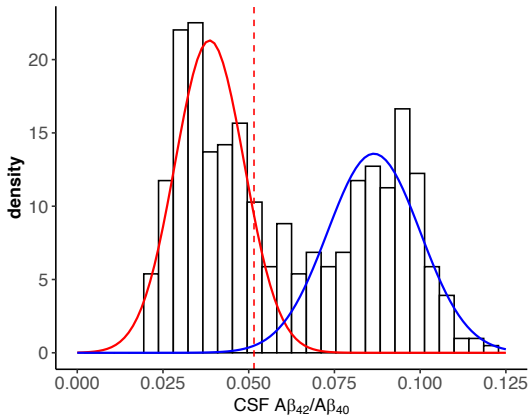
Supplemental Material

Cutoff of CSF $A\beta_{42}/A\beta_{40}$

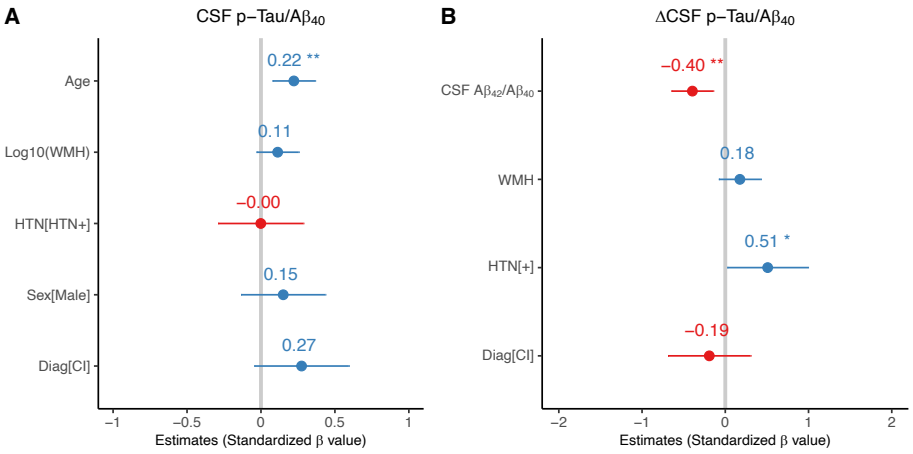


Supplemental fig.1. *Estimates of 2 gaussian distributions of high CSF $A\beta_{42}/A\beta_{40}$ (blue curve) and low CSF $A\beta_{42}/A\beta_{40}$ (red curve) of among all 474 (251 CU, 184 MCI and 39 AD) ADNI participants with CSF $A\beta_{42}/A\beta_{40}$ ratio. Red dashed vertical line reflects the Aβ+ threshold of CSF $A\beta_{42}/A\beta_{40}$ ratio 0.051, which corresponds to a 90% probability of belonging to the low CSF $A\beta_{42}/A\beta_{40}$ distribution.*

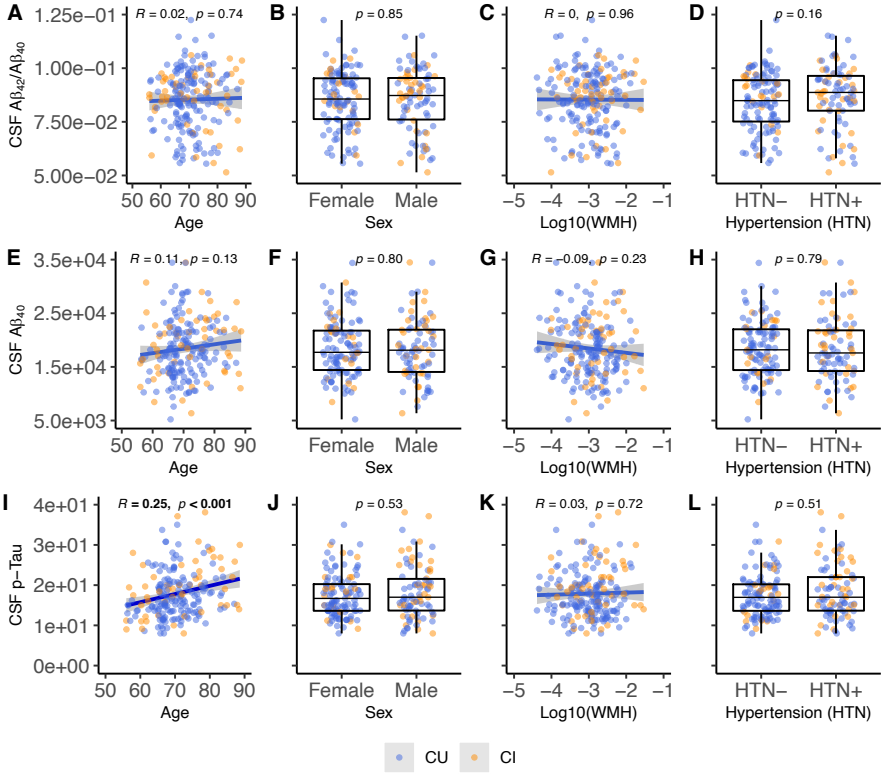
Supplemental table1. Demographics of longitudinal data

Diagnosis	Cognitively unimpaired	Cognitively impaired
56 participants with ≥ 2 CSF measurements		
Sample size	36	20
Duration of follow-up, year, (Mean (SD))	5.9 (2.9)	3.9 (1.8)
Visits of CSF, No., (Mean (SD))	2.8 (0.6)	2.8 (0.9)
61 participants with ≥ 2 aHCV		
Sample size	29	32
Duration of follow-up, year, (Mean (SD))	6.5(1.7)	3.8(2.6)
Visits of aHCV, (Mean (SD))	6.4(1.5)	5.2(2.5)
39 participants with ≥ 2 FDG PET		
Sample size	22	17
Duration of follow-up, year, (Mean (SD))	2.4(1.4)	3.7(2.1)
Visits of FDG PET, (Mean (SD))	2.1(0.3)	2.3(0.5)
74 participants with ≥ 2 cognition		
Sample size	29	45
Duration of follow-up, year, (Mean (SD))	6.8(1.3)	3.5(2.7)
Visits of PACC scores, (Mean (SD))	6.4(1.0)	4.6(2.8)

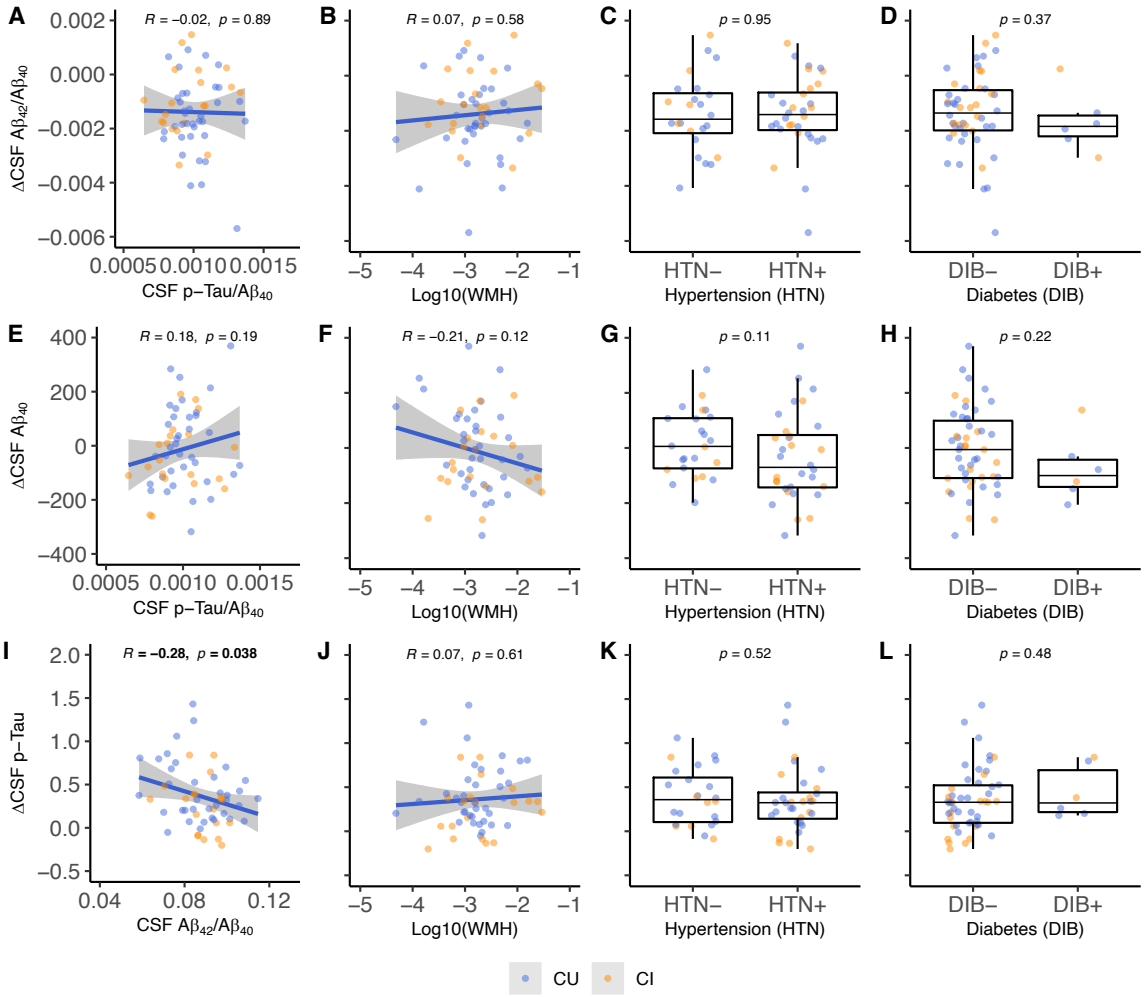
The associations of age, vascular disease and CSF Aβ$_{40}$, CSF Aβ$_{42}$/Aβ$_{40}$ and CSF p-Tau/Aβ$_{40}$



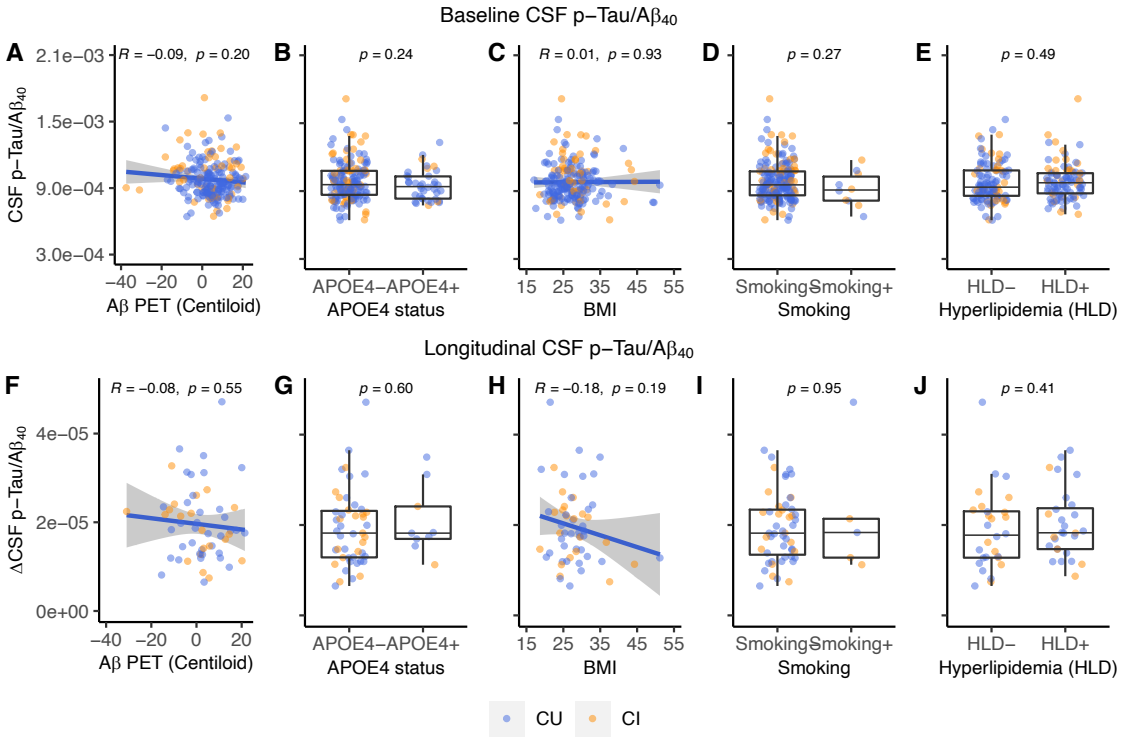
Supplemental fig. 2. *(A). Associations of baseline CSF p-Tau/Aβ$_{40}$ with age, white matter hyperintensities (WMH), hypertension (HTN), sex and diagnosis in one model. (B). Associations of longitudinal CSF p-Tau/Aβ$_{40}$ changes (ΔCSF p-Tau/Aβ$_{40}$) with CSF Aβ$_{42}$/Aβ$_{40}$, WMH, HTN and diagnosis in one model.*



Supplemental fig. 3. *The association of age, sex, WMH and HTN with (A-D) CSF Aβ$_{42}$/Aβ$_{40}$, (E-H) CSF Aβ$_{40}$ and (I-L) CSF p-Tau alone in Aβ- individuals.*

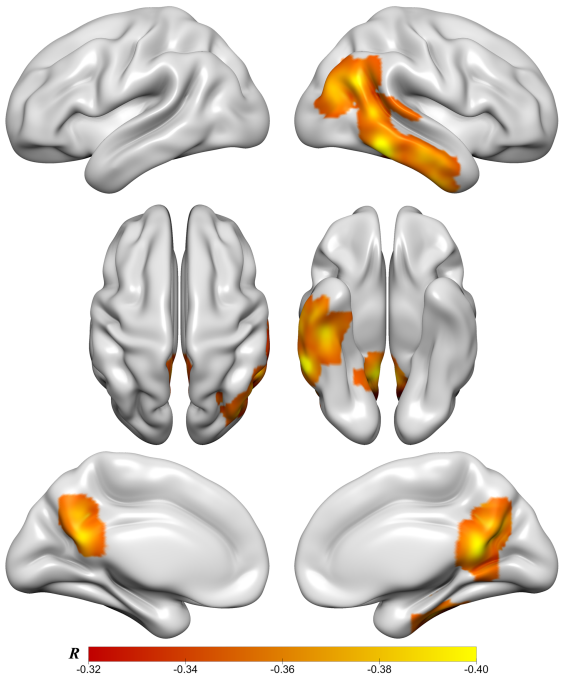


Supplemental fig. 4. *The association of age, sex, WMH and HTN with (A-D) ΔCSF $Aβ_{42}/Aβ_{40}$, (E-H) ΔCSF $Aβ_{40}$ and (I-L) ΔCSF p-Tau alone in Aβ- individuals.*

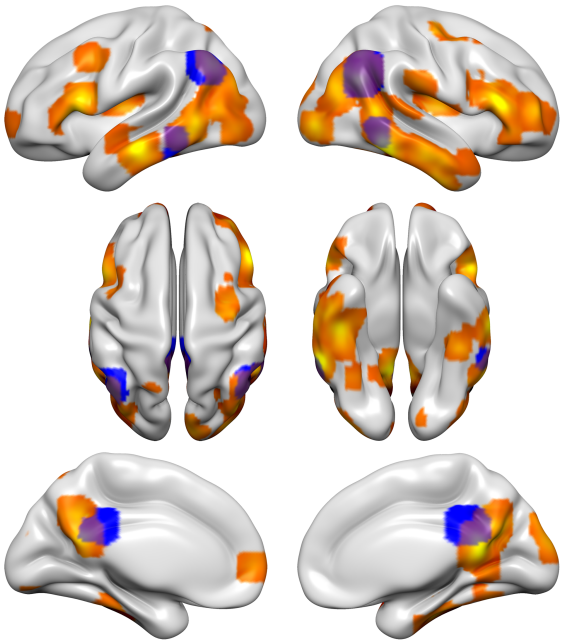


Supplemental fig. 5. Risk factors not related to CSF p-Tau/Aβ$_{40}$ increase in Aβ- individuals.

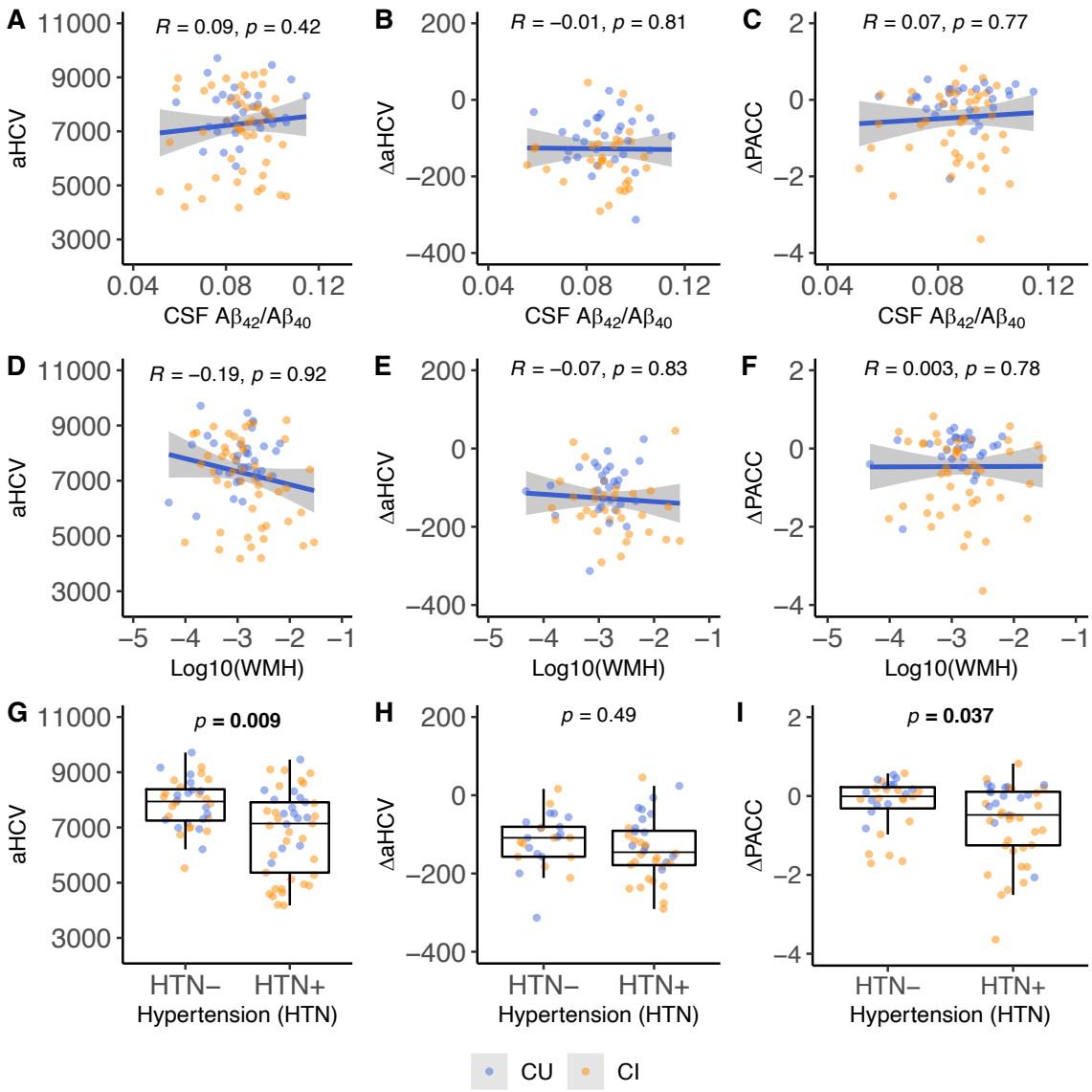
The associations of risk factors with (A-E) baseline CSF p-Tau/Aβ$_{40}$ and (F-J) longitudinal CSF p-Tau/Aβ$_{40}$ changes (ΔCSF p-Tau/Aβ$_{40}$).



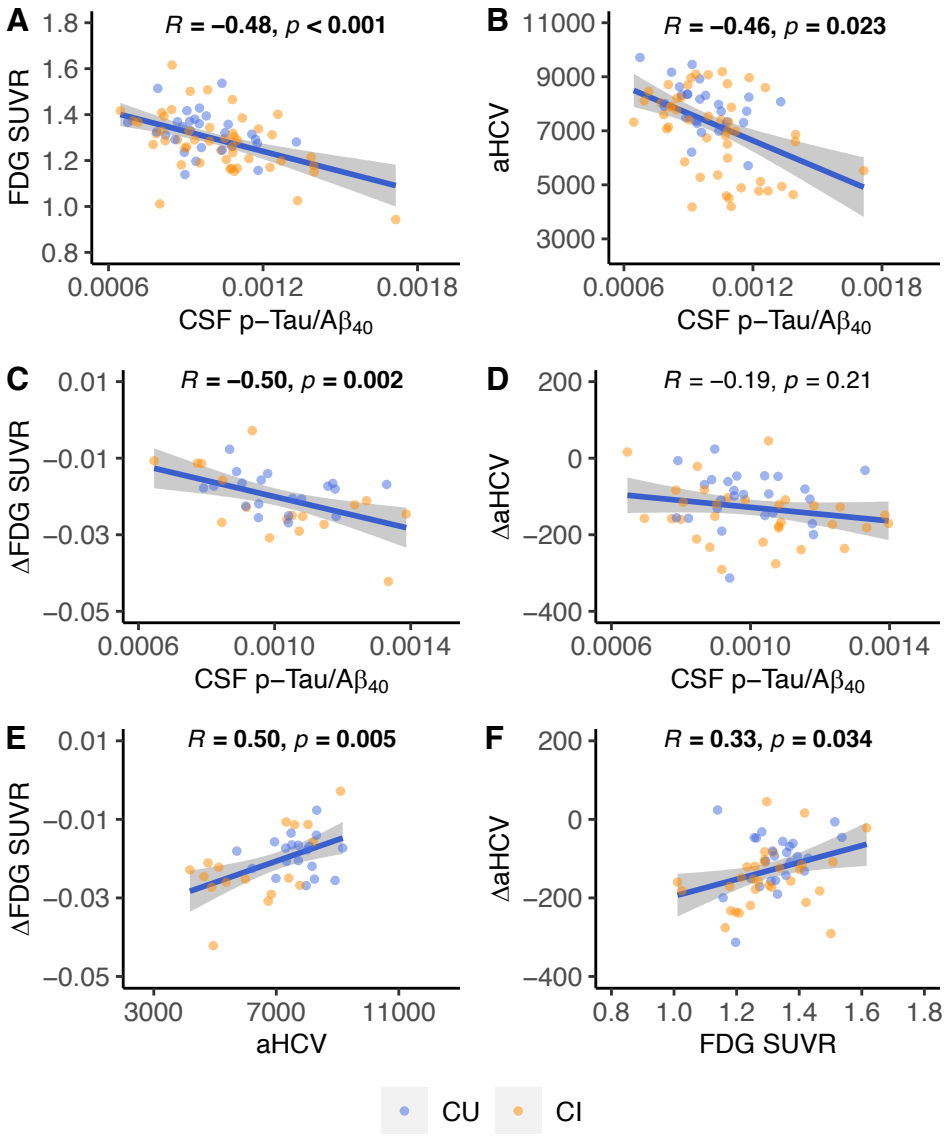
Supplemental fig. 6. *Voxel-wise correlation between CSF p-Tau/Aβ$_{40}$ and FDG PET with family-wise error (FWE) corrected p < 0.05 at cluster level.*



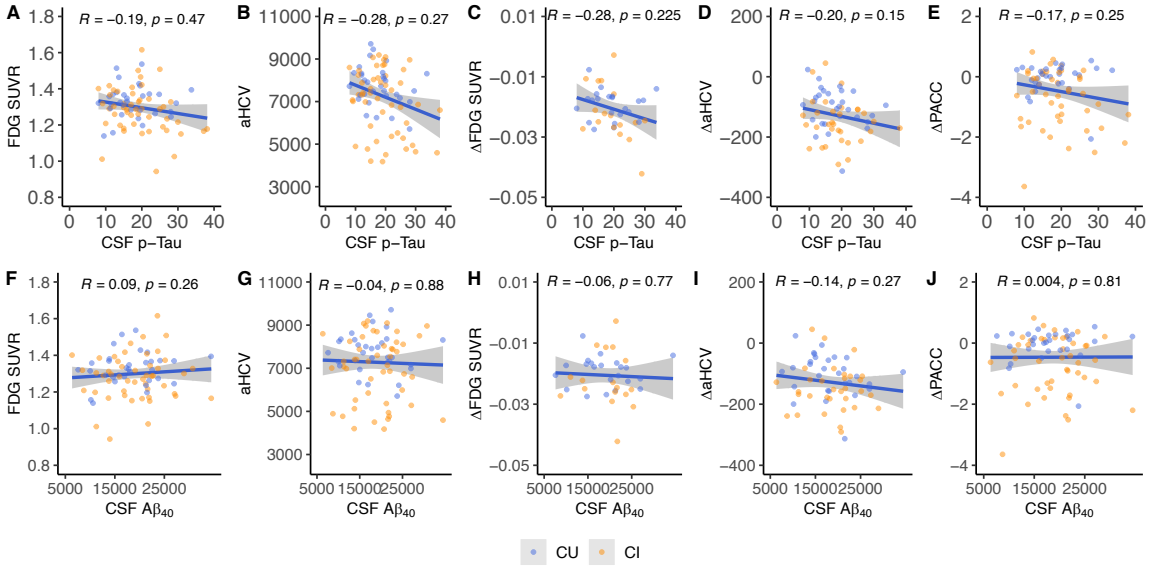
Supplemental fig. 7. *Overlap (purple) of significant brain regions (red-yellow) between FDG SUVR and CSF p-Tau/Aβ$_{40}$ with Alzheimer's metaROI (left angular gyrus, right angular gyrus, bilateral posterior cingulate, left inferior temporal gyrus, right inferior temporal gyrus) region (blue)of hypometabolism.*



Supplemental fig. 8. *Associations of $A\beta_{42}/A\beta_{40}$, White Matter Hypertension (WMH), Hypertension (HTN), adjusted hippocampal volume (aHCV) and PACC Slope (ΔPACC).*



Supplemental fig. 9. Associations of elevated tau, hypometabolism and hippocampal atrophy in Aβ- individuals after excluding Aβ status converters. *Cross-sectional associations between CSF p-Tau/Aβ$_{40}$, and (A) FDG SUVR (metaROIs) and (B)aHCV. Prediction of ΔFDG SUVR by baseline (C) CSF p-Tau/Aβ$_{40}$, and (E) aHCV. Prediction of ΔaHCV by baseline (D) CSF p-Tau/Aβ$_{40}$, and (F) FDG SUVR (metaROIs).*



Supplemental fig. 10. Associations of CSF p-Tau alone, CSF Aβ$_{40}$, hypometabolism, hippocampal atrophy and cognitive decline in Aβ- individuals. *Cross-sectional associations between CSF p-Tau, and (A) FDG SUVR (metaROIs) and (B)aHCV. Prediction of (C) ΔFDG SUVR (metaROIs), (D) ΔaHCV and (E) ΔPACC by baseline CSF p-Tau. Cross-sectional associations between CSF Aβ$_{40}$, and (F) FDG SUVR (metaROIs) and (G)aHCV. Prediction of (H) ΔFDG SUVR (metaROIs), (I) ΔaHCV and (J) ΔPACC by baseline CSF Aβ$_{40}$.*