Supplemental Online Content

Mielke MM, Frank RD, Dage JL, et al. Comparison of plasma phosphorylated tau species with amyloid and tau positron emission tomography, neurodegeneration, vascular pathology, and cognitive outcomes. *JAMA Neurol*. Published online July 26, 2021. doi:10.1001/jamaneurol.2021.2293

eTable 8. Multivariable associations between the plasma p-tau species and neuroimaging and cognitive *z* scores among the 164 participants with all plasma p-tau species

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

1. Participant Assessment

MCSA visits include an interview by a study coordinator, physician examination, and neuropsychological testing.[1] Clinical follow-up visits occur at 15 month intervals. Participant demographics (age, sex, and years of education) and medical history were ascertained at the in-clinic examination. The cognitive battery included 9 tests covering 4 domains: memory, language, executive function, and visuospatial. Sample-specific z-scores for all cognitive tests were calculated; domain-specific z-scores were created by averaging the z-scores for the individual tests within each domain. A global cognitive z-score was created by averaging the z-scores of the four domains.

Participant demographics (age, sex, and years of education) were ascertained at the in-clinic examination. Participants' height (cm) and weight (kg) were measured and used to calculate body mass index (BMI) (kg/m^2). Nurse abstractors confirmed medical conditions based on medical record review using the REP medical records-linkage system.[2] Apolipoprotein E (*APOE*) ε4 genotyping was performed from a blood sample.

2. Mild Cognitive Impairment (MCI) and Dementia Diagnostic Determination

Clinical diagnoses were determined by a consensus committee of those who evaluated each participant. Cognitive performance was compared with the age-adjusted scores of CU individuals previously obtained using Mayo's Older American Normative Studies.[3] Participants with scores around 1.0 SD below the age-specific mean in the general population were considered for possible cognitive impairment. The operational definition of MCI was based on clinical judgment including a history from the patient and informant. Published criteria were used for the diagnosis: cognitive complaint, cognitive function not normal for age, essentially normal functional activities, no dementia.[4] A final decision was made after considering education, occupation, visual or hearing deficits, and reviewing all other participant information. The diagnosis of dementia was based on published criteria.[5] Participants who performed in the normal range and did not meet criteria for MCI or dementia were deemed CU. The consensus committee was blinded to blood P-tau and neuroimaging results when determining the clinical diagnosis.

3. Plasma P-tau Assays

Plasma phospho-Tau 181 (pTau-181) was measured on the Quanterix HD-X analyzer using the Simoa® pTau-181 Advantage V2 kit per manufacturer's instructions (Quanterix, Billerica, MA, United States). Briefly, after thawing and mixing, plasma samples were centrifuged 5 minutes x 10,000 g. Samples were diluted 1:4 using the instrument's onboard dilution protocol and run in duplicate from a single well each on a 96-well plate. 7-point calibration curves and sample measurements were determined on Simoa® HD-X Analyzer software using a weighting factor $1/Y^2$ and a 4 parameter logistic curve fitting algorithm. Paramagnetic beads in the pTau-181 Advantage V2 kits are coated with a phospho-tau 181 monoclonal capture antibody (AT270) with an immunogen designed to target paired helical filament tau. The biotinylated detector antibody (Tau12) is a mouse monoclonal antibody mapped to amino acids 6 to 18 at the N-terminal of Tau. This assay has previously been developed as a so-called homebrew assay and described in detail in Karikari et al.[6] Two levels of quality control material were included, flanking the samples at the front and end of each batch. In internal studies of inter-assay imprecision at approximate concentrations of 3.82 and 62.6 pg/mL were 7.8% and 11.2%, respectively. Plasma P-tau231 was measured using an in-house SiMoA method based on a monoclonal antibody for P-tau231, ADx253, for capture and a biotin-conjugated N-terminal tau monoclonal antibody (Tau12) for detection. A full-length recombinant tau 441 phosphorylated in vitro by GSK-3β was used as the calibrator. The validation and assay performance details have been described in detail elsewhere.[7]

Both P-tau181 and P-tau217 levels were measured in duplicate on the MSD platform by electrochemiluminescence using proprietary assays developed by Lilly Research Laboratories as previously described.[8] Briefly, samples were diluted 1:2 and 50 uL of diluted sample was used for each replicate. The assay was performed on a streptavidin small spot plate using the Meso Scale Discovery platform. P-tau181 used Biotinylated-AT270 (mIgG1) as the capture and P-tau217 used Biotinylated-IBA493 (mIgG1) as the capture. In this study, both assays used SULFO-4G10-E2 (anti-tau monoclonal antibody developed by Lilly Research Laboratories) as the detector. Each assay was calibrated using a unique synthetic P-tau peptide coupled with a polyethylene glycol linker to a second tau peptide matching amino acid 111-130 according to the Tau441 sequence numbering.

4. Amyloid and Tau PET Imaging

Aβ PiB-PET and Tau PET images were acquired using a PET/CT scanner (DRX, GE Healthcare) operating in 3-dimensional mode.[9] Pittsburgh compound B (PiB)–PET scan, consisting of 4 5-minute dynamic frames, was acquired from 40 to 60 minutes after injection.[10,11] Tau PET was performed using AV1451 and images were acquired from 80-100 minutes after injection.

Quantitative image analysis for PiB and AV1451 was done using our in-house fully automated image processing pipeline.[12] A global cortical PiB-PET retention ratio was computed by calculating the median uptake over voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest for each participant and dividing this by the median uptake over voxels in the cerebellar crus. A tau PET temporal meta region of interest (ROI) was used in this analysis which included the amygdala, entorhinal cortex, fusiform, parahippocampal, and inferior temporal and middle temporal gyri. In addition, we also examined the entorhinal cortex (ERC) as a single ROI. No partial volume correction was used. The atlas and image recognition steps were based on a 3D T1-weighted volume MRI sequence. We dichotomized participants as A+ based on a cutoff of 1.48 standard uptake value ratio (SUVR) using the reliable worsening method, as previously described.[13] Participants were dichotomized as T+ based on the tau PET temporal meta ROI defined as >1.29 SUVR and ERC defined as >1.27 SUVR based on autopsy diagnosis and Braak NFT stage.[14]

5. Structural MRI Outcomes

Structural magnetic resonance imaging (MRI) was acquired using standardized Magnetization Prepared – Rapid Gradient Echo (MPRAGE) sequences on 3T GE scanners (GE Medical Systems, Milwaukee, WI). FreeSurfer (version 5.3) was run on the MPRAGE scans; a temporal meta ROI using a cortical thickness composite of entorhinal, fusiform, inferior temporal, and middle temporal ROIs which includes regions that are typically impacted by aging and AD was computed.[13]

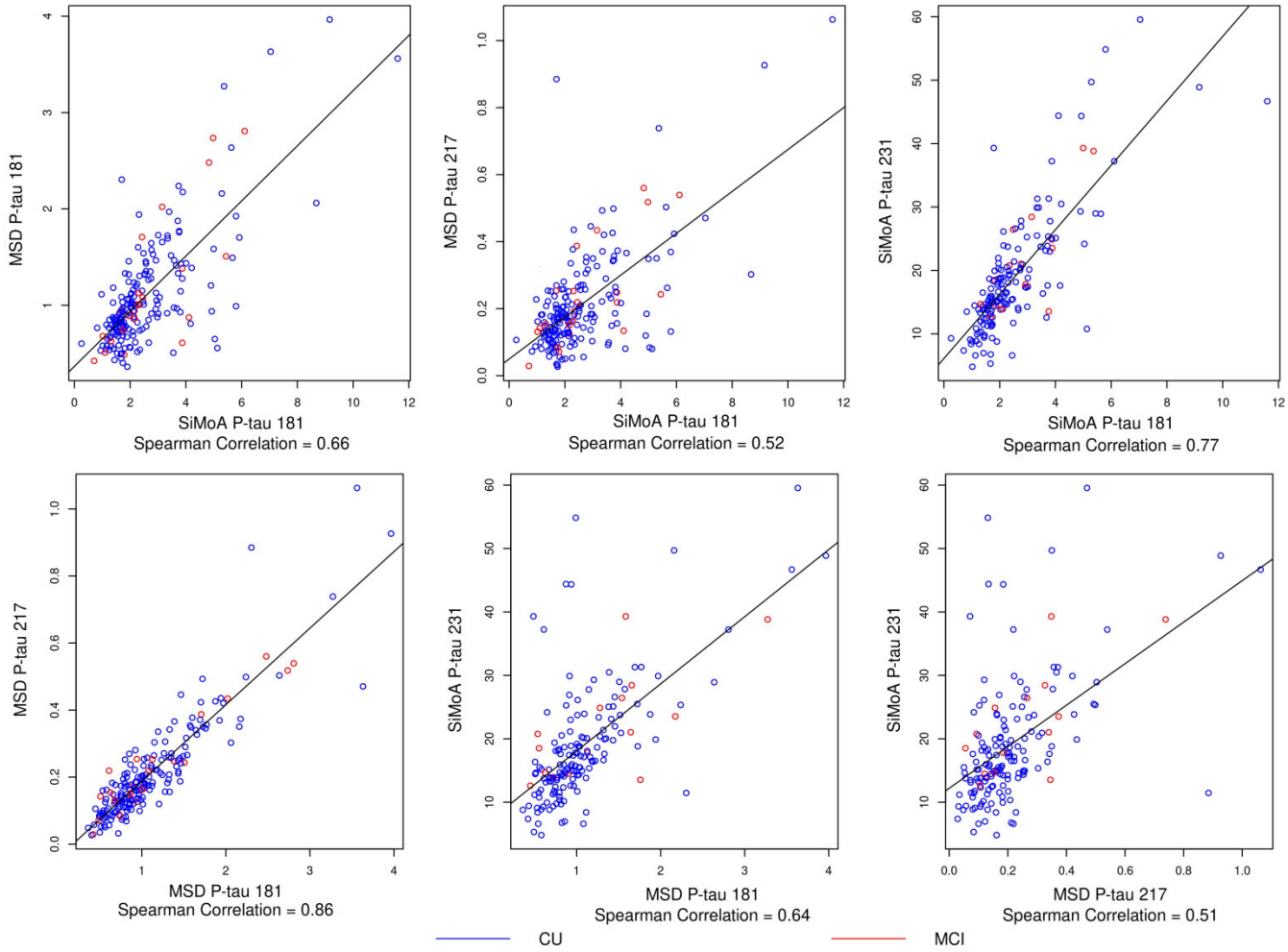
Diffusion Tensor Imaging (DTI) sequences were processed and analyzed for fractional anisotropy (FA) of the genu of the corpus callosum (FA-Genu) and of the hippocampal cingulum bundle (HCB).[15,16] The JHU atlas was used to regionally measure FA from DTI scans.[17] FA-Genu is a useful biomarker of cerebrovascular disease because loss of microstructural integrity in this region has previously been shown with worsening of system vascular health and cerebrovascular injury even after account for AD pathology.[16] FA-HCB is known to be susceptible to AD pathology, especially neurofibrillary tangles.

White matter hyperintensities (WMH) on standard 2-dimensional Fluid-attenuated inversion recovery (FLAIR) imaging were segmented and edited by a trained imaging analyst using a semi-automated method, as previously described.[18] WMH volume is presented as the percentage of total intracranial volume (TIV).

eReferences

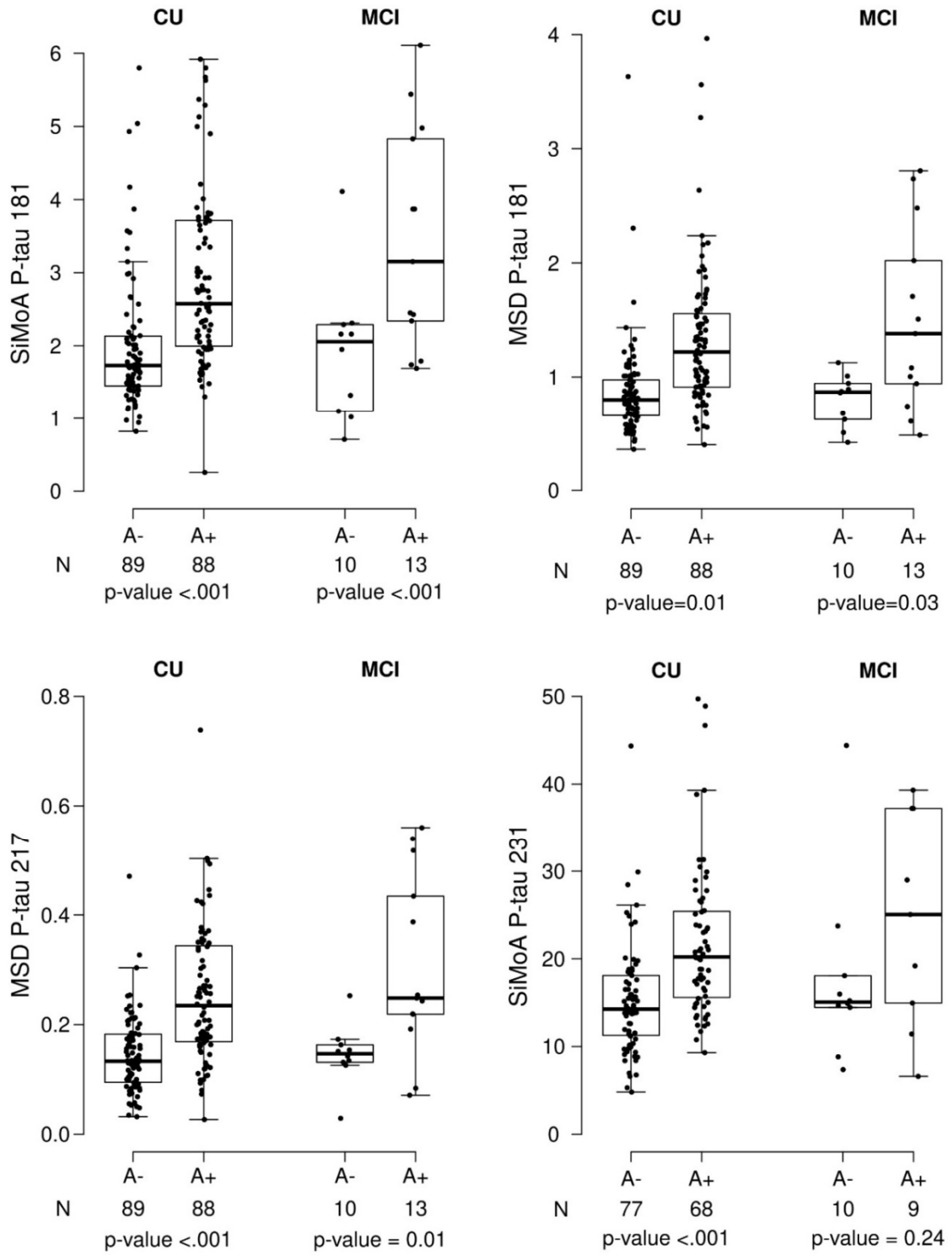
1. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology.* 2008;30(1):58-69.
2. St. Sauver JL, Grossardt BR, Yawn BP, et al. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol.* 2012;41(6):1614-1624.
3. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's Older Americans Normative Studies: updated AVLT norms for ages 56 to 97. *Clin Neuropsychol.* 1992;6(Supplement):83-104.
4. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med.* 2004;256(3):183-194.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
6. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol.* 2020;19(5):422-433.
7. Ashton NJ, Pascoal TA, Karikari TK, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol.* doi: 10.1007/s00401-021-02275-6. Online ahead of print.
8. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study. *Alzheimers Dement.* doi: 10.1002/alz.12301. Online ahead of print.
9. Lowe VJ, Kemp BJ, Jack CR Jr, et al. Comparison of 18F-FDG and PiB PET in cognitive impairment. *J Nucl Med.* 2009;50(6):878-886.
10. Price JC, Klunk WE, Lopresti BJ, et al. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *J Cereb Blood Flow Metab.* 2005;25(11):1528-1547.
11. McNamee RL, Yee SH, Price JC, et al. Consideration of optimal time window for Pittsburgh compound B PET summed uptake measurements. *J Nucl Med.* 2009;50(3):348-355.
12. Jack CR Jr, Lowe VJ, Senjem ML, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain.* 2008;131(Pt 3):665-680.
13. Jack CR Jr, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement.* 2017;13(3):205-216.
14. Lowe VJ, Lundt ES, Albertson SM, et al. Tau-positron emission tomography correlates with neuropathology findings. *Alzheimers Dement.* 2020;16(3):561-571.
15. Ramanan VK, Przybelski SA, Graff-Radford J, et al. Statins and brain health: Alzheimer's disease and cerebrovascular disease biomarkers in older adults. *J Alzheimers Dis.* 2018;65(4):1345-1352.
16. Vemuri P, Lesnick TG, Przybelski SA, et al. Development of a cerebrovascular magnetic resonance imaging biomarker for cognitive aging. *Ann Neurol.* 2018;84(5):705-716.
17. Oishi K, Faria A, Jiang H, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. *Neuroimage.* 2009;46(2):486-499.

eFigure 1. Scatterplots and spearman correlations between plasma p-tau measures



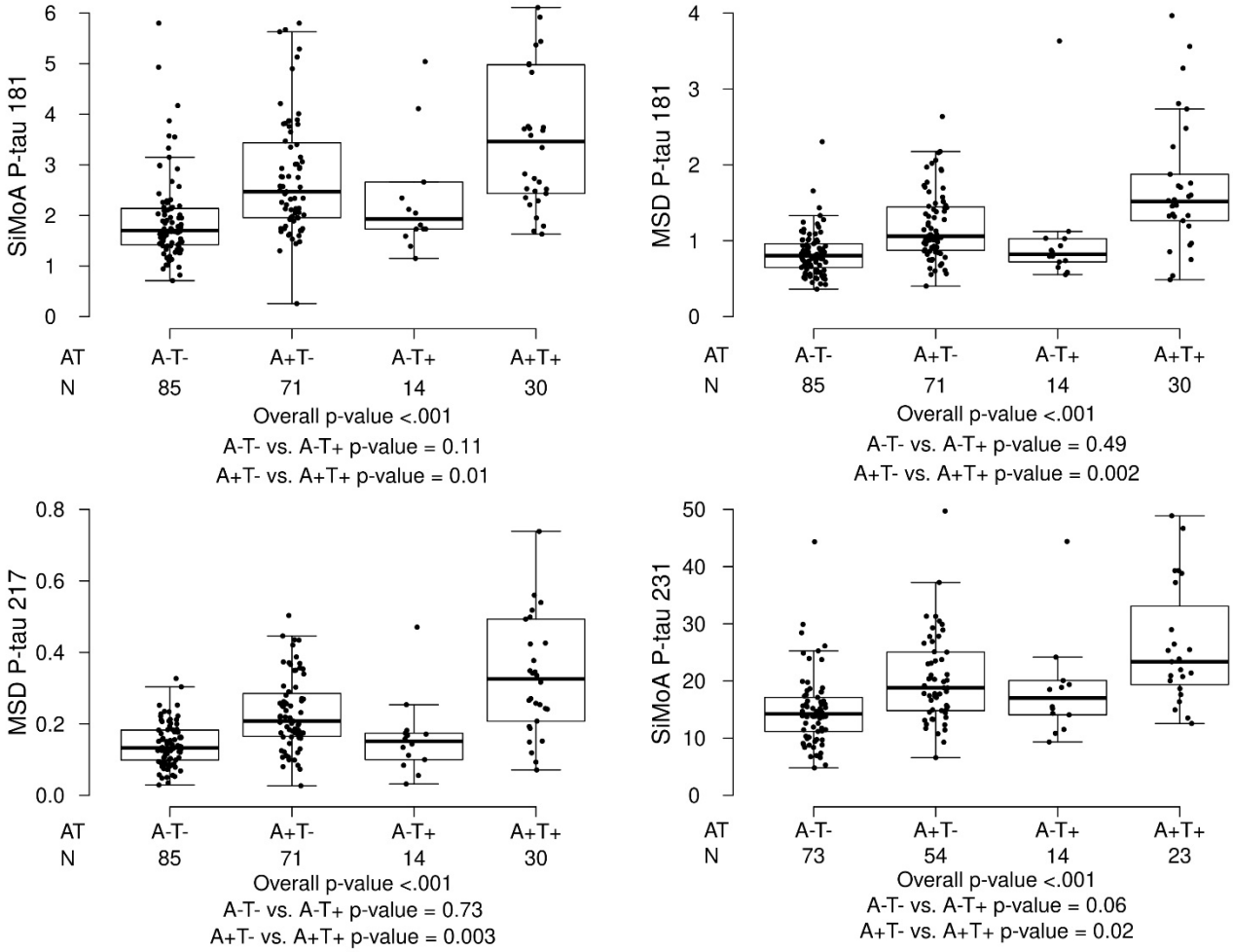
Abbreviations: MSD, Meso Scale Discovery; SiMoA, Single molecular array.

eFigure 2. Boxplots of plasma p-tau measures by clinical diagnosis and elevated amyloid PET



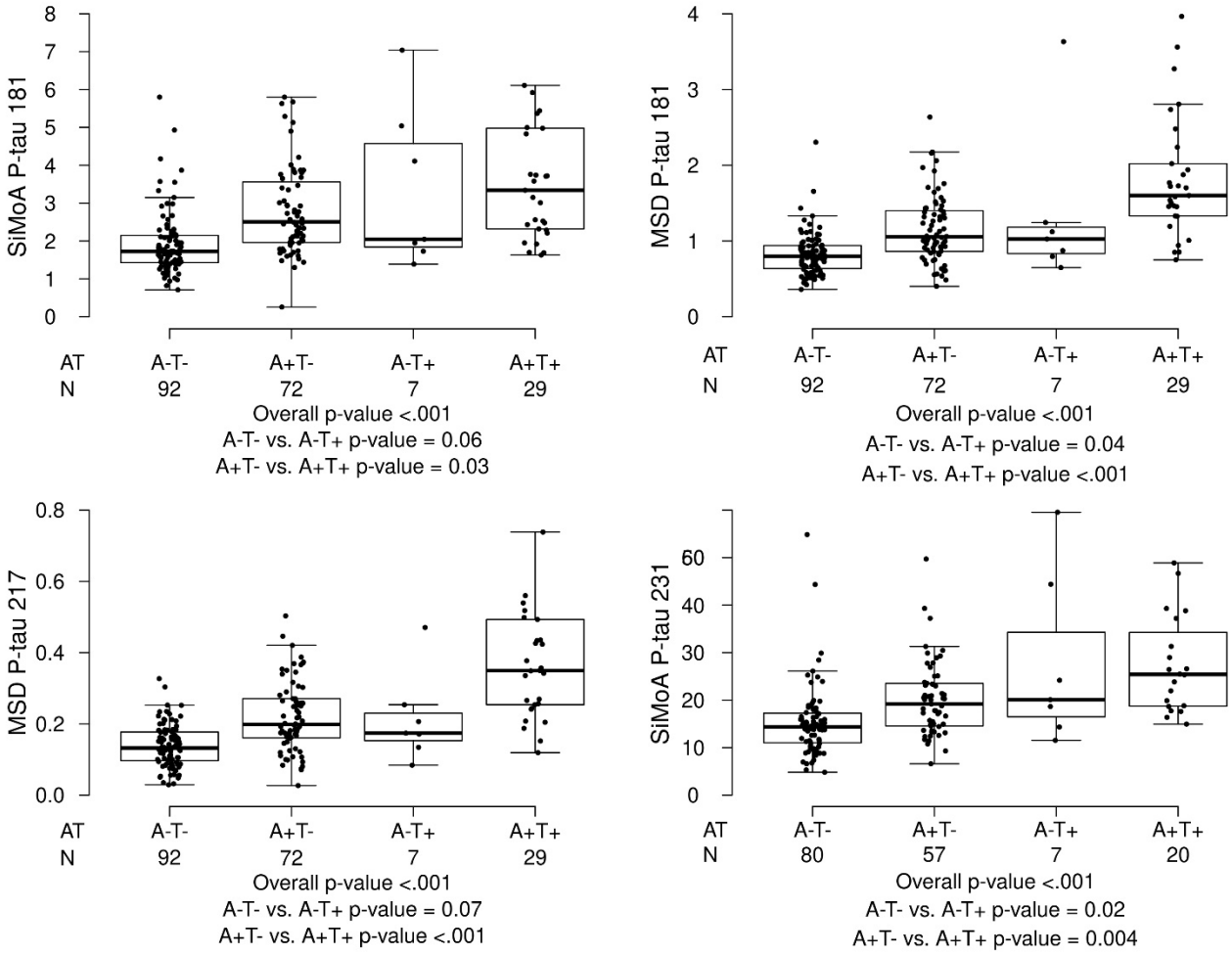
Abbreviations: CU, cognitively unimpaired; MCI, mild cognitive impairment; MSD, Meso Scale Discovery; PET, positron emission tomography; SiMoA, Single molecular array.

eFigure 3. Boxplots of plasma p-tau measures by clinical diagnosis and amyloid and meta-ROI tau PET



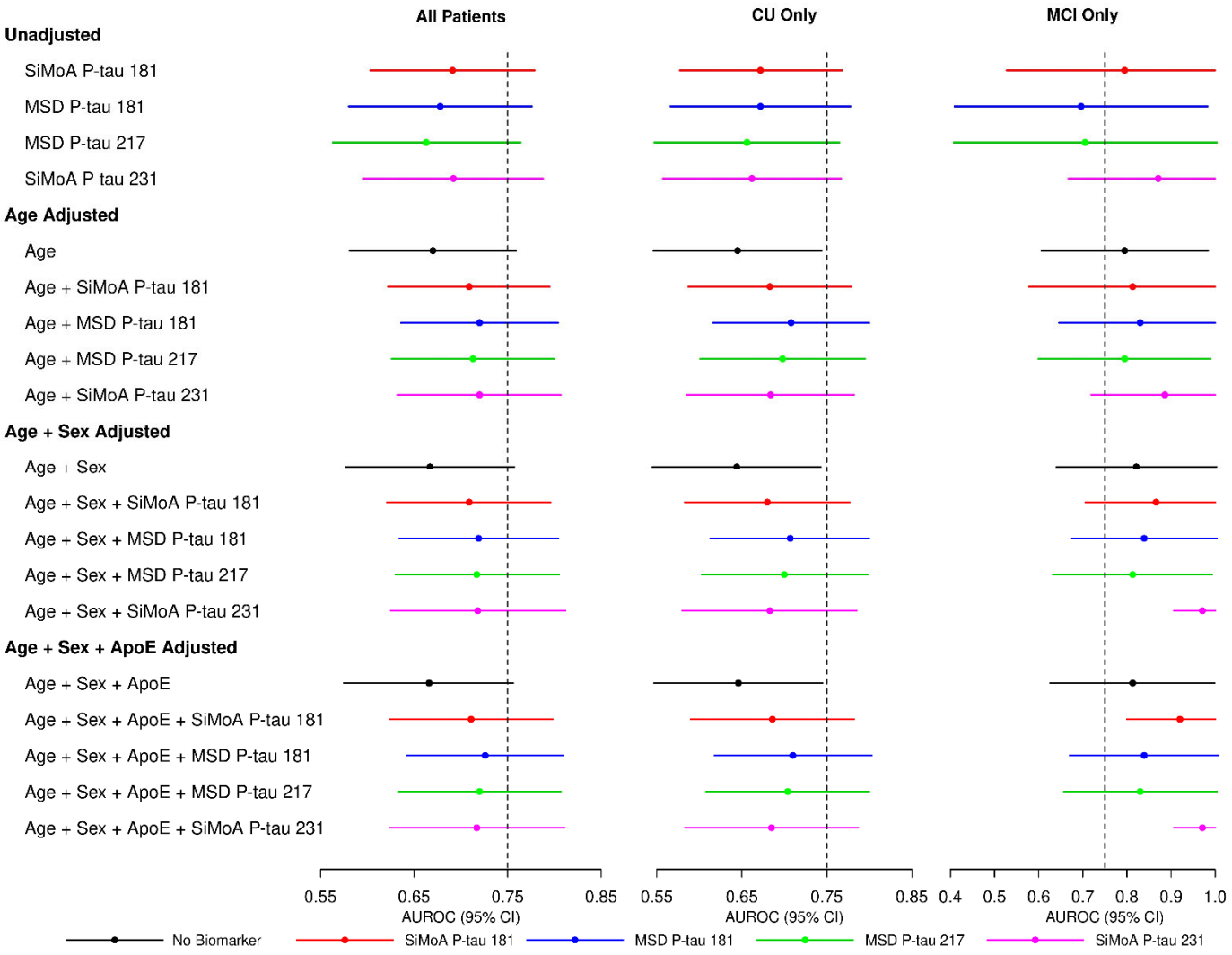
Abbreviations: MSD, Meso Scale Discovery; PET, positron emission tomography; ROI, region of interest; SiMoA, Single molecular array.

eFigure 4. Boxplots of plasma p-tau measures by diagnosis and amyloid and entorhinal cortex tau PET



Abbreviations: MSD, Meso Scale Discovery; PET, positron emission tomography; SiMoA, Single molecular array.

eFigure 5. Comparison of the accuracy of the 4 plasma p-tau measures for a tau PET metaregion of interest



eTable 1. Predictive accuracy of continuous plasma p-tau biomarkers in predicting elevated amyloid PET

Variable	All AUROC (95% CI)	CU only AUROC (95% CI)	MCI only AUROC (95% CI)
All (N=200)			
Age	0.69 (0.62, 0.77)	0.67 (0.59, 0.75)	0.86 (0.70, 1.02)
Age+Sex	0.70 (0.63, 0.77)	0.67 (0.59, 0.75)	0.88 (0.73, 1.03)
Age+Sex+*APOE*	0.77 (0.70, 0.83)	0.75 (0.68, 0.82)	0.90 (0.76, 1.04)
SiMoA ptau-181 (N=200)			
Ptau-181	0.77 (0.71, 0.84)	0.77 (0.70, 0.84)	0.82 (0.63, 1.00)
Ptau-181+Age	0.77 (0.71, 0.84)	0.77 (0.70, 0.84)	0.85 (0.69, 1.02)
Ptau-181+Age+Sex	0.78 (0.71, 0.84)	0.77 (0.70, 0.84)	0.90 (0.77, 1.03)
Ptau-181+Age+Sex+*APOE*	0.81 (0.75, 0.87)	0.80 (0.74, 0.87)	0.90 (0.76, 1.04)
MSD ptau-181 (N=200)			
Ptau-181	0.79 (0.72, 0.85)	0.79 (0.72, 0.86)	0.78 (0.58, 0.98)
Ptau-181+Age	0.80 (0.73, 0.86)	0.79 (0.72, 0.86)	0.87 (0.72, 1.02)
Ptau-181+Age+Sex	0.80 (0.74, 0.86)	0.80 (0.73, 0.86)	0.89 (0.75, 1.03)
Ptau-181+Age+Sex+*APOE*	0.83 (0.77, 0.89)	0.82 (0.76, 0.89)	0.90 (0.76, 1.04)
MSD ptau-217 (N=200)			
Ptau-217	0.79 (0.72, 0.85)	0.78 (0.71, 0.85)	0.82 (0.63, 1.02)
Ptau-217+Age	0.79 (0.73, 0.86)	0.78 (0.72, 0.85)	0.88 (0.73, 1.04)
Ptau-217+Age+Sex	0.79 (0.73, 0.86)	0.78 (0.72, 0.85)	0.91 (0.77, 1.05)
Ptau-217+Age+Sex+*APOE*	0.82 (0.76, 0.88)	0.81 (0.75, 0.88)	0.91 (0.77, 1.05)
SiMoA ptau-231 (N=164)			
Ptau-231	0.73 (0.66, 0.81)	0.74 (0.66, 0.83)	0.67 (0.39, 0.95)
Ptau-231+Age	0.73 (0.65, 0.81)	0.74 (0.66, 0.82)	0.81 (0.60, 1.02)
Ptau-231+Age+Sex	0.74 (0.66, 0.81)	0.73 (0.65, 0.81)	0.82 (0.61, 1.03)
Ptau-231+Age+Sex+*APOE*	0.77 (0.70, 0.84)	0.78 (0.71, 0.86)	0.84 (0.64, 1.05)

Abbreviations: APOE, apolipoprotein E; AUROC, area under the receiver operating curve; CU, cognitively unimpaired; MCI, mild cognitive impairment; MSD, Meso Scale Discovery; PET, positron emission tomography; SiMoA = Single molecular array.

eTable 2. Predictive accuracy of continuous plasma p-tau biomarkers in predicting elevated tau PET meta-ROI

Variable	All AUROC (95% CI)	CU only AUROC (95% CI)	MCI only AUROC (95% CI)
All (N=200)			
Age	0.67 (0.58, 0.76)	0.65 (0.55, 0.74)	0.79 (0.61, 0.98)
Age+Sex	0.67 (0.58, 0.76)	0.64 (0.55, 0.74)	0.82 (0.64, 1.00)
Age+Sex+*APOE*	0.67 (0.58, 0.76)	0.65 (0.55, 0.74)	0.81 (0.63, 1.00)
SiMoA ptau-181 (N=200)			
Ptau-181	0.69 (0.60, 0.78)	0.67 (0.58, 0.77)	0.79 (0.53, 1.06)
Ptau-181+Age	0.71 (0.62, 0.80)	0.68 (0.59, 0.78)	0.81 (0.58, 1.05)
Ptau-181+Age+Sex	0.71 (0.62, 0.80)	0.68 (0.58, 0.78)	0.87 (0.71, 1.03)
Ptau-181+Age+Sex+*APOE*	0.71 (0.62, 0.80)	0.69 (0.59, 0.78)	0.92 (0.80, 1.04)
MSD ptau-181 (N=200)			
Ptau-181	0.68 (0.58, 0.78)	0.67 (0.57, 0.78)	0.70 (0.41, 0.98)
Ptau-181+Age	0.72 (0.64, 0.80)	0.71 (0.62, 0.80)	0.83 (0.65, 1.01)
Ptau-181+Age+Sex	0.72 (0.63, 0.80)	0.71 (0.61, 0.80)	0.84 (0.67, 1.00)
Ptau-181+Age+Sex+*APOE*	0.73 (0.64, 0.81)	0.71 (0.62, 0.80)	0.84 (0.67, 1.01)
MSD ptau-217 (N=200)			
Ptau-217	0.66 (0.56, 0.76)	0.66 (0.55, 0.76)	0.71 (0.41, 1.00)
Ptau-217+Age	0.71 (0.63, 0.80)	0.70 (0.60, 0.79)	0.79 (0.60, 0.99)
Ptau-217+Age+Sex	0.72 (0.63, 0.80)	0.70 (0.60, 0.80)	0.81 (0.63, 0.99)
Ptau-217+Age+Sex+*APOE*	0.72 (0.63, 0.81)	0.70 (0.61, 0.80)	0.83 (0.66, 1.00)
SiMoA ptau-231 (N=164)			
Ptau-231	0.69 (0.60, 0.79)	0.66 (0.56, 0.77)	0.87 (0.67, 1.08)
Ptau-231+Age	0.72 (0.63, 0.81)	0.68 (0.58, 0.78)	0.89 (0.72, 1.05)
Ptau-231+Age+Sex	0.72 (0.62, 0.81)	0.68 (0.58, 0.79)	0.97 (0.91, 1.04)
Ptau-231+Age+Sex+*APOE*	0.72 (0.62, 0.81)	0.69 (0.58, 0.79)	0.97 (0.91, 1.04)

Abbreviations: APOE, apolipoprotein E; AUROC, area under the receiver operating curve; CU, cognitively unimpaired; MCI, mild cognitive impairment; MSD, Meso Scale Discovery; PET, positron emission tomography; ROI, region of interest; SiMoA, Single molecular array.

eTable 3. Predictive accuracy of continuous plasma p-tau biomarkers in predicting elevated tau PET ERC

Variable	All AUROC (95% CI)	CU only AUROC (95% CI)	MCI only AUROC (95% CI)
All (N=200)			
Age	0.64 (0.54, 0.74)	0.59 (0.48, 0.70)	0.84 (0.67, 1.01)
Age+Sex	0.64 (0.54, 0.74)	0.59 (0.48, 0.71)	0.86 (0.70, 1.02)
Age+Sex+*APOE*	0.66 (0.56, 0.76)	0.60 (0.49, 0.71)	0.89 (0.76, 1.03)
SiMoA ptau-181 (N=200)			
Ptau-181	0.73 (0.64, 0.82)	0.70 (0.60, 0.80)	0.88 (0.66, 1.09)
Ptau-181+Age	0.74 (0.65, 0.82)	0.71 (0.61, 0.80)	0.88 (0.69, 1.08)
Ptau-181+Age+Sex	0.76 (0.68, 0.84)	0.72 (0.63, 0.82)	0.95 (0.84, 1.06)
Ptau-181+Age+Sex+*APOE*	0.76 (0.68, 0.84)	0.72 (0.63, 0.82)	0.95 (0.84, 1.06)
MSD ptau-181 (N=200)			
Ptau-181	0.81 (0.73, 0.89)	0.80 (0.71, 0.89)	0.86 (0.67, 1.04)
Ptau-181+Age	0.81 (0.74, 0.89)	0.79 (0.69, 0.89)	0.92 (0.81, 1.03)
Ptau-181+Age+Sex	0.83 (0.75, 0.90)	0.81 (0.72, 0.90)	0.92 (0.81, 1.03)
Ptau-181+Age+Sex+*APOE*	0.83 (0.75, 0.90)	0.81 (0.72, 0.90)	0.92 (0.80, 1.04)
MSD ptau-217 (N=200)			
Ptau-217	0.82 (0.74, 0.90)	0.81 (0.72, 0.90)	0.87 (0.67, 1.06)
Ptau-217+Age	0.82 (0.74, 0.90)	0.81 (0.72, 0.90)	0.90 (0.78, 1.03)
Ptau-217+Age+Sex	0.82 (0.74, 0.90)	0.81 (0.72, 0.90)	0.90 (0.77, 1.03)
Ptau-217+Age+Sex+*APOE*	0.82 (0.74, 0.90)	0.81 (0.72, 0.90)	0.92 (0.80, 1.04)
SiMoA ptau-231 (N=164)			
Ptau-231	0.78 (0.70, 0.87)	0.78 (0.68, 0.87)	0.80 (0.54, 1.06)
Ptau-231+Age	0.78 (0.70, 0.87)	0.77 (0.67, 0.87)	0.87 (0.70, 1.04)
Ptau-231+Age+Sex	0.80 (0.71, 0.89)	0.79 (0.69, 0.89)	0.88 (0.72, 1.04)
Ptau-231+Age+Sex+*APOE*	0.80 (0.71, 0.89)	0.79 (0.69, 0.90)	0.88 (0.73, 1.04)

Abbreviations: APOE, apolipoprotein E; AUROC, area under the receiver operating curve; CU, cognitively unimpaired; ERC, Entorhinal cortex; SiMoA, Single molecular array; MCI, mild cognitive impairment; MSD, Meso Scale Discovery.

eTable 4. Univariable associations between the plasma p-tau isoforms and neuroimaging and cognitive *z* scores

Neuroimaging measures	*N*	*b (95% CI)*	*p-value*	R^2	*Cognitive measures*	*N*	*b (95% CI)*	*p-value*	R^2
Cortical Thickness					**Global Z-score**				
SiMoA P-tau181	200	-0.043 (-0.056, -0.031)	<.001	0.184	SiMoA P-tau181	178	-0.148 (-0.241, -0.055)	0.002	0.047
MSD P-tau181	200	-0.037 (-0.050, -0.024)	<.001	0.133	MSD P-tau181	178	-0.198 (-0.287, -0.110)	<.001	0.095
MSD P-tau217	200	-0.033 (-0.046, -0.020)	<.001	0.106	MSD P-tau217	178	-0.185 (-0.273, -0.097)	<.001	0.082
SiMoA P-tau231	164	-0.053 (-0.073, -0.032)	<.001	0.132	SiMoA P-tau231	143	-0.203 (-0.341, -0.064)	0.005	0.048
WMH volume					**Memory Z-score**				
SiMoA P-tau181	199	6.816 (4.997, 8.635)	<.001	0.211	SiMoA P-tau181	199	-0.154 (-0.246, -0.063)	0.001	0.048
MSD P-tau181	199	6.630 (4.832, 8.428)	<.001	0.206	MSD P-tau181	199	-0.205 (-0.293, -0.117)	<.001	0.091
MSD P-tau217	199	7.153 (5.387, 8.919)	<.001	0.239	MSD P-tau217	199	-0.178 (-0.268, -0.089)	<.001	0.068
SiMoA P-tau231	163	4.539 (1.781, 7.297)	0.002	0.055	SiMoA P-tau231	163	-0.255 (-0.397, -0.114)	<.001	0.066
FA-Genu					**Attention Z-score**				
SiMoA P-tau181	200	-0.012 (-0.016, -0.007)	<0.001	0.117	SiMoA P-tau181	191	-0.174 (-0.270, -0.078)	<.001	0.057
MSD P-tau181	200	-0.012 (-0.016, -0.007)	<0.001	0.120	MSD P-tau181	191	-0.184 (-0.277, -0.092)	<.001	0.070
MSD P-tau217	200	-0.013 (-0.017, -0.099)	<0.001	0.153	MSD P-tau217	191	-0.185 (-0.277, -0.093)	<.001	0.070
SiMoA P-tau231	164	-0.008 (-0.015, -0.001)	0.022	0.026	SiMoA P-tau231	156	-0.158 (-0.301, -0.015)	0.032	0.023
FA-HCB					**Language Z-Score**				
SiMoA P-tau181	200	-0.006 (-0.009, -0.002)	<0.001	0.051	SiMoA P-tau181	196	-0.137 (-0.232, -0.042)	0.005	0.034
MSD P-tau181	200	-0.007 (-0.010, -0.004)	<0.001	0.283	MSD P-tau181	196	-0.136 (-0.229, -0.043)	0.005	0.035
MSD P-tau217	200	-0.007 (-0.010, -0.004)	<0.001	0.314	MSD P-tau217	196	-0.131 (-0.225, -0.038)	0.007	0.033
SiMoA P-tau231	164	-0.008 (-0.013, -0.003)	0.004	0.104	SiMoA P-tau231	160	-0.216 (-0.362, -0.071)	0.004	0.045
Amyloid PET					**VisualSpatial Z-score**				
SiMoA P-tau181	200	0.135 (0.097, 0.174)	<0.001	0.190	SiMoA P-tau181	183	-0.040 (-0.133, 0.053)	0.396	-0.002
MSD P-tau181	200	0.163 (0.127, 0.199)	<0.001	0.283	MSD P-tau181	183	-0.110 (-0.199, -0.020)	0.017	0.026
MSD P-tau217	200	0.172 (0.137, 0.207)	<0.001	0.314	MSD P-tau217	183	-0.108 (-0.196, -0.018)	0.019	0.024
SiMoA P-tau231	164	0.139 (0.078, 0.200)	<0.001	0.104	SiMoA P-tau231	148	-0.117 (-0.255, 0.022)	0.101	0.012

Abbreviations: FA, fractional anisotropy; FA-Genu, genu of corpus callosum; FA-HCB, hippocampal cingulum bundle;
MCI, mild cognitive impairment; MSD, Meso Scale Discovery; SiMoA, Single molecular array; WMH, white matter hyperintensities.

eTable 5. Predictive accuracy of continuous plasma biomarkers in predicting elevated amyloid PET among the 164 participants with all plasma p-tau species

Variable	All AUROC	CU only AUROC	MCI only AUROC
All			
Age	0.66 (0.57, 0.74)	0.64 (0.54, 0.73)	0.81 (0.60, 1.02)
Age+Sex	0.67 (0.59, 0.76)	0.65 (0.56, 0.74)	0.82 (0.61, 1.03)
Age+Sex+*APOE*	0.75 (0.68, 0.83)	0.74 (0.66, 0.83)	0.84 (0.64, 1.05)
Simoa plasma ptau-181			
ptau-181	0.76 (0.68, 0.83)	0.75 (0.67, 0.83)	0.76 (0.52, 0.99)
ptau-181+Age	0.76 (0.69, 0.84)	0.76 (0.68, 0.84)	0.81 (0.60, 1.02)
ptau-181+Age+Sex	0.77 (0.69, 0.84)	0.76 (0.68, 0.84)	0.86 (0.68, 1.03)
ptau-181+Age+Sex+*APOE*	0.80 (0.73, 0.87)	0.81 (0.73, 0.88)	0.83 (0.62, 1.05)
Lilly plasma ptau-181			
ptau-181	0.78 (0.70, 0.85)	0.79 (0.71, 0.86)	0.68 (0.41, 0.94)
ptau-181+Age	0.78 (0.70, 0.85)	0.79 (0.71, 0.86)	0.82 (0.62, 1.03)
ptau-181+Age+Sex	0.79 (0.72, 0.86)	0.79 (0.72, 0.86)	0.84 (0.65, 1.04)
ptau-181+Age+Sex+*APOE*	0.81 (0.75, 0.88)	0.82 (0.75, 0.89)	0.86 (0.65, 1.06)
Lilly plasma ptau-217			
ptau-217	0.77 (0.70, 0.84)	0.77 (0.70, 0.85)	0.74 (0.48, 1.01)
ptau-217+Age	0.77 (0.70, 0.84)	0.77 (0.70, 0.85)	0.84 (0.63, 1.05)
ptau-217+Age+Sex	0.78 (0.71, 0.85)	0.78 (0.70, 0.85)	0.87 (0.67, 1.07)
ptau-217+Age+Sex+*APOE*	0.81 (0.74, 0.88)	0.81 (0.74, 0.88)	0.87 (0.67, 1.07)
Plasma ptau-231			
ptau-231	0.73 (0.66, 0.81)	0.74 (0.66, 0.83)	0.67 (0.39, 0.95)
ptau-231+Age	0.73 (0.65, 0.81)	0.74 (0.66, 0.82)	0.81 (0.60, 1.02)
ptau-231+Age+Sex	0.74 (0.66, 0.81)	0.73 (0.65, 0.81)	0.82 (0.61, 1.03)
ptau-231+Age+Sex+*APOE*	0.77 (0.70, 0.84)	0.78 (0.71, 0.86)	0.84 (0.64, 1.05)

Abbreviations: APOE, apolipoprotein E; AUROC, area under the receiver operating curve; CU, cognitively unimpaired; MCI, mild cognitive impairment; SiMoA = single molecular array; MSD=Meso Scale Discovery.

eTable 6. Predictive accuracy of continuous plasma biomarkers in predicting elevated meta-ROI tau PET among the 164 participants with all plasma p-tau species

Variable	All AUROC	CU only AUROC	MCI only AUROC
All			
Age	0.67 (0.57, 0.77)	0.65 (0.55, 0.76)	0.79 (0.57, 1.00)
Age+Sex	0.67 (0.57, 0.77)	0.65 (0.54, 0.76)	0.81 (0.60, 1.02)
Age+Sex+*APOE*	0.67 (0.57, 0.77)	0.65 (0.54, 0.76)	0.83 (0.63, 1.03)
Simoa plasma ptau-181			
ptau-181	0.67 (0.57, 0.77)	0.66 (0.55, 0.76)	0.73 (0.39, 1.07)
ptau-181+Age	0.70 (0.61, 0.80)	0.68 (0.58, 0.79)	0.77 (0.50, 1.04)
ptau-181+Age+Sex	0.71 (0.61, 0.81)	0.69 (0.58, 0.80)	0.89 (0.73, 1.04)
ptau-181+Age+Sex+*APOE*	0.72 (0.62, 0.82)	0.69 (0.58, 0.80)	0.90 (0.76, 1.04)
Lilly plasma ptau-181			
ptau-181	0.66 (0.55, 0.77)	0.66 (0.54, 0.77)	0.63 (0.27, 0.99)
ptau-181+Age	0.72 (0.62, 0.81)	0.70 (0.60, 0.81)	0.83 (0.62, 1.04)
ptau-181+Age+Sex	0.72 (0.63, 0.82)	0.71 (0.60, 0.81)	0.89 (0.72, 1.06)
ptau-181+Age+Sex+*APOE*	0.73 (0.64, 0.82)	0.71 (0.61, 0.82)	0.89 (0.72, 1.06)
Lilly plasma ptau-217			
ptau-217	0.64 (0.52, 0.75)	0.64 (0.52, 0.76)	0.64 (0.25, 1.03)
ptau-217+Age	0.71 (0.62, 0.81)	0.70 (0.59, 0.81)	0.81 (0.60, 1.03)
ptau-217+Age+Sex	0.72 (0.62, 0.82)	0.70 (0.59, 0.81)	0.86 (0.66, 1.06)
ptau-217+Age+Sex+*APOE*	0.73 (0.63, 0.83)	0.71 (0.60, 0.82)	0.86 (0.66, 1.06)
Plasma ptau-231			
ptau-231	0.69 (0.60, 0.79)	0.66 (0.56, 0.77)	0.87 (0.67, 1.08)
ptau-231+Age	0.72 (0.63, 0.81)	0.68 (0.58, 0.78)	0.89 (0.72, 1.05)
ptau-231+Age+Sex	0.72 (0.62, 0.81)	0.68 (0.58, 0.79)	0.97 (0.91, 1.04)
ptau-231+Age+Sex+*APOE*	0.72 (0.62, 0.81)	0.69 (0.58, 0.79)	0.97 (0.91, 1.04)

Abbreviations: APOE, apolipoprotein E; AUROC, area under the receiver operating curve; CU, cognitively unimpaired; MCI = mild cognitive impairment; MSD, Meso Scale Discovery; PET, positron emission tomography; ROI, Region of interest; SiMoA, single molecular array.

eTable 7. Predictive accuracy of continuous plasma biomarkers in predicting elevated ERC tau PET among the 164 participants with all plasma p-tau species

Variable	All AUROC	CU only AUROC	MCI only AUROC
All			
Age	0.61 (0.49, 0.72)	0.57 (0.44, 0.70)	0.85 (0.67, 1.03)
Age+Sex	0.62 (0.50, 0.73)	0.60 (0.47, 0.72)	0.82 (0.59, 1.04)
Age+Sex+*APOE*	0.65 (0.54, 0.76)	0.62 (0.49, 0.74)	0.85 (0.66, 1.04)
Simoa plasma ptau-181			
ptau-181	0.73 (0.62, 0.83)	0.71 (0.59, 0.83)	0.82 (0.45, 1.18)
ptau-181+Age	0.73 (0.62, 0.84)	0.71 (0.59, 0.83)	0.85 (0.59, 1.11)
ptau-181+Age+Sex	0.78 (0.69, 0.87)	0.76 (0.66, 0.87)	0.90 (0.74, 1.06)
ptau-181+Age+Sex+*APOE*	0.78 (0.68, 0.87)	0.76 (0.66, 0.87)	0.93 (0.79, 1.08)
Lilly plasma ptau-181			
ptau-181	0.82 (0.73, 0.91)	0.82 (0.72, 0.92)	0.78 (0.51, 1.06)
ptau-181+Age	0.82 (0.73, 0.91)	0.82 (0.71, 0.92)	0.90 (0.76, 1.04)
ptau-181+Age+Sex	0.84 (0.75, 0.92)	0.84 (0.75, 0.94)	0.92 (0.77, 1.06)
ptau-181+Age+Sex+*APOE*	0.84 (0.76, 0.92)	0.84 (0.75, 0.94)	0.90 (0.73, 1.07)
Lilly plasma ptau-217			
ptau-217	0.81 (0.71, 0.90)	0.81 (0.71, 0.92)	0.80 (0.48, 1.12)
ptau-217+Age	0.81 (0.71, 0.90)	0.82 (0.71, 0.93)	0.88 (0.72, 1.04)
ptau-217+Age+Sex	0.84 (0.75, 0.93)	0.84 (0.75, 0.94)	0.90 (0.73, 1.07)
ptau-217+Age+Sex+*APOE*	0.84 (0.75, 0.93)	0.85 (0.75, 0.94)	0.90 (0.73, 1.07)
Plasma ptau-231			
ptau-231	0.78 (0.70, 0.87)	0.78 (0.68, 0.87)	0.80 (0.54, 1.06)
ptau-231+Age	0.78 (0.70, 0.87)	0.77 (0.67, 0.87)	0.87 (0.70, 1.04)
ptau-231+Age+Sex	0.80 (0.71, 0.89)	0.79 (0.69, 0.89)	0.88 (0.72, 1.04)
ptau-231+Age+Sex+*APOE*	0.80 (0.71, 0.89)	0.79 (0.69, 0.90)	0.88 (0.73, 1.04)

Abbreviations: APOE, apolipoprotein E; AUROC, area under the receiver operating curve; CU, cognitively unimpaired; ERC, entorhinal cortex; MCI, mild cognitive impairment; MSD, Meso Scale Discovery; PET, positron emission tomography; SiMoA, single molecular array.

eTable 8. Multivariable associations between the plasma p-tau species and neuroimaging and cognitive *z* scores among the 164 participants with all plasma p-tau species

Neuroimaging measures	*N*	*b (95% CI)**	*p-value*	R^2 *full model*	R^2 *covariables only*	*Cognitive measures*	*N*	*b (95% CI)**	*p-value*	R^2 *full model*	R^2 *covariables only*
Cortical Thickness						**Global Z-score**					
SiMoA P-tau181	164	-0.024 (-0.039, -0.009)	0.002	0.313	0.274	SiMoA P-tau181	143	-0.063 (-0.163, 0.037)	0.217	0.271	0.268
MSD P-tau181	164	-0.018 (-0.032, -0.004)	0.013	0.298	0.274	MSD P-tau181	143	-0.049 (-0.141, 0.044)	0.304	0.268	0.268
MSD P-tau217	164	-0.013 (-0.027, 0.001)	0.061	0.286	0.274	MSD P-tau217	143	-0.049 (-0.139, 0.040)	0.281	0.269	0.268
SiMoA P-tau231	164	-0.026 (-0.046, -0.005)	0.015	0.297	0.274	SiMoA P-tau231	143	-0.103 (-0.240, 0.035)	0.146	0.274	0.268
WMH volume						**Memory Z-score**					
SiMoA P-tau181	163	2.467 (0.472, 4.461)	0.017	0.244	0.220	SiMoA P-tau181	163	-0.096 (-0.200, 0.008)	0.073	0.253	0.243
MSD P-tau181	163	3.387 (1.589, 5.184)	<.001	0.279	0.220	MSD P-tau181	163	-0.109 (-0.205, -0.013)	0.028	0.261	0.243
MSD P-tau217	163	4.291 (2.567, 6.015)	<.001	0.320	0.220	MSD P-tau217	163	-0.081 (-0.175, 0.014)	0.097	0.251	0.243
SiMoA P-tau231	163	1.071 (-1.700, 3.841)	0.450	0.218	0.220	SiMoA P-tau231	163	-0.149 (-0.291, -0.006)	0.042	0.258	0.243
FA-Genu						**Attention Z-score**					
SiMoA P-tau181	164	-0.004 (-0.009, 0.002)	0.18	0.214	0.210	SiMoA P-tau181	156	-0.032 (-0.128, 0.063)	0.508	0.361	0.363
MSD P-tau181	164	-0.005 (0.010, -0.0004)	0.035	0.227	0.210	MSD P-tau181	156	0.009 (-0.080, 0.097)	0.851	0.359	0.363
MSD P-tau217	164	-0.008 (-0.12, -0.003)	0.001	0.258	0.210	MSD P-tau217	156	-0.017 (-0.103, 0.070)	0.709	0.360	0.363
SiMoA P-tau231	164	0.001 (-0.006, 0.008)	0.828	0.205	0.210	SiMoA P-tau231	156	0.001 (-0.130, 0.131)	0.992	0.359	0.363
FA-HCB						**Language Z-Score**					
SiMoA P-tau181	164	-0.002 (-0.006, 0.001)	0.234	0.230	0.228	SiMoA P-tau181	160	-0.035 (-0.147, 0.078)	0.545	0.176	0.180
MSD P-tau181	164	-0.003 (-0.006, 0.0004)	0.089	0.237	0.228	MSD P-tau181	160	-0.020 (-0.123, 0.084)	0.714	0.175	0.180
MSD P-tau217	164	-0.003 (-0.006, 0.0004)	0.089	0.237	0.228	MSD P-tau217	160	-0.023 (-0.124, 0.079)	0.664	0.175	0.180
SiMoA P-tau231	164	-0.002 (-0.007, 0.003)	0.382	0.226	0.228	SiMoA P-tau231	160	-0.139 (-0.291, 0.012)	0.074	0.191	0.180
Amyloid PET						**VisualSpatial Z-score**					
SiMoA P-tau181	164	0.119 (0.073, 0.165)	<0.001	0.264	0.146	SiMoA P-tau181	148	-0.028 (-0.136, 0.080)	0.612	0.116	0.121
MSD P-tau181	164	0.129 (0.088, 0.170)	<0.001	0.311	0.146	MSD P-tau181	148	-0.013 (-0.113, 0.088)	0.806	0.115	0.121
MSD P-tau217	164	0.130 (0.090, 0.170)	<0.001	0.320	0.146	MSD P-tau217	148	-0.022 (-0.119, 0.075)	0.658	0.115	0.121
SiMoA P-tau231	164	0.116 (0.051, 0.181)	<0.001	0.203	0.146	SiMoA P-tau231	148	-0.088 (-0.235, 0.060)	0.248	0.123	0.121

Abbreviations: FA, fractional anisotropy; FA-Genu, genu of corpus callosum; FA-HCB, hippocampal cingulum bundle;
MSD, Meso Scale Discovery; MSD, Meso Scale Discovery; PET, positron emission tomography; SiMoA, single molecular array; WMH, white matter hyperintensities.

*Multivariable models adjust for age, sex, any *APOE* Ɛ4 allele, years of education, body mass index, and chronic kidney disease