


## BRIEF COMMUNICATION

# Correlation of plasma and neuroimaging biomarkers in Alzheimer's disease

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## Introduction

The development of blood-based biomarkers to estimate the amyloid ('A'), tau ('T'), and neurodegenerative ('N') features of Alzheimer's disease (AD) has increased the ability to study disease in diverse populations. Plasma concentrations of phosphorylated tau at threonine 181 and 217 (Ptau 181 and Ptau 217) along with neurofilament light (NfL) chain were elevated in multi-racial/ethnic, community based, older adults diagnosed clinically, and pathologically with AD,<sup>1</sup> consistent with other studies.<sup>2-7</sup> We found increased Ptau 181 and Ptau 217 concentrations and decreased A $\beta$ 42/A $\beta$ 40 ratios were associated with higher risk of AD after an average of 4 years.

Fluid and imaging biomarkers allow for incorporation of pathophysiological data into diagnosis according to the

## Abstract

Blood-based phosphorylated tau (Ptau) 181 and 217 biomarkers are sensitive and specific for Alzheimer's disease. In this racial/ethnically diverse cohort study, participants were classified as biomarker positive (Ptau+) or negative (Ptau-) based on Ptau 181 and 217 concentrations and as cognitively impaired (Sym) or unimpaired (Asym). The four groups, Ptau-/Asym, Ptau+/Asym, Ptau-/Sym, and Ptau+/Sym, differed by age, *APOE-4* allele frequency, total tau, neurofilament light chain, and cortical thickness measured by MRI. Our results add to increasing evidence that plasma Ptau 181 and 217 concentrations are valid Alzheimer's disease biomarkers in diverse populations.

ATN framework without explicit consideration of cognitive or clinical symptoms.<sup>8</sup> The goal of this study was to examine demographic (i.e., age, sex/gender, race/ethnicity), genetic (i.e., *APOE*  $\epsilon$ 4 allele), amyloid (A $\beta$ 42/A $\beta$ 40), tau (total tau concentration), neurodegeneration (NfL, cortical atrophy) variables across older adults classified by Ptau cutpoint and clinical status in a multi-ethnic cohort.

## Methods

### Participants and diagnostic procedures

This follow-up study included 300 participants from the Washington Heights-Inwood Columbia Aging Project (WHICAP) selected for equal representation from race/ethnicity groups: non-Latinx White, Latinx/Hispanic, and

non-Latinx African American/Black) with similar numbers with an AD clinical diagnosis at their last longitudinal assessment. Race and ethnicity were self-reported and coded via standardized criteria.<sup>9</sup> A goal for the current analyses was to define four groups based on symptom and biomarker status. A consensus committee, including clinicians with expertise in dementia, reviewed neuropsychological, medical, and neurological data (but not biomarker data) for clinical diagnoses. A clinical diagnosis of AD was assigned using research criteria<sup>10</sup> and a Clinical Dementia Rating<sup>11</sup> of 0.5 or higher. To derive a diagnostic threshold score for Ptau biomarker concentration, we examined data from autopsied WHICAP participants with stored plasma ( $n = 113$ ) as described previously.<sup>1</sup> A pathological assignment of AD was made according to the National Institute on Aging-Alzheimer's Association criteria, as previously described,<sup>1</sup> with case status assigned to those deemed with high AD neuropathological changes (ADNC) and controls to those without pathological AD or with low or intermediate ADNC.

### Plasma biomarkers

Plasma biomarker concentrations were measured as described previously.<sup>1</sup> Briefly stored aliquoted plasma was used to determine A $\beta$ <sub>42</sub>, A $\beta$ <sub>40</sub>, t-tau, NfL, Ptau 181, and Ptau 217 concentrations. For A $\beta$ <sub>42</sub>, A $\beta$ <sub>40</sub>, and t-tau we used Simoa (Quanterix) technology on the SR-X platform with the multiplex Neuro 2-plex A (#101995) and NfL (#103400) kits. Each plate assayed in duplicate 38 samples, 8 calibrators, and 2 controls. The ratio of A $\beta$ <sub>42</sub> to A $\beta$ <sub>40</sub> was considered as the primary biomarker for amyloid. Ptau 181 and Ptau 217 concentrations were determined on a Meso Scale Discovery (MSD) platform as described previously.<sup>1</sup> Briefly, for Ptau 181, Biotinylated-AT270 (MN1050, ThermoFisher) was used as a capture antibody and SULFOTAG-Ru-4G10-E2 (Eli Lilly) for the detector. For Ptau217, Biotinylated-IBA493 (Eli Lilly) was used as a capture antibody and SULFO-TAG-Ru-4G10-E2 (Eli Lilly) for the detector.

### Neuropsychological assessment

At each visit, participants are evaluated with a comprehensive set of neuropsychological tests<sup>12</sup> in their preferred language (English or Spanish). Based on the factor structure of the neuropsychological battery,<sup>13</sup> summary scores were derived for memory, language, visuospatial function, and speed/executive function by averaging z-scores for individual tests in each domain.

### Magnetic resonance imaging

Magnetic resonance imaging (MRI) was available for a subset of participants ( $n = 223$ ) included in the analyses. T1-

weighted anatomical images were acquired on a 3 T Philips (Best, the Netherlands) Intera scanner (TR = 6.6 ms; TE = 3.0 ms; flip angle = 8°; FOV = 256 × 200 × 165 mm; slice thickness = 0.6 mm) or 1.5 T Philips Intera scanner (TR = 20 ms, TE = 2.1 ms, FOV = 240 × 256 × 160 mm, slice thickness = 1.3 mm). FreeSurfer<sup>14</sup> was used to derive regional cortical thickness and an "AD signature" was calculated by averaging cortical thickness in the entorhinal cortex, parahippocampus, inferior parietal lobe, pars opercularis, pars orbitalis, pars triangularis, inferior temporal lobe, temporal pole, precuneus, supramarginal gyrus, superior parietal lobe, and superior frontal lobe across hemispheres.

### Statistical analysis

We used receiver operating characteristic (ROC) curves to evaluate the area under the curve (AUC) to assess Ptau 217 and Ptau 181 concentrations with high ADNC relative to controls. We calculated Youden's index<sup>15</sup> to derive the respective Ptau concentration cutoff scores with the highest combination of sensitivity and specificity. This allowed us to define four distinct groups: low Ptau concentration (Ptau181 and Ptau217) without clinical diagnosis of AD (Ptau-, Asym), high Ptau concentration without clinical diagnosis (Ptau+, Asym), low Ptau concentration with clinical diagnosis (Ptau-, Sym), and high Ptau concentration with clinical diagnosis (Ptau+, Sym). We compared age, sex/gender, and race/ethnicity across the four groups using chi-squared and general linear models. Next, we examined differences in AD-relevant variables, including *APOE*  $\epsilon 4$  allele frequency; plasma biomarker concentrations for A $\beta$ <sub>42</sub>/A $\beta$ <sub>40</sub>, t-tau, and NfL; cognitive domain scores; and cortical thickness on MRI using general linear models and Chi-squared tests. Post hoc analyses contrasted participant groups to Ptau-/Asym group as reference.

### Results

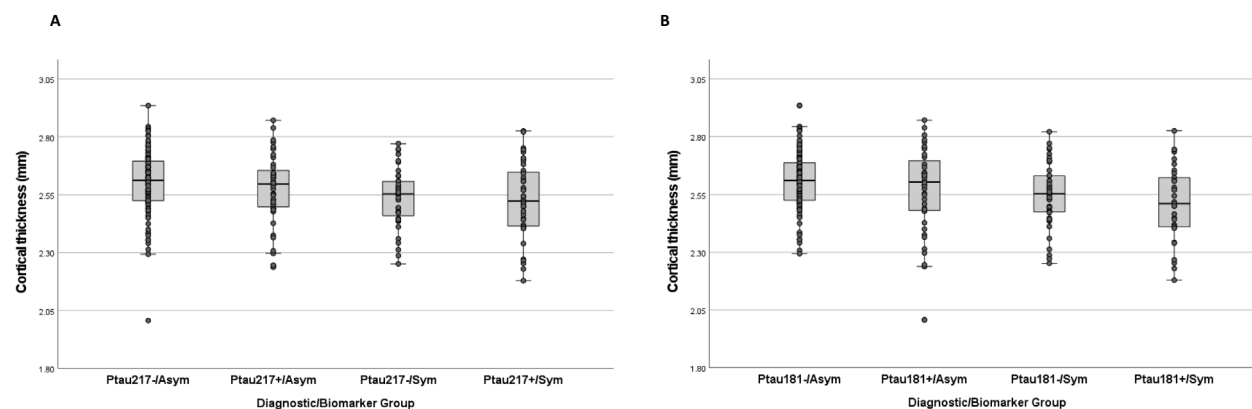
The Youden Index for Ptau 217 was 0.21 pg/mL, yielding a diagnostic sensitivity and specificity of 0.84 and 0.77, respectively, as previously reported.<sup>1</sup> Relative to individuals classified as Ptau-/Asym, those who were Ptau+/Sym were older, but similar in sex/gender and race/ethnicity (Table 1). Ptau+ individuals regardless of cognitive status were more likely to have at least one *APOE*  $\epsilon 4$  allele. The four groups did not differ in A $\beta$ <sub>42</sub>/A $\beta$ <sub>40</sub> ratio. Compared with participants classified as Ptau-/Asym, Ptau+/Asym, and Ptau+/Sym had higher total tau concentrations. Participants classified as Ptau+/Asym, Ptau-/Sym, or Ptau+/Sym had higher NfL concentrations compared with the Ptau-/Asym group. Cortical thickness was lower in the Ptau-/Sym and Ptau+/Sym compared with the Ptau-/

**Table 1.** Differences across biomarker/clinical groups in demographic and Alzheimer's disease-related measures.

	Ptau-/Asym	Ptau+/Asym	Ptau-/Sym	Ptau+/Sym	Total sample	Statistic
Ptau 217						
N	119 (40%)	54 (18%)	60 (20%)	67 (22%)	300	-
Age mean (SD) yrs	80.75 (6.36)	81.41 (6.15)	82.00 (6.36)	84.13 (6.51)	81.87 (6.45)	F = 4.17, p = 0.006
N (%) women	81 (68%)	31 (57%)	42 (70%)	46 (69%)	200 (66.7%)	$\chi^2 = 2.60$ , p = 0.45
Race/ethnicity N (%)					100 (33.3%)	$\chi^2 = 5.90$ , p = 0.43
White N (%)	46 (39%)	18 (33%)	14 (23%)	22 (33%)	100 (33.3%)	
Black N (%)	38 (32%)	17 (32%)	20 (33%)	25 (37%)	100 (33.3%)	
Hispanic N (%)	35 (29%)	19 (35%)	26 (43%)	20 (30%)	100 (33.3%)	
APOE, N (%) with at least one $\epsilon 4$ allele	21 (18%)	28 (52%)	8 (13%)	27 (40%)	84 (28%)	$\chi^2 = 32.99$ , p < 0.001
A $\beta_{42}$ /A $\beta_{40}$ mean (SD) concentration	0.060 (0.01)	0.057 (0.01)	0.63 (0.02)	0.057 (0.01)	0.059 (0.01)	F = 2.39, p = 0.06
T-tau mean (SD) concentration, pg/mL	4.63 (1.91)	5.54 (2.39)	4.58 (2.05)	5.24 (2.08)	4.92 (2.09)	F = 3.40, p = 0.01
NFL mean (SD) concentration, pg/mL	27.53 (19.12)	38.45 (41.99)	35.57 (30.81)	38.43 (18.07)	33.48 (27.25)	F = 3.52, p = 0.01
Cognition mean (SD) standard score	0.46 (0.54)	0.32 (0.57)	-0.69 (0.67)	-0.89 (0.70)	-0.07 (0.85)	F = 92.73, p < 0.001
Language	0.52 (0.51)	0.55 (0.56)	-0.41 (0.60)	-0.24 (0.50)	0.17 (0.68)	F = 60.21, p < 0.001
Speed/executive function	0.44 (0.80)	0.51 (0.69)	-0.59 (1.08)	-0.49 (1.06)	0.12 (0.99)	F = 23.71, p < 0.001
Visuospatial function	0.58 (0.43)	0.54 (0.56)	-0.18 (0.61)	-0.03 (0.62)	0.30 (0.63)	F = 37.15, p < 0.01
Cortical thickness mean (SD) mma	2.60 (0.14)	2.57 (0.14)	2.53 (0.14)	2.52 (0.16)	2.57 (0.14)	F = 3.50, p = 0.016
Ptau 181						
N	123 (41%)	49 (16%)	68 (23%)	59 (20%)	300	-
Age mean (SD) yrs	80.40 (6.26)	82.33 (6.25)	82.34 (6.56)	84.03 (6.37)	81.87 (6.47)	F = 4.68, p = 0.08
Race/ethnicity N (%)	45 (36.7)	19 (39)	18 (26.5)	18 (30.5)	100 (33.3)	$\chi^2 = 5.53$ , p = 0.47
White N (%)	39 (32)	15 (31)	21 (31)	24 (41)	100 (33.3)	
Black N (%)	39 (32)	15 (31)	29 (42.6)	17 (29)	100 (33.3)	
Hispanic N (%)	26 (21)	22 (45)	12 (17.6)	23 (39)	83 (28)	$\chi^2 = 17.04$ , p = 0.001
APOE, N (%) with at least one $\epsilon 4$ allele	0.060 (0.01)	0.058 (0.01)	0.062 (0.02)	0.057 (0.01)	0.059 (0.01)	F = 1.57, p = 0.196
A $\beta_{42}$ /A $\beta_{40}$ mean (SD) concentration	4.58 (1.88)	5.75 (2.41)	4.40 (1.68)	5.54 (2.23)	4.92 (2.09)	F = 7.21, p < 0.001
T-tau mean (SD) concentration, pg/mL	26.84 (18.57)	40.56 (43.87)	32.51 (26.52)	42.30 (21.75)	33.46 (27.29)	F = 5.85, p < 0.001
NFL mean (SD) concentration, pg/mL	0.44 (0.54)	0.35 (0.58)	-0.72 (0.63)	-0.88 (0.75)	-0.07 (0.85)	F = 90.81, p < 0.001
Cognition mean (SD) standard score	0.49 (0.49)	0.60 (0.62)	-0.37 (0.57)	-0.27 (0.53)	0.17 (0.68)	F = 59.45, p < 0.001
Language	0.41 (0.79)	0.56 (0.71)	-0.59 (1.03)	-0.47 (1.11)	0.12 (0.99)	F = 23.79, p < 0.001
Speed/executive function	0.55 (0.46)	0.62 (0.51)	-0.16 (0.62)	-0.04 (0.61)	0.30 (0.63)	F = 36.58, p < 0.001
Visuospatial function	2.60 (0.12)	2.56 (0.18)	2.54 (0.13)	2.51 (0.16)	2.57 (0.14)	F = 4.20, p = 0.006
Cortical thickness mean (SD) mma						

The four groups: Ptau-/Asym, Ptau+/Asym, and Ptau-/Sym, and Ptau+/Sym, differed significantly by age, APOE-4 allele frequency, total tau, NFL, and cortical thickness on MRI. Ptau+ regardless of their symptomatic status were similar with only slight differences in cortical thickness. There were no difference by sex/gender or race/ethnicity across the four groups.

<sup>a</sup>Available for n = 223 participants.



**Figure 1.** Differences across biomarker/clinical groups in cortical thickness in Alzheimer's signature regions for groups defined by Pttau 217 cutpoint (A) and by Pttau 181 cutpoint (B).

Asym group, respectively (Fig. 1 and Table 1). Cortical thickness values decreased linearly ( $p = 0.02$ ) across groups as seen in Figure 1. For Pttau 181, the Youden Index was calculated as 0.95 pg./mL, yielding a sensitivity and specificity of 0.84 and 0.59, respectively. Results were similar for groups defined by Pttau 181 compared with Pttau 217 with the exception of a slight difference in the age and the significant difference in cortical thickness (Table 1).

## Discussion

Groups defined by Pttau 217 and Pttau 181 yielded similar results. Compared to those with low Pttau concentrations, with elevated Pttau concentrations, were slightly older but did not differ in race/ethnicity or sex/gender especially when symptomatic. The results here indicate that in a community-representative sample, biomarkers and clinical diagnoses do not vary by demographic factors. Groups with increased Pttau concentration irrespective of dementia status had a higher *APOE*  $\epsilon 4$  allele frequency. Interestingly, those diagnosed clinically without biomarker evidence of AD had a similar proportion of *APOE*  $\epsilon 4$  carriers as those who were asymptomatic and biomarker negative.

In assessing biological differences among groups, several important patterns emerged. Our previous analyses showed that  $A\beta_{42}/A\beta_{40}$  concentration ratios may be prognostically useful; those with lower values were more likely to progress to dementia but the values did not discriminate prevalent cases from unimpaired control participants.<sup>1</sup> The analyses here confirm that these plasma amyloid biomarkers in this community-based sample do not track as well with other AD biomarkers or with clinical status, providing additional evidence that implementation of a single Pttau value may be sufficient for characterizing AD pathophysiology.

Mass spectrometry approaches to estimate amyloid pathology from plasma samples may be more accurate than immunoassays.<sup>16</sup> Consideration of the three biological markers that reflect neurodegeneration: t-tau, NFL, and cortical thickness, provides additional insight into the biological basis of the diagnostic groups. Although t-tau measurements are considered markers of neurodegeneration<sup>17</sup> they appear to track most with Pttau elevation and not with clinical status. Neurofilament light chain concentrations, conversely, appeared elevated among individuals with either elevated Pttau concentrations or a dementia diagnosis. Similarly, cortical thickness, a reflection of neurodegeneration in the form of brain atrophy, decreased across diagnostic groups (Fig. 1), but tracked with dementia. We conclude that plasma NFL concentrations and cortical thinning reflect neurodegeneration, irrespective of a specific AD pathophysiological process. Our observed sensitivities and specificities are slightly lower than what has been reported previously, including recent papers from Thijssen *et al.*<sup>18</sup> and Palmqvist *et al.*<sup>19</sup> We speculate that differences reflect the design and composition of our study cohort. Ours is a community-based study, the average age at death is older than the other two studies, and the interval between the antemortem collection and death is somewhat longer. These factors are likely contributors to the differences in diagnostic accuracy among studies.

The existence of two discordant groups: those with elevated Pttau concentrations but asymptomatic and those who were symptomatic but without elevated Pttau concentrations are of great interest. In the first group, despite evidence of neurodegenerative changes, there may be factors that mitigate the impact of neurodegenerative pathology on its clinical manifestations, while in the second group, other pathophysiological factors are likely driving the diagnosis of dementia. AD pathology per se is only

one of the myriad factors that contributes to emergence of dementia. Indeed, pathological data suggest that the defining feature of symptomatic AD in older adults is the presence of multiple pathologies.<sup>20</sup> Future studies should continue to examine biological and social correlates of biomarker and clinical features of AD without discounting either.

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## Author Contributions

AMB: Conception and design, acquisition and analysis of data, drafting manuscript. JJM: Conception and design, acquisition and analysis of data, drafting manuscript. LSH: Analysis of data. DS: Acquisition of data. DR-D: Acquisition of data. RAL: Acquisition and analysis of data. JPV: Acquisition and analysis of data. AFT: Acquisition and analysis of data. MSK: Analysis of data. JLD: Acquisition and analysis of data. RM: Conception and design, acquisition and analysis of data, drafting manuscript.

## Conflict of Interest

Jeffrey L. Dage is a minor stockholder and receives some research support from Eli Lilly and Company. Additionally, Jeffrey L. Dage is an inventor on patents and/or patent applications of Eli Lilly and Company relating to the ptau217 assay, methods, reagents, and/or compositions of matter used in this research.

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