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Plasma Aβ but Not Tau is Related to Brain PiB Retention in Early Alzheimer's Disease

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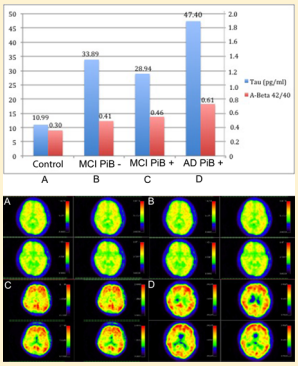
ABSTRACT: Recent advances in biomarkers provide the possibility of early or preclinical diagnosis of Alzheimer's pathology. Currently, decreased levels of Aβ-42 and increased levels of tau proteins in cerebral spinal fluid are considered reliable biomarkers of Alzheimer's disease (AD); however, little evidence exists for the use of amyloid and tau protein levels in the plasma as useful biomarkers. We investigated the potential use of plasma biomarkers to diagnose AD and explored their relationships with brain Aβ deposition in amyloid imaging. We used an immunomagnetic reduction assay to measure the plasma levels of Aβ40, Aβ42, and tau proteins in 20 older control participants and 25 participants who had either mild cognitive impairment due to AD or early AD dementia. All participants received ^{11}C-labeled Pittsburgh compound B PET scans. The sensitivity of the plasma tau level at the cutoff value of 28.27 pg/mL was 92%, and the specificity was 100%; the sensitivity of the Aβ42/40 ratio at the cutoff value of 0.3693 was 84%, and the specificity was 100%. Regression analyses of the effects of plasma protein levels on brain amyloid retention, as determined by standard uptake value ratios in either side of the frontal, parietal, and temporal lobes and the precuneus, are predicted only by ratios of plasma Aβ42/40 (R^2 0.326−0.449, all $p < 0.001$) but not by plasma tau levels. Plasma Aβ in terms of Aβ42/40 might provide an indirect estimation of Aβ deposition in the brain.



KEYWORDS: *^{11}C-PiB, plasma biomarker, cognitive function, mild cognitive impairment, AD pathology, beta amyloid, tau*

Amyloid beta (Aβ)-rich senile plaques and tau-positive neurofibrillary tangles are the major pathological indicators of Alzheimer's disease (AD) in the brains of patients. The role of Aβ proteins in the pathogenesis of AD and the significance of Aβ as a primary causal factor of neurodegeneration remain controversial.[1,2] Cognitive function is only weakly associated with the amount of fibrillary Aβ accumulated in the brain.[3] The finding that normal elderly participants retain a significant portion of Aβ according to Pittsburg compound B positron emission tomography (PiB PET) scans partially accounts for this apparent mismatch.[4,5] On the other hand, participants with mild cognitive impairment (MCI) who have positive brain amyloid depositions are at a higher risk of AD than those who do not.[6]

The number of neurofibrillary tangles is significantly correlated with both cognitive function and clinical staging.[3,7] Previous studies have also correlated hippocampal atrophy, a characteristic feature of AD, with tau markers in the cerebral spinal fluid (CSF).[8,9] In addition, our previous work found an association between hippocampal atrophy and total plasma tau levels as well as between hippocampal atrophy and cognitive functioning.[10]

Recent studies have provided new insights regarding that pathological processes associated with AD, which precede the onset of clinical dementia by many years.[10−12] A longitudinal study of participants with dominantly inherited AD (the DIAN study) found brain Aβ deposition and CSF tau elevation 15−20 years prior to the onset of dementia symptoms, thereby confirming this possibility.[13]

According to the diagnostic guidelines recommended by the National Institute on Aging-Alzheimer's Association (NIA-AA) work groups, decreased levels of Aβ42 and increased total levels of tau in the CSF are potential biomarkers of AD.[14] These low levels of Aβ42 in the CSF might reflect the entrapment of Aβ in senile plaques, whereas elevated levels of tau might be related with axonal and neuronal destruction.[15] Amyloid imaging such as ^{11}C labeled Pittsburgh compound B positron emission tomography (^{11}C-PiB PET) defined fibrillary Aβ and was demonstrated to have a strong correlation with post-mortem plaque counts especially with diffuse plaques.[16]

However, the routine diagnosis of AD based on CSF components has several drawbacks. Most importantly, this technique might not be suitable for general screening in a large-scale study or a longitudinal follow-up assessment especially in some Asian countries. Research concerning blood-based

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Table 1. Demographic Data and Plasma Protein Levels of Controls and Patients[a]

	group (*n*)			
	controls (20)	MCI_{AD} (11)	ADD (14)	all (25)
age (years)	63.7 ± 7.9	69.2 ± 10.4	64.9 ± 11.5	66.8 ± 11
female/male	10/10	5/6	10/4	15/10
APOEε4 (0/1/2)	15/4/1	6/4/1	5/4/5	11/8/6
education (years)	12.4 ± 3.5	11.9 ± 4.2	9.9 ± 4.7	10.8 ± 4.5
CDR (0/0.5/1)	20/0/0	0/11/0	0/7/7	0/18/7
MMSE	29.0 ± 1.1	26.5 ± 2.5	20.7 ± 4.6	23.5 ± 4.7**
tau (pg/mL)	13.5 ± 5.5	33.5 ± 2.2	46.7 ± 2.0	40.9 ± 10.8**
Aβ42 (pg/mL)	15.9 ± 0.3	17.2 ± 0.3	18.9 ± 0.3	18.2 ± 1.7**
Aβ40 (pg/mL)	60.9 ± 6.4	41.4 ± 1.8	36.9 ± 1.6	38.9 ± 5.8**
Aβ42/Aβ40	0.26 ± 0.03	0.42 ± 0.07	0.52 ± 0.07	0.48 ± 0.09**

[a]Mean ± SD. MCI_{AD}, mild cognitive impairment due to Alzheimer's disease; ADD, Alzheimer's disease dementia; analysis of variance was performed by using multivariate General Linear Model of SPSS to compare the between-group differences for plasma levels and demographic data; *, significance level of $p < 0.05$ and **, $p < 0.001$. No significant between-group differences were found for gender (Pearson's $\chi^2 = 2.13$, $p = 0.344$), ApoE ε4 (Pearson's $\chi^2 = 8.352$, $p = 0.08$) and for age ($t = -1.052$, $p = 0.299$).

indicators should begin with accepted biomarkers such as Aβ or tau.[17] However, measuring Aβ42 concentration in plasma is difficult. In addition to the low levels of Aβ42 in plasma, this peptide can bind to plasma proteins such as albumin, lipoproteins, and complement factors.[18] These technical difficulties at least partially account for the conflicting results found regarding the use of plasma Aβ as a diagnostic biomarker for AD.[19−24]

Our previous work developed an immunomagnetic reduction (IMR) method capable of accurately quantifying the plasma levels of Aβ42, Aβ40, and tau proteins.[10,25,26] Therefore, this study uses the same IMR method to measure the plasma levels of Aβ and tau in healthy control (HC) participants, those with MCI due to AD, and those with early AD dementia. Since the cutoff values used for diagnosis should come out from an independent larger population, we applied the optimal cutoff values of plasma levels obtained from our previous reports.[10,27,28]

Then, we correlated plasma Aβ levels with the amount of amyloid depositions revealed by using ^{11}C-PiB PET to determine whether plasma Aβ can be used as a surrogate biomarker for the brain pathology found among patients with AD[13,16] and examine the relationship between plasma Aβ, tau proteins, and brain amyloid deposition.

RESULTS AND DISCUSSION

Biochemical Measures. There were significant between-group differences in the levels of plasma Aβ40, Aβ42, and tau proteins. We further compute the Aβ42/40 ratios to improve the differential sensitivity.[27,28] With the most useful cutoff values obtained from our previous work,[10,27,28] the sensitivity of the plasma tau at the cutoff value of 28.27 pg/mL was 92%, and the specificity was 100%; the sensitivity of the Aβ42/Aβ40 ratio at the cutoff value of 0.3693 was 84%, and the specificity was 100%, tested on this independent cohort in the diagnosis of MCI due to AD and AD dementia. As for the level of plasma Aβ42, the specificity went down to 75% though the specificity remained 100% at the cutoff value of 16.1 pg/mL. There were no useful cutoff values available for plasma Aβ40 that both sensitivity and specificity were below 40%. Therefore, we only used plasma Aβ42/Aβ40 and tau levels for further analyses.

Performance of the plasma tau biomarker or Aβ42/Aβ40 ratios was no worse than those biomarkers in CSF. In brief, direct IMR measures for plasma Aβ42, total tau and ratios of Aβ42/Aβ40 are capable of discriminating normal controls from patients with early or prodromal AD.

A marked 50% decrease in Aβ42 in the CSF can discriminate between patients with AD dementia and normal aging with a sensitivity and specificity greater than 85%.[29,30] CSF p-tau can reliably predict AD in subjects with MCI with high accuracy (80%) as a single biomarker in a relatively short observation interval of 1.5 years in a large-scale multicenter study.[31] AD can be discriminated from normal aging by increased CSF total tau with a mean sensitivity and specificity of approximately 82% and 88%, respectively. Mean total tau levels in AD patients were three times higher than those in controls.[29,30] Previous studies also have shown that a combination of the three CSF biomarkers, namely tau, p-tau, and Aβ42, can be used to detect incipient AD in subjects with MCI with mean sensitivity and specificity ranging from 80 to 100%.[32−34] However, because blood is much more accessible than CSF technically or due to some psychosociocultural reasons in many Asian countries, searching for reliable blood biomarkers for AD is thus desirable. Due to the filtering effects of the blood−brain barrier, dilution in the large plasma volume, easy self-aggregation or adhesion to tissue or cell membrane, and enzymatic degradation or sequestration by various reticular tissue systems, concentrations of brain-derived proteins in the blood are lower than those in the CSF, which makes this task a great challenge.[35] Therefore, Aβ and tau levels measured in plasma compartments and CSF compartments do not always correlate.[35−37] Previous studies have found conflicting results regarding the levels and significance of Aβ-related proteins in plasma. These findings have been controversial because they have found that elevated levels of plasma Aβ42 and Aβ40 might predict development of AD, reduced[40] or no association in patients with AD.[23,42] Also controversial is Aβ42/40 ratios: some found that elevation of the Aβ42/40 ratios predicts AD, and some reported the opposite or no difference.[23,42]

In recent studies, however, elevated plasma Aβ42 levels have been reported in different research groups.[13,27,28,44] In one study, high levels of plasma Aβ42 were related to more rapid decline of cognitive functions among AD patients.[47] Certain studies have tested patients who have genetic risk factors for AD.[13,45] Plasma Aβ42 levels were elevated in mutation carriers, compared with noncarriers. In the same study, the 50% decrease in Aβ42 and the increase in tau in the CSF were similar to those typically observed in late-onset sporadic AD.[13]

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Table 2. Brain Amyloid Retention of the Controls and Patients[a]

SUVR of ROI	controls (20)	MCI_{AD} (11)	ADD (14)	all (25)
L frontal lobe	1.10 ± 0.23	1.62 ± 0.39	1.97 ± 0.62	1.82 ± 0.55*
R frontal lobe	1.08 ± 0.24	1.56 ± 0.33	1.85 ± 0.55	1.77 ± 0.51*
L parietal lobe	1.10 ± 0.16	1.37 ± 0.33	1.82 ± 0.54	1.62 ± 0.51*
R parietal lobe	1.10 ± 0.13	1.38 ± 0.26	1.71 ± 0.41	1.62 ± 0.51*
L temporal lobe	1.10 ± 0.19	1.47 ± 0.39	1.67 ± 0.39	1.58 ± 0.39*
R temporal lobe	1.07 ± 0.16	1.38 ± 0.33	1.71 ± 0.41	1.62 ± 0.51*
L precuneus	1.13 ± 0.18	1.54 ± 0.36	1.94 ± 0.59	1.76 ± 0.54*
R precuneus	1.17 ± 0.16	1.54 ± 0.38	1.90 ± 0.59	1.74 ± 0.53*

[a]Mean ± SD. SUVR, standardized uptake value ratio; MCI_{AD}, mild cognitive impairment due to Alzheimer's disease; ADD, Alzheimer's disease dementia; analysis of variance was performed by using multivariate General Linear Model of SPSS to compare the between-group differences in levels of plasma biomarkers and brain SUVR of regions of interest. We used Bonferroni correction to adjust multiple comparisons.*, level of $p < 0.001$.

In this study, mean total plasma tau levels in AD patients were about several times higher than those of controls, which is similar to the findings in CSF.[29,30,37] This is compatible with a recent study in which Zetterberg et al. used an ultrasensitive new assay and found tau levels in plasma were significantly higher in AD patients compared with both controls and MCI patients with a dimension of about two times; while MCI patients who developed AD during follow-up had tau levels similar to those of patients with stable MCI and cognitively normal controls.[37] The former findings support our results, but the latter is different from our results in appearance. However, we measured those plasma tau levels on a group of image-biomarker-validated patients with early AD whether in the stage of MCI or very mild dementia. Therefore, our subjects with MCI due to AD may not be at a same stage of Alzheimer's pathology as theirs.

Aβ Deposition. We computed the mean SUVR of the ROI against the cerebellum. The PiB PET scan showed significant between-group differences that all ROIs showed significantly increased amyloid retention including the bilateral frontal, parietal, and temporal cortices and the bilateral precuneus of patients (multivariate GLM with Bonferroni correction for multiple comparisons, all $p < 0.001$; Table 3). If we used 1.5 as a standardized uptake value ratio (SUVR) threshold,[46] we got 85.7% (12/14) positive rate for patients with AD dementia, 81.8% (9/11) positive for MCI due to AD, and 10% (2/20) positive for older controls. To separate controls from early AD, the PiB amyloid imaging has 84% sensitivity and 90% specificity.

Table 3. Regression Analyses between Plasma Proteins and SUVR of PiB-PET[a]

Model $I_{PlasmaA\beta42/A\beta40}$	*B* [95% CI]	*β*	R^2	*P*
L frontal lobe	2.831 [1.777−3.886]	0.637	0.405	0.000
R frontal lobe	2.702 [1.780−3.623]	0.67	0.449	0.000
L parietal lobe	2.239 [1.342−3.136]	0.609	0.371	0.000
R parietal lobe	2.224 [1.339−3.108]	0.612	0.374	0.000
R temporal lobe	1.978 [1.250−2.707]	0.641	0.411	0.000
L precuneus	2.482 [1.476−3.487]	0.605	0.326	0.000
R precuneus	2.221 [1.239−3.204]	0.571	0.366	0.000
Global mean	2.325 [1.492−3.157]	0.652	0.425	0.000
Model $I^*_{PlasmaA\beta40}$	*B* [95% CI]	*β*	R^2	*P*
L temporal lobe	−0.019 [−0.027 ∼ −0.012]	−0.612	0.374	0.000

[a]Excluded variables in Model $I_{PlasmaA\beta42/A\beta40}$: levels of plasma Aβ42, Aβ40 and tau proteins, clinical dementia rating, age, gender. Excluded variables in Model $I^*_{PlasmaA\beta40}$: levels of plasma Aβ42, and tau proteins, and ratios of plasma Aβ42/Aβ40, clinical dementia rating, age, gender.

Regression Analyses. In this study, we showed that amyloid depositions in terms of PiB PET SUVR in the bilateral frontal, parietal, and temporal lobes and precuneus were predicted by plasma Aβ42/Aβ40 ratio (R^2 0.326−0.449, all $p < 0.001$) but not by plasma tau levels (all $p > 0.05$) (Table 3; Figure 1).

Combined use of CSF and imaging biomarkers can predict the conversion from MCI to AD dementia and enable the early diagnosis of AD, even at a preclinical stage.[47,48] In addition, in one of our previous studies, we also reported that hippocampal volume was negatively associated with plasma tau levels but positively associated with episodic memory.[10]

The association of CSF levels of amyloid proteins and amyloid deposition measured by PiB PET must be further clarified.[49] Inversed association of CSF Aβ42 levels to amyloid deposition measured by PiB PET has been reported.[49] Another study reported that plasma Aβ showed inversed association in patients with MCI.[50]

In brief, the degree of amyloid deposition revealed by ^{11}C-PiB PET was strongly related to the Aβ system but not the tau system in the periphery. In the brain, amyloid depositions revealed by ^{11}C PiB PET were more correlated with the diffuse plaque count, but less to the neuritic plaques in a post-mortem study.[16] Our study is not without limitations. First, we measured plasma Aβ and tau levels without a cross check of the Aβ and tau levels in the CSF of the same population; Aβ and tau levels measured in the plasma compartment and the CSF compartment do not correlate.[29−31] Second, this is a cross-sectional study, and observation of the timeline of disease progression in terms of the plasma and imaging biomarkers used in this study is not yet available. A longitudinal cohort study is warranted. Thus, care must be taken when generalizing our findings at this stage.

In conclusion, in this study, we proposed that plasma Aβ in terms of Aβ42/Aβ40 might be able to provide an indirect estimation of Aβ deposition in the brain, whereas plasma tau might unravel hippocampal volume as shown in our previous study. A combination of plasma Aβ and tau may discriminate normal aging from AD[28] and predict hippocampal atrophy and brain Aβ deposition. Together with imaging biomarkers, we explored on the disease landmarks in patients in the early or prodromal stages of AD, and at the same time provide convenient indices for possible disease modifying therapy.

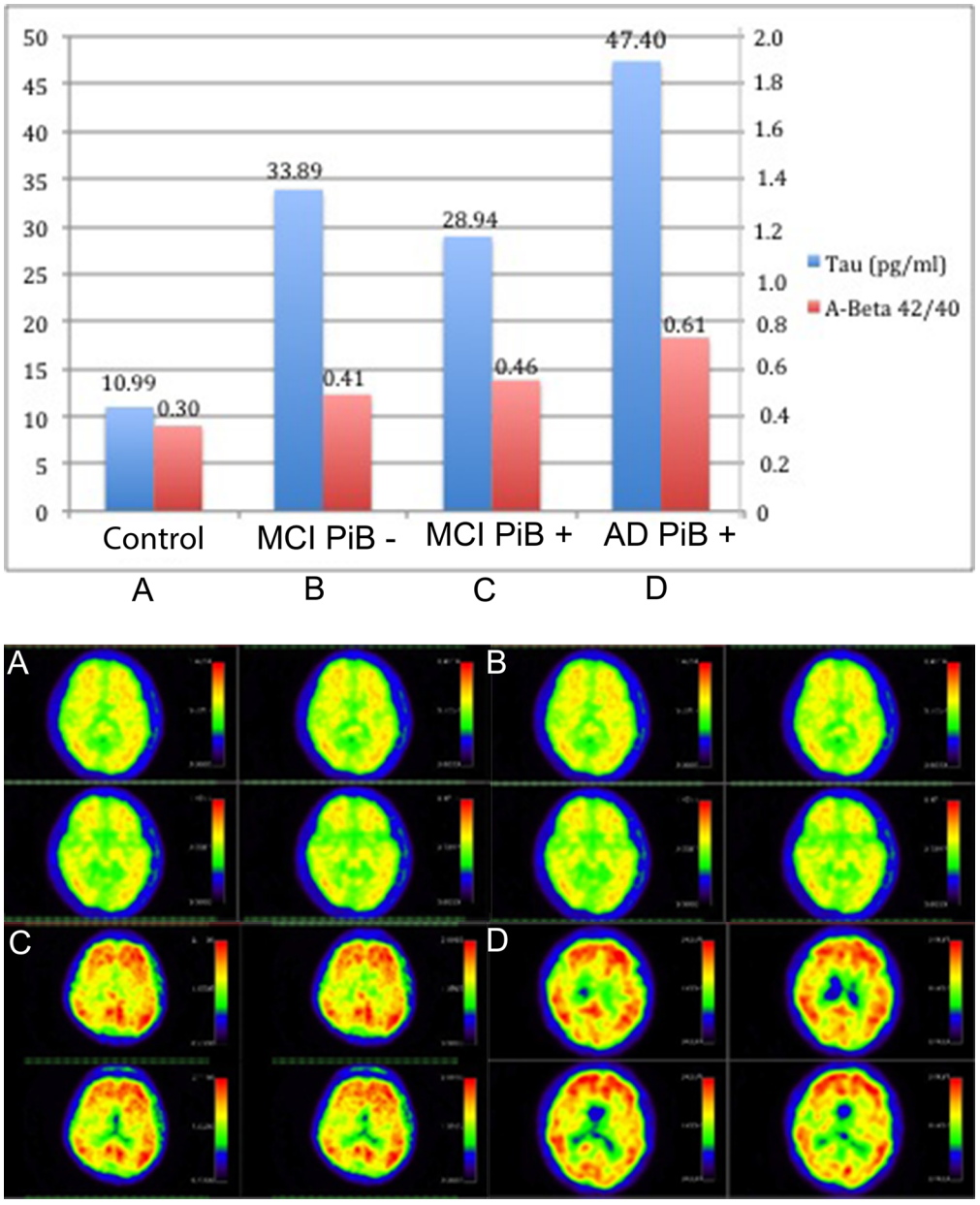

Figure 1. Results from four examplar participants. The upper row shows the plasma total tau levels (blue) in pg/mL and the Aβ42/Aβ40 ratios (red) of the respective participants. The lower row shows ^{11}C-PiB deposition in the brain: (A) Control, an elderly control; (B) MCI PiB−, a patient with MCI with little amyloid deposition; (C) MCI PiB+, a patient with MCI with positive amyloid deposition; and (D) AD PiB+, a patient with AD dementia with positive amyloid deposition.

METHODS

All participants provided written informed consent or assented via proxy consent. The Research Ethics Committee of the National Taiwan University Hospital (NTUH) approved this study.

Clinical Assessments. *Participants.* We recruited 25 participants who had MCI or mild AD (age = 63.7 ± 7.9; 10 men; Clinical Dementia Rating (CDR) = 0.5, 18 subjects; CDR = 1, 7 subjects) and 20 control participants (age = 66.8 ± 11.0; 10 men; all CDR = 0) (Table 1). Significant between-group differences were not found for gender (Pearson's χ^2 = 0.450, p = 0.52) or for age (t = −1.052, p = 0.299). Control participants had more years of education (12.4 ± 3.5 versus 10.8 ± 4.5 years, p = 0.198) and higher MMSE scores (29.0 ± 1.1 versus 23.2 ± 4.7, p < 0.001) than patients (Table 1). Participants with MCI or AD were recruited from the memory clinic at the NTUH. All participants with dementia met the diagnostic guidelines for probable AD dementia proposed by the NIA-AA workgroups in 2011.[51] The MCI diagnosis due to AD was also in accordance with the NIA-AA's diagnostic guidelines.[52] To diagnose MCI due to AD, we used a formal cognitive test with the cutoff value set at or below the fourth percentile (i.e., lower than 1.5 SDs) of the scale scores based on age- and education-matched control participants. The control participants were healthy volunteers who had participated in our previous MCI studies.[53] After undergoing routine tests at the memory clinic, each participant received a comprehensive clinical examination that included a review of his or her medical history, a physical and neurological examination, laboratory tests, and neuroimaging studies. All participants received the same diagnostic evaluation. Neuroimaging biomarkers[54] were applied on an individual basis for the temporoparietal hypometabolism measured by FDG-PET, or the decreased hippocampal volume as measured by either volumetry (with volumes less than 95% of the healthy elderly controls) or the Visual Rating System.[55] One blood sample was taken within 1 month of the neuropsychological test and the MRI brain scan and PiB PET scan.

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Neuropsychological Testing. The neuropsychological battery assessed participant memory, executive function, attention, visuospatial ability, and psychomotor speed. The battery included the Wisconsin Card Sorting Test (WCST), Color Trail Tests I and II (CTT I and II), two subtests of the Wechsler Memory Scale Version III (WMS-III; logical memory and visual reproduction), subtests of the Wechsler Adult Intelligence Scale Version III, and a semantic verbal fluency test.

PET Images. PET data were acquired using a GE Healthcare Discovery ST4 PET/CT scanner (2D mode, 47 image planes, 15.0 cm axial field of view) after injecting 370−555 MBq of ^{11}C PiB. PET data were acquired over 30 min (40−70 min post injection). Emission data were corrected for attenuation, scatter, and radioactive decay and reconstructed using OSEM with Iteration 2, Subset 15. The reconstructed image resolution was 6 mm full width at half-maximum in the transverse and axial planes. Before the PET session, a cranial computer tomography (CT) scan was obtained for each participant so that the CT/PET image coregistration could be performed. By using the cranial CT scan as an anatomic guide, we were able to draw various regions of interest (ROIs) for the cerebral and cerebellar cortices following the method used in a previous study.[56] We modified the method to use elliptical ROIs instead of hand-drawn irregularly shaped ROIs to include cerebellar cortex. The SUV_{max} value of each ROI was measured and was used to calculate the mean cerebellar cortical uptake from the three SUV_{max} values. We used the hand-drawn irregular-shape ROIs and also measured SUV_{max} instead of $SUV_{average}$ for the calculation of SUVR for cerebral cortexes. Increased ^{11}C PiB retention (in terms of higher SUVR) indicates increased binding to fibrillary amyloids.

Biochemical Analysis. *Specimen Collection and Preparation.* Participants provided a 10 mL nonfasting venous blood sample (K3 EDTA, lavender-top tube). Each sample was assigned a registry number following the sampling sequence; thus, colleagues in the laboratory were blind to the clinical status and demographic data of participants. The blood samples were centrifuged (2500*g* for 15 min) within 1 h of collection, and plasma was aliquoted into cryotubes and stored at −80 °C for less than 3 months until thawed for measurement.

Magnetic Reagent Preparation. Ferrous oxide (Fe_3O_4) magnetic nanoparticles were synthesized in a solution consisting of a 1:2 stoichiometric ratio of ferrous sulfate heptahydrate ($FeSO_4{\cdot}7H_2O$) and ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), and this solution was mixed with an equal volume of aqueous dextran. To specifically label Aβ40, Aβ42, and tau protein in samples, magnetic nanoparticles (MF-DEX-0060, MagQu) coated with antibodies against Aβ40 (A3981, SIGMA), Aβ42 (A8354, SIGMA), and tau protein (T9450, SIGMA) were dispersed in pH 7.4 phosphate buffered saline (PBS) solution. The solution with anti-Aβ40 is referred to as Aβ40 reagent, the solution with anti-Aβ42 is referred to as Aβ42 reagent, and the solution with anti-tau is referred to as tau reagent. The saturated magnetization of these three reagents is 0.3 emu/g measured with a vibration sample magnetometer (model 4500, EG&G). The antibodies were added to the dextran of the magnetic nanoparticles to create aldehyde groups (−CHO). Dextran then reacted with the antibodies via a −CH═N− functional group. To prepare the final anti-Aβ40, anti-Aβ42, and anti-tau reagents, the magnetic antibody conjugates were removed from the unbound antibodies via magnetic separation.

The samples for building up the standards were prepared by diluting Aβ40 (A3981, SIGMA), Aβ42 (A9810, SIGMA), or tau protein (T7951, SIGMA) with PBS solution to desired concentrations. The solution was mixed with its corresponding reagent for IMR measurement. The volumes of solutions and reagents used are as follows: solution/reagent for Aβ40 (40/80 μL), Aβ42 (60/60 μL), and tau protein (40/80 μL). The real-time signal of a mixture is recorded by using the SQUID-based ac magnetosusceptometer (XacPro-S, MagQu). With these real-time signals, the IMR signals for each concentration and samples can be detected.

IMR Measurements. IMR works by determining the percent of reduction in the magnetic field produced by an alternating current (ac). This reduction is due to a decrease in the magnetic susceptibility (χ_{ac}) of a biofunctionalized magnetic nanoparticle reagent due to its association with target biomolecules. The percent reduction of the χ_{ac} of the reagent was measured using an ac magnetosusceptometer (XacPro-S, MagQu) equipped with a high-T_c superconducting quantum-interference device (SQUID) magnetometer as a magnetic sensor. After the magnetic nanoparticles bind to the Aβ molecules, and the χ_{ac} signal of the mixture decreases. The percent reduction of the χ_{ac} signal (i.e., the IMR signal) for the sample is determined based on the first and last χ_{ac} values. The IMR signal reduction values were then compared with standard curves to determine the amounts of Aβ and tau in the plasma. The lower limits of quantification (LLoQ) in IMR are approximately 1−10 pg/mL for Aβ40 (linearity maintained at 10 pg/mL), 1−10 pg/mL for Aβ42 (linearity at approximately 20−30 pg/mL), and 0.1−1 pg/mL for total tau (linearity at 1 pg/mL). By using a triple-test with a four-channel SQUID-based ac magnetosusceptometer, the coefficient of variation (CV) of IMR signals for 50 pg/mL Aβ1−40 was estimated to be less than 3%. For further technical details, please refer to our previous reports.[10,25−28]

Statistical Analyses. Demographic data and clinical information were examined by independent *t* test analysis or Pearson χ^2 analysis. Analysis of variance was performed by using the multivariate General Linear Model of SPSS to compare the between-group differences in levels of plasma biomarkers and brain SUVR of regions of interest. We used Bonferroni correction to adjust multiple comparisons. A stepwise multiple linear regression analysis of the plasma Aβ and tau levels on the measurements of PiB brain structures was used to identify possible predictors in terms of plasma protein levels. The data were analyzed using SPSS (version 16.0; SPSS Inc., Chicago, IL).

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Notes

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