

SUPPLEMENTARY FILE

The potential of Alzheimer's plasma biomarkers to mimic tau PET MUBADA-based disease staging

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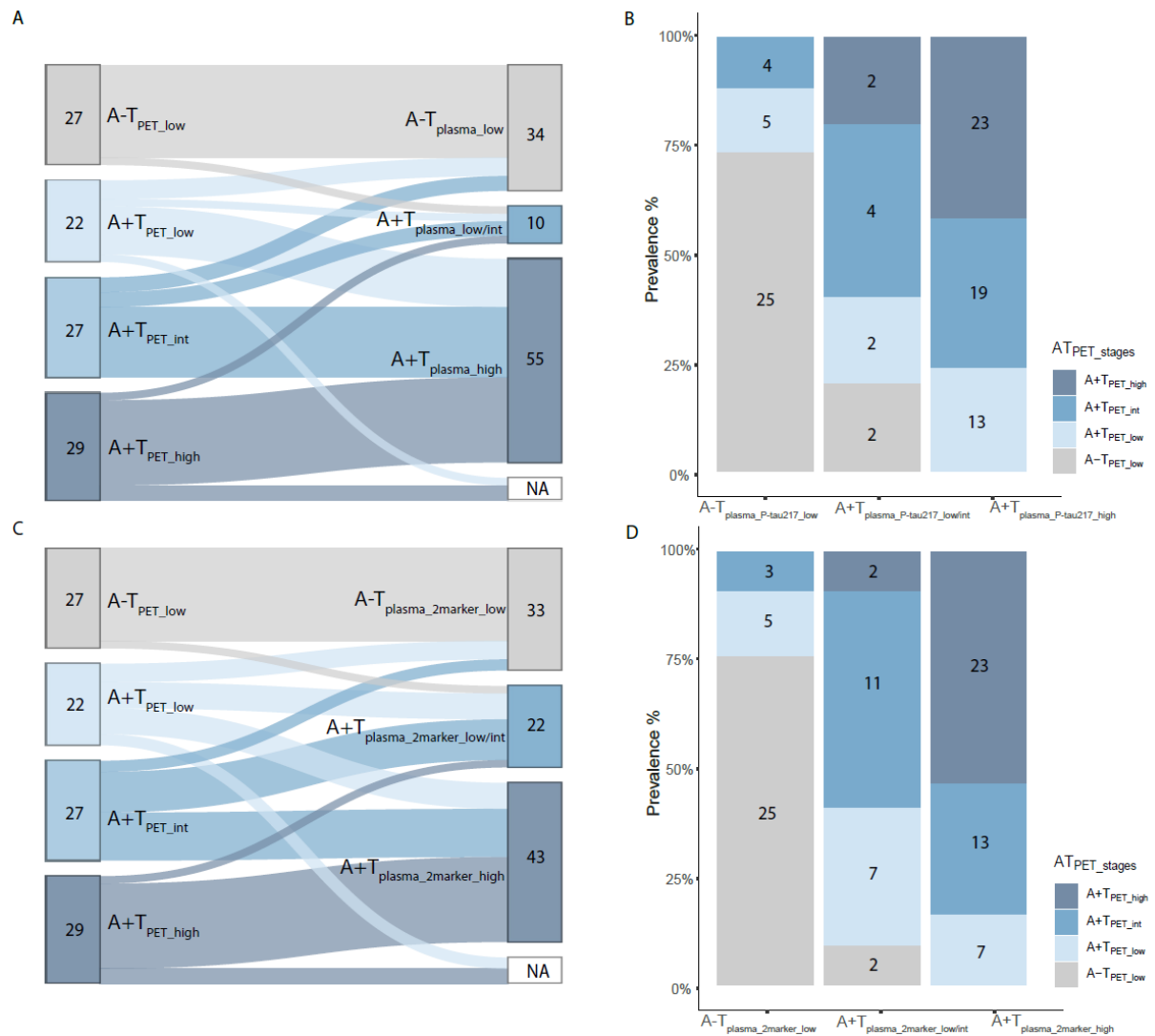
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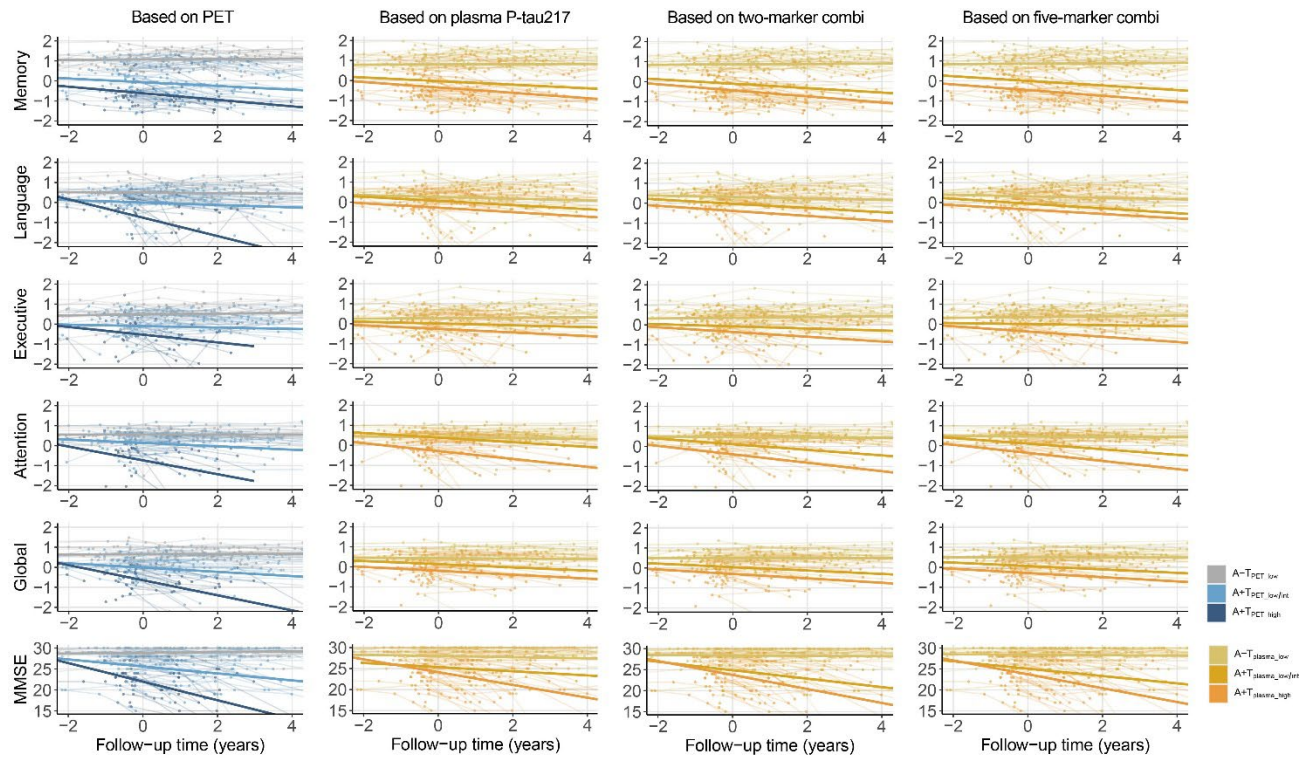
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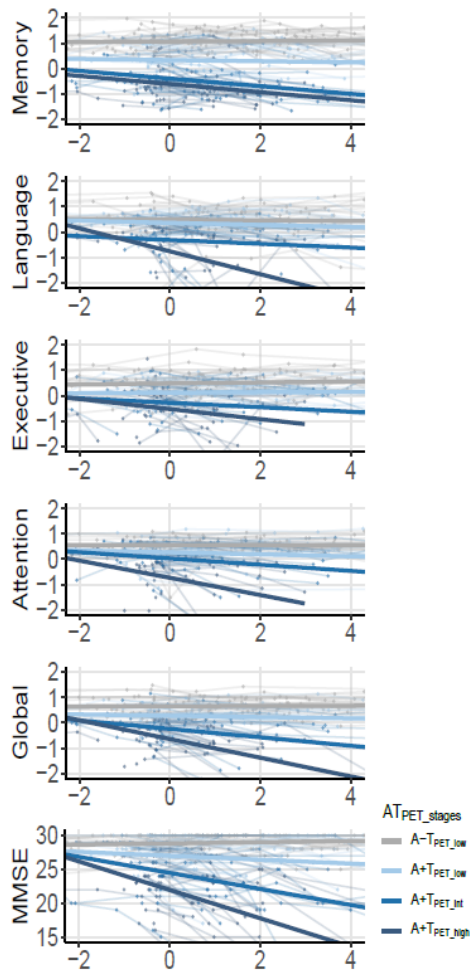


Supplementary figure 1. Sankey plot (A/C) and prevalence plot (B/D) visualizing the AT_{PET_stages} groups versus the developed AT_{plasma_P-tau217_stages} (top) and AT_{plasma_2marker_stages} (bottom) groups. The AT_{PET_stages} groups are based on amyloid (A) status (-/+) according to cerebrospinal fluid testing or amyloid PET and tau (T) according to positron emission tomography (PET) scanning, where the tau-PET scan was interpreted according to the MUBADA SUVR and visual read. The AT_{plasma_P-tau217_stages} groups are based on the plasma P-tau217 levels predicting the AT_{PET_stages}, with thresholds set at >90% specificity. The AT_{plasma_P-tau217_stages} groups are based on the two-marker combinations (P-tau217 and Aβ42/40 for A-T_{PET_low} versus A+T_{PET_low/int}, and P-tau217 and P-tau181 for A+T_{PET_low/int} versus A+T_{PET_high}) predicting the AT_{PET_stages} with thresholds set at >90% specificity. 6 participants are classified as not available (NA) in AT_{plasma_P-tau217_stages} groups and 7 participants are classified as NA in AT_{plasma_2marker_stages} due to missing plasma biomarker levels. Int = intermediate.



Supplementary figure 2. Spaghetti plots visualizing the association of AT_{PET_stages} (first column), $AT_{plasma_P\text{-}tau217_stages}$ (second column), $AT_{plasma_2\text{-}marker_stages}$ (third column) and $AT_{plasma_5marker_stages}$ (right column) with longitudinal cognitive performance across domains, and global cognition and MMSE.

A = amyloid, T = tau, Int = intermediate, MMSE = mini-mental state examination.



Supplementary figure 3. Spaghetti plots visualizing the association of AT_{PET_stages} with longitudinal cognitive performance across domains, and global cognition and MMSE, where AT_{PET_stages} are splitted across four groups: $A-T_{PET_low}$, $A+T_{PET_low}$, $A+T_{PET_int}$ and $A+T_{PET_high}$. A = amyloid, T = tau, Int = intermediate, $MMSE$ = mini-mental state examination.

Supplementary table 1. Associations of AT_{plasma_P-tau217_stages} and AT_{PET_stages} with cross-sectional and longitudinal cognitive performance across cognitive domains and global cognition.

Cognitive domain	A-T _{PET_low} VS A+T _{PET_low/int}		A+T _{PET_low/int} VS A+T _{PET_high}		A-T _{plasma_P-tau217_low} VS A+T _{plasma_P-tau217_low/int}		A+T _{plasma_P-tau217_low/int} VS A+T _{plasma_P-tau217_high}	
	Concurrent	Annual change	Concurrent	Annual change	Concurrent	Annual change	Concurrent	Annual change
Memory	-1.14[0.16]***	-0.10[0.02]***	-0.60[0.17]***	-0.08[0.03]**	-0.89[0.27]**	-0.10[0.03]*	-0.27[0.26]	-0.05[0.03]
Language	-0.49[0.21]*	-0.05[0.03]	-0.81[0.22]***	-0.42[0.07]***	-0.24[0.35]	-0.06[0.06]	-0.30[0.33]	-0.01[0.06]
Executive functioning	-0.58[0.15]***	-0.06[0.02]**	-0.55[0.17]**	-0.18[0.05]***	-0.36[0.26]	-0.05[0.04]	-0.21[0.25]	-0.05[0.04]
Attention	-0.44[0.18]*	-0.09[0.04]	-0.88[0.19]***	-0.28[0.06]***	-0.05[0.31]	-0.10[0.08]	-0.65[0.30]*	-0.08[0.08]
Global cognition	-0.67[0.13]***	-0.11[0.04]*	-0.65[0.13]***	-0.13[0.03]***	-0.39[0.22]	-0.07[0.03]*	-0.27[0.21]	-0.02[0.03]
MMSE	-0.78[0.19]***	-0.22[0.05]***	-0.94[0.20]***	-0.34[0.07]***	-0.71[0.32]*	-0.09[0.11]	-0.24[0.30]	-0.24[0.11]*

Standardized β and standard error of linear mixed models associating AT_{PET_stages} (left) or AT_{plasma_P-tau217_stages} (right) groups with longitudinal cognitive domain scores, corrected for age, sex and education, are presented. The standardized beta represents either the cross-sectional difference in cognitive performance at time of the PET imaging, or the annual standard deviation change in cognitive performance, for subsequent stages. A = amyloid status, Int = intermediate, In bold font, * $p < 0.05^{FDR}$, ** $p < 0.01^{FDR}$, *** $p < 0.001^{FDR}$; in regular font, * $p < 0.05$ prior to FDR correction.

Supplementary table 2. Associations of AT_{plasma_stages} based on 2-marker and 5-marker combinations with cross-sectional and longitudinal cognitive performance across cognitive domains and global cognition.

Cognitive domain	A-T _{plasma_low} VS A+T _{plasma_int} Based on 2-marker combination		A+T _{plasma_int} VS A+T _{plasma_high} Based on 2-marker combination		A-T _{plasma_low} VS A+T _{plasma_int} Based on 5-marker combination		A+T _{plasma_int} VS A+T _{plasma_high} Based on 5-marker combination	
	Concurrent	Annual change	Concurrent	Annual change	Concurrent	Annual change	Concurrent	Annual change
Memory	-1.01[0.21]***	-0.12[0.02]***	-0.28[0.21]	-0.04[0.03]	-0.87[0.21]***	-0.12[0.02]***	-0.46[0.20]*	-0.03[0.06]
Language	-0.39[0.27]	-0.07[0.04]	-0.29[0.27]	-0.03[0.05]	-0.39[0.27]	-0.08[0.04]	-0.29[0.27]	-0.001[0.05]
Executive functioning	-0.45[0.20]*	-0.08[0.03]*	-0.28[0.20]	-0.06[0.04]	-0.35[0.09]	-0.05[0.03]	-0.41[0.20]*	-0.10[0.04]**
Attention	-0.39[0.23]	-0.13[0.05]*	-0.46[0.23]*	-0.07[0.06]	-0.38[0.24]	-0.13[0.06]*	-0.45[0.23]	-0.07[0.06]
Global cognition	-0.50[0.17]**	-0.09[0.02]***	-0.29[0.17]	-0.03[0.02]	-0.46[0.17]*	-0.09[0.02]***	-0.34[0.17]*	-0.03[0.02]
MMSE	-0.91[0.24]***	-0.23[0.08]*	-0.23[0.23]	-0.15[0.08]	-0.83[0.24]***	-0.20[0.09]*	-0.32[0.24]	-0.18[0.09]*

Standardized β and standard error of linear mixed models associating AT_{plasma_stages} based on two-marker combinations (left) or all-5-marker combinations (right) groups with longitudinal cognitive domain scores, corrected for age, sex and education, are presented. The standardized beta represents either the cross-sectional difference in cognitive performance at time of the PET imaging, or the annual standard deviation change in cognitive performance, for subsequent stages. The two-marker combinations employed P-tau217 + A β 42/40 to discriminate A-T_{PET_low} from A+T_{PET_low} and P-tau217 + P-tau181 to discriminate A+T_{PET_high} from A+T_{PET_low/int}. The 5-marker combination included P-tau217, P-tau181, A β 42/40, GFAP and NfL. Predicted values from logistic regression models combining the plasma biomarkers were used in the linear mixed models. A = amyloid status, Int = intermediate, In bold font, * $p < 0.05^{FDR}$, ** $p < 0.01^{FDR}$, *** $p < 0.001^{FDR}$; in regular font, * $p < 0.05$ prior to FDR correction.