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RESEARCH ARTICLE

Predicting continuous amyloid PET values with CSF and plasma A β 42/A β 40

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Abstract

Introduction: Continuous measures of amyloid burden as measured by positron emission tomography (PET) are being used increasingly to stage Alzheimer's disease (AD). This study examined whether cerebrospinal fluid (CSF) and plasma amyloid beta (A β)42/A β 40 could predict continuous values for amyloid PET.

Methods: CSF A β 42 and A β 40 were measured with automated immunoassays. Plasma A β 42 and A β 40 were measured with an immunoprecipitation–mass spectrometry assay. Amyloid PET was performed with Pittsburgh compound B (PiB). The continuous relationships of CSF and plasma A β 42/A β 40 with amyloid PET burden were modeled.

Results: Most participants were cognitively normal (427 of 491 [87%]) and the mean age was 69.0 \pm 8.8 years. CSF A β 42/A β 40 predicted amyloid PET burden until a relatively high level of amyloid accumulation (69.8 Centiloids), whereas plasma A β 42/A β 40 predicted amyloid PET burden until a lower level (33.4 Centiloids).

Discussion: CSF A β 42/A β 40 predicts the continuous level of amyloid plaque burden over a wider range than plasma A β 42/A β 40 and may be useful in AD staging.

KEYWORDS

biomarker concordance, CSF A β 42/A β 40, machine learning, PET, plasma A β 42/A β 40

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Highlights

- Cerebrospinal fluid (CSF) amyloid beta ($A\beta$)₄₂/ $A\beta$ ₄₀ predicts continuous amyloid positron emission tomography (PET) values up to a relatively high burden.
- Plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ is a comparatively dichotomous measure of brain amyloidosis.
- Models can predict regional amyloid PET burden based on CSF $A\beta$ ₄₂/ $A\beta$ ₄₀.
- CSF $A\beta$ ₄₂/ $A\beta$ ₄₀ may be useful in staging AD.

1 | INTRODUCTION

Alzheimer's disease (AD) is a slowly progressive neurodegenerative disorder characterized by the presence of amyloid plaques and neurofibrillary tangles.¹⁻³ The burden of amyloid plaques in the brain can be quantified in vivo with positron emission tomography (PET) tracers such as Pittsburgh compound B (PiB).⁴ Amyloid PET is well correlated with AD neuropathology,⁵⁻⁷ and is often used as the reference standard for brain amyloidosis.^{8,9} Amyloid PET positivity is also used as an enrollment criterion for clinical trials, including trials in cognitively normal individuals that are designed to prevent or slow AD symptom onset.^{10,11} Multiple studies have demonstrated that amyloid plaques, as measured by PET, accumulate consistently across individuals during preclinical AD (when individuals are amyloid positive but cognitively normal), enabling staging of preclinical AD with continuous measures of amyloid PET.¹²⁻¹⁷

Cerebrospinal fluid (CSF) and plasma amyloid beta ($A\beta$)₄₂/ $A\beta$ ₄₀ have also been found to be accurate biomarkers of brain amyloidosis.^{8,18} However, although amyloid PET quantifies the lifetime accumulation of amyloid plaques, CSF and plasma concentrations of $A\beta$ ₄₂ and $A\beta$ ₄₀ represent the overall production and clearance of $A\beta$ peptides at the time of collection.^{19,20} Sequestration of $A\beta$ ₄₂ into amyloid plaques may be reflected by lower levels of $A\beta$ ₄₂ in the CSF and plasma,¹⁹⁻²¹ whereas $A\beta$ ₄₀ remains relatively stable in the presence of amyloid plaques and, therefore, can be used to normalize for overall protein production.^{20,22} Although the $A\beta$ ₄₂ to $A\beta$ ₄₀ ratio as measured in either CSF or plasma strongly predicts dichotomous amyloid PET status,^{8,9,18,23-26} the relationships of CSF and plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ with continuous values for amyloid PET burden are non-linear, and it is unclear whether CSF or plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ can be used as continuous measures of brain amyloidosis.

Because CSF and plasma measures of amyloid change monotonically over time²⁷⁻³⁰ and amyloid burden accumulates in a generally consistent pattern,¹²⁻¹⁷ it is possible that CSF and plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ may predict amyloid burden as measured by amyloid PET. Here we evaluated the relationships between CSF and plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ and continuous values for amyloid PET burden. We used high-performance measures of amyloid: CSF $A\beta$ ₄₂/ $A\beta$ ₄₀ by automated immunoassays, plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ by a high-precision immunoprecipitation-mass spectrometry assay, and amyloid PET with PiB. We generated three types of models (linear models, generalized additive models, and artificial neural networks) to predict mean cortical and regional

amyloid burden based on CSF and/or plasma $A\beta$ ₄₂/ $A\beta$ ₄₀. In addition, we implemented a recently published approach to staging AD based on regional amyloid PET values and compared disease stage based on actual amyloid PET with predicted regional amyloid PET values.

2 | METHODS

2.1 | Participants

Community-dwelling older adults enrolled in studies at the Knight Alzheimer's Disease Research Center (Knight ADRC) at Washington University in St. Louis were considered for inclusion based on the following criteria: (1) plasma and CSF collected on the same day with available $A\beta$ ₄₂/ $A\beta$ ₄₀ data, and (2) amyloid PET with PiB obtained within 2 years of the plasma and CSF collection. Written informed consent was obtained from all participants and their study partners. All procedures were approved by Washington University's Human Research Protection Office.

Participants underwent clinical assessments using the Uniform Data Set (UDS)³¹ that included the Clinical Dementia Rating (CDR).³² A CDR of 0 indicates no cognitive impairment, a CDR of 0.5 indicates very mild impairment, and a CDR of 1 indicates mild cognitive impairment. Race and gender were self-identified. Apolipoprotein E (APOE) genotyping was performed using either an Illumina 610 or OmniExpress chip as described previously.³³

2.2 | Cerebrospinal fluid (CSF) and plasma biomarkers

CSF and blood samples from each participant were collected at a single session at \approx 8 a.m. following overnight fasting as described previously.^{8,21} Concentrations of CSF $A\beta$ ₄₀ and $A\beta$ ₄₂ were measured by chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE G1200, Fujirebio, Malvern, PA, USA). Plasma $A\beta$ ₄₂ and $A\beta$ ₄₀ were measured by the C2N Diagnostics commercial laboratory using an immunoprecipitation-mass spectrometry assay (St. Louis, MO, USA).²⁴ All assays were performed by personnel who were blinded to participant information.

RESEARCH IN CONTEXT

- 1. Systematic Review:** Continuous measures of mean cortical and regional amyloid burden as measured by positron emission tomography (PET) are being used increasingly to stage Alzheimer's disease (AD). Cerebrospinal fluid (CSF) and plasma amyloid beta (A β)₄₂/A β ₄₀ have a non-linear relationship with amyloid PET measures. To facilitate comparisons of fluid biomarkers and amyloid PET, these measures are often dichotomized, which reduces the information represented by these measures.
- 2. Interpretation:** CSF A β ₄₂/A β ₄₀ predicts continuous values for mean cortical amyloid PET burden over a wider range than plasma A β ₄₂/A β ₄₀, potentially because of biological differences in these measures. CSF A β ₄₂/A β ₄₀ also predicts regional amyloid PET burden. These characteristics suggest that CSF A β ₄₂/A β ₄₀ may be useful in staging AD.
- 3. Future Directions:** Validation of the utility of CSF A β ₄₂/A β ₄₀ for disease staging using additional cohorts and study designs is needed. Further studies of CSF and plasma A β metabolism are needed to understand the differences between these measures of amyloidosis.

2.3 | Structural magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) images were obtained on 3T Siemens scanners. T1-weighted scans were segmented with FreeSurfer 5.3 (Martinos Center for Biomedical Imaging, Charlestown, MA, USA), and the Desikan-Killiany atlas was applied. Partial volume correction of amyloid PET images used volumes obtained from structural MRI.

2.4 | Positron emission tomography (PET) imaging

Amyloid PET scans with ¹¹C-Pittsburgh Compound B (or PiB) were obtained via previously described methods, and images were processed using the PET unified pipeline (PUP, <https://github.com/ysu001/PUP>).^{34,35} Briefly, dynamically acquired PET data were reconstructed into frames that underwent affine registration to correct for inter-frame motion.^{36,37} Standardized uptake value ratios (SUVRs) from the 30–60 min post-injection window were calculated using the cerebellar gray matter as the reference region.^{34,38} Images were smoothed using a gaussian kernel to achieve a spatial resolution of 8 mm. Data were then summarized in regions of interest defined by the Desikan-Killiany atlas derived from the MRI. Partial volume correction was implemented via a geometric transfer matrix approach.^{35,39} An amyloid PET summary value was calculated from the arithmetic mean of SUVRs for the following bilateral regions (average of right- and

left-sided structures): precuneus, superior frontal and rostral middle frontal regions, lateral orbitofrontal and medial orbitofrontal regions, and superior temporal and middle temporal regions.³⁴ Individuals were classified as amyloid positive if the mean cortical SUVR was greater than 1.42.³⁴ Centiloid values were calculated using Equation 1.⁴⁰

$$\text{Centiloid} = 45.0 * \text{mean cortical SUVR} - 47.5 \quad (1)$$

2.5 | Statistical analysis

Differences in participant characteristics by amyloid PET status were calculated using Student's *t*-tests for continuous variables and chi-square tests for categorical variables. Spearman correlations were used to evaluate the non-parametric relationships between biomarkers.

2.6 | Model development and architecture

We constructed linear, generalized additive models (GAMs) and artificial neural networks (ANNs) to predict both mean cortical and regional cortical SUVRs based on CSF and plasma A β ₄₂/A β ₄₀. For all models, we used an 80–20 train-test split after stratifying by PET amyloid status. In addition to models based only on fluid biomarkers, we considered models with age, number of APOE ϵ 4 alleles (using target encoding), and their interaction as potential covariates. For GAMs we fit cubic regression splines with a maximum allowed *k* of 4. For GAM model confidence intervals, we performed a 1000-iteration bootstrap and used a sliding window (*N* = 50) to evaluate the mean average percent error (MAPE) associated with the model fit relative to amyloid burden. We next constructed feedforward ANNs that used CSF or plasma A β ₄₂/A β ₄₀ to predict 37 bilateral regional PET-PiB SUVR values. ANNs were designed in R Studio v4.0 (R Core Development Team, 2013) using the Keras package. Feedforward ANNs map an input to an output using a directed acyclic graph composed of sets of smaller functions.⁴¹ The ANNs consisted of an input layer, three hidden layers with Relu activation functions, and an output layer with a linear activation function (Figure 1). Dropout was used between hidden layers in the model.⁴² Input features were scaled and centered, and the ANNs were trained with adaptive moment estimation (Adam) optimization with training terminated after 100 epochs.⁴³ The parameters for each ANN were identified with hyperparameter optimization via a coarse grid search (Table S1). Confidence intervals (Cis) were estimated from a 500-iteration bootstrap procedure.

2.7 | Inference from developed models

After training and optimizing the neural network models, we generated regional SUVR predictions. The range of fluid biomarkers that predicted mean cortical SUVRs was evaluated by asymptotic regression as described by Equation 2, where A and B were determined using a

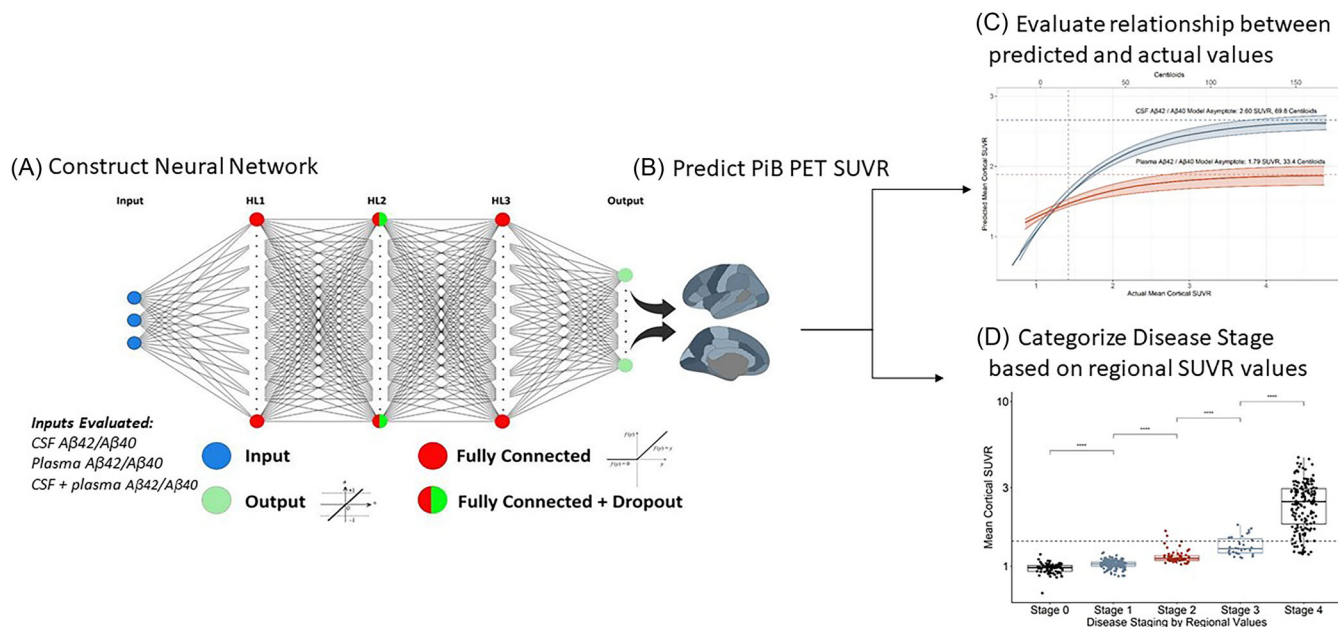


FIGURE 1 Overview of study. The objectives of this study were to examine the continuous relationships of amyloid positron emission tomography (PET) with cerebrospinal fluid (CSF) and plasma amyloid beta ($A\beta$)42/ $A\beta$ 40, and to determine whether these fluid biomarkers could be used to stage amyloidosis. We built a three-layer neural network with dropout to predict amyloid PET standardized uptake value ratio (SUVR) using CSF and plasma $A\beta$ 42/ $A\beta$ 40 (A). We evaluated the accuracy of these predictions (B), including across the range of amyloid PET SUVR values (C). We categorized individuals according to regional amyloid PET as described by Collij et al.¹³ (D) and compared the stages to those predicted by CSF $A\beta$ 42/ $A\beta$ 40.

non-linear least-squares model fitted via `nls()`, a function in the R package `nlme`.

$$\lim_{x \rightarrow \infty} A + Be^{-x} \quad (2)$$

2.8 | Staging by regional amyloid PET values

We next examined the relationship between fluid biomarkers and AD stage based on regional amyloid PET values. We categorized individuals into five disease stages based on regional amyloid PET.¹³ The same individuals were then categorized based on predicted values for regional SUVRs. Using accuracy and Kendall's tau, we compared the concordance of the disease stage based on actual and predicted regional amyloid PET values. Finally, we constructed a multinomial model to directly predict disease stage with CSF $A\beta$ 42/ $A\beta$ 40 as the sole input and the disease stages¹³ as a categorical output. We compared the performance of this direct multinomial model to the disease stages derived from the predicted regional PiB values on the basis of both Kendall's tau and confusion matrices.

3 | RESULTS

3.1 | Participants

Most participants were cognitively normal (427 of 491 [87%] were rated CDR 0) and the mean age was 69.0 with a standard deviation (SD)

of 8.8 years (Table 1). The cohort included 157 amyloid PET-positive and 334 amyloid PET-negative participants. The amyloid PET-positive group was older (73.2 ± 6.8 years vs 67.1 ± 8.9 years, $p < 0.001$), was more likely to have cognitive impairment as defined by a CDR > 0 (31% vs 6%, $p < 0.001$), and was more likely to carry an APOE $\epsilon 4$ allele (64% vs 25%, $p < 0.001$) compared to the amyloid PET-negative group.

Amyloid PET scans were typically performed within 2 weeks of fluid biomarker collection (median 8.1 days, range 0 days to 2 years); previous studies have demonstrated similar correlations between amyloid PET and CSF biomarkers when CSF was collected up to 6 years prior to or 2 years after amyloid PET.⁴⁴ There was no systematic bias whereby PET was more frequently collected either before or after the fluid biomarkers (Figure S1). CSF and plasma were collected on the same day.

3.2 | Correlations of CSF and plasma $A\beta$ 42/ $A\beta$ 40 with amyloid PET

Within the entire cohort, CSF $A\beta$ 42/ $A\beta$ 40 was well correlated with amyloid PET as measured by mean cortical SUVR (Spearman $\rho = -0.73$ (95% CI -0.78 to -0.70)), and plasma $A\beta$ 42/ $A\beta$ 40 was moderately correlated with mean cortical SUVR (Spearman $\rho = -0.56$, 95% CI -0.64 to -0.50) (Figure 2). Within the amyloid PET-positive group (mean cortical SUVR > 1.42 , $N = 157$), the correlation between CSF $A\beta$ 42/ $A\beta$ 40 and mean cortical SUVR was reduced, but there was still a moderate correlation (Spearman $\rho = -0.43$, 95% CI -0.55 to -0.30). Within

TABLE 1 Participant characteristics.

	Entire cohort	PET Amyloid Negative	PET Amyloid Positive	<i>p</i>
N	491	334	157	
Age in years (mean ± SD)	69.0 ± 8.8	67.1 ± 8.9	73.2 ± 6.8	<0.001
Gender, female n (%)	270 (55%)	194 (58%)	76 (48%)	0.06
CDR				<0.001
0	427 (87%)	316 (95%)	111 (71%)	
0.5	54 (11%)	16 (5%)	38 (26%)	
1	10 (2%)	2 (0.6%)	8 (5%)	
APOE genotype, n (%)				<0.001
ε2/ε2	1 (0.2%)	1 (0.3%)	0 (0%)	
ε2/ε3	51 (11%)	48 (15%)	3 (2%)	
ε2/ε4	15 (3%)	9 (3%)	6 (4%)	
ε3/ε3	248 (52%)	197 (60%)	54 (35%)	
ε3/ε4	138 (29%)	67 (20%)	71 (46%)	
ε4/ε4	28 (6%)	7 (2%)	21 (14%)	
Race, n (%)				0.02
White	438 (89%)	289 (87%)	149 (95%)	
Black	48 (10%)	42 (13%)	6 (4%)	
Other	5 (1%)	3 (0.9%)	2 (1.2%)	
Years of education (mean ± SD)	16.0 ± 2.6	16.2 ± 2.4	15.7 ± 2.8	0.09
Years between amyloid PET and fluid biomarker collection ^a (mean ± SD)	-0.03 (0.57)	-0.04 (0.55)	-0.03 (0.61)	0.835
Mean cortical SUVR (mean ± SD)	1.52 ± 0.79	1.06 ± 0.11	2.50 ± 0.73	<0.001
Mean cortical Centiloids (mean ± SD)	20.94 ± 35.66	0.19 ± 4.84	64.97 ± 32.68	<0.001
CSF Aβ42/Aβ40 (mean ± SD)	0.073 ± 0.023	0.086 ± 0.014	0.046 ± 0.011	<0.001
Plasma Aβ42/Aβ40 (mean ± SD)	0.101 ± 0.009	0.104 ± 0.008	0.094 ± 0.007	<0.001

^aNegative sign indicates that amyloid positron emission tomography (PET) imaging occurred after fluid biomarker collection.

the group with high amyloid PET burden (mean cortical SUVR > 2.0, N = 109), there was only a trend toward a correlation between CSF Aβ42/Aβ40 and mean cortical SUVR (Spearman $\rho = -0.18$, 95% CI -0.36 to 0.00). There was no significant correlation between plasma Aβ42/Aβ40 and mean cortical SUVR in the amyloid PET-positive group (Spearman $\rho = -0.09$, 95% CI -0.20 to 0.01) or in the group with high amyloid PET burden (Spearman $\rho = 0.10$, 95% CI -0.09 to 0.28). Correlations of CSF and plasma Aβ42/Aβ40 with regional mean cortical SUVR are shown in Figure S2.

Within the entire cohort, CSF Aβ42/Aβ40 was well correlated with plasma Aβ42/Aβ40 (Spearman $\rho = 0.64$, 95% CI 0.58 to 0.69). The correlation between CSF and plasma Aβ42/Aβ40 was stronger in the amyloid PET-negative group ($\rho = 0.404$, $p < 0.001$) than the amyloid PET-positive group ($\rho = 0.184$, $p = 0.022$) (Figure S3). There was no significant correlation between CSF and plasma Aβ42/Aβ40 in the group with high amyloid PET burden (Spearman $\rho = 0.019$, 95% CI -0.17 to 0.21).

A GAM for mean cortical SUVR as a function of CSF Aβ42/Aβ40 had a good fit ($R^2_{\text{adj}} = 0.662$, Figure 2A); a GAM for mean cortical SUVR

as a function of plasma Aβ42/Aβ40 had a moderate fit ($R^2_{\text{adj}} = 0.275$, Figure 2B). A comparison of the MAPE for the GAM models based on CSF or plasma Aβ42/Aβ40 demonstrated that both analytes were highly predictive of very low mean cortical amyloid PET burden, that is, both analytes identified individuals who did not have amyloid plaques (Figure 2C). However, as amyloid plaque burden increased in the brain, CSF Aβ42/Aβ40 remained predictive of continuous mean cortical SUVRs even after individuals passed the threshold for amyloid PET positivity, whereas plasma Aβ42/Aβ40 had a greater error in prediction starting with the relatively low amyloid burden.

3.3 | Artificial neural network models

ANN models were constructed to predict amyloid PET SUVR based on CSF and/or plasma Aβ42/Aβ40 (Figure S4). Models that predicted mean cortical SUVR using either a combination of CSF and plasma Aβ42/Aβ40 or CSF Aβ42/Aβ40 alone performed similarly (MAPE 14.8%, 95% CI 13.1% to 17.4% vs 14.2%, 95% CI 13.3% to 15.8%,

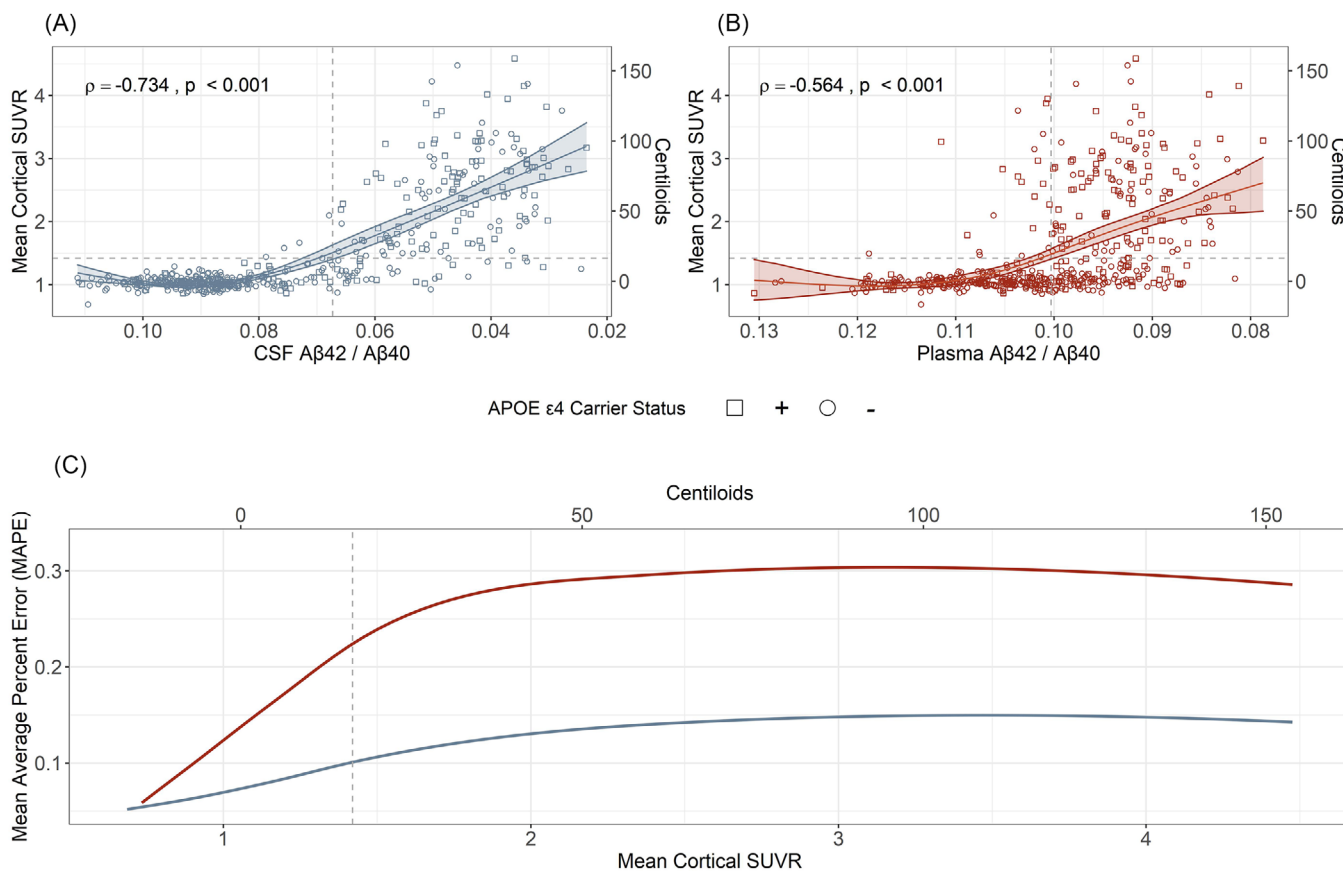


FIGURE 2 Correlations of amyloid positron emission tomography (PET) with cerebrospinal fluid (CSF) and plasma amyloid beta ($A\beta$)42/ $A\beta$ 40. The relationship of amyloid PET with CSF $A\beta$ 42/ $A\beta$ 40 (A) or plasma $A\beta$ 42/ $A\beta$ 40 (B) is shown with Spearman correlations. Horizontal dashed lines denote the established cutoff for amyloid PET (standardized uptake value ratio [SUVR] 1.42). The line of best fit for (A) and (B) was determined using a generalized additive model (GAM) with bootstrapped confidence intervals (Cis). The mean average percent error (MAPE) associated with the GAM model fit for the previous 50 values is shown (C). For low amyloid PET values, the MAPE is low (good prediction) for both CSF $A\beta$ 42/ $A\beta$ 40 (blue) and plasma $A\beta$ 42/ $A\beta$ 40 (red). As amyloid burden increases, the sliding window MAPE increases more rapidly for the plasma $A\beta$ 42/ $A\beta$ 40 GAM than the CSF $A\beta$ 42/ $A\beta$ 40 GAM. A vertical line shows the established cutoff for amyloid PET positivity.

respectively) (Figure 3). In contrast, the ANN predicting mean cortical SUVR using plasma $A\beta$ 42/ $A\beta$ 40 had a MAPE of 29.3% (95% CI 22.6% to 35.9%). Note that a lower MAPE indicates better prediction. Because of their nearly equivalent performance, we focused on the CSF-based model rather than the combination of CSF and plasma. The addition of age and number of *APOE* ε4 alleles did not significantly improve the performance of the CSF-based model; however, the number of *APOE* ε4 alleles did improve the plasma-based model to a MAPE of 23.2% (Figure S5). The addition of age did not improve the performance of any models. ANN models were compared to statistical models of amyloid PET as a function of CSF and/or plasma $A\beta$ 42/ $A\beta$ 40. The ANN models substantially outperformed the linear models and outperformed the generalized additive models (Figure S6). The linear model and GAM predicting mean cortical SUVR based on CSF $A\beta$ 42/ $A\beta$ 40 had a MAPE of 23.8% (95% CI 22.5% to 24.3%) and 15.1% (95% CI 14.2% to 16.1%), respectively.

After developing and tuning these models, the predicted and actual mean cortical SUVRs were compared (Figure 4). ANNs using CSF or plasma $A\beta$ 42/ $A\beta$ 40 under-predicted mean cortical SUVRs for individ-

uals with higher amyloid PET values, suggesting that the CSF or plasma $A\beta$ 42/ $A\beta$ 40 only predicted continuous SUVRs until a certain threshold value. We performed asymptotic regression analyses to find the maximum SUVR that could be predicted by CSF or plasma $A\beta$ 42/ $A\beta$ 40. This approach found that the models predicted mean cortical SUVR until the following levels: CSF and plasma $A\beta$ 42/ $A\beta$ 40, 2.49 SUVR (64.6 Centiloids); CSF $A\beta$ 42/ $A\beta$ 40, 2.60 SUVR (69.5 Centiloids); and plasma $A\beta$ 42/ $A\beta$ 40, 1.79 SUVR (33.1 Centiloids). Notably, the amyloid positivity threshold for amyloid PET with PiB is SUVR 1.42 (16.4 Centiloids).

3.4 | Disease stage classification

Although mean cortical amyloid burden has been used as a measure of AD stage, another recent approach to staging emphasizes regional spread as the primary marker of disease severity and uses the number of brain regions where amyloid SUVR is higher than a relatively low threshold.¹³ Individuals with virtually no amyloid accumulation

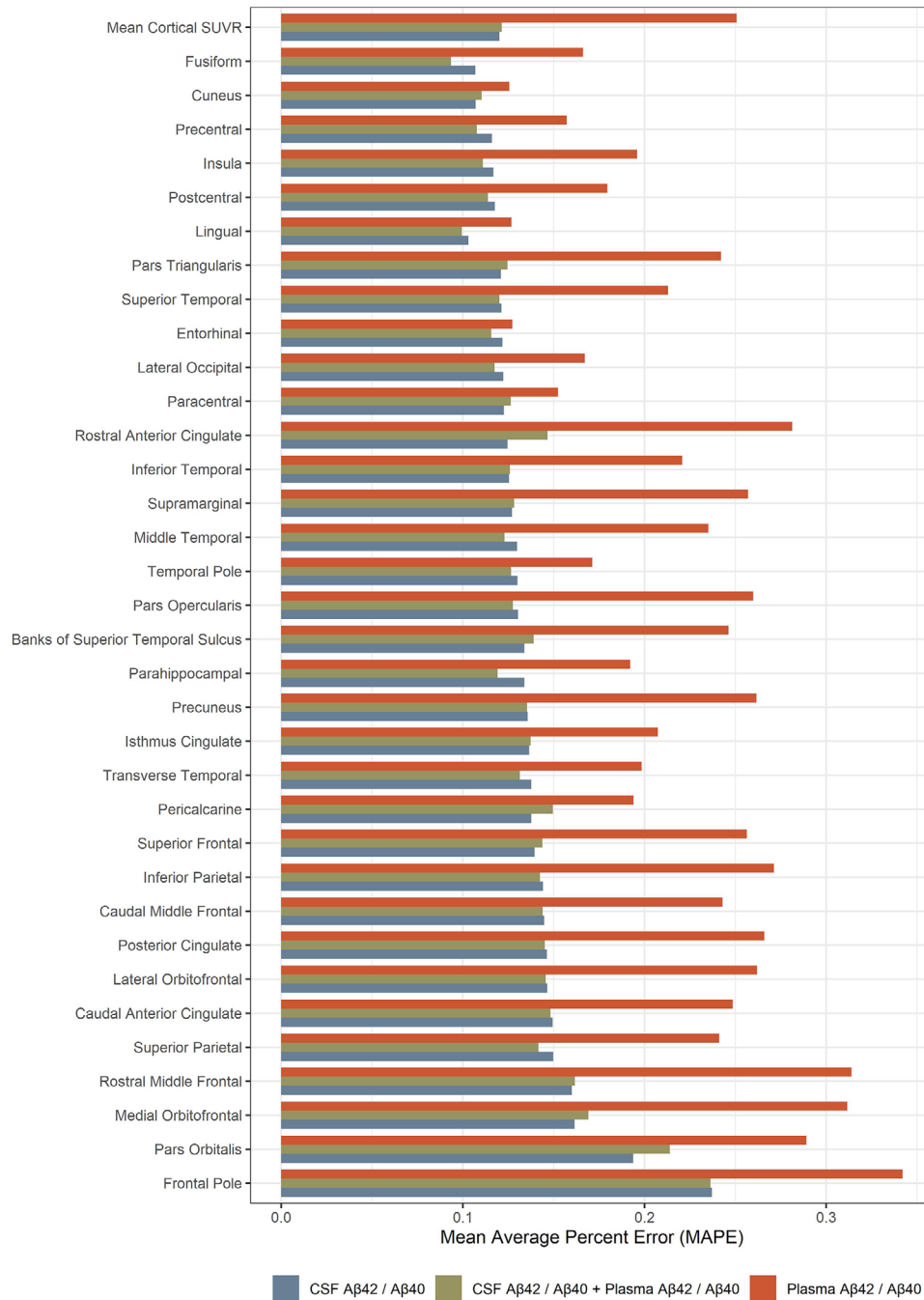


FIGURE 3 Prediction of regional amyloid positron emission tomography (PET) standardized uptake value ratio (SUVR) by neural network models. The mean average percent error (MAPE) for prediction of mean cortical SUVR and regional amyloid PET (average of right- and left-sided structures) is shown for cerebrospinal fluid (CSF) amyloid beta ($A\beta$)₄₂/ $A\beta$ ₄₀, CSF and plasma $A\beta$ ₄₂/ $A\beta$ ₄₀, and plasma $A\beta$ ₄₂/ $A\beta$ ₄₀. The most accurate prediction, by a small margin, was the combined CSF and plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ model (average MAPE over all regions, $MAPE_{avg} = 13.3\%$). The CSF $A\beta$ ₄₂/ $A\beta$ ₄₀ model performed almost as well ($MAPE_{avg} = 14.1\%$). The plasma $A\beta$ ₄₂/ $A\beta$ ₄₀ model did not perform as well as models that included CSF $A\beta$ ₄₂/ $A\beta$ ₄₀ ($MAPE_{avg} = 23.6\%$), but performance improved with the inclusion of APOE genotype in the model (Figure S4).

are considered Disease Stage 0, whereas those with amyloid burden in most regions of the brain are considered Disease Stage 4. Participants were classified into each of the five disease stages based on actual regional amyloid PET SUVR values (Figure S7) and based on predicted regional SUVRs. The concordance between disease stage based on actual regional amyloid PET SUVRs and values predicted by the

model based on CSF $A\beta$ ₄₂/ $A\beta$ ₄₀ had high concordance ($\tau_{Kendall} = 0.655$, $p < 0.001$); they were the same for 61% of individuals and within one stage for 90% of individuals (Figure S8). The CSF $A\beta$ ₄₂/ $A\beta$ ₄₀ model resulted in a more bimodal distribution than amyloid PET, classifying nearly all individuals as either Stage 1 or Stage 4, but it did identify some individuals as Stages 2 or 3 (Table S2). The model based on

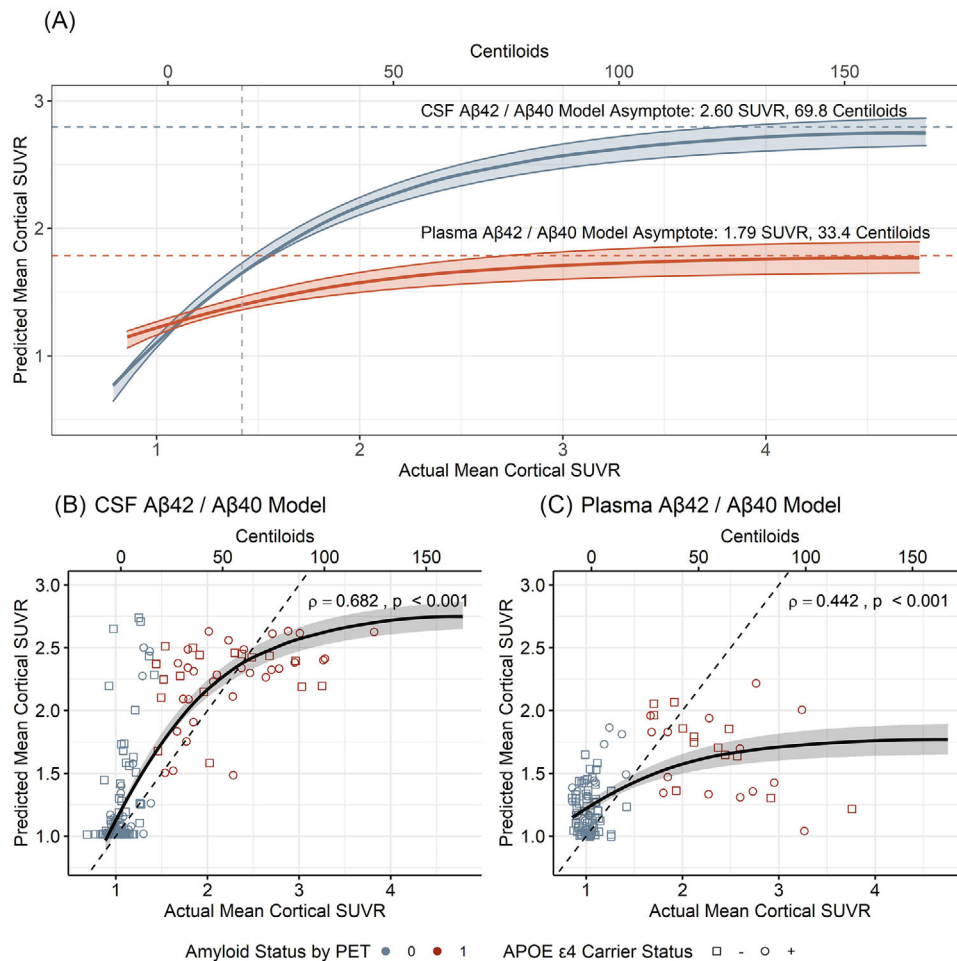


FIGURE 4 Prediction of mean cortical standardized uptake value ratio (SUVR) by neural network models. The relationship between predicted and actual mean cortical SUVR for models using cerebrospinal fluid (CSF) (A, B) or plasma amyloid beta (A β)42/A β 40 (A, C) are shown. Asymptotic regression was used to identify the maximum level of amyloid burden at which CSF and plasma A β 42/A β 40 accurately predicted mean cortical SUVR (A).

plasma A β 42/A β 40 did not categorize individuals reliably by disease stage (Table S3). We then constructed a multinomial model to directly predict disease stage using CSF A β 42/A β 40 as the model input. Direct prediction of disease stage from CSF A β 42/A β 40 resulted in a similar overall performance ($\tau_{Kendall} = 0.627$); however, this approach failed to categorize any individuals into the intermediate stages (Stage 2 or Stage 3) (Table S4).

4 | DISCUSSION

Multiple studies using amyloid PET have shown that amyloid plaque burden accumulates in a generally consistent manner across individuals.¹²⁻¹⁷ As amyloid burden increases, CSF A β 42 levels and plasma A β 42/A β 40 decrease and then appear to plateau.^{21,28,29,45,46} In this study, we sought to clarify the continuous relationships of CSF and plasma A β 42/A β 40 with amyloid plaque burden as measured by amyloid PET. Most studies have performed Spearman correlations to quantify these non-linear relationships,^{8,9,18,23-26} although some

have performed more sophisticated modeling.^{28,30,47} We found that CSF A β 42/A β 40 predicted mean cortical SUVR until 69.8 Centiloids, which includes most of the range of amyloid PET values that are associated with preclinical and early symptomatic AD,¹⁶ whereas plasma A β 42/A β 40 predicted mean cortical SUVR until 33.4 Centiloids, which is above the threshold for amyloid positivity (16.4 Centiloids), but did not distinguish between moderate to high amyloid burden. In addition, we found that a single CSF A β 42/A β 40 measurement could be used to categorize individuals into a disease stage representing the regional spread of amyloidosis. Using CSF A β 42/A β 40 to first predict regional amyloid PET values via a neural network model and then predicting disease stage better identified individuals in the intermediate disease stages (Stage 2 and Stage 3) compared to directly predicting disease stage from CSF A β 42/A β 40. Although the accuracy of these predictions was limited, this finding demonstrates that the regional distribution of amyloid plaques is strongly related to the global level of brain amyloidosis as reflected by CSF A β 42/A β 40.

Overall, these analyses demonstrate key differences in amyloid PET, CSF A β 42/A β 40, and plasma A β 42/A β 40 as measures of

amyloidosis. The dynamic range over which CSF and plasma A β ₄₂/A β ₄₀ reflect amyloid burden is smaller for plasma A β ₄₂/A β ₄₀, consistent with a previous report.³⁰ The different relationships of CSF and plasma A β ₄₂/A β ₄₀ with amyloid PET are likely related to differences in A β metabolism in the CSF and plasma. A β peptides that are generated by the brain enter the interstitial fluid, where they can interact directly with extracellular amyloid plaques and enter the CSF. The lower CSF A β ₄₂/A β ₄₀ levels found in individuals with brain amyloidosis likely represent the preferential sequestration of A β ₄₂ compared to A β ₄₀ into amyloid plaques.²⁰ In contrast, plasma A β has multiple sources: A β peptides in the brain interstitial fluid are transported across the blood-brain barrier into the blood; A β peptides in the CSF are resorbed into venous blood; and A β peptides are produced in the periphery, including by platelets.⁴⁸ The more complex origin of plasma A β ₄₂/A β ₄₀ may explain why brain amyloidosis is associated with an \approx 40% lower CSF A β ₄₂/A β ₄₀, but only 10% lower plasma A β ₄₂/A β ₄₀.⁸ Furthermore, studies of A β kinetics suggest that differences in the balance between the peripheral and central nervous system (CNS) contributions may vary by amyloid status.¹⁹ The reduced correlation between CSF and plasma A β ₄₂/A β ₄₀ in amyloid PET-positive individuals further supports the idea that relationships between these biomarkers change with amyloid plaque deposition. Changes in plasma A β metabolism that occur with amyloidosis could underlie our finding that plasma A β behaves as a relatively dichotomous marker of amyloidosis, rather than a continuous measure that steadily changes with increasing amyloid plaque burden.

Consideration of the number of APOE ϵ 4 alleles improved prediction of mean cortical SUVR in a model based on plasma A β ₄₂/A β ₄₀ but not CSF A β ₄₂/A β ₄₀, consistent with previous work demonstrating that APOE ϵ 4 status affects the likelihood of amyloid PET positivity by plasma A β ₄₂/A β ₄₀.^{8,24,26,49} In contrast, including age did not improve the prediction of mean cortical SUVR in models based on either plasma or CSF A β ₄₂/A β ₄₀. Moreover, inclusion of age worsened the prediction of mean cortical SUVR, suggesting that age was simply adding noise to the prediction. Previous studies have varied in finding significant effects of age on the relationship between plasma A β ₄₂/A β ₄₀ and amyloid PET^{8,23,25,26,49}; this association may be affected by the mean age and size of the cohort, as well as the PET tracer.

Limitations of this study include the relatively low frequency of individuals with high amyloid burden. Extension of this work into a cohort that includes more individuals with high amyloid burden would provide greater confidence in the range of CSF and plasma A β ₄₂/A β ₄₀ that predicts continuous values for amyloid PET. Notably, few cohorts currently have large data sets on plasma A β ₄₂/A β ₄₀ measured with a high-precision assay, and more widely available assays may have significantly lower performance that would make interpretation less clear.²³ We used the PiB radiotracer in this study, which may be more sensitive than other amyloid PET tracers⁵⁰ and has demonstrated very consistent longitudinal trajectories in our cohort that make it ideal for staging.¹⁶ Furthermore, although the cross-sectional design enabled modeling of the relationships between biomarkers performed at a single time, longitudinal studies are needed to examine how these relationships change within individuals over time.

In conclusion, we observed a non-linear but continuous relationship between CSF A β ₄₂/A β ₄₀ and amyloid PET that persisted throughout much of the range of amyloid PET values that are associated with preclinical AD. In contrast, plasma A β ₄₂/A β ₄₀ behaved as a more dichotomous measure of amyloid plaque burden. Although CSF and plasma A β ₄₂/A β ₄₀ and amyloid PET have high agreement as dichotomous measures of amyloid, and amyloid status (positive or negative) is often used in clinical practice and clinical studies, continuous levels of these measures are not interchangeable, especially at high levels of amyloid burden.

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REFERENCES

- Jack CR Jr, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *2016*;87(5):539-47. doi:10.1212/WNL.0000000000002923
- Thal DR, Rüb U, Orantes M, Braak H. Phases of A β -deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58(12):1791-1800.
- Thal DR, Capetillo-Zarate E, del Tredici K, Braak H. The development of amyloid beta protein deposits in the aged brain. *Review Sci Aging Knowledge Environ*. 2006;2006(6):re1. <http://sageke.sciencemag.org/cgi/content/full/2006/6/re1>
- Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. *Ann Neurol*. 2004;55(3):306-319.
- Clark CM, Pontecorvo MJ, Beach TG, et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid- β plaques: a prospective cohort study. *Lancet Neurol*. 2012;11(8):669-678.
- Ikonomic MD, Buckley CJ, Abrahamson EE, et al. Post-mortem analyses of PiB and flutemetamol in diffuse and cored amyloid- β plaques in Alzheimer's disease. *Acta Neuropathol*. 2020;140(4):463-476.
- Chen CD, Joseph-Mathurin N, Sinha N, et al. Comparing amyloid- β plaque burden with antemortem PiB PET in autosomal dominant and late-onset Alzheimer disease. *Acta Neuropathol*. 2021;142(4):689-706.
- Schindler SE, Bollinger JG, Ovod V, et al. High-precision plasma β -amyloid 42/40 predicts current and future brain amyloidosis. *Neurology*. 2019;93(17):E1647-59.
- Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimer's Dement*. 2018;14(11):1460-1469.
- Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? *Sci Transl Med*. 2014;6(228):228fs13. doi:10.1126/scitranslmed.3007941
- Rafii MS, Sperling RA, Donohue MC, et al. The AHEAD 3-45 study: design of a prevention trial for Alzheimer's disease. *Alzheimer's Dement*. 2022.
- Grothe MJ, Barthel H, Sepulcre J, Dyrba M, Sabri O, Teipel SJ. In vivo staging of regional amyloid deposition. *Neurology*. 2017;89(20):2031-2038.
- Collij LE, Heeman F, Salvadó G, et al. Multitracer model for staging cortical amyloid deposition using PET imaging. *Neurology*. 2020;95(11):e1538-e1553.
- Mattsson N, Palmqvist S, Stomrud E, Vogel J, Hansson O. Staging β -amyloid pathology with amyloid positron emission tomography. *JAMA Neurol*. 2019;76(11):1319-1329.
- Koscik RL, Betthausen TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. *Alzheimer's Dement*. 2020;12(1):e12007. doi:10.1002/dad2.12007
- Schindler SE, Li Y, Buckles VD, et al. Predicting symptom onset in sporadic Alzheimer disease with amyloid PET. *Neurology*. 2021;97(18):e1823-e1834.
- Betthausen TJ, Bilgel M, Koscik RL, et al. Multi-method investigation of factors influencing amyloid onset and impairment in three cohorts. *Brain*. 2022;45(11):4065-4079. doi:10.1093/brain/awac213
- Lewczuk P, Matzen A, Blennow K, et al. Cerebrospinal fluid A β 42/40 corresponds better than A β 42 to amyloid PET in Alzheimer's disease. *J Alzheimer's Dis*. 2016;55(2):813-822.
- Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimer's Dement*. 2017;13(8):841-849.
- Patterson BW, Elbert DL, Mawuenyega KG, et al. Age and amyloid effects on human central nervous system amyloid-beta kinetics. *Ann Neurol*. 2015;78(3):439-453.
- Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta₄₂ in humans. *Ann Neurol*. 2006;59(3):512-519.
- Graff-Radford J, Jones DT, Wiste HJ, et al. Cerebrospinal fluid dynamics and discordant amyloid biomarkers. *Neurobiol Aging*. 2022;110:27-36. <https://linkinghub.elsevier.com/retrieve/pii/S0197458021003298>
- Janelidze S, Teunissen CE, Zetterberg H, et al. Head-to-head comparison of 8 plasma amyloid- β 42/40 assays in Alzheimer disease. *JAMA Neurol*. 2021;78(11):1375.
- Hu Y, Kirmess KM, Meyer MR, et al. Assessment of a plasma amyloid probability score to estimate amyloid positron emission tomography findings among adults with cognitive impairment. *JAMA Netw Open*. 2022;5(4):e228392.
- Zicha S, Bateman RJ, Shaw LM, et al. Comparative analytical performance of multiple plasma A β 42 and A β 40 assays and their ability to predict positron emission tomography amyloid positivity. *Alzheimer's Dement*. 2022. doi:10.1002/alz.12697. Epub ahead of print.
- Li Y, Schindler SE, Bollinger JG, et al. Validation of plasma amyloid- β 42/40 for detecting Alzheimer disease amyloid plaques. *Neurology*. 2022;98(7):e688-99.
- Sutphen CL, Jasielec MS, Shah AR, et al. Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer disease during middle age. *JAMA Neurol*. 2015;72(9):1029.
- Toledo JB, Bjerke M, Da X, et al. Nonlinear association between cerebrospinal fluid and florbetapir F-18 β -amyloid measures across the spectrum of Alzheimer disease. *JAMA Neurol*. 2015;72(5):571.
- de Wolf F, Ghanbari M, Licher S, et al. Plasma tau, neurofilament light chain and amyloid- β levels and risk of dementia; a population-based cohort study. *Brain*. 2020;143(4):1220-1232.
- Palmqvist S, Insel PS, Stomrud E, et al. Cerebrospinal fluid and plasma biomarker trajectories with increasing amyloid deposition in Alzheimer's disease. *EMBO Mol Med*. 2019;11(12):e11170. doi:10.15252/emmm.201911170
- Dodge HH, Goldstein FC, Wakim NI, et al. Differentiating among stages of cognitive impairment in aging: version 3 of the uniform data set (UDS) neuropsychological test battery and MoCA index scores. *Alzheimer's Dement*. 2020;6(1):e12103.
- Morris JC. Clinical Dementia rating: a reliable and valid diagnostic and staging measure for Dementia of the Alzheimer type. *Int Psychogeriatr*. 1997;9(1):173-176. doi:10.1017/S1041610297004870
- Cruchaga C, Kauwe J, Harari O, et al. GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. *Neuron*. 2013;78:256-268. <https://www.sciencedirect.com/science/article/pii/S0896627313001840>
- Su Y, D'Angelo GM, Vlassenko AG, et al. Quantitative analysis of PiB-PET with FreeSurfer ROIs. *PLoS One*. 2013;8(11):e73377. doi:10.1371/journal.pone.0073377
- Su Y, Blazey TM, Snyder AZ, et al. Partial volume correction in quantitative amyloid imaging. *Neuroimage*. 2015;107:55-64. <https://www.sciencedirect.com/science/article/pii/S1053811914009884>

36. Eisenstein SA, Koller JM, Piccirillo M, et al. Characterization of extrastriatal D2 in vivo specific binding of [18F](N-methyl)benperidol using PET. *Synapse*. 2012;66(9):770-780.
37. Hajnal JV, Saeed N, Soar EJ, Oatridge A, Young IR, Bydder GM. A registration and interpolation procedure for subvoxel matching of serially acquired MR images. *J Comput Assist Tomogr*. 1995;19(2):289-296.
38. Mintun MA, LaRossa GN, Sheline YI, et al. [11C]PIB in a nondemented population. *Neurology*. 2006;67(3):446-452. doi:10.1212/01.wnl.0000228230.26044.a. <http://www.neurology.org/cgi/content/full/67/3/446>
39. Rousset OG, Ma Y, Evans AC. Correction for partial volume effects in PET: principle and validation. *J Nucl Med*. 1998;39(5):904-911.
40. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimer's Dement*. 2015;11(1):1-15.e4. <https://www.sciencedirect.com/science/article/pii/S155252601402500X>
41. Lockett PH, McCullough A, Gordon BA, et al. Modeling autosomal dominant Alzheimer's disease with machine learning. *Alzheimer's Dement*. 2021;17(6):1005-1016.
42. Srivastava N, Hinton G, Krizhevsky A, Salakhutdinov R. Dropout: a simple way to prevent neural networks from overfitting. *J Mach Learn Res*. 2014;15(1):1929-1958.
43. Kingma DP, Ba J. Adam: A Method for Stochastic Optimization. arXiv. 2014; <http://arxiv.org/abs/1412.6980>
44. Boerwinkle AH, Wisch JK, Chen CD, et al. Temporal correlation of CSF and neuroimaging in the amyloid-Tau-neurodegeneration model of Alzheimer disease. *Neurology*. 2021;97(1):e76-e87. doi:10.1212/WNL.00000000000012123
45. Lopez OL, Klunk WE, Mathis CA, et al. Relationship of amyloid- β 1-42 in blood and brain amyloid: ginkgo evaluation of memory study. *Brain Commun*. 2020;2(1):fz038. doi:10.1093/braincomms/fz038
46. Winder Z, Sudduth TL, Fardo D, et al. Hierarchical clustering analyses of plasma proteins in subjects with cardiovascular risk factors identify informative subsets based on differential levels of angiogenic and inflammatory biomarkers. *Front Neurosci*. 2020;14:84. doi: 10.3389/fnins.2020.00084
47. Milà-Alomà M, Ashton NJ, Shekari M, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid- β pathology in preclinical Alzheimer's disease. *Nat Med*. 2022;28(9):1797-1801. doi:10.1038/s41591-022-01925-w
48. Roberts KF, Elbert DL, Kasten TP, et al. Amyloid- β efflux from the central nervous system into the plasma. *Ann Neurol*. 2014;76(6):837-844.
49. West T, Kirmess KM, Meyer MR, et al. A blood-based diagnostic test incorporating plasma A β 42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. *Mol Neurodegener*. 2021;16(1):30.
50. Su Y, Flores S, Wang G, et al. Comparison of Pittsburgh compound B and florbetapir in cross-sectional and longitudinal studies. *Alzheimer's Dement*. 2019;11(1):180-190.

SUPPORTING INFORMATION

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

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