
Supplementary information

**Biomarker modeling of Alzheimer's disease
using PET-based Braak staging**

In the format provided by the
authors and unedited

Supplemental Table 1. Summary of statistical comparisons of regional tau-PET SUVRs across individuals at different *in vivo* Braak stages

Braak I Regions	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.424	-0.564 to -0.283	<0.0001
I vs II	-0.776	-0.991 to -0.559	<0.0001
I vs III	-0.897	-1.465 to -0.329	<0.0001
I vs IV	-1.707	-2.115 to -1.299	<0.0001
I vs V	-1.823	-2.360 to -1.286	<0.0001
I vs VI	-2.020	-2.398 to -1.643	<0.0001

Braak II Regions	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.244	0.171 to 0.317	<0.0001
I vs II	-0.322	-0.476 to -0.166	<0.0001
I vs III	-0.693	-1.268 to -0.118	<0.0001
I vs IV	-0.936	-1.224 to -0.649	<0.0001
I vs V	-1.011	-1.381 to -0.640	<0.0001
I vs VI	-1.137	-1.393 to -0.880	<0.0001

Braak III Regions	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.048	-0.026 to 0.121	0.2428
I vs II	-0.082	-0.157 to -0.006	0.0141
I vs III	-0.243	-0.333 to -0.152	<0.0001
I vs IV	-0.409	-0.662 to -0.154	<0.0001
I vs V	-0.832	-1.227 to -0.436	<0.0001
I vs VI	-1.878	-2.215 to -1.540	<0.0001

Braak IV Regions	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.039	-0.030 to 0.110	0.3667
I vs II	-0.076	-0.148 to -0.003	0.0173
I vs III	-0.121	-0.284 to 0.041	0.1008
I vs IV	-0.407	-0.595 to -0.219	<0.0001
I vs V	-1.102	-1.457 to -0.745	<0.0001
I vs VI	-1.996	-2.381 to -1.612	<0.0001

Braak V Regions	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.041	-0.023 to 0.105	0.2618
I vs II	-0.020	-0.088 to 0.048	0.9268
I vs III	-0.051	-0.204 to 0.102	0.7348
I vs IV	-0.152	-0.241 to -0.062	<0.0001
I vs V	-0.681	-0.967 to -0.395	<0.0001
I vs VI	-1.820	-2.193 to -1.446	<0.0001

Braak VI Regions	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.058	-0.013 to 0.128	0.0872
I vs II	0.010	-0.065 to 0.086	0.9985
I vs III	0.034	-0.133 to 0.201	0.9579
I vs IV	-0.037	-0.143 to 0.068	0.8421
I vs V	-0.073	-0.167 to 0.020	0.1211
I vs VI	-1.114	-1.431 to -0.7977	<0.0001

All analyses conducted with ANOVA (Brown-Forsythe) test. All ANOVAs significant at $p < 0.001$. Adjusted *p* values reflect *p* values after multiple comparisons correction with Dunnett's T3 multiple comparisons test.

Supplementary Table 2. Summary of Amyloid-PET statistical comparisons between Braak stages

Amyloid-PET SUVR	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.228	-0.550 to 0.095	0.1810
0 vs II	-0.520	-0.766 to -0.274	<0.0001
0 vs III	-0.753	-1.334 to -0.172	0.0071
0 vs IV	-1.085	-1.362 to -0.807	<0.0001
0 vs V	-1.143	-1.391 to -0.894	<0.0001
0 vs VI	-1.082	-1.271 to -0.892	<0.0001
IV vs V	-0.058	-0.375 to 0.259	0.9417
IV vs VI	0.0031	-0.289 to 0.295	>0.9999
V vs VI	0.061	-0.207 to 0.329	0.8964

Supplementary Table 3. Summary of CSF A β 42/A β 40 ratio statistical comparisons between Braak stages

CSF A β 42/A β 40 ratio	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.119	-1.731 to 1.494	0.9992
0 vs II	-1.073	-1.989 to -0.157	0.0069
0 vs III	-1.692	-2.624 to -0.7603	0.0018
0 vs IV	-2.084	-2.991 to -1.178	<0.0001
0 vs V	-2.163	-2.961 to -1.365	<0.0001
0 vs VI	-1.849	-2.314 to -1.384	<0.0001
IV vs V	-0.078	-0.986 to 0.830	0.9887
IV vs VI	0.235	-0.581 to 1.052	0.7310
V vs VI	0.313	-0.400 to 1.028	0.4016

Supplemental Table 4. Percentage of amyloid-positive individuals according to PET and CSF modalities at each Braak stage in the cross-sectional cohort

PET-Based Braak Stage	% Amyloid-PET +	% CSF Aβ +
0	17%	25%
I	42%	40%
II	64%	72%
III	100%	100%
IV	100%	100%
V	100%	100%
VI	96%	100%

The amyloid-negative individuals at stage VI may represent cases of Neurofibrillary Tangle-Predominant Dementia ¹, who display high levels of neurofibrillary tangle pathology in the absence of elevated amyloid-beta and present with a phenotype indistinguishable from Alzheimer's clinical syndrome. The amyloid-PET negative Braak stage VI individuals did not have CSF evaluations.

Supplemental Table 5. Summary of statistical comparisons of CSF and plasma phosphorylated tau species across Braak stages

CSF pTau181	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.927	-3.615 to 1.760	0.4629
0 vs II	-1.191	-2.327 to -0.055	0.0176
0 vs III	-3.139	-8.072 to 1.794	0.0447
0 vs IV	-6.664	-13.51 to 0.1811	0.0279
0 vs V	-7.612	-15.16 to -0.060	0.0243
0 vs VI	-6.455	-9.874 to -3.035	<0.0001
IV vs V	-0.947	-7.691 to 5.796	0.9514
IV vs VI	0.209	-5.515 to 5.934	0.9992
V vs VI	1.157	-4.692 to 7.006	0.8808

CSF pTau217	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.586	-3.001 to 1.826	0.7277
0 vs II	-1.164	-2.015 to -0.312	0.0017
0 vs III	-2.768	-5.435 to -0.101	0.0225
0 vs IV	-4.943	-10.42 to 0.533	0.0395
0 vs V	-5.691	-10.04 to -1.342	0.0095
0 vs VI	-5.738	-9.124 to -2.351	0.0002
IV vs V	-0.748	-5.764 to 4.269	0.9429
IV vs VI	-0.794	-5.767 to 4.178	0.9477
V vs VI	-0.049	-3.944 to 3.850	>0.9999

CSF pTau231	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.935	-4.444 to 2.575	0.5099
0 vs II	-1.493	-2.308 to -0.678	<0.0001
0 vs III	-1.968	-3.097 to -0.839	0.0032
0 vs IV	-3.744	-7.547 to 0.058	0.0268
0 vs V	-4.279	-6.920 to -1.637	0.0042
0 vs VI	-4.521	-7.426 to -1.616	0.0005
IV vs V	-0.534	-3.883 to 2.814	0.9315
IV vs VI	-0.776	-4.468 to 2.915	0.8982
V vs VI	-0.242	-3.167 to 2.683	0.9931

CSF pTau235	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.257	-1.788 to 1.273	0.9498
0 vs II	-0.833	-1.594 to -0.071	0.0122
0 vs III	-2.657	-5.979 to 0.664	0.0463
0 vs IV	-3.953	-7.887 to -0.018	0.0245
0 vs V	-4.303	-7.578 to -1.028	0.0093
0 vs VI	-4.710	-7.177 to -2.242	<0.0001
IV vs V	-0.350	-3.895 to 3.194	0.9832
IV vs VI	-0.757	-4.320 to 2.807	0.8890
V vs VI	-0.406	-3.267 to 2.454	0.9641

Plasma pTau181	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.111	-0.979 to 0.757	0.9979
0 vs II	-0.352	-0.867 to 0.164	0.2452
0 vs III	-0.684	-3.190 to 1.822	0.6460
0 vs IV	-1.446	-2.832 to -0.060	0.0188
0 vs V	-2.147	-3.729 to -0.564	0.0026
0 vs VI	-2.431	-3.283 to -1.579	<0.0001
IV vs V	-0.701	-2.432 to 1.031	0.5806
IV vs VI	-0.984	-2.359 to 0.390	0.1434
V vs VI	-0.284	-1.811 to 1.242	0.9296

Plasma pTau231	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.424	-1.293 to 0.446	0.5187
0 vs II	-0.599	-1.177 to -0.022	0.0182
0 vs III	-1.309	-2.813 to 0.194	0.0502
0 vs IV	-1.022	-2.264 to 0.220	0.0799
0 vs V	-1.645	-3.064 to -0.226	0.0085
0 vs VI	-2.431	-3.154 to -1.708	<0.0001
IV vs V	-0.623	-2.180 to 0.933	0.5951
IV vs VI	-1.409	-2.624 to -0.194	0.0084
V vs VI	-0.785	-2.140 to 0.568	0.2846

All analyses conducted with ANOVA (Brown-Forsythe) test. All ANOVAs significant at $p < 0.001$. Adjusted *p* values reflect *p* values after multiple comparisons correction with Dunnett's T3 multiple comparisons test. *P*-values for differences between stages were considered statistically

significant at $p < 0.01$ after multiple comparisons correction. All CSF pTau species had detectable differences by Braak stage III. CSF pTau181, 217, 231 and 235 were all significantly different from stage 0 by stage II. Plasma pTau231 was significantly different by Braak stage II and plasma pTau181 was significantly different by stage VI.

Supplementary Table 6. Summary of statistical comparisons of cognitive outcomes between Braak stages

Memory Composite	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.4307	-0.940 to 1.802	0.8521
0 vs II	0.6456	-0.002 to 1.293	0.0256
0 vs III	1.195	-1.283 to 3.673	0.0880
0 vs IV	2.014	0.914 to 3.113	0.0001
0 vs V	2.551	1.589 to 3.514	<0.0001
0 vs VI	3.099	2.618 to 3.581	<0.0001

Executive Composite	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.04131	-1.114 to 1.196	>0.9999
0 vs II	0.3904	-0.142 to 0.923	0.1717
0 vs III	0.8023	-2.802 to 4.406	0.8576
0 vs IV	0.6201	-0.634 to 1.875	0.4846
0 vs V	1.432	-0.211 to 3.075	0.0557
0 vs VI	2.403	1.658 to 3.147	<0.0001

Language Composite	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.2798	-0.801 to 0.241	0.4549
0 vs II	0.3168	-0.170 to 0.804	0.2950
0 vs III	0.01543	-2.688 to 2.719	>0.9999
0 vs IV	1.016	-0.999 to 3.031	0.4532
0 vs V	0.4675	-0.750 to 1.686	0.6165
0 vs VI	3.055	1.112 to 4.998	0.0003

Visuospatial composite	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	-0.1264	-1.158 to 0.904	0.9983
0 vs II	0.3601	-0.419 to 1.140	0.6461
0 vs III	0.7250	-2.570 to 4.020	0.8630
0 vs IV	0.2478	-1.193 to 1.689	0.9899
0 vs V	0.8388	-0.887 to 2.566	0.4229
0 vs VI	3.413	1.405 to 5.421	0.0001

MMSE	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.1644	-0.657 to 0.986	0.9890
0 vs II	0.1561	-0.585 to 0.897	0.9890
0 vs III	0.5561	-1.366 to 2.478	0.8628
0 vs IV	1.723	0.195 to 3.250	0.0090
0 vs V	3.623	1.622 to 5.624	<0.0001
0 vs VI	11.02	8.612 to 13.43	<0.0001

MOCA	Mean difference	95% CI of difference	Adjusted <i>p</i> value
0 vs I	0.1877	-2.883 to 3.259	>0.9999
0 vs II	0.8911	-0.522 to 2.305	0.3089
0 vs III	4.073	-2.363 to 10.51	0.1540
0 vs IV	5.249	1.438 to 9.060	0.0025
0 vs V	6.121	1.812 to 10.43	0.0032
0 vs VI	14.64	9.706 to 19.58	<0.0001

All analyses conducted with ANOVA (Brown-Forsythe) test. All ANOVAs significant at $p < 0.001$. Adjusted p values reflect p values after multiple comparisons correction with Dunnett's T3 multiple comparisons test.

Years to onset of symptoms: ANOVA: $F = 31.59$; $p < 0.0001$, $R^2 = 0.9186$.

Supplementary Table 7. Clinical, demographic and summary biomarker data for sub-sample with longitudinal tau-PET.

	CU	MCI	<i>p</i> value	Alzheimer syndrome	<i>p</i> value
No.	87	45	—	27	—
Age, y, mean (SD)	70.83 (7.16)	70.11 (8.3)	0.61	67.21 (8.7)	0.03
Female, no. (%)	53 (61)	24 (53)	0.40	13 (48)	0.40
Education, y, mean (SD)	15.20 (3.82)	14.59 (3.61)	0.41	14.28 (4.03)	0.65
APOE $\epsilon 4$ carriers, %	24 (28)	16 (36)	0.34	13 (48)	0.04
MMSE, mean (SD)	29.06 (1.19)	28.16 (1.59)	<0.0001	21.07 (5.66)	<0.0001
Neocortical [^{18}F]AZD4694 SUVR (SD)	1.41 (0.32)	1.91 (0.59)	<0.0001	2.38 (0.59)	<0.0001
Temporal Meta-ROI [^{18}F]MK6240 (SD)	1.05 (0.14)	1.39 (0.43)	<0.0001	2.78 (0.96)	<0.0001
Hippocampal volume, mm³ (SD)	3.59 (0.43)	3.21 (0.49)	<0.0001	2.88 (0.54)	<0.0001

p values reported are for comparisons to cognitively unimpaired (CU) subjects. *p* values indicate values assessed with independent samples t-tests for each variable except sex and APOE $\epsilon 4$ status, where contingency χ^2 tests were performed. MMSE = Mini-Mental State Examination; SUVR = Standardized Uptake Value Ratio; CU = Cognitively Unimpaired; MCI = Mild Cognitive Impairment.