

Results

Cross-sectional Association Between Individual CSF and Florbetapir-PET Aβ Measures

The first and second columns in Figure 1 show the CSF and PET Aβ levels for the participants included in the training and test sets, respectively, and the fitted models (the solid gray areas show disagreement in participant classification between both biomarkers).

Coefficients of determination (R^2) for the different models are summarized in eTable 2 in the Supplement. In all comparisons, the linear model showed the worst performance in the training and test sets, whereas the hyperbolic and MARS models showed overall the best performance.

APOE genotype influenced the relationship; an increasing number of ε4 copies were associated with lower CSF Aβ1–42 levels for the same PET SUVR in all models. In all MARS models, the first hinge was located in a narrow range of Aβ1–42 levels (225–288 pg/mL for participants with 0 copies of the *APOE* ε4 allele and 208–214 pg/mL for participants with 1 copy of the *APOE* ε4 allele), and the second hinge showed a slightly higher variability (137–144 pg/mL for participants with 0 copies of the *APOE* ε4 allele and 119–132 pg/mL for participants with 1 copy of the *APOE* ε4 allele). The PET SUVRs could not accurately predict CSF Aβ1–42 levels before the first hinge (R^2 = 0.01–0.10) and after the second hinge (R^2 = 0.11–0.26). We tested whether clinical diagnosis was a significant predictor, but it was not selected in any of the MARS models. Similar results that included 2 hinges in the MARS were obtained when CSF Aβ1–42 level was selected as the predictor and the florbetapir measures were selected as outcomes (data not shown).

eTable 3 in the Supplement shows PET SUVRs that corresponded to the CSF Aβ1–42 cutoff level of 192 pg/mL for participants with 0 copies or 1 copy of the *APOE* ε4 allele. Table 2 summarizes the κ coefficients and overall percentage agreement for each pair of biomarkers. There was a substantial agreement between the CSF Aβ1–42–defined groups and the groups that were defined based on the different florbetapir-derived measures (κ = 0.69–0.76), but it was lower than the excellent agreement observed for the different florbetapir-PET measures (κ = 0.80–0.91). Most of the participants who were classified differently by CSF and PET Aβ measures presented with abnormal CSF Aβ1–42 levels and normal PET SUVRs (8.9%-12.5%) compared with participants with normal CSF Aβ1–42 levels and abnormal PET SUVRs (0.7%-4.5%). We compared clinical characteristics in the groups with mismatched biomarker results (eTables 4 and 5 in the Supplement). Although there were a larger number of participants who were cognitively impaired in the group that had only abnormal CSF Aβ1–42 levels compared with the group that had only abnormal summary cerebellum values, the differences were not significant (P = .50). Whereas there were no differences in the Alzheimer's Disease Assessment Scale– cognitive subscale (ADAS-cog) scores between groups at the 12-month follow-up, the participants who had only abnormal CSF Aβ1–42 levels showed memory decline, and the participants who had only abnormal summary cerebellum values showed executive decline.

The different PET SUVRs obtained with the different references and pipelines were highly correlated (eFigure 2 in the Supplement), with correlation coefficients between 0.81 and 0.95, although the values were not comparable and needed a transformation between pipelines (eTable 6 in the Supplement). When we tested the ability of florbetapir-PET measures and CSF Aβ1–42 levels to predict the ADAS-cog score, the summary composite measure (R^2 = 0.36) outperformed the Aβ1–42 level (R^2 = 0.25) in a cross-validated MARS model that included age as a covariate (Figure 2A and B).The MARS model fits calculated for each of the clinical diagnostic groups are summarized in eTable 7 in the Supplement. Results were similar for other PET Aβ measures.

Longitudinal CSF and PET Aβ Measurements

Figure 2C–F shows baseline SUVRs for each of the PET measurements (x-axis) and the corresponding yearly change (y-axis) for participants with 2 PET measurements, and Figure 2G shows the changes in the CSF Aβ1–42 level for the same period. For 304 participants who had 2 PET scans and CSF samples obtained during the baseline visit, only the group with abnormal Aβ1–42 levels and abnormal PET SUVR summary measures showed a greater increase during follow-up (Figure 2H and I).

A total of 150 participants (53 cognitively normal participants, 90 participants with mild cognitive impairment, and 7 participants with AD) had 2 CSF and PET Aβ measurements obtained during the same visits, with the second set of measurements occurring within 2 years (ie, mean [SD], 729.7 [20.8] days) of the first. Figure 3 displays scatter plots with the yearly value changes during follow-up for the CSF Aβ1–42 and florbetapir-PET measurements below the diagonal and their correlation above the diagonal (eFigure 3 in the Supplement also shows associations between the PET SUVRs). There was no correlation between CSF and PET amyloid value changes, while the different PET Aβ amyloid measurements correlated with a higher degree. The correlation between CSF Aβ1–42 level and florbetapir-PET measure did not improve when only participants with Aβ1–42 levels between both MARS hinges (140–215 pg/mL) were included (data not shown).

Discussion

Cross-sectional CSF Aβ1–42 levels and florbetapir-PET measures were associated for a limited middle range of values that included the cutoffs, and they were consistent with AD. The association was significantly modified by the number of *APOE* ε4 alleles. Nevertheless, there was a large agreement for the classification of participants as having an AD-like Aβ burden between the different measures. Different approaches converged on a similar cutoff for pathological Aβ deposition across platforms. However, there was no correlation between longitudinal changes observed after 2 years of follow-up.

Previous studies[16,19] have mainly analyzed the agreement between CSF and PET Aβ measures in the same cohort using a single florbetapir-PET measure or using Pearson correlation or linear regressions assuming a linear association.[18] Good agreement between CSF Aβ1–42 level and florbetapir-PET SUVR has been previously reported using a single pipeline for the latter.[16,19] In the present study, we found an excellent correlation-classification agreement using 4 separate SUVRs obtained in 2 different laboratories using 2 distinct pipelines. Including different processing pipelines used in the 2 laboratories allowed us to analyze how the use of different pipelines and references can affect comparisons across studies. We showed that cross-sectional SUVRs were highly correlated and that different processing pipelines and choices of references led to a disagreement of 5% to 10%, and κ coefficients between 0.80 and 0.91 in a large sample of participants processed in 4 different ways, which could be a potential important source of variability between studies. Thus, each pipeline needs to establish its own cutoffs. Recently, a new method has been proposed to compare values across different PET ligands and processing pipelines.[30] Nevertheless, CSF Aβ1–42 levels and florbetapir-PET measures showed much higher agreement and much

higher κ coefficients than the ones observed when the different neuronal injury biomarkers were studied in the same cohort.[31]

The validity of the cutoffs has been previously demonstrated in a 3-fold manner: (1) the CSF Aβ1–42 level cutoff was initially demonstrated using autopsy-validated diagnoses[25] to prevent biases due to clinical diagnostic uncertainties,[5] (2) this cutoff was then validated using a "diagnosis-free"–driven mixture model analysis of CSF Aβ1–42 levels,[28] and (3) for florbetapir-PET SUVRs, investigators used young controls[32] and autopsy cases.[2] In the mixture model analysis of summary CB values that we performed, 1.12 was designated as the cutoff that corresponds to an SUVR of 1.11 using the semiautomated quantification applied by Avid and, therefore, overlaps with their validated cutoff[32] (eFigure 4 in the Supplement). Furthermore, the 1.12 summary CB cutoff value is close to the average of the transformation of the CSF Aβ1–42 autopsy-validated cutoff level for participants with 0 or 1 *APOE* ε4 allele. In addition, using a mixture-modeling approach in a sample of 1005 levels of CSF Aβ1–42, we reached the same level as the one previously described in our autopsy study.[25]

Therefore, we confirmed the previous florbetapir-PET cutoff established based on young controls using an unsupervised classification method, in a sample that included a large number of cognitively normal participants, participants with mild cognitive impairment, and participants with AD, and the CSF Aβ1–42 autopsy-validated cutoff level in a larger sample using the approach applied by De Meyer et al[28] in a larger sample. Most importantly, we demonstrated that the conversion of the values across different platforms and methods converges robustly on the similar burden of Aβ pathology. However, we emphasize that recommended SUVR cutoffs vary according to the pipeline that was used, and therefore any modification in the pipeline must be followed by a validation of new cutoffs. Previous studies[16,19] have described groups of participants that show disagreement in classification between CSF Aβ1–42 levels and florbetapir-PET measures. The size of these groups varies depending on the reference region, and the disagreement decreases when white matter regions are used as a reference. This might be explained by the fact that the cerebellum is affected in latter stages of AD,[33] and therefore reference regions might be affected differently in later stages of disease.

Recently, a lower cutoff level for CSF Aβ1–42 (ie, 157 pg/mL) and an average cerebellum with a cutoff SUVR of 1.26 that is skewed toward more abnormal values of pathological Aβ biomarkers were suggested.[19] These values were obtained using clinical diagnosis as the gold standard and contradict evidence from previous autopsy-based studies using unsupervised diagnosis-independent methods.[25,28,32] This can be explained by our current understanding of the pathological Aβ biomarker model for AD,[34] which describes biomarker and neuropathological changes that precede cognitive changes and that are being used for the staging of preclinical AD in cognitively normal participants,[35] and by autopsy studies[36–38] showing that 44.2% of cognitively normal participants have Consortium to Establish a Registry for Alzheimer's Disease B and C scores and that 22.5% of cognitively normal participants have an intermediate probability of AD neuropathological changes. Hence, these and other studies[2] emphasize that optimizing cutoffs based on clinical diagnosis to classify all participants with normal cognition as healthy controls will

contradict the neuropathological findings for many participants and prevent an accurate preclinical diagnosis of the underlying Aβ pathology. This is of critical importance for the design and conduct of clinical trials of new therapies targeting pathological Aβ biomarkers in participants with underlying AD pathology who are cognitively normal.[39–41]

One previous study[9] pursued efforts to transform CSF Aβ1–42 levels to Pittsburg Compound B–PET SUVRs, and vice versa, and used a $\log_2$ transformation for both values owing to the lack of a linear association. However, the goal of our study was to transform the values between the different methods and to understand how both are related (in order to interpret differences in the timing of the biomarker changes for both biomarkers across the whole clinical spectrum) and the implications there of. Based on the MARS models, it can be concluded that there is only a strong association between CSF and florbetapir-PET Aβ values for the midrange values of both measures, which include the currently applied CSF Aβ1–42 level measured using the multiplex xMAP Luminex platform[25] and the florbetapir-PET Aβ amyloid measure normalized to cerebellum[2,32] cutoff values. It is also in this range where most of the discrepant classification appears. This could be due, in part, to the variability inherent to any clinical measure that can have an important effect for cases with values close to a dichotomic cutoff.

Another explanation for this disagreement might be the lower affinity of PET amyloid ligands for diffuse plaques[2,42] and the differential effect of the *APOE* genotype on biomarker values. Different amyloid PET ligands share their binding site and show a higher affinity for neuritic amyloid plaques compared with diffuse amyloid plaques, which can lead to false negatives.[3,42–45] While it is thought that the decrease in CSF Aβ1–42 levels, but not in other Aβ levels,[18] reflects brain Aβ deposition, more mature forms might not be in equilibrium with CSF and, therefore, might lead to the plateau observed in the CSF Aβ1–42 level, or later stages might represent Aβ levels that are not in equilibrium with the CSF. Therefore, the wider range of CSF Aβ1–42 levels in the lower range of florbetapir-PET SUVRs might imply a stronger association of the CSF Aβ1–42 level with diffuse amyloid plaques, which appear in earlier phases without the presence of neuritic plaques.[46]

Another explanation is that different sensitivities or ceiling effects of the assays could account for the strong association between CSF Aβ1–42 levels and florbetapir-PET Aβ measures only for the midrange values of these 2 most widely used measures of pathological Aβ deposition. However, the CSF Aβ1–42 level plateau is well above the lower detection limit of the Luminex assay. Furthermore, *APOE* ε4 is associated with a higher proportion of fibrillar amyloid and neurotic plaques,[47,48] which show a higher affinity for amyloid PET ligands and, therefore, would explain the higher SUVRs, and this would explain why the presence of *APOE* ε4 had different effects on both the CSF Aβ1–42 levels and the florbetapir-PET measures across all pipelines. For the same CSF Aβ1–42 levels, participants with no ε4 alleles had lower florbetapir-PET SUVRs. We performed several analyses to assess the clinical correlations of participants who showed either abnormal CSF Aβ1–42 levels or abnormal florbetapir-PET measures and found differences in the cognitive changes, but a longer follow-up (including autopsies) will be needed to characterize these small groups of participants.

Surprisingly, there was no correlation between the changes in CSF Aβ1–42 levels and the changes in florbetapir-PET measures after a 2-year follow-up. There are several non–mutually exclusive explanations for this finding: (1) the changes are small and might not be detected owing to the inherent variability of the measurements, (2) a longer follow-up is needed to see larger changes, and (3) the different dynamic ranges of these 2 biomarkers could lead to different rates of changes in them across the biomarker spectrum. This might be due to the fact that these 2 biomarkers reflect different aspects of disease mechanisms, leading to Aβ fibrillation and deposition, as well as different floor and ceiling effects as already noted. However, another factor that might explain these differences is the sensitivity of the measures of CSF Aβ1–42 level and florbetapir-PET SUVR to track small changes during a 2-year follow-up. In any case, it is not surprising that the methods used to measure CSF Aβ1–42 level and brain Aβ amyloid deposits do, in fact, measure different aspects of pathological Aβ amyloid as previously discussed.

Florbetapir-PET SUVRs showed a stronger association with ADAS-cog scores, which can be explained by the absence of the floor effect observed for CSF Aβ1–42 levels, and thus can offer a larger dynamic range along disease progression. Nevertheless, the association with cognition is lower than the one observed for neuronal injury neuroimaging biomarkers.[49]

Conclusions

Thus, in conclusion, although CSF Aβ1–42 levels and florbetapir-PET Aβ measures show a high-classification agreement for dementia due to underlying AD pathology, these are clearly different measures of pathological Aβ amyloidosis that converge to similar diagnostic cutoffs across different cohorts, methods, and amyloid biomarkers, but they do not closely correlate in the cross-sectional low and high range of values. Notably, this extends to a lack of correlation for the longitudinal changes in these 2 biomarkers during a 2-year follow-up. Hence, our novel findings are significant for understanding how to interpret CSF Aβ1–42 levels and florbetapir-PET Aβ measures for diagnosis and for understanding the mechanisms of Aβ amyloidosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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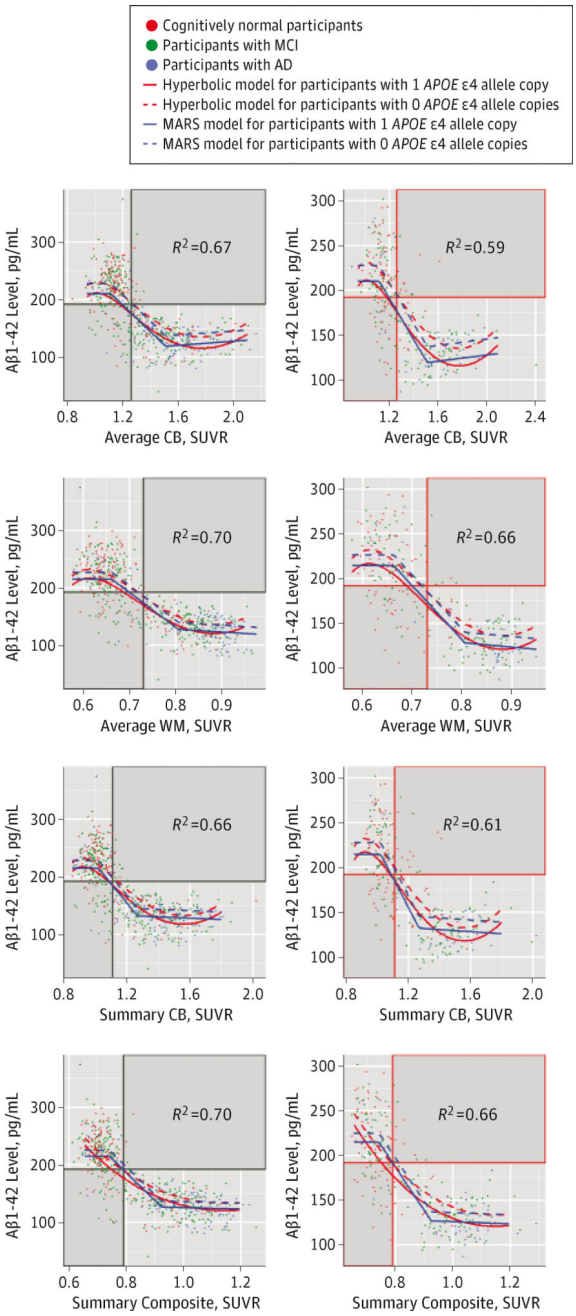

Figure 1. Association Between CSF Aβ1–42 Levels and Florbetapir F-18 PET SUVRs

A model for participants with 2 *APOE* ε4 copies is not included. The solid gray areas indicate disagreement in the classification based on the pair of Aβ measures. Aβ indicates β-amyloid; AD, Alzheimer disease; CB, cerebellum; CSF, cerebrospinal fluid; MARS, multivariate adaptive regression spline; MCI, mild cognitive impairment; PET, positron emission tomographic; SUVR, standardized uptake value ratio; and WM, white matter.

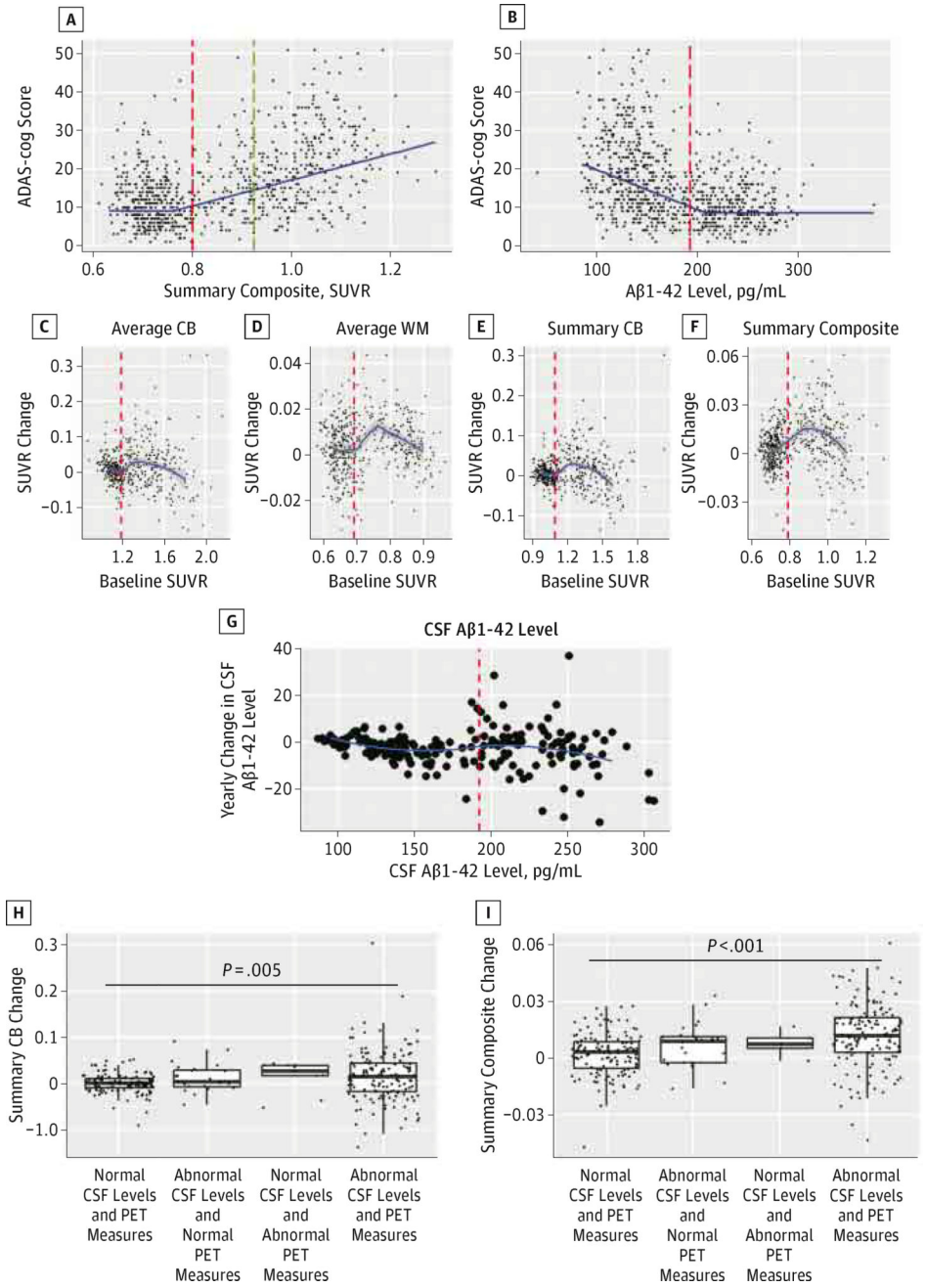

Figure 2. Clinical Associations and Longitudinal Changes of PET SUVRs

Scatterplots showing the association between Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) scores on the y-axis and the summary composite standardized uptake value ratios (SUVRs) (A) and the cerebrospinal fluid (CSF) β-amyloid 1–42 (Aβ1–42) levels (B) on the x-axis. The blue continuous line represents the multivariate adaptive regression spline for a 65-year-old participant. The red dashed line represents the cutoff for the biomarker represented in the plot, and the green dashed line represents the value at which the CSF Aβ1–42 level plateaus. Longitudinal SUVR yearly changes (after a 2-year follow-up) for the average cerebellum (CB) (C), the average white matter (WM) (D),

the summary CB (E), and the summary composite (F) are shown on the y-axes, with the x-axes representing baseline SURVs. G, Longitudinal changes in CSF Aβ1–42 level after a 2-year follow-up are shown. The red dashed line represents the value that corresponds to the CSF Aβ1–42 level of 192 pg/mL. Yearly changes in the summary CB (H) and the summary composite (I) values during follow-up (y-axis) are based on the presence of normal or abnormal baseline CSF Aβ1–42 levels and florbetapir F-18–positron emission tomographic (PET) measures. The horizontal line in each box indicates the median, while the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box mark the 90th and 10th percentiles, respectively. The points beyond the whiskers are outliers beyond the 90th and 10th percentiles.

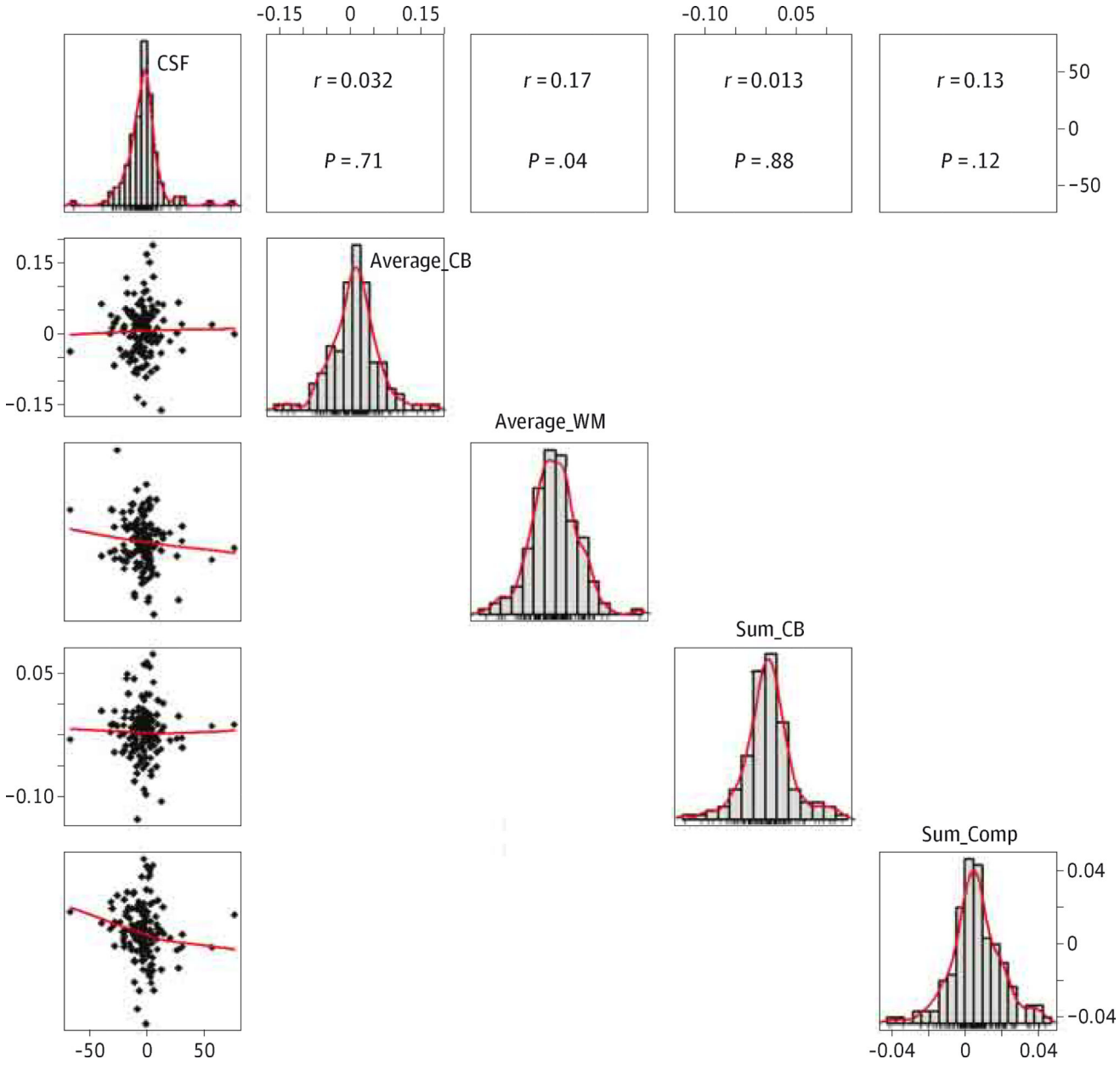

Figure 3. Association Between CSF Aβ1–42 Level and Florbetapir F-18–PET Measure Longitudinal Changes

Matrix showing the individual scatterplots depicting the association between cerebrospinal fluid (CSF) β-amyloid 1–42 (Aβ1–42) level (x-axis) and florbetapir F-18–positron emission tomographic (PET) standardized uptake value ratio (y-axis) changes during a 2-year follow-up (below the diagonal) and the corresponding Pearson correlation coefficient and *P* value (above the diagonal). The panels in the diagonal direction depict histograms showing the distribution of CSF Aβ1–42 levels and PET SUVRs. Average_CB indicates average cerebellum; Average_WM, average white matter; Sum_CB, summary cerebellum; and Sum_Comp, summary composite.

Table 1

Characteristics of the ADNI Participants Included in the Study at the Time of the Scan

Characteristic	Cognitively Normal Participants (n = 259)	Participants With MCI (n = 415)	Participants With AD (n = 146)	*P* Value
Age at time of scan, mean (SD), y	72.8 (5.9)	71.3 (7.4)	73.5 (8.5)	.002
Male sex, %	45.2	56.0	58.3	.009
ADAS-cog score, mean (SD)	9.0 (4.4)	15.0 (6.8)	30.9 (8.9)	<.001
SUVR, median (Q1-Q3)				
Average CB	1.17 (1.12–1.32)	1.27 (1.13–1.53)	1.54 (1.37–1.68)	<.001
Average WM	0.66 (0.63–0.72)	0.74 (0.66–0.84)	0.87 (0.83–0.90)	<.001
Summary CB	1.06 (1.00–1.17)	1.18 (1.02–1.39)	1.42 (1.27–1.53)	<.001
Summary composite	0.73 (0.70–0.82)	0.83 (0.72–0.99)	1.03 (0.94–1.09)	<.001
Aβ1–42 level, median (Q1-Q3), pg/mL	209.3 (159.2–237.6)	160.9 (131.9–214.4)	131.8 (114.4–150.7)	<.001

Abbreviations: Aβ, β-amyloid; AD, Alzheimer disease; ADAS-cog, Alzheimer Disease Assessment Scale–cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; CB, cerebellum; MCI, mild cognitive impairment; Q1, first quarter; Q3, third quarter; SUVR, standardized uptake value ratio; WM, white matter.

Table 2

Matrix Showing Agreement Between the Different Aβ Measures[a]

	CSF Aβ1–42 Level	Average CB	Average WM	Summary CB	Summary Composite
CSF Aβ1–42 level		84.5	86.7	86.6	88.2
Average CB	0.69 (0.64–0.74)		90.2	92.4	90.8
Average WM	0.74 (0.69–078)	0.80 (0.76–0.84)		89.9	95.3
Summary CB	0.73 (0.68–0.77)	0.85 (0.81–0.89)	0.80 (0.74–0.84)		92.9
Summary Composite	0.76 (0.72–0.81)	0.82 (0.78–0.86)	0.91 (0.88–0.94)	0.86 (0.82–0.89)	

Abbreviations: Aβ, β-amyloid; CB, cerebellum; CSF, cerebrospinal fluid; WM, white matter.

[a]Values below the diagonal space show the κ coefficient, and values above the diagonal space show percentage agreement.