

SUPPLEMENTARY INFORMATION

Supplementary Method: Participants selection

Supplementary Fig. 1: Distribution of plasma biomarkers across diagnostic groups

Supplementary Fig. 2: Stage-specific changes in plasma biomarkers across the tau continuum

Supplementary Fig. 3: Pairwise correlations among plasma and PET biomarkers in the total group

Supplementary Fig 4: Association of plasma biomarkers with A β PET, and MTL and NeoC tau PET among cognitively impaired patients

Supplementary Fig. 5 Association of plasma biomarkers with A β PET, tau PET, and cognition among cognitively impaired participants

Supplementary Fig. 6: ROC curves of plasma biomarkers for regional tau PET positivity

Supplementary Fig. 7 Sensitivity analysis of longitudinal cognitive trajectory using complete biomarker cases

Supplementary Fig. 8: Predictive value of plasma biomarkers for longitudinal cognitive change in the total group

Supplementary Fig. 9: Predictive value of plasma biomarkers for longitudinal cognitive change in the A β ⁺ subgroup

Supplementary Fig. 10: Predictive value of plasma biomarkers for longitudinal cognitive change in the A β ⁺ CI subgroup

Supplementary Fig. 11: Marginal R² of plasma biomarkers for longitudinal cognitive decline among cognitively impaired participants

Supplementary Table 1: Demographics, clinical, and biomarker characteristics of participants included in the C2N_LC-MS/MS platform

Supplementary Table 2: Demographics, clinical, and biomarker characteristics of participants included in the UGOT_Simoa platform

Supplementary Table 3: Demographics, clinical, and biomarker characteristics of participants included in the Lilly_MSD platform

Supplementary Table 4: Demographics, clinical, and biomarker characteristics of participants included in the Roche_Elecsys platform

Supplementary Table 5: Associations of baseline plasma biomarkers with longitudinal regional tau PET accumulation

Supplementary Table 6: Performance and optimal cutoff values of plasma biomarkers for regional tau PET positivity (MTL)

Supplementary Table 7: Longitudinal associations between plasma biomarkers and cognitive decline

Supplementary Table 8: Analytical validation of the C2N research-use-only assays (eMTBR-tau243 and %p-tau-MAA)

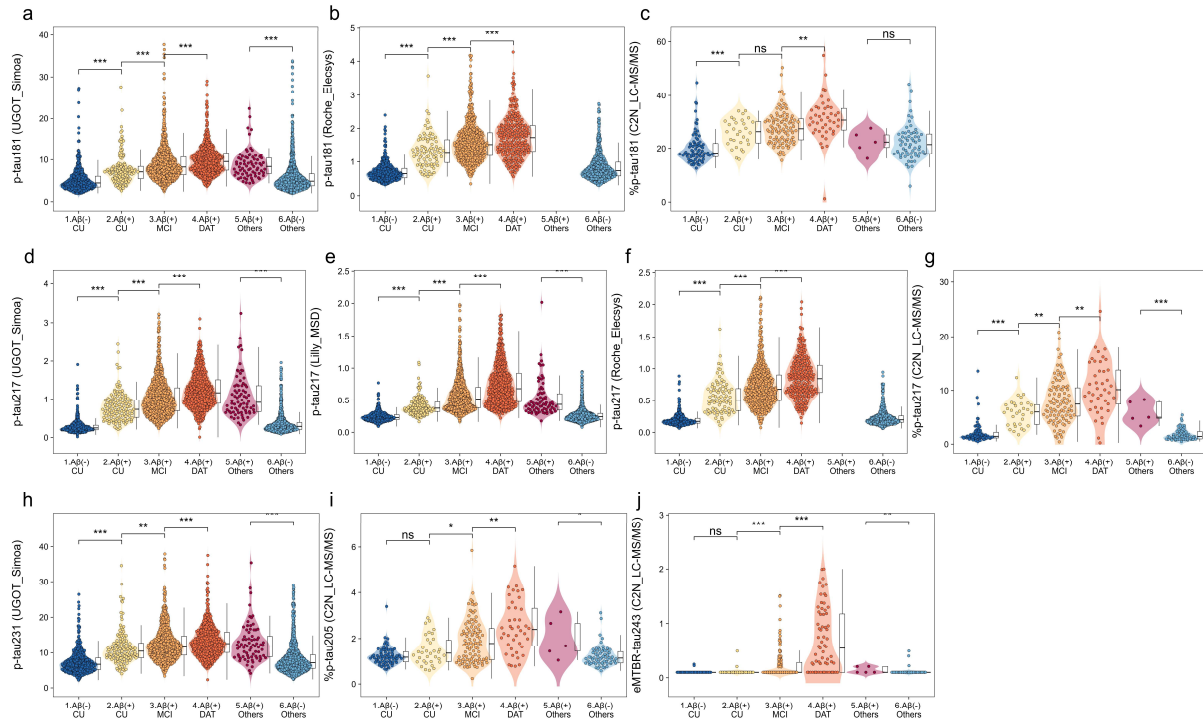
Supplementary Table 9: Proportion of plasma eMTBR-tau243 measurements below the limit of detection by diagnostic group

Supplementary Method: Participants selection

Participants were classified into one of the following diagnostic categories: cognitively unimpaired (CU), mild cognitive impairment (MCI), dementia of Alzheimer's type ($A\beta(+)$ DAT), or others. The category of others included individuals with clinically diagnosed subcortical vascular cognitive impairment (SVCI), frontotemporal dementia (FTD) syndrome, or cognitively impaired (CI) of undetermined underlying pathology. This group was further divided into others $A\beta$ -negative and $A\beta$ -positive ($A\beta(-)$ others and $A\beta(+)$ others, respectively). CU participants were identified according to the following criteria: (1) absence of any medical history that is likely to affect cognitive function and (2) normal cognitive performance across all cognitive domains, defined as scores above -1.0 standard deviation (SD) of age- and education-adjusted norms for memory and above -1.5 SD for other cognitive domains in SNSB [1]. MCI was diagnosed based on the specified criteria [2]: (1) subjective cognitive decline reported by the participants or caregiver; (2) objective cognitive impairment in one or more cognitive domains, defined as scores below -1.0 SD in memory and/or below -1.5 SD in other cognitive domains relative to age- and education-matched norms; (3) preserved independence in activities of daily living; and (4) not demented. DAT was diagnosed based on the National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic criteria [3]. SVCI was diagnosed based on the following criteria: (1) subjective cognitive decline reported by the participants or caregiver; (2) objective cognitive impairment below the -1.0 SD in any cognitive domain; and (3) evidence of severe ischemic changes on brain MRI, defined as periventricular white matter hyperintensities (WMH) > 10 mm and deep WMH > 25 mm, following a modified Fazekas scale [4]. FTD syndromes were diagnosed based on established consensus criteria [5-9].

All participants underwent routine laboratory evaluations to exclude secondary medical causes of cognitive impairment. These assessments included complete blood counts,

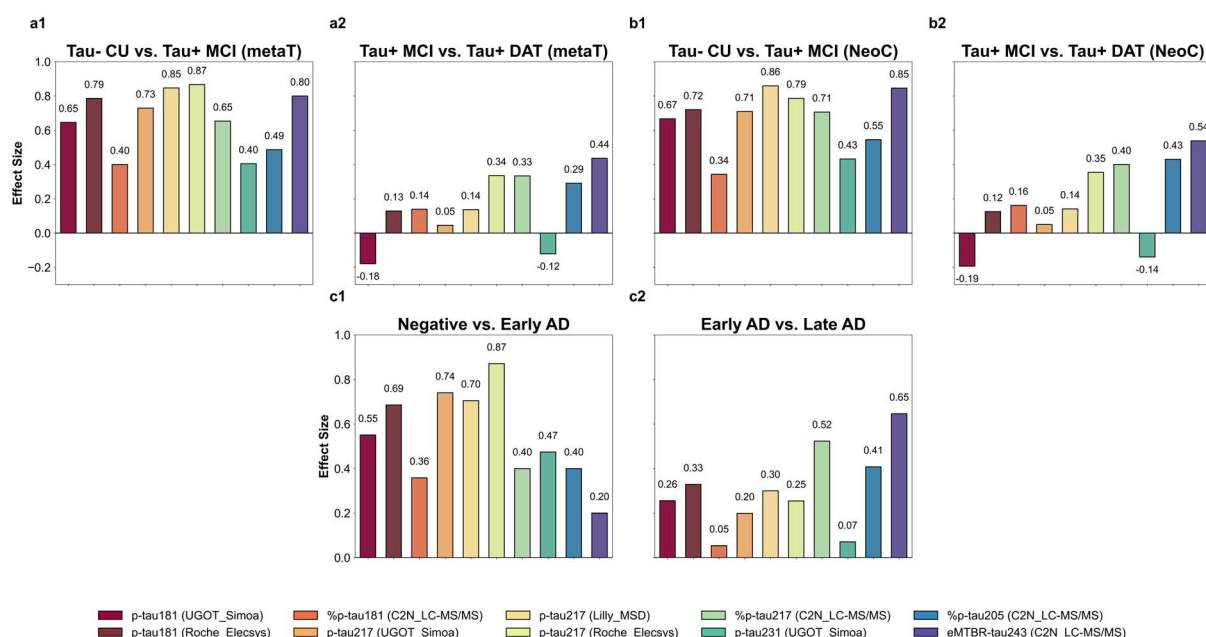
hepatic and renal function tests, vitamin B12/folate levels, thyroid function tests, and syphilis serology. Patients with structural brain abnormalities on MRI, such as territorial infarctions, brain tumors, or white matter lesions caused by other than small vessel ischemic injury were also excluded.



Supplementary Fig. 1: Distribution of plasma biomarkers across diagnostic groups

Violin plots showing the distribution and group-wise differences of plasma biomarkers (p-tau181, %p-tau181, %p-tau205, p-tau217, %p-tau217, p-tau231, eMTBR-tau243) across diagnostic categories. Median and interquartile ranges are overlaid to visualize central tendency and variability. Group differences were assessed using ANCOVA followed by Turkey-corrected post-hoc pairwise comparisons. All statistical tests were two-sided, and source data are provided as a Source data file. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Abbreviations: A β (-) CU, amyloid-negative cognitively unimpaired; A β (+) CU, amyloid-positive cognitively unimpaired; A β (+) MCI, amyloid-positive mild cognitive impairment; A β (+) DAT, amyloid-positive dementia of the Alzheimer type; A β (+) Others, amyloid-positive cognitively impaired with other etiologies; A β (-) Others, amyloid-negative cognitively impaired with other etiologies; A β , amyloid- β ; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg;

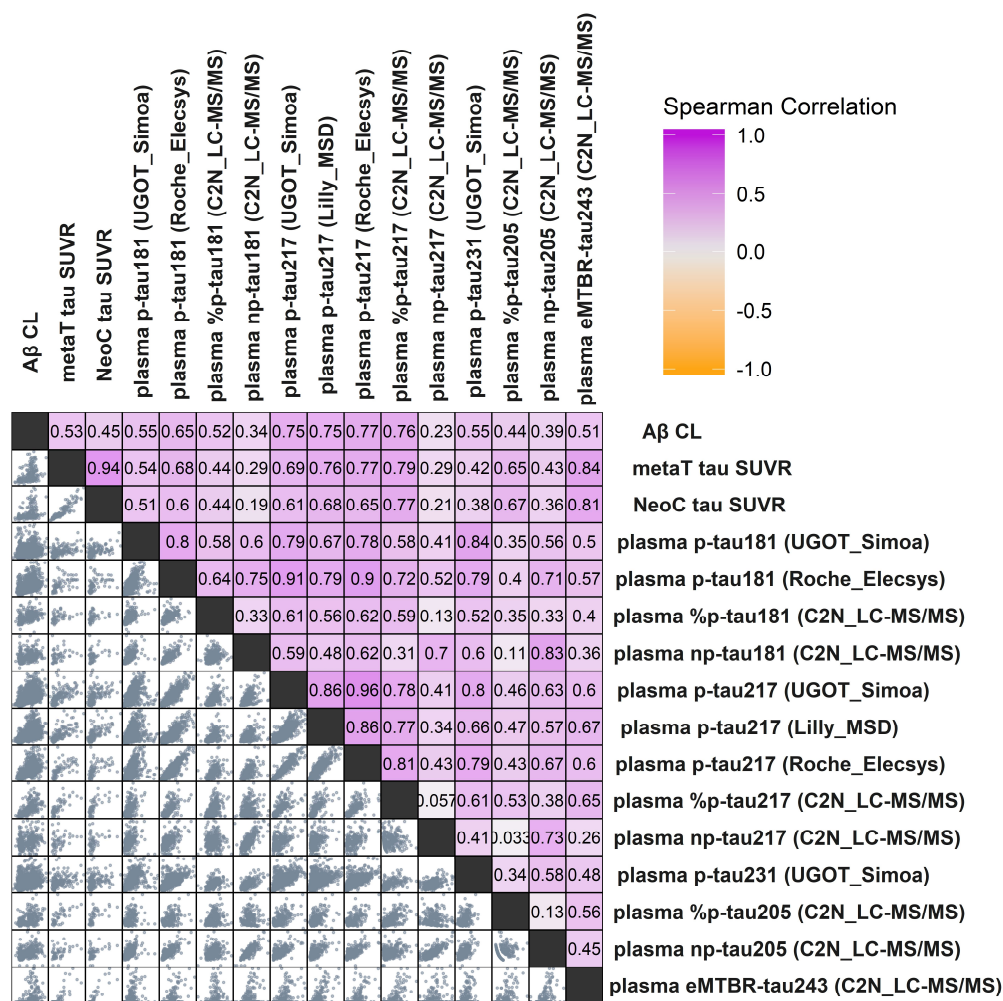
Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly;
Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit
framework at Roche Diagnostics.



Supplementary Fig. 2: Stage-specific changes in plasma biomarkers across the tau continuum

A. Cliff's Delta effect sizes for plasma biomarkers based on meta-temporal tau PET positivity. Comparisons were performed between Tau- CU and Tau+ MCI participants (A1) and between Tau+ MCI and Tau+ DAT participants (A2). B. Cliff's Delta effect sizes for plasma biomarkers based on neocortical tau PET positivity. Comparisons were performed between Tau- CU and Tau+ MCI participants (B1) and between Tau+ MCI and Tau+ DAT participants (B2). C. Cliff's Delta effect sizes for plasma biomarkers across PET-based tau stages. Comparisons were performed between negative and early stages (C1) and between early and late stages (C2). Tau stages were defined according to the PET-based topographic staging framework used in the main analyses: negative (metaT-/NeoC-), early (metaT+/NeoC-), and late (NeoC+ regardless of metaT status). Effect sizes were calculated using log-transformed biomarker values. Absolute values of 0.147, 0.330, and 0.474 were interpreted as small, medium, and large effects, respectively. Source data are provided as a Source data file. Abbreviations: AD, Alzheimer's disease; tau- CU, tau-negative cognitively unimpaired; tau+ MCI, tau-positive mild cognitive impairment; tau+ DAT, tau-positive

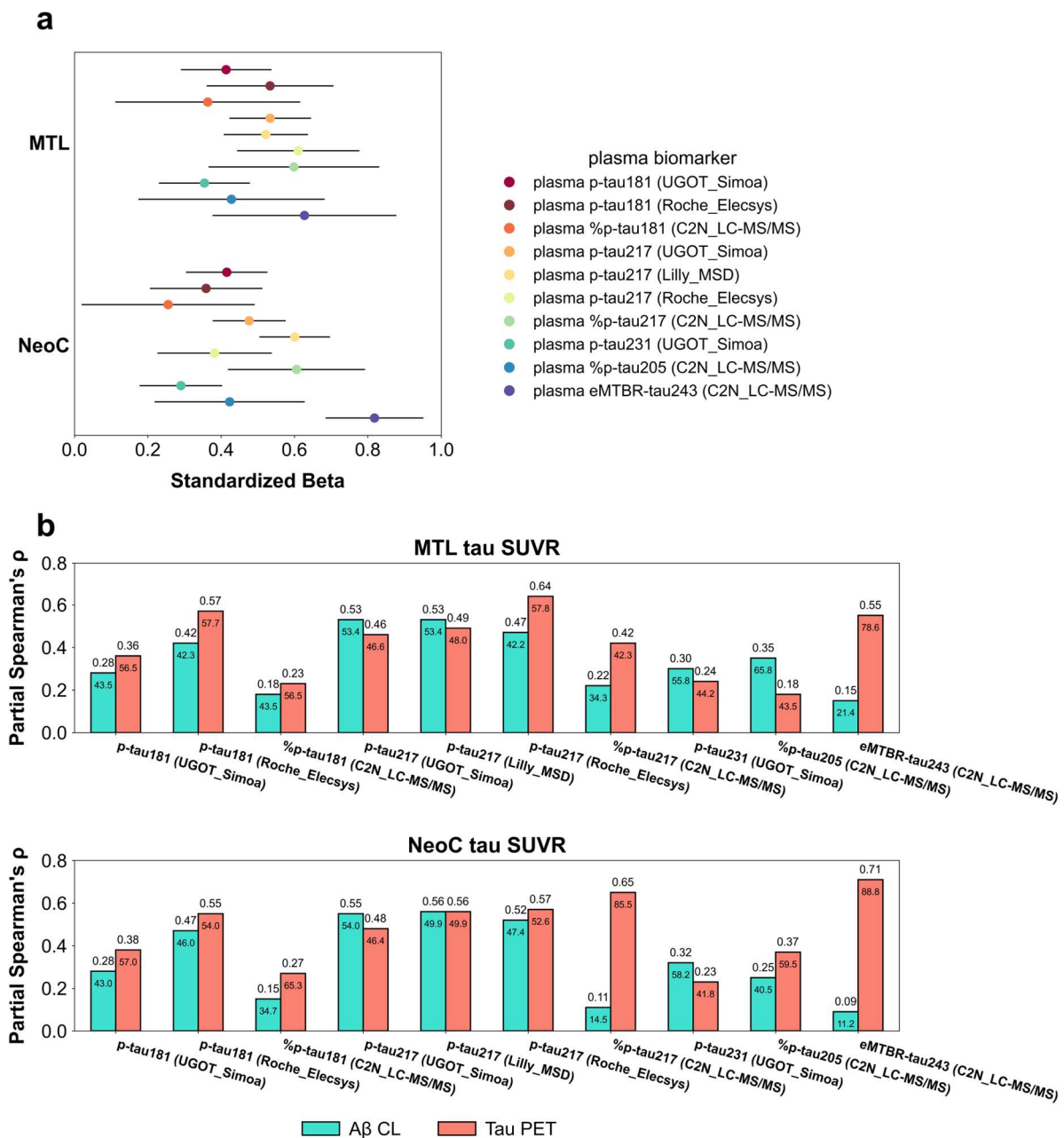
dementia of the Alzheimer type; metaT, meta-temporal; NeoC, neocortical; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics



Supplementary Fig. 3: Pairwise correlations among plasma and PET biomarkers in the total group

Correlation matrix illustrating pairwise relationships between plasma biomarkers, Aβ PET Klunk CL, and regional tau PET SUVRs assessed by Spearman's correlation. Source data are provided as a Source data file. Abbreviations: Aβ, amyloid-β; PET, positron emission tomography; SUVR, standardized uptake value ratio; CL, Centiloid; metaT, meta-temporal; NeoC, neocortical; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype

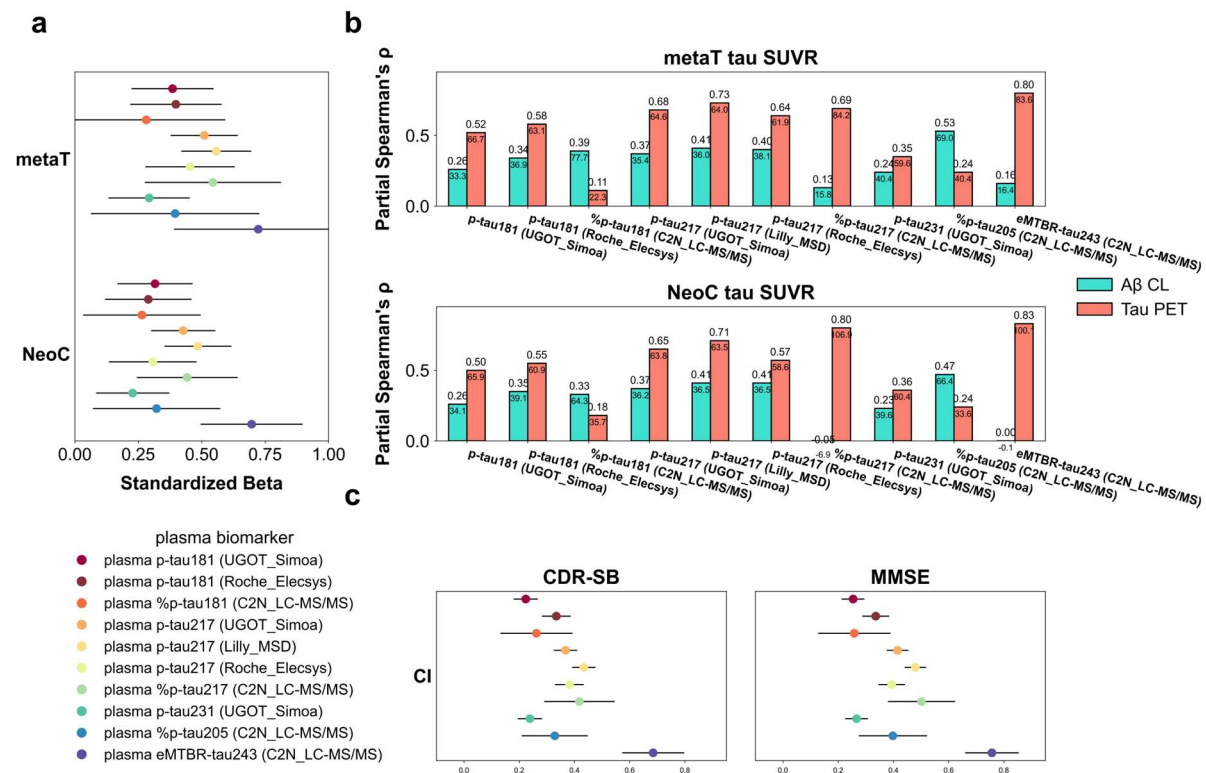
Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics.



Supplementary Fig 4: Association of plasma biomarkers with Aβ PET, and MTL and NeoC tau PET

A. Associations of plasma biomarkers with regional tau PET SUVRs in MTL and NeoC ROIs were assessed using linear regression. Points represent standardized β coefficients and error bars represent 95% confidence intervals. **B.** The relative association of Aβ PET and tau PET with plasma biomarker levels were assessed using partial Spearman's correlation. All statistical tests were two-sided, and source data are provided as a Source data file. * $P < 0.05$,

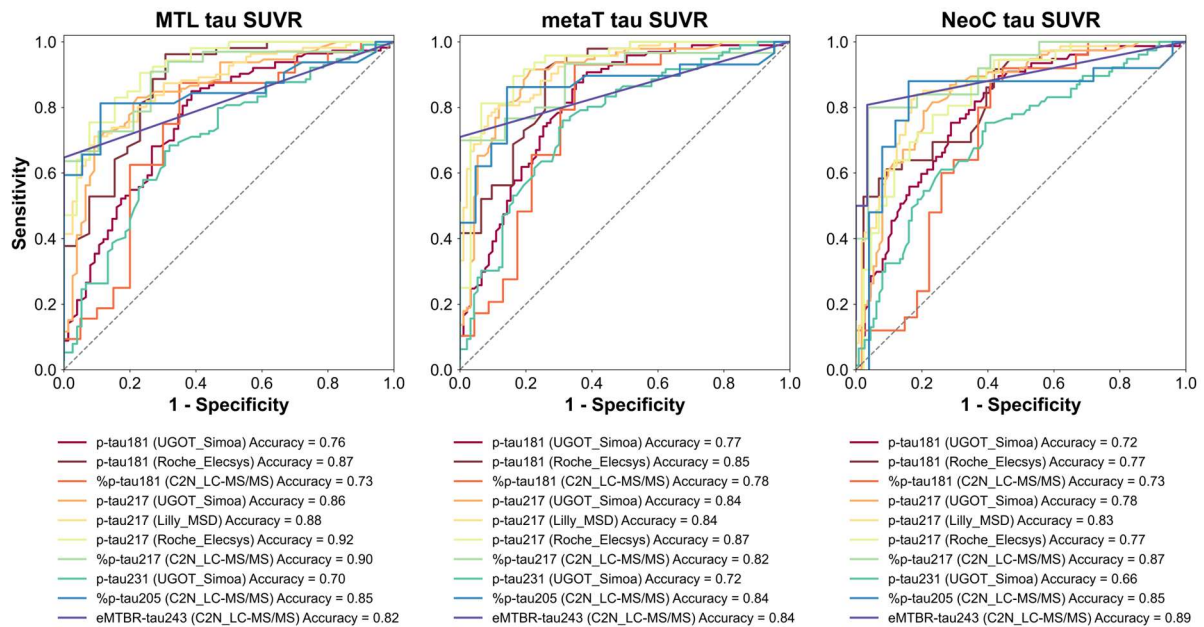
****P < 0.01, ***P < 0.001.** Abbreviations: A β , amyloid- β ; A β + CI, amyloid-positive cognitive impairment; SUVR, standardized uptake value ratio; ROI, region-of-interest; MTL, medial temporal; NeoC, neocortical; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics



Supplementary Fig. 5 Association of plasma biomarkers with Aβ PET, tau PET, and cognition among cognitively impaired participants

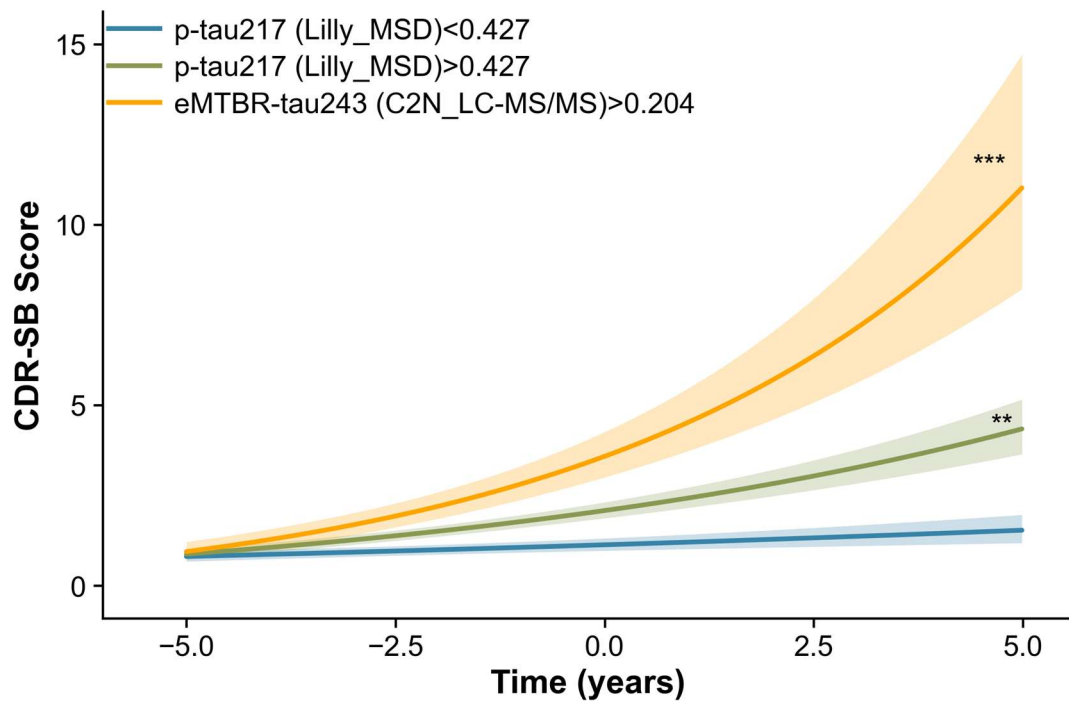
A. Associations of plasma biomarkers with regional tau PET SUVRs in metaT and NeoC ROIs among cognitively impaired participants irrespective of Aβ status were assessed using linear regression. Points represent standardized β coefficients and error bars represent 95% confidence intervals. **B.** The relative associations of Aβ PET and tau PET with plasma biomarker levels among cognitively impaired participants irrespective of Aβ status were assessed using partial Spearman's correlation. **C.** Associations between plasma biomarkers and cognitive measures among cognitively impaired participants irrespective of Aβ status were assessed using multiple linear regression. Points represent standardized β coefficients and error bars represent 95% confidence intervals. All statistical tests were two-sided. Source data are provided as a Source data file. Abbreviations: CI, cognitively impaired; Aβ, amyloid-β; SUVR, standardized uptake value ratio; ROI, region-of-interest; metaT, meta-

temporal; NeoC, neocortical; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination.



Supplementary Fig. 6: ROC curves of plasma biomarkers for regional tau PET positivity

ROC curves were derived from univariate logistic regression models, with each plasma biomarker as the predictor and tau PET positivity as the binary outcome, to evaluate the ability of plasma biomarkers to discriminate tau PET positivity in the medial temporal, meta-temporal and neocortical regions. Corresponding AUC values are shown. Source data are provided as a Source data file. Abbreviations: ROC, Receiver operating characteristic; AUC, area under the curve; SUVR, standardized uptake value ratio; metaT, meta-temporal; MTL, medial temporal; NeoC, neocortical; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics.

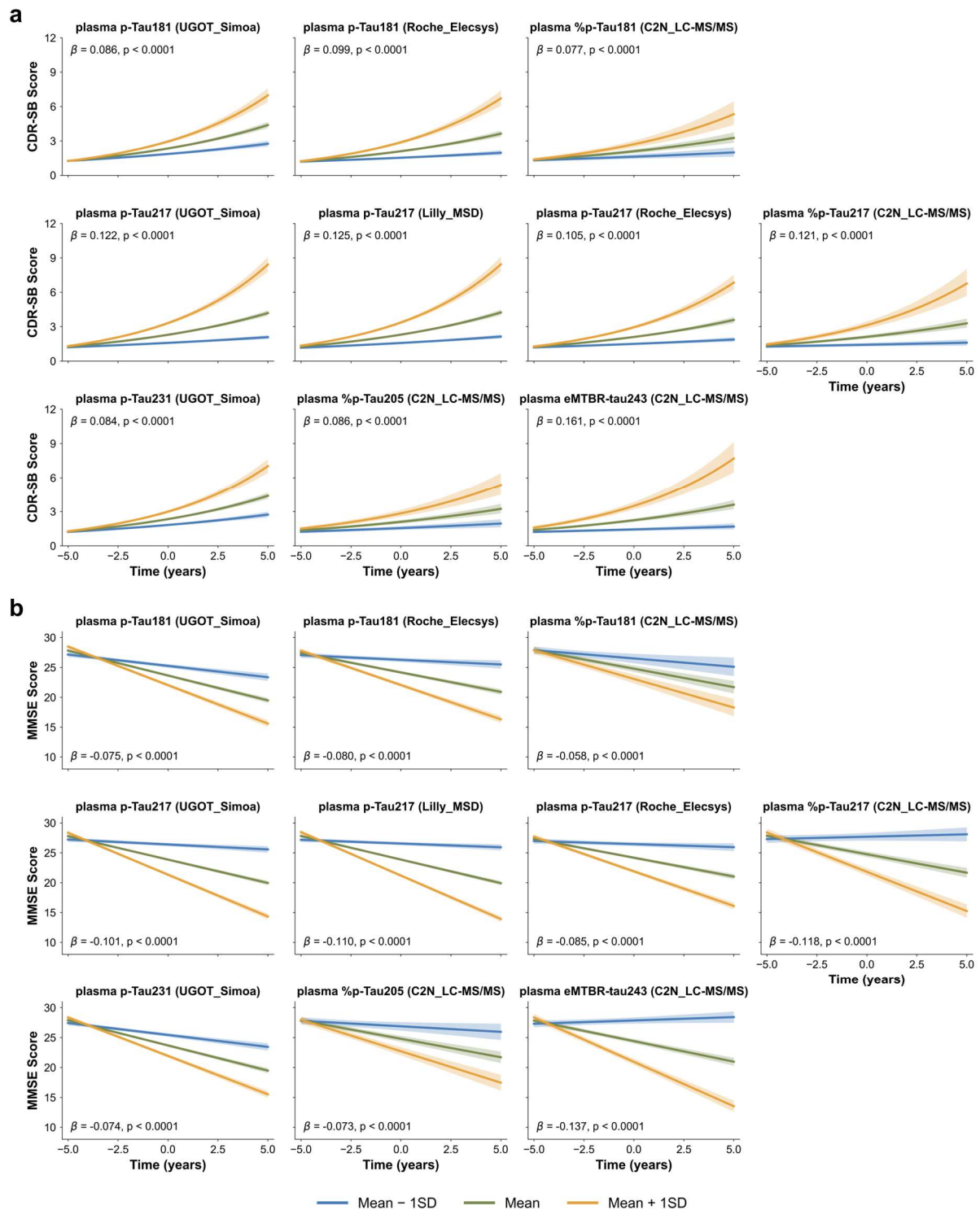


tau PET ROI	Beta	SE	p-value	marginal R ²	conditional R ²
p-tau217 < 0.427	ref				
p-tau217 > 0.427 & eMTBR < 0.204	0.102	0.039	0.010	0.353	0.757
eMTBR > 0.204	0.280	0.039	0.000		

Supplementary Fig. 7 Sensitivity analysis of longitudinal cognitive trajectory using complete biomarker cases

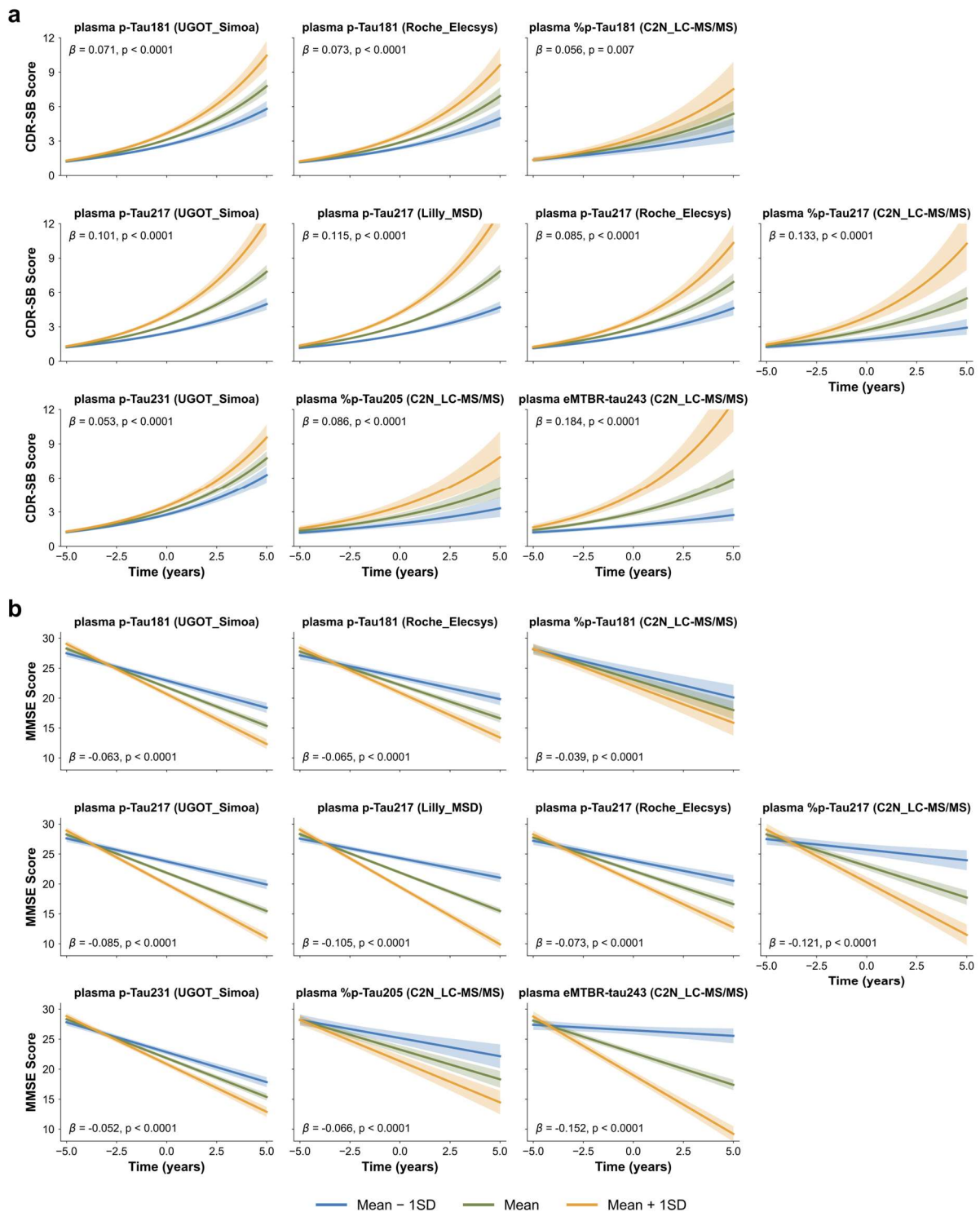
Longitudinal CDR-SB trajectories across negative, early, and late tau stages defined by plasma-based tau staging in 198 participants with measurements available for all plasma biomarkers. Plasma-based tau stages were defined using the same cutoffs as in the primary analysis. Trajectories were analyzed using linear mixed-effects models, and shaded areas represent 95% confidence intervals. All statistical tests were two-sided. Source data are provided as a Source data file. *P < 0.05, **P < 0.01, ***P < 0.001. Abbreviations: CDR-SB, Clinical Dementia Rating sum of boxes; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem

mass spectrometry assay at C2N Diagnostics; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly.



Supplementary Fig. 8: Predictive value of plasma biomarkers for longitudinal cognitive change in the total group

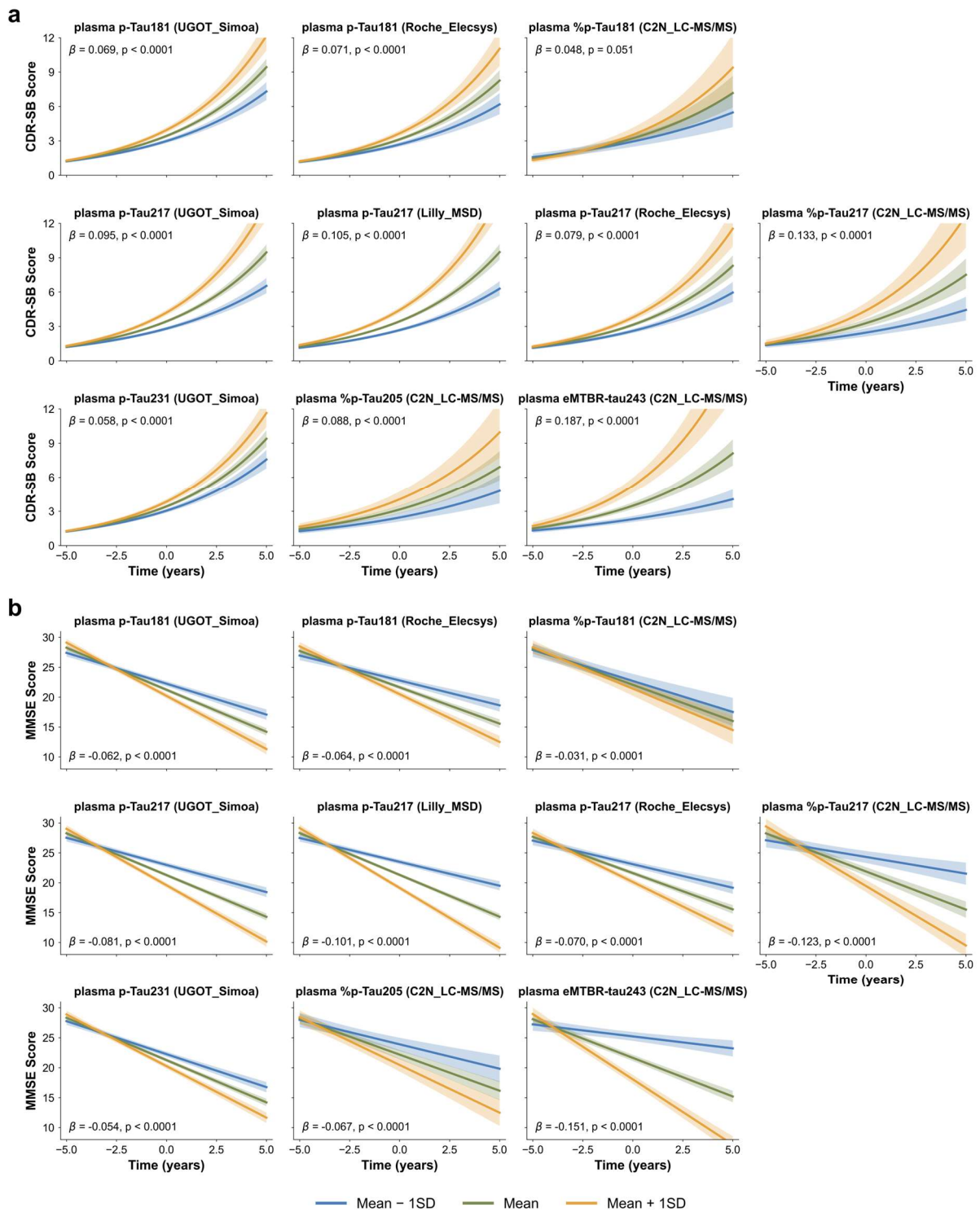
Associations between baseline plasma biomarkers and longitudinal **A. CDR-SB** and **B. MMSE** change analyzed using LMMs adjusted for age, APOE $\epsilon 4$ status, and education in the total group. Participants were stratified into low (values more than 1 SD below the mean), average (within 1 SD of the mean), and high (values more than 1 SD above the mean) plasma biomarker groups to illustrate differences in cognitive trajectories. All statistical test were two-sided, and source data are provided as a Source data file. Abbreviations: SD, standard deviation; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics



Supplementary Fig. 9: Predictive value of plasma biomarkers for longitudinal cognitive change in the A β ⁺ subgroup

Associations between baseline plasma biomarkers and longitudinal **A. CDR-SB** and **B. MMSE** change analyzed using LMMs adjusted for age, APOE ϵ 4 status, and education in the A β ⁺

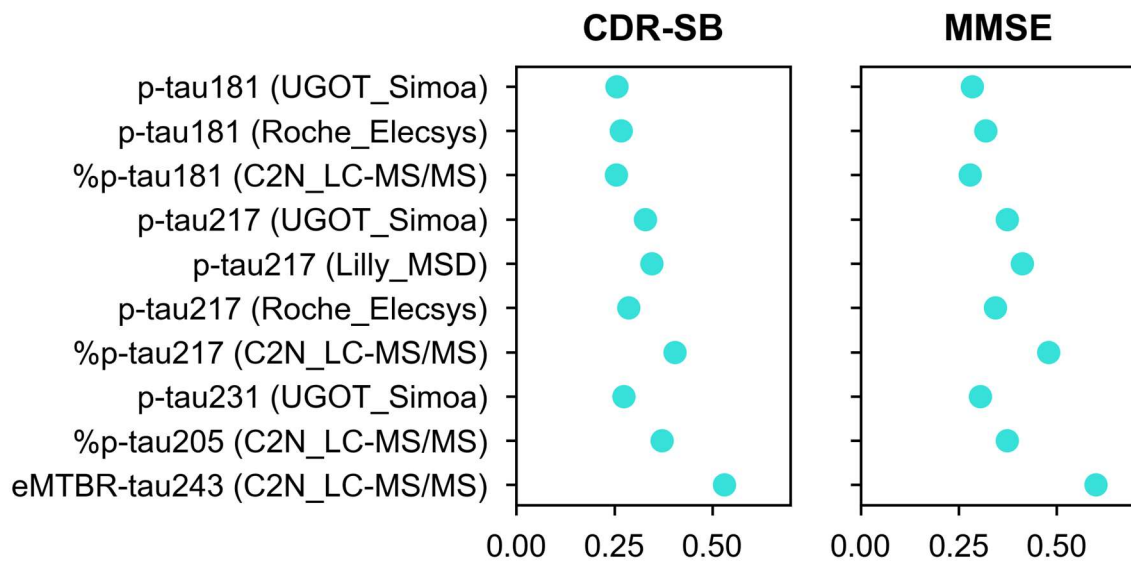
subgroup. Participants were stratified into low (values more than 1 SD below the mean), average (within 1 SD of the mean), and high (values more than 1 SD above the mean) plasma biomarker groups to illustrate differences in cognitive trajectories. All statistical test were two-sided, and source data are provided as a Source data file. Abbreviations: A β , amyloid- β ; SD, standard deviation; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics.



Supplementary Fig. 10: Predictive value of plasma biomarkers for longitudinal cognitive change in the A β + CI subgroup

Associations between baseline plasma biomarkers and longitudinal **A. CDR-SB** and **B. MMSE** change analyzed using LMMs adjusted for age, APOE ϵ 4 status, and education in the A β + CI

subgroup. Participants were stratified into low (values more than 1 SD below the mean), average (within 1 SD of the mean), and high (values more than 1 SD above the mean) plasma biomarker groups to illustrate differences in cognitive trajectories. All statistical test were two-sided, and source data are provided as a Source data file. Abbreviations: A β +CI, amyloid-positive cognitive impairment; SD, standard deviation; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics.



Supplementary Fig. 11: Marginal R^2 of plasma biomarkers for longitudinal cognitive decline among cognitively impaired participants

Forest plot showing the marginal R^2 values for the associations between baseline plasma biomarker levels and longitudinal CDR-SB and MMSE among cognitively impaired participants irrespective of $A\beta$ status. Marginal R^2 values were derived from linear mixed-effects models adjusted for age, sex, *APOE* $\epsilon 4$ status, and education. Source data are provided as a Source data file. Abbreviations: CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics.

Supplementary Table 1. Demographics, clinical, and biomarker characteristics of participants included in the C2N_LC-MS/MS platform

	A β - CU	A β + CU	A β + MCI	β + DAT	A β + others	A β - others
Demographics and clinical characteristics						
N	87	43	121	67	5	78
Age, years	71 [64, 74]	75 [70, 79]	73 [69, 79]	70 [60, 76]	76 [74, 78]	73 [68, 77]
Female, n (%)	49 (56.3)	27 (62.8)	81 (66.9)	40 (59.7)	4 (80.0)	48 (61.5)
Education, years	12 [9, 16]	12 [6, 16]	12 [6, 16]	12 [9, 16]	12 [10, 16]	12 [9, 16]
APOE ϵ 4, n (%)	16 (18.4)	17 (39.5)	70 (57.9)	36 (53.7)	4 (80.0)	20 (25.6)
A β PET positivity, n (%)	0 (0.0)	43 (100.0)	121 (100.0)	67 (100.0)	5 (100.0)	0 (0.0)
Tau PET positivity, n (%)	0 (0.0)	2 (25.0)	15 (75.0)	11 (91.7)	3 (75.0)	0 (0.0)
MMSE	29 [28, 30]	29 [27, 30]	25 [22, 27]	19 [15, 22]	22 [22, 26]	27 [24, 28]
CDR-SB	0.5 [0.5, 1.0]	0.5 [0.5, 0.5]	2.0 [1.0, 3.0]	6.0 [4.5, 8.0]	3.5 [2.0, 5.0]	1.0 [0.5, 2.0]
Biomarker values						
%p-tau181	18.2 [16.8, 21.9]	26.3 [21.8, 30.3]	27.4 [23.2, 31.3]	30.7 [26.8, 35.1]	22.4 [20.3, 25.1]	21.4 [18.0, 25.5]
%p-tau205	1.2 [1.0, 1.4]	1.4 [1.0, 2.0]	1.8 [1.1, 2.5]	2.4 [1.6, 3.3]	1.7 [1.5, 2.7]	1.1 [0.9, 1.4]
%p-tau217	1.5 [1.1, 2.2]	6.0 [3.6, 7.4]	7.4 [5.2, 10.6]	10.1 [7.5, 13.8]	5.0 [4.8, 7.8]	1.4 [0.9, 2.4]
eMTBR-tau243	0.1 [0.1, 0.1]	0.1 [0.1, 0.1]	0.1 [0.1, 0.3]	0.6 [0.1, 1.2]	0.1 [0.1, 0.2]	0.1 [0.1, 0.1]

Demographic, clinical, and biomarker characteristics of participants included in the C2N_LC-MS/MS platform, stratified by diagnostic group. Biomarker measurements included %p-tau181, %p-tau205, %p-tau217, and eMTBR-tau243. A β PET positivity was defined using a cutoff value of 25 Klunk CL. Tau PET positivity was defined as an SUVR greater than 1.31 in the meta-temporal ROI. Values are presented as median [IQR] or mean (SD) for continuous variables and number (%) for categorical variables, unless otherwise specified.

Supplementary Table 2. Demographics, clinical, and biomarker characteristics of participants included in the UGOT_Simoa platform

	A β - CU	A β + CU	A β + MCI	β + DAT	A β + others	A β - others
Demographics and clinical characteristics						
N	511	130	686	499	75	992
Age, years	70 [63, 75]	75 [70, 78]	74 [68, 78]	70 [63, 77]	79 [74, 84]	73 [66, 79]
Female, n (%)	334 (65.4)	83 (63.8)	463 (67.5)	316 (63.3)	53 (70.7)	592 (59.7)
Education, years	12 [9, 16]	12 [6, 16]	12 [6, 15]	12 [6, 14]	9 [6, 14]	12 [6, 14]
APOE ϵ 4, n (%)	98 (19.2)	63 (48.5)	438 (63.8)	294 (58.9)	29 (38.7)	172 (17.3)
A β PET positivity, n (%)	0 (0.0)	130 (100.0)	686 (100.0)	499 (100.0)	75 (100.0)	0 (0.0)
Tau PET positivity, n (%)	1 (6.7)	4 (26.7)	33 (70.2)	41 (95.3)	12 (48.0)	7 (14.9)
MMSE	28 [27, 30]	28 [26, 29]	25 [22, 27]	19 [15, 22]	23 [17, 26]	25 [21, 28]
CDR-SB	0.5 [0.5, 0.5]	0.5 [0.5, 1.0]	1.5 [1.0, 2.5]	5.0 [4.0, 8.0]	2.5 [1.5, 6.5]	1.5 [0.5, 3.0]
Biomarker values						
p-tau181	4.4 [3.5, 6.1]	7.1 [5.4, 8.4]	8.2 [6.4, 10.7]	9.6 [7.5, 11.6]	8.4 [6.7, 10.4]	4.9 [3.8, 6.6]
p-tau217	0.25 [0.20, 0.32]	0.74 [0.52, 0.98]	0.98 [0.70, 1.30]	1.17 [0.89, 1.52]	0.92 [0.67, 1.36]	0.29 [0.21, 0.39]
p-tau231	6.7 [5.2, 8.5]	10.5 [8.5, 12.7]	11.7 [9.3, 14.7]	12.6 [10.1, 15.8]	11.9 [8.9, 14.7]	7.1 [5.6, 9.4]

Demographic, clinical, and biomarker characteristics of participants included in the UGOT_Simoa platform, stratified by diagnostic group.

Biomarker measurements included p-tau181, p-tau217, and p-tau231. A β PET positivity was defined using a cutoff value of 25 Klunk CL.

Tau PET positivity was defined as an SUVR greater than 1.31 in the meta-temporal ROI. Values are presented as median [IQR] or mean (SD) for continuous variables and number (%) for categorical variables, unless otherwise specified.

Supplementary Table 3. Demographics, clinical, and biomarker characteristics of participants included in the Lilly_MSD platform

	Aβ- CU	Aβ+ CU	Aβ+ MCI	β+ DAT	Aβ+ others	Aβ- others
Demographics and clinical characteristics						
N	510	130	684	495	75	979
Age, years	70 [63, 75]	75 [70, 78]	74 [68, 78]	70 [63, 77]	79 [74, 84]	73 [66, 79]
Female, n (%)	333 (65.3)	83 (63.8)	463 (67.7)	314 (63.4)	53 (70.7)	580 (59.2)
Education, years	12 [9, 16]	12 [6, 16]	12 [6, 15]	12 [6, 14]	9 [6, 14]	12 [6, 14]
APOE ε4, n (%)	98 (19.2)	63 (48.5)	437 (63.9)	293 (59.2)	29 (38.7)	170 (17.4)
Aβ PET positivity, n (%)	0 (0.0)	130 (100.0)	684 (100.0)	495 (100.0)	75 (100.0)	0 (0.0)
Tau PET positivity, n (%)	1 (6.7)	4 (26.7)	33 (70.2)	38 (95.0)	12 (48.0)	5 (11.1)
MMSE	28 [27, 30]	28 [26, 29]	25 [22, 27]	19 [15, 22]	23 [17, 26]	25 [22, 28]
CDR-SB	0.5 [0.5, 0.5]	0.5 [0.5, 1.0]	1.5 [1.0, 2.5]	5.0 [4.0, 8.0]	2.5 [1.5, 6.5]	1.5 [0.5, 3.0]
Biomarker values						
p-tau217	0.23 [0.19, 0.27]	0.37 [0.32, 0.47]	0.52 [0.38, 0.70]	0.68 [0.48, 0.92]	0.43 [0.35, 0.61]	0.24 [0.20, 0.29]

Demographic, clinical, and biomarker characteristics of participants included in the Lilly_MSD platform, stratified by diagnostic group.

Biomarker measurement included p-tau217. Aβ PET positivity was defined using a cutoff value of 25 Klunk CL. Tau PET positivity was defined as an SUVR greater than 1.31 in the meta-temporal ROI. Values are presented as median [IQR] or mean (SD) for continuous variables and number (%) for categorical variables, unless otherwise specified.

Supplementary Table 4. Demographics, clinical, and biomarker characteristics of participants included in the Roche_Elecsys platform

	A β - CU	A β + CU	A β + MCI	β + DAT	A β + others	A β - others
Demographics and clinical characteristics						
N	362	86	466	269	0	610
Age, years	69 [63, 74]	74 [69, 78]	75 [69, 79]	72 [63, 78]	-	73 [66, 79]
Female, n (%)	244 (67.4)	54 (62.8)	315 (67.6)	166 (61.7)	-	367 (60.2)
Education, years	12 [9, 16]	12 [6, 14]	11 [6, 13]	12 [6, 14]	-	11 [6, 14]
APOE ϵ 4, n (%)	70 (19.3)	35 (40.7)	287 (61.6)	160 (59.5)	-	111 (18.2)
A β PET positivity, n (%)	0 (0.0)	86 (100.0)	466 (100.0)	269 (100.0)	-	0 (0.0)
Tau PET positivity, n (%)	1 (10.0)	2 (28.6)	15 (60.0)	30 (93.8)	-	0 (0.0)
MMSE	28 [27, 29]	28 [26, 29]	24 [21, 26]	19 [16, 23]	-	26 [22, 28]
CDR-SB	0.5 [0.5, 0.5]	0.5 [0.5, 0.5]	1.5 [1.0, 2.5]	5.0 [4.0, 8.0]	-	1.0 [0.5, 2.0]
Biomarker values						
p-tau181	0.65 [0.53, 0.81]	1.28 [0.98, 1.66]	1.52 [1.19, 1.87]	1.73 [1.31, 2.09]	-	0.73 [0.58, 0.99]
p-tau217	0.17 [0.14, 0.22]	0.51 [0.34, 0.69]	0.68 [0.50, 0.90]	0.84 [0.63, 1.06]	-	0.20 [0.16, 0.26]

Demographic, clinical, and biomarker characteristics of participants included in the Roche_Elecsys platform, stratified by diagnostic group.

Biomarker measurements included p-tau181 and p-tau217. A β PET positivity was defined using a cutoff value of 25 Klunk CL. Tau PET

positivity was defined as an SUVR greater than 1.31 in the meta-temporal ROI. Values are presented as median [IQR] or mean (SD) for continuous variables and number (%) for categorical variables, unless otherwise specified.

Supplementary Table 5: Associations of baseline plasma biomarkers with longitudinal regional tau PET accumulation

outcome	biomarker	n	adjusted beta	95% CI		p-value
metaT	log_ptau181_simoa	73	0.002	-0.242	0.246	0.988
	log_ptau181_Roche	38	0.044	-0.306	0.395	0.799
	log_ptau181_c2n_ratio	24	0.167	-0.270	0.603	0.433
	log_ptau217_simoa	74	0.025	-0.214	0.264	0.837
	log_ptau217_MSD	74	-0.083	-0.323	0.157	0.492
	log_ptau217_Roche	38	0.074	-0.276	0.424	0.670
	log_ptau217_c2n_ratio	24	0.080	-0.431	0.591	0.747
	log_ptau231_simoa	73	0.017	-0.223	0.258	0.885
	log_ptau205_c2n_ratio	23	0.014	-0.496	0.523	0.955
	log_tau243_MTBR	24	-0.266	-0.729	0.197	0.243
NeoC	log_ptau181_simoa	62	0.206	-0.046	0.458	0.107
	log_ptau181_Roche	29	0.254	-0.166	0.674	0.224
	log_ptau181_c2n_ratio	21	0.113	-0.374	0.599	0.629
	log_ptau217_simoa	63	0.235	-0.016	0.485	0.065
	log_ptau217_MSD	63	0.160	-0.096	0.416	0.216
	log_ptau217_Roche	29	0.303	-0.121	0.728	0.153
	log_ptau217_c2n_ratio	21	0.215	-0.347	0.777	0.428
	log_ptau231_simoa	62	0.169	-0.081	0.419	0.182
	log_ptau205_c2n_ratio	20	0.155	-0.417	0.728	0.570
	log_tau243_MTBR	21	-0.093	-0.631	0.446	0.719

Associations between baseline plasma biomarker levels and annualized regional tau PET slopes in the meta-temporal and neocortical regions. Associations were assessed using linear regression models adjusted models included age, sex, education, and APOE ε4 status. All statistical tests were two-sided. Abbreviations: metaT, meta-temporal; NeoC, neocortical

Supplementary Table 6: Performance and optimal cutoff values of plasma biomarkers for regional tau PET positivity (MTL)

Tau PET ROI	biomarkers	Tau-PET Positivity, n		Optimal cut-off	Sensitivity	Specificity	accuracy
		Low-risk	High-risk				
MTL	p-tau181 (SIMOA)	76	116	6.20	0.83	0.62	0.74
	p-tau181 (Roche)	26	53	0.965	0.96	0.69	0.87
	%p-tau181 (C2N)	21	34	22.08	0.82	0.67	0.76
	p-tau217 (SIMOA)	76	116	0.68	0.80	0.78	0.79
	p-tau217 (MSD)	76	111	0.427	0.71	0.91	0.79
	p-tau217 (Roche)	26	53	0.568	0.83	0.85	0.84
	%p-tau217 (C2N)	21	34	4.88	0.88	0.76	0.84
	p-tau231 (SIMOA)	76	116	10.5	0.67	0.68	0.68
	%p-tau205 (C2N)	21	34	1.95	0.76	0.90	0.82
	eMTBR-tau243 (C2N)	21	34	0.204	0.65	1.00	0.78

For each plasma biomarker, the optimal cutoff value for determine tau PET positivity in medial temporal ROI was derived using the Youden index. The corresponding sensitivity, specificity, and accuracy are shown in the right columns. Abbreviations: MTL, medial temporal; ROI, region-of-interest.

Supplementary Table 7: Longitudinal associations between plasma biomarkers and cognitive decline

	CDR-SB	effect	n	Beta	SE	pvalue	marginal R ²	Conditional R ²
Total	p-tau181 (SIMOA)	Time_y*ptau181_simoa	1,786	0.086	0.007	0.0000	0.248	0.878
	p-tau181 (Roche)	Time_y*ptau181_Roche	1,185	0.099	0.008	0.0000	0.285	0.874
	%p-tau181 (C2N)	Time_y*ptau181_C2N_r	241	0.077	0.013	0.0000	0.223	0.876
	p-tau217 (SIMOA)	Time_y*ptau217_Simoa	1,802	0.122	0.006	0.0000	0.333	0.876
	p-tau217 (MSD)	Time_y*ptau217_MSD	1,803	0.125	0.006	0.0000	0.353	0.870
	p-tau217 (Roche)	Time_y*ptau217_Roche	1,181	0.105	0.008	0.0000	0.302	0.872
	%p-tau217 (C2N)	Time_y*ptau217_C2N_r	232	0.121	0.011	0.0000	0.388	0.871
	p-tau231 (SIMOA)	Time_y*ptau231_simoa	1,793	0.084	0.007	0.0000	0.257	0.879
	%p-tau205 (C2N)	Time_y*ptau205_C2N_r	240	0.086	0.011	0.0000	0.327	0.873
	eMTBR-tau243 (C2N)	Time_y*tau243_eMTBR	298	0.161	0.009	0.0000	0.525	0.861
Aβ+	p-tau181 (SIMOA)	Time_y*ptau181_simoa	1,011	0.071	0.011	0.0000	0.290	0.876
	p-tau181 (Roche)	Time_y*ptau181_Roche	625	0.073	0.013	0.0000	0.275	0.870
	%p-tau181 (C2N)	Time_y*ptau181_C2N_r	144	0.056	0.020	0.0072	0.252	0.908
	p-tau217 (SIMOA)	Time_y*ptau217_Simoa	1,018	0.101	0.010	0.0000	0.331	0.876
	p-tau217 (MSD)	Time_y*ptau217_MSD	1,019	0.115	0.010	0.0000	0.356	0.871
	p-tau217 (Roche)	Time_y*ptau217_Roche	625	0.085	0.013	0.0000	0.292	0.870

Aβ+ CI	%p-tau217 (C2N)	Time_y*ptau217_C2N_r	140	0.133	0.017	0.0000	0.390	0.908
	p-tau231 (SIMOA)	Time_y*ptau231_simoa	1,014	0.053	0.011	0.0000	0.283	0.876
	%p-tau205 (C2N)	Time_y*ptau205_C2N_r	144	0.086	0.018	0.0000	0.361	0.911
	eMTBR-tau243 (C2N)	Time_y*tau243_eMTBR	185	0.184	0.014	0.0000	0.548	0.892
	p-tau181 (SIMOA)	Time_y*ptau181_simoa	912	0.069	0.012	0.000	0.295	0.864
	p-tau181 (Roche)	Time_y*ptau181_Roche	565	0.071	0.014	0.000	0.262	0.855
	%p-tau181 (C2N)	Time_y*ptau181_C2N_r	117	0.048	0.024	0.051	0.290	0.908
	p-tau217 (SIMOA)	Time_y*ptau217_Simoa	919	0.095	0.011	0.000	0.336	0.865
	p-tau217 (MSD)	Time_y*ptau217_MSD	920	0.105	0.010	0.000	0.358	0.861
	p-tau217 (Roche)	Time_y*ptau217_Roche	564	0.079	0.014	0.000	0.284	0.856
	%p-tau217 (C2N)	Time_y*ptau217_C2N_r	112	0.133	0.020	0.000	0.417	0.907
	p-tau231 (SIMOA)	Time_y*ptau231_simoa	915	0.058	0.011	0.000	0.296	0.864
	%p-tau205 (C2N)	Time_y*ptau205_C2N_r	115	0.088	0.022	0.000	0.404	0.913
	eMTBR-tau243 (C2N)	Time_y*tau243_eMTBR	149	0.187	0.016	0.000	0.560	0.889
Total	MMSE	effect	n	Beta	SE	pvalue	marginal R ²	Conditional R ²
	p-tau181 (SIMOA)	Time_y*ptau181_simoa	1,970	-0.075	0.005	0.0000	0.278	0.882
	p-tau181 (Roche)	Time_y*ptau181_Roche	1,280	-0.080	0.005	0.0000	0.339	0.864

Aβ+

%p-tau181 (C2N)	Time_y*ptau181_C2N_r	257	-0.058	0.011	0.0000	0.256	0.889
p-tau217 (SIMOA)	Time_y*ptau217_Simoa	1,982	-0.101	0.004	0.0000	0.384	0.878
p-tau217 (MSD)	Time_y*ptau217_MSD	1,983	-0.110	0.004	0.0000	0.425	0.876
p-tau217 (Roche)	Time_y*ptau217_Roche	1,277	-0.085	0.005	0.0000	0.365	0.867
%p-tau217 (C2N)	Time_y*ptau217_C2N_r	249	-0.118	0.009	0.0000	0.469	0.885
p-tau231 (SIMOA)	Time_y*ptau231_simoa	1,977	-0.074	0.005	0.0000	0.291	0.882
%p-tau205 (C2N)	Time_y*ptau205_C2N_r	257	-0.073	0.009	0.0000	0.340	0.883
eMTBR-tau243 (C2N)	Time_y*tau243_eMTBR	324	-0.137	0.007	0.0000	0.587	0.885
p-tau181 (SIMOA)	Time_y*ptau181_simoa	1,124	-0.063	0.007	0.0000	0.304	0.891
p-tau181 (Roche)	Time_y*ptau181_Roche	688	-0.065	0.008	0.0000	0.301	0.875
%p-tau181 (C2N)	Time_y*ptau181_C2N_r	157	-0.039	0.015	0.0106	0.281	0.902
p-tau217 (SIMOA)	Time_y*ptau217_Simoa	1,129	-0.085	0.007	0.0000	0.352	0.886
p-tau217 (MSD)	Time_y*ptau217_MSD	1,130	-0.105	0.006	0.0000	0.403	0.884
p-tau217 (Roche)	Time_y*ptau217_Roche	689	-0.073	0.008	0.0000	0.322	0.875
%p-tau217 (C2N)	Time_y*ptau217_C2N_r	153	-0.121	0.013	0.0000	0.455	0.900
p-tau231 (SIMOA)	Time_y*ptau231_simoa	1,128	-0.052	0.007	0.0000	0.298	0.889
%p-tau205 (C2N)	Time_y*ptau205_C2N_r	157	-0.066	0.014	0.0000	0.356	0.898
eMTBR-tau243 (C2N)	Time_y*tau243_eMTBR	207	-0.152	0.011	0.0000	0.595	0.894

Aβ+CI	p-tau181 (SIMOA)	Time_y*ptau181_simoa	1,022	-0.062	0.008	0.0000	0.313	0.882
	p-tau181 (Roche)	Time_y*ptau181_Roche	625	-0.064	0.009	0.0000	0.294	0.863
	%p-tau181 (C2N)	Time_y*ptau181_C2N_r	129	-0.031	0.018	0.0837	0.314	0.899
	p-tau217 (SIMOA)	Time_y*ptau217_Simoa	1,027	-0.081	0.007	0.0000	0.361	0.878
	p-tau217 (MSD)	Time_y*ptau217_MSD	1,028	-0.101	0.007	0.0000	0.405	0.877
	p-tau217 (Roche)	Time_y*ptau217_Roche	625	-0.070	0.009	0.0000	0.319	0.865
	%p-tau217 (C2N)	Time_y*ptau217_C2N_r	124	-0.123	0.015	0.0000	0.475	0.899
	p-tau231 (SIMOA)	Time_y*ptau231_simoa	1,026	-0.054	0.008	0.0000	0.314	0.880
	%p-tau205 (C2N)	Time_y*ptau205_C2N_r	127	-0.067	0.017	0.0001	0.391	0.899
	eMTBR-tau243 (C2N)	Time_y*tau243_eMTBR	170	-0.151	0.012	0.0000	0.606	0.890

Summary of linear mixed-effects model showing the associations between baseline plasma biomarker levels and longitudinal cognitive outcomes (CDR-SB and MMSE) across the total, A β +, and A β +CI subgroups. All statistical tests were tow-sided, and p-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate correction. Abbreviations: A β , amyloid- β ; A β +CI, amyloid-positive cognitive impairment; SE, standard error; CDR-SB, Clinical Dementia Rating sum of boxes; MMSE, Mini-Mental State Examination; C2N_LC-MS/MS, immunoprecipitation-liquid chromatography–tandem mass spectrometry assay at C2N Diagnostics; UGOT_Simoa, immunoassay on the Single Molecule Array platform at the University of Gothenburg; Lilly_MSD, customized immunoassay on the Meso Scale Discovery platform at Eli Lilly; Roche_Elecsys, prototype Elecsys immunoassay developed within the Neuro ToolKit framework at Roche Diagnostics

**Supplementary Table 8: Analytical validation of the C2N research-use-only assays
(eMTBR-tau243 and %p-tau-MAA)**

Measurand	LoD (pg/mL)	LoQ (pg/mL)	Reproducibility CV (%)	Repeatability, within-day CV (%)
eMTBR-tau243	0.11	0.2	9.8–18.3 ^a	8.0–18.5
p-tau217	0.938	= LoD	4.3–12.6	3.2–10.9
p-tau205	1.214	= LoD	5.2–10.6	4.4–11.6
p-tau181	1.262	= LoD	5.0–8.0	3.6–6.7
np-tau217	6.846	= LoD	2.4–12.8	3.6–8.3
np-tau205	8.375	= LoD	1.5–11.5	2.4–4.3
np-tau181	5.598	= LoD	1.1–6.0	1.6–3.3

Reproducibility CV corresponds to within-laboratory imprecision for eMTBR-tau243 (superscript a) and to within-device imprecision for the %p-tau-MAA measurands; repeatability CV corresponds to within-day imprecision. For eMTBR-tau243: LoB = 0.10 pg/mL, LoQ set to the lower limit of the measurable interval (0.2 pg/mL), accuracy 90.2–107.2%, carryover 0.42%, and no interference observed for any tested interferent. For the %p-tau-MAA, LoQ equals LoD for each measurand. Validation followed CLSI guidance; sources: C2N-RUO-P0005 eMTBR-tau243 Analytical Validation Report (doc. 135087.2413) and C2N-RUO-P0008 Analytical Validation Summary Report (doc. 135087.2447). Abbreviations: LoD, limit of detection; LoQ, limit of quantitation; CV, coefficient of variation

Supplementary Table 9: Proportion of plasma eMTBR-tau243 measurements below the limit of detection by diagnostic group

Diagnostic group	n	≤ LoD (n)	% ≤ LoD
Aβ- CU	86	84	97.7%
Aβ+ CU	41	39	95.1%
Aβ+ MCI	119	76	63.9%
Aβ+ DAT	69	21	30.4%
Aβ+ Others	7	5	71.4%
Aβ- Others	77	74	96.1%

eMTBR-tau243 values below the assay's measurable interval (0.2 pg/mL) were assigned the floor value of 0.1 pg/mL; all such values were at or below the LoD. Abbreviations: n, number of participants with an available eMTBR-tau243 measurement; ≤ LoD (n), number at or below the limit of detection (0.11 pg/mL); CU, cognitively unimpaired; MCI, mild cognitive impairment; DAT, dementia of the Alzheimer type; LoD, limit of detection

[reference]

1. Ahn, H.J., et al., *Seoul Neuropsychological Screening Battery-dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients*. J Korean Med Sci, 2010. **25**(7): p. 1071-6.
2. Albert, M.S., et al., *The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease*. Alzheimer's & dementia, 2011. **7**(3): p. 270-279.
3. McKhann, G.M., et al., *The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease*. Alzheimers Dement, 2011. **7**(3): p. 263-9.
4. Fazekas, F., et al., *MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging*. AJR Am J Roentgenol, 1987. **149**(2): p. 351-6.
5. Armstrong, M.J., et al., *Criteria for the diagnosis of corticobasal degeneration*. Neurology, 2013. **80**(5): p. 496-503.
6. Gorno-Tempini, M.L., et al., *Classification of primary progressive aphasia and its variants*. Neurology, 2011. **76**(11): p. 1006-14.
7. Litvan, I., et al., *Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop*. Neurology, 1996. **47**(1): p. 1-9.
8. Rascovsky, K., et al., *Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia*. Brain, 2011. **134**(Pt 9): p. 2456-77.

9. Strong, M.J., et al., *Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria*. Amyotroph Lateral Scler Frontotemporal Degener, 2017. **18**(3-4): p. 153-174.