Supplementary Material

Cerebrospinal Fluid Biomarkers in Cerebral Amyloid Angiopathy

SUPPLEMENTARY RESULTS

Aβ ratios

$A\beta_{42}:A\beta_{40}$ ratio

There was a significant difference between the three groups (Supplementary Table 1; Supplementary Figure 2A; p=0.0001). In post-hoc comparisons, patients with CAA had significantly lower CSF $A\beta_{42}:A\beta_{40}$ ratio than the CS group (corrected p=0.00003), but not the AD group (corrected p=0.06). Patients with AD had a lower $A\beta_{42}:A\beta_{40}$ ratio than the CS group (corrected p=0.0036). In age-adjusted quantile regression, there was a significant difference between the three groups (p=0.0003). Pairwise comparison of the medians found significant differences between CAA and CS groups, and the AD and CS groups. The difference between the CAA and AD groups did not reach statistical significance.

$A\beta_{40}: A\beta_{38}$ ratio

There was a significant difference between the three groups (Supplementary Table 1; Supplementary Figure 2B; p=0.0001). In post-hoc comparisons, patients with CAA had significantly lower CSF $A\beta_{40}:A\beta_{38}$ ratio than the AD group (corrected p=0.0039), but not the CS group (corrected p=0.22). There was no significant difference between the AD and CS groups (corrected p=0.28). In age-adjusted quantile regression, there was no significant difference between the three groups (p=0.77).

<u>Aβ$_{42}$: Aβ$_{38}$ ratio</u>

There was a significant difference between the three groups (Supplementary Table 1; Supplementary Figure 1C; p=0.0003). In post-hoc comparisons, patients with CAA had significantly lower CSF Aβ$_{42}$: Aβ$_{38}$ ratio than both the CS (corrected p=0.00003) and AD (corrected p=0.0273) groups. Patients with AD had a lower CSF Aβ$_{42}$: Aβ$_{38}$ ratio than the CS group (corrected p=0.0345). In age-adjusted quantile regression, there was as significant difference between the three groups (p=0.0013). Pairwise comparison of the medians found significant differences between CAA and CS groups and the AD and CS groups. The difference between the CAA and AD groups did not reach statistical significance.

Exploratory comparisons with amyloid-negative CAA group

Having performed post-hoc analyses comparing the CSF profiles of CAA patients with amyloid-PET positive and negative scans, we performed a further comparison, in which amyloid-PET negative CAA patients were compared with AD and CS groups. Comparisons between amyloid-PET negative CAA patients, the AD and CS groups were made using the Kruskal-Wallis and then Dunn's test for post-hoc comparisons (for group comparisons with p<0.05).

We found similar results to those identified in the full analysis (where comparisons were made with all CAA patients); patients with amyloid-PET negative CAA still had lower Aβ$_{38}$, Aβ$_{40}$, and Aβ$_{42}$ than both AD (Aβ$_{38}$ corrected p=0.0021, Aβ$_{40}$ corrected p=0.0015, Aβ$_{42}$ corrected p=0.0138) and CS (Aβ$_{38}$ corrected p=0.0036, Aβ$_{40}$ corrected p=0.0036, Aβ$_{42}$ corrected p=0.0003) groups, with no statistically significant differences between the AD and CS groups for

all three markers. There were no significant differences in sAβPPα and sAβPPβ between the three groups, and the results for t-tau, p-tau, NFL, and sTREM2 were similar to those identified in the original analyses. However, in contrast to the original analysis, neurogranin in amyloid-PET negative CAA was significantly lower than the AD group (corrected p=0.0036). Comparison of Aβ ratios found similar results (i.e., statistically significant reductions in $A\beta_{42}$: $A\beta_{40}$ and $A\beta_{42}$: $A\beta_{38}$ ratios for the CAA and AD groups compared with the CS group) to the original analysis.

Supplementary Table 1. Univariable and age-adjusted quantile regression for Aβ ratios. Univariable p-values are from Kruskal-Wallis tests.

Ratio	Group	Univariable comparison		Age-adjusted quantile regression		
		Median (IQR)	p	β (SE)	Predicted median, (95% CI)	p
$A\beta_{42}$: $A\beta_{40}$ ratio	CAA	0.032 (0.028 to 0.042)		*Reference group*	0.034 (0.019 to 0.048)	
	AD	0.049 (0.040 to 0.055)	0.0001	0.015 (0.01)	0.049 (0.040 to 0.058)	0.0003
	CS	0.076 (0.068 to 0.110)		0.043 (0.01)	0.077 (0.064 to 0.090)	
$A\beta_{40}$: $A\beta_{38}$ ratio	CAA	2.069 (1.777 to 2.209)		*Reference group*	2.201 (1.994 to 2.408)	
	AD	2.375 (2.174 to 2.477)	0.0104	0.095 (0.13)	2.295 (2.164 to 2.427)	0.7714
	CS	2.312 (2.020 to 2.393)		0.066 (0.15)	2.267 (2.083 to 2.451)	
$A\beta_{42}$: $A\beta_{38}$ ratio	CAA	0.068 (0.050 to 0.095)		*Reference group*	0.086 (0.046 to 0.126)	
	AD	0.114 (0.091 to 0.138)	0.0003	0.025 (0.03)	0.112 (0.086 to 0.137)	0.0013
	CS	0.181 (0.130 to 0.268)		0.101 (0.03)	0.187 (0.152 to 0.223)	

Supplementary Figure 1. Scatter plots of each biomarker by age.

A) Aβ38

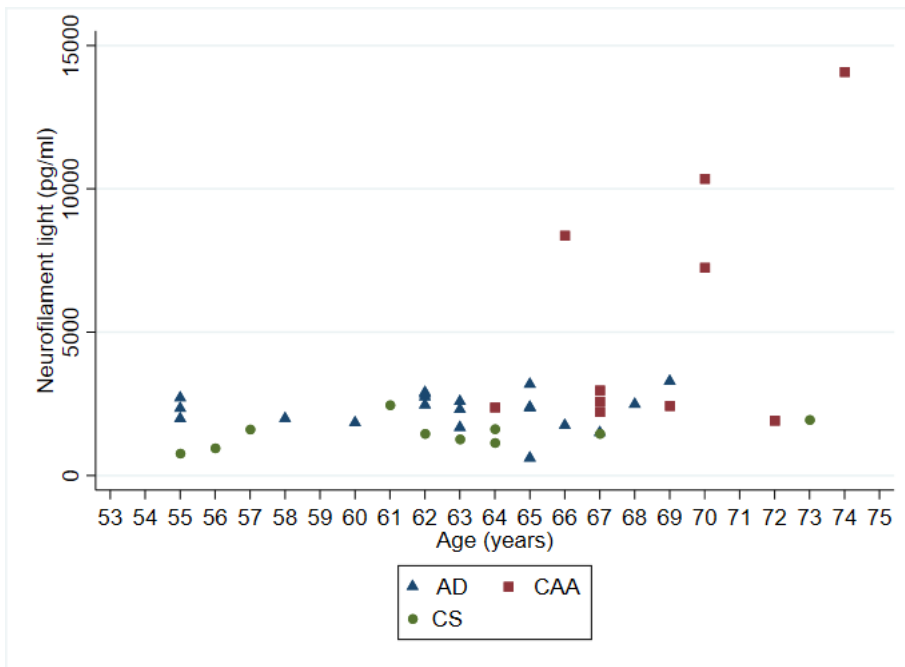**B) Aβ40**

C) Aβ₄₂

D) sAβPPα

E) sAβPPβ
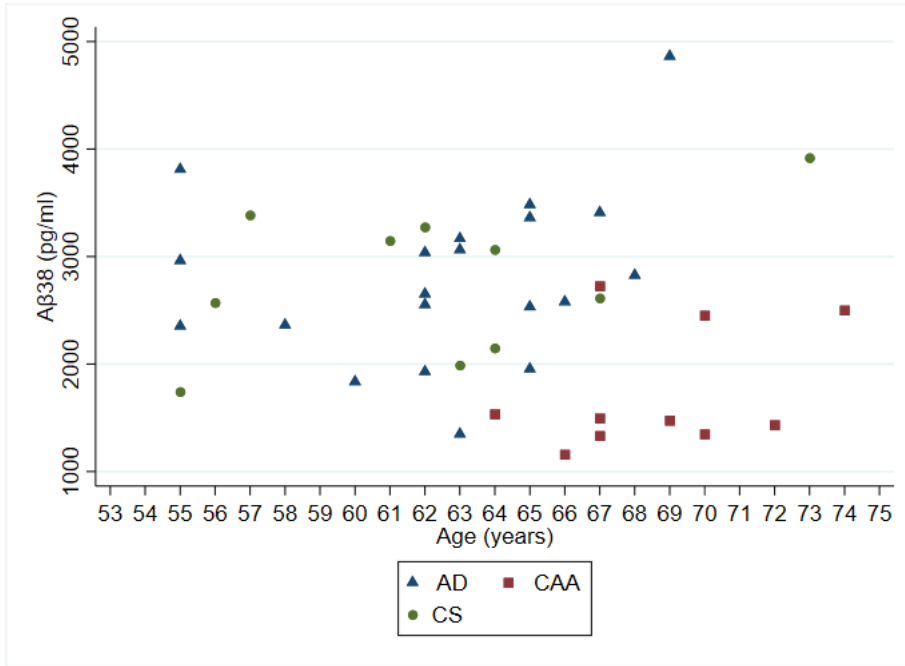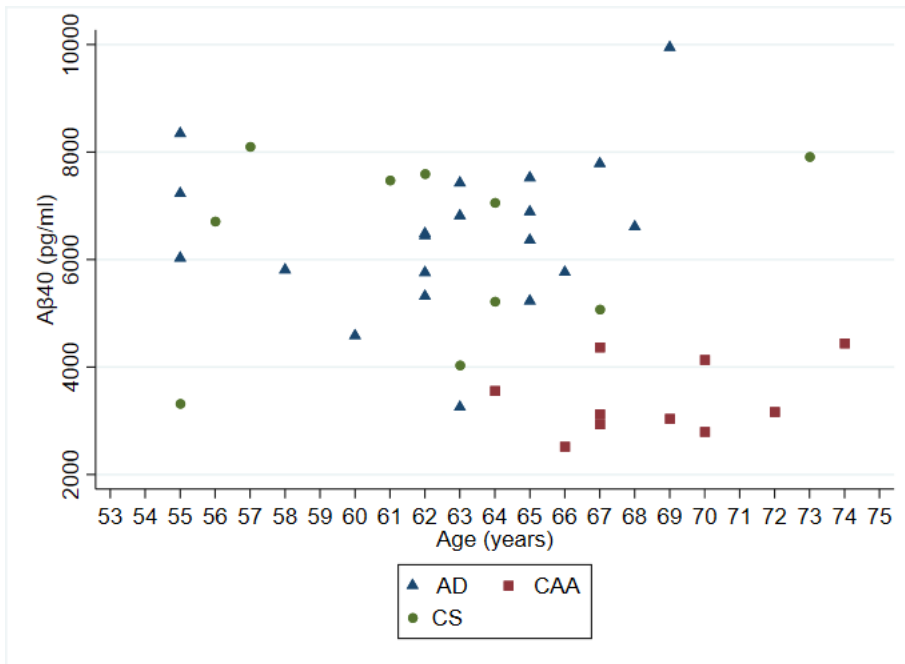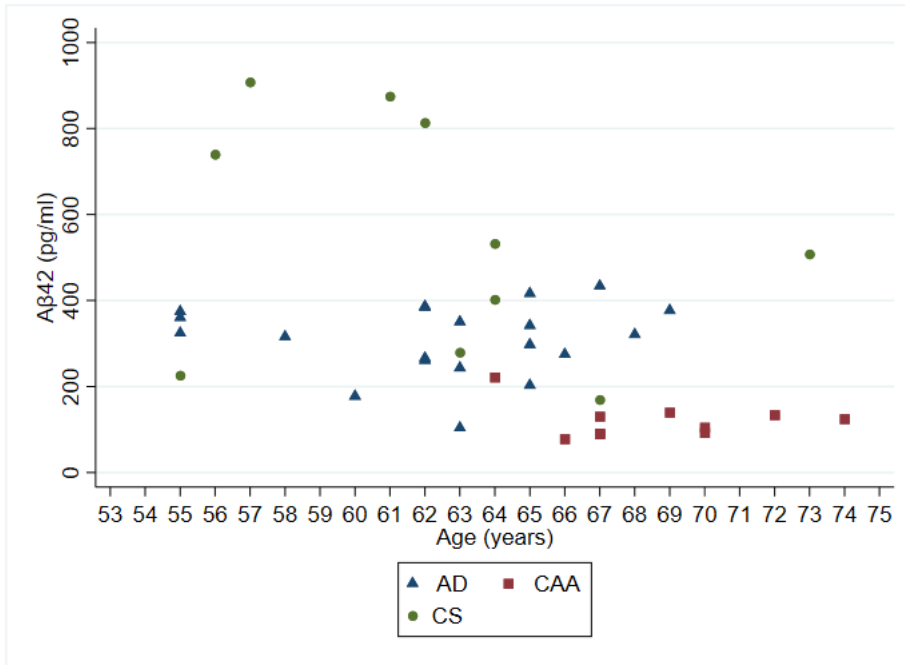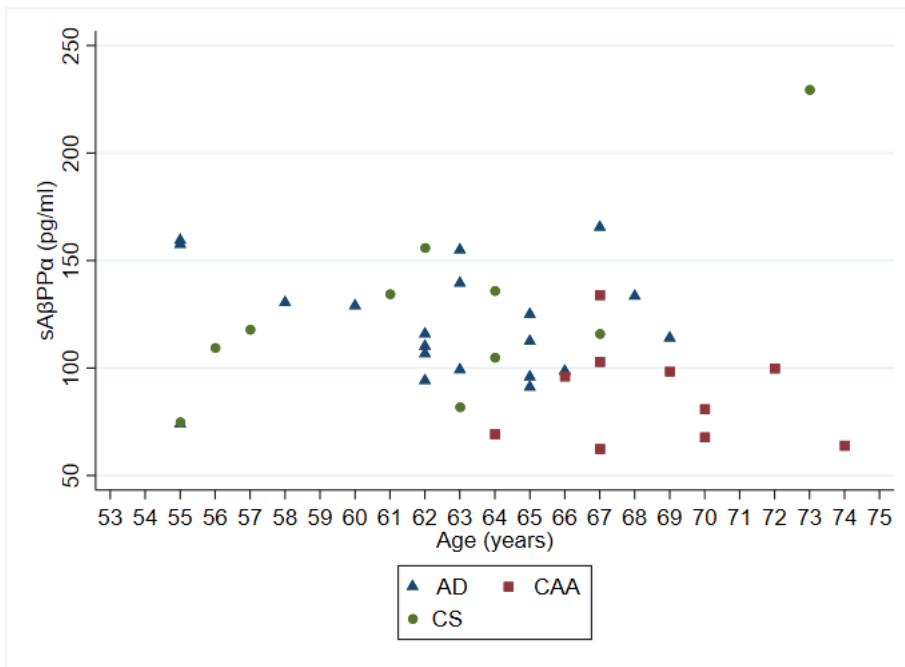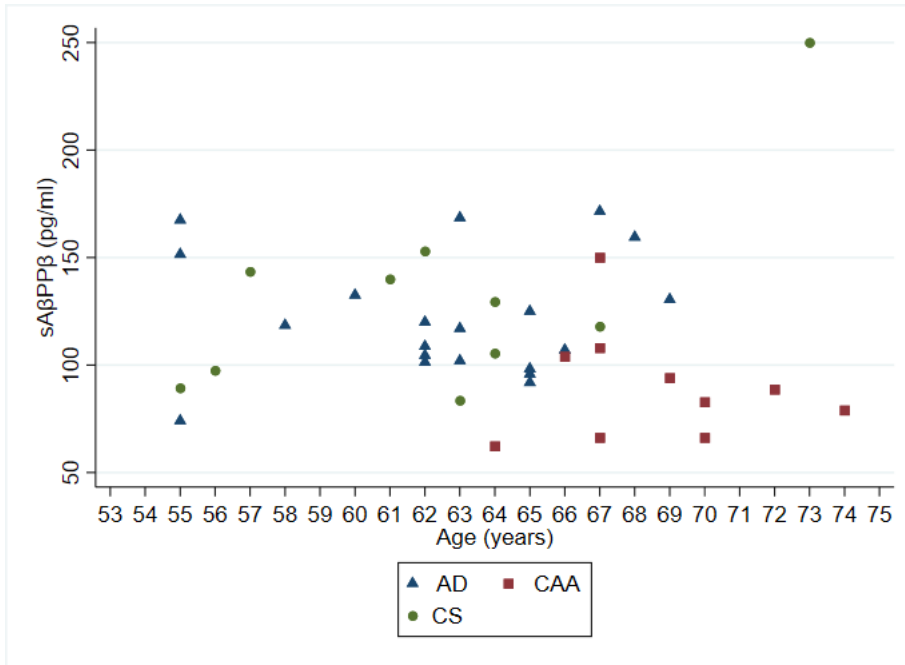
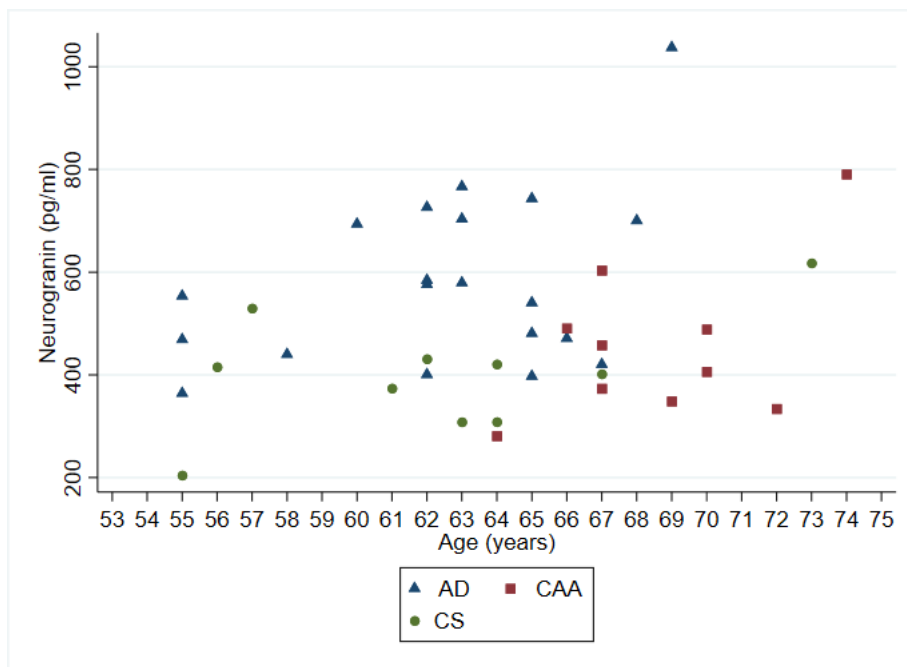**F) Total tau**
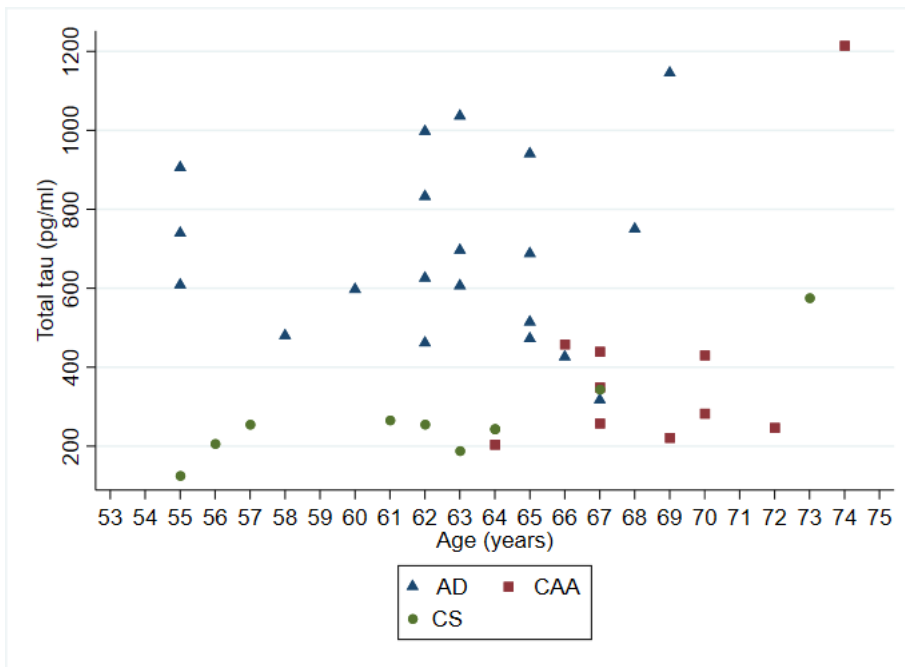
G) Phospho-tau
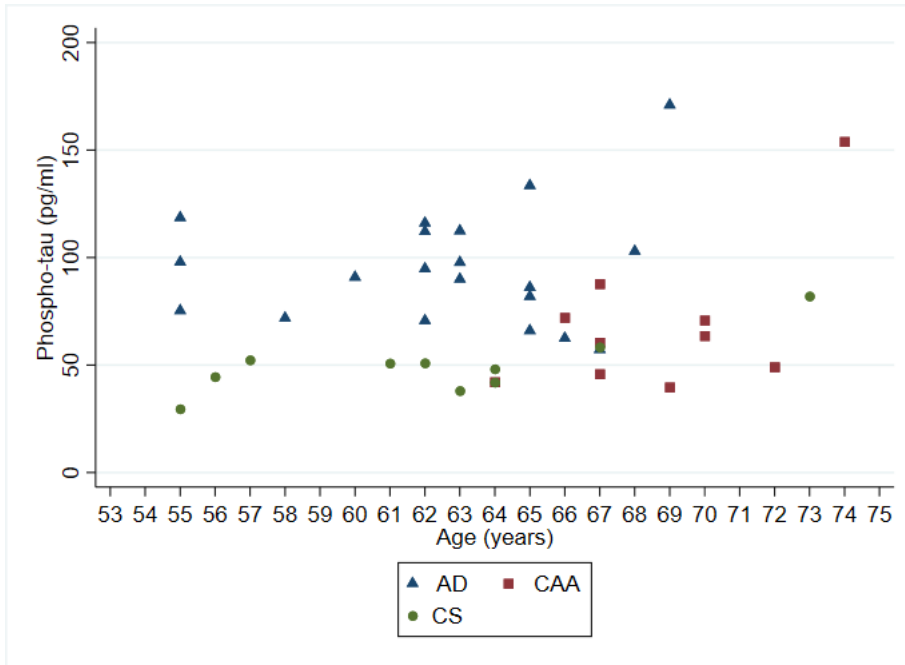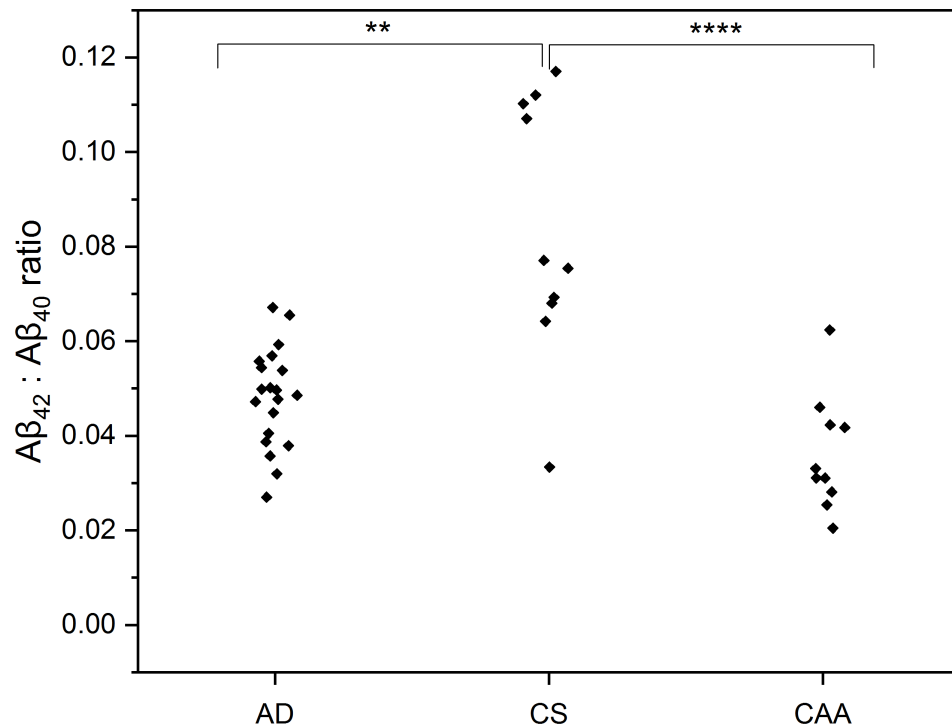

H) Neurofilament light
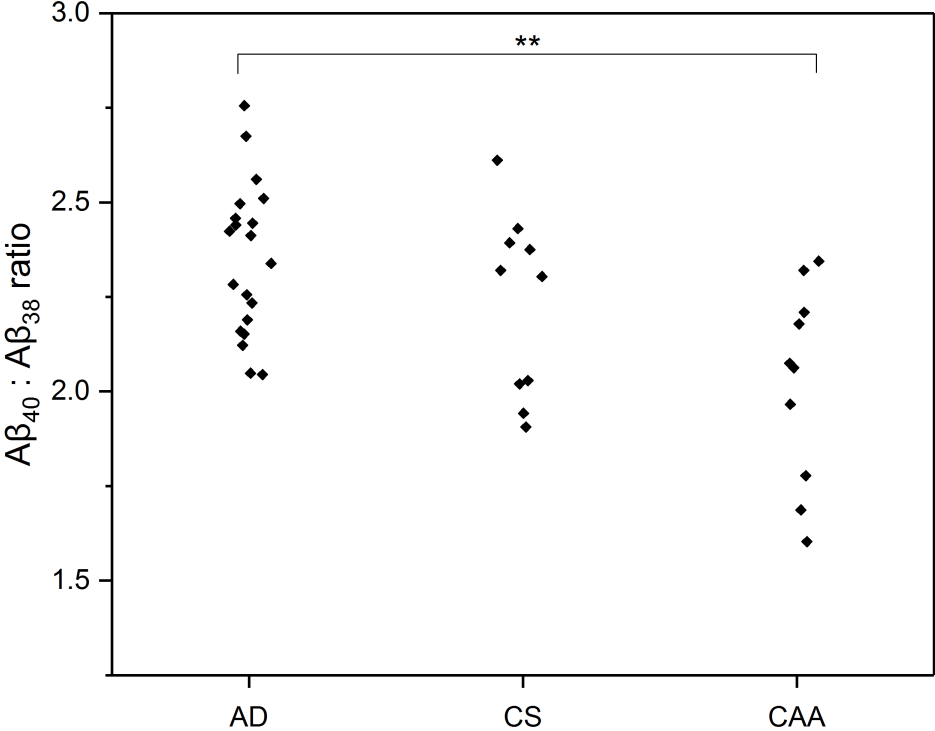
I) sTREM2
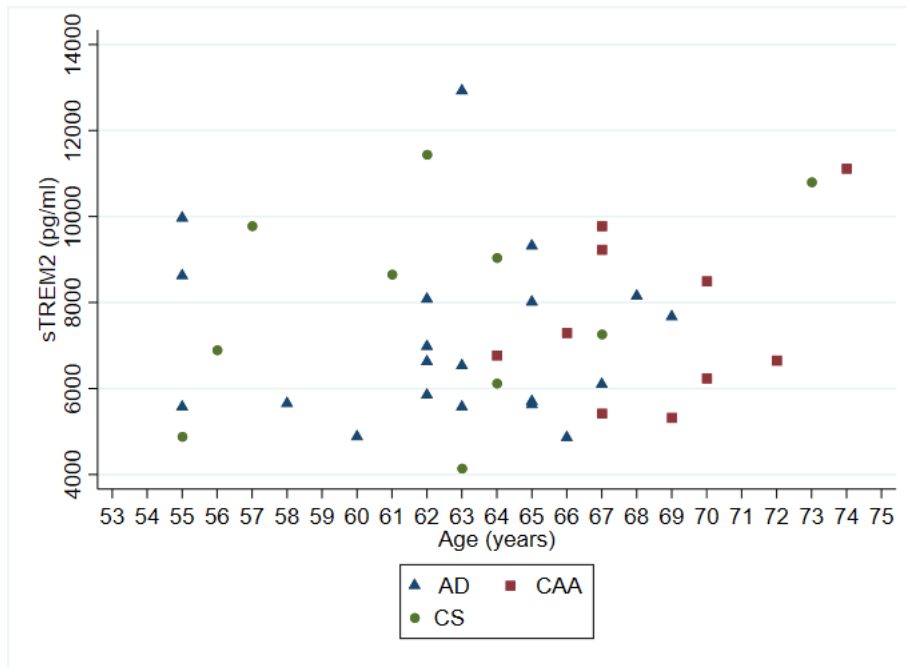
J) Neurogranin

Supplementary Figure 2. Comparison of Aβ ratios in AD, CAA, and control participant (CS) groups. Each diamond indicates an individual data point. p values are derived from post-hoc Dunn's test and have been Bonferroni-corrected. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$

A) Aβ$_{42}$: Aβ$_{40}$ ratio

B) Aβ$_{40}$: Aβ$_{38}$ ratio

C) Aβ$_{42}$: Aβ$_{38}$ ratio
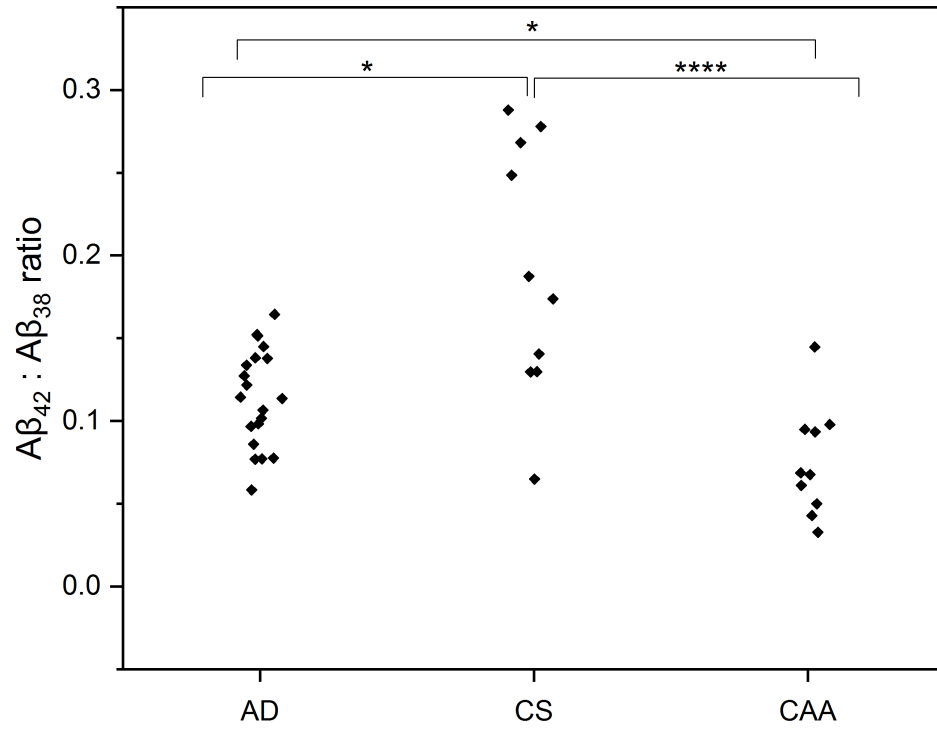
Supplementary Figure 3. Comparison of CSF biomarker profiles in PET positive and negative patients with CAA. Horizontal line indicates median value per group. Each diamond indicates an individual data point.
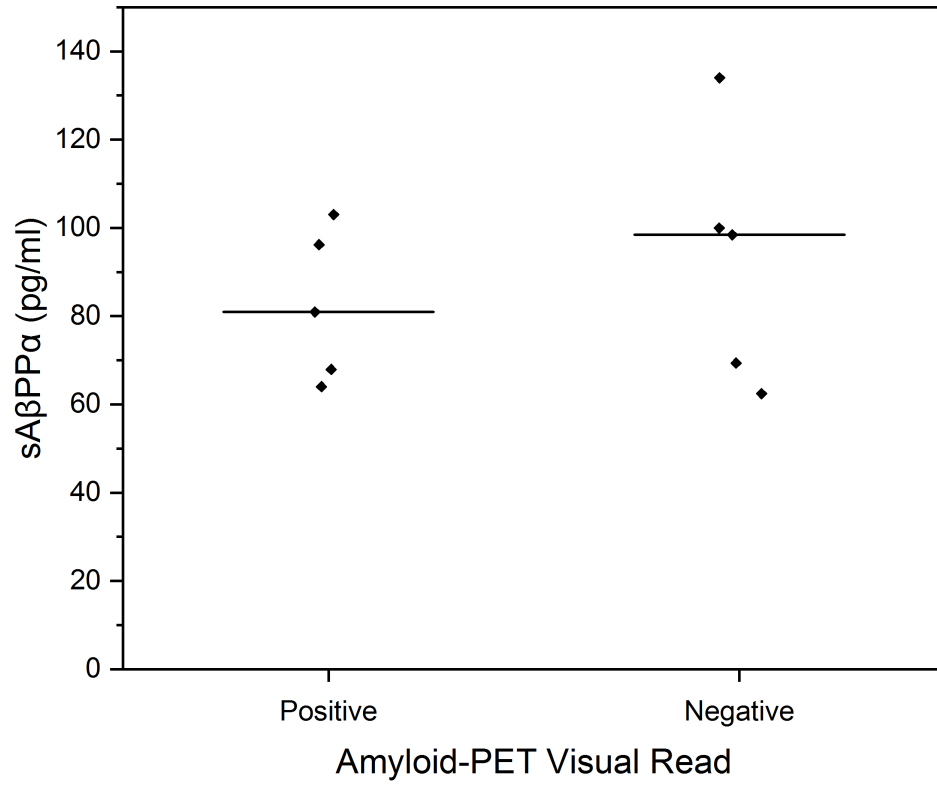
A) Aβ38

B) Aβ₄₀
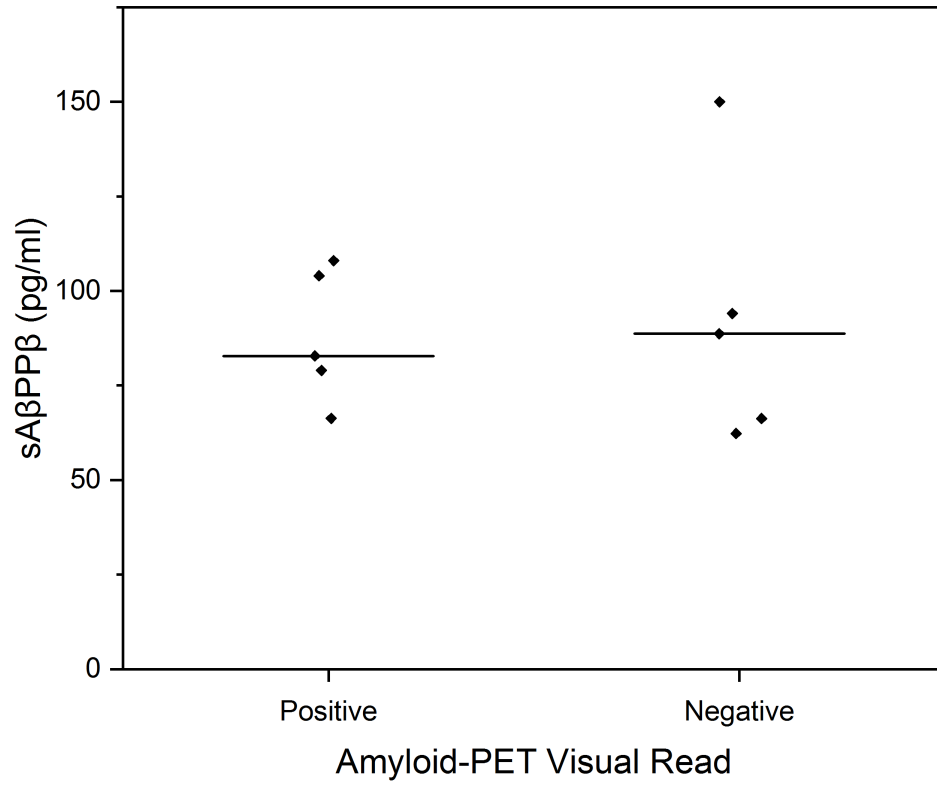
C) Aβ$_{42}$

D) sAβPPα

E) sAβPPβ
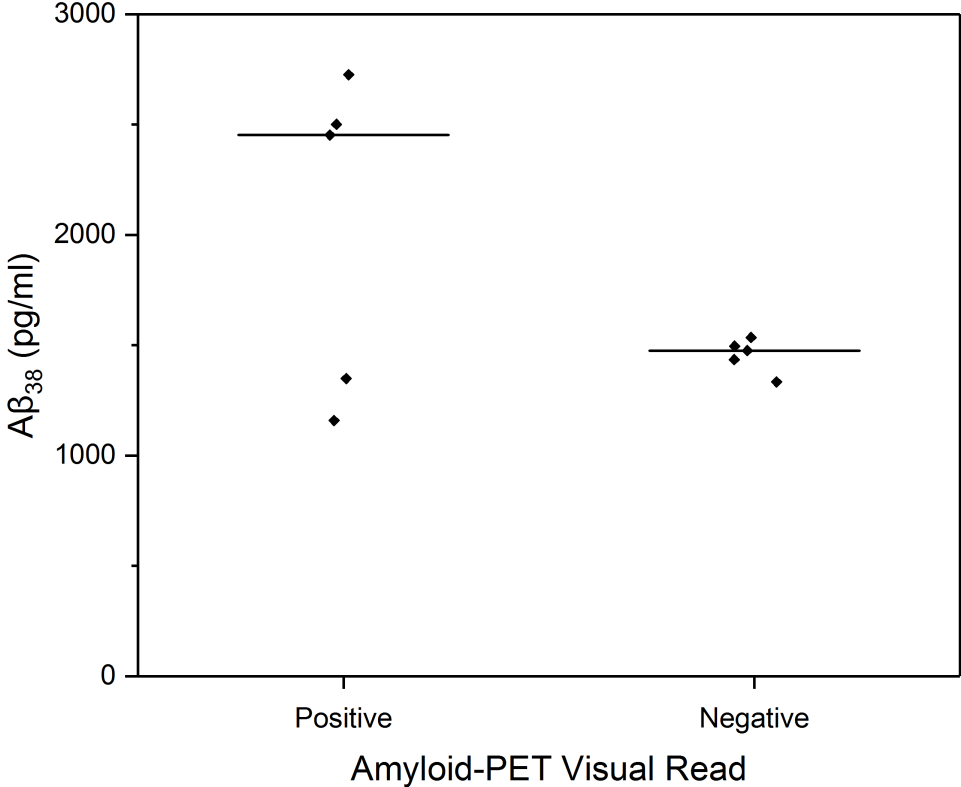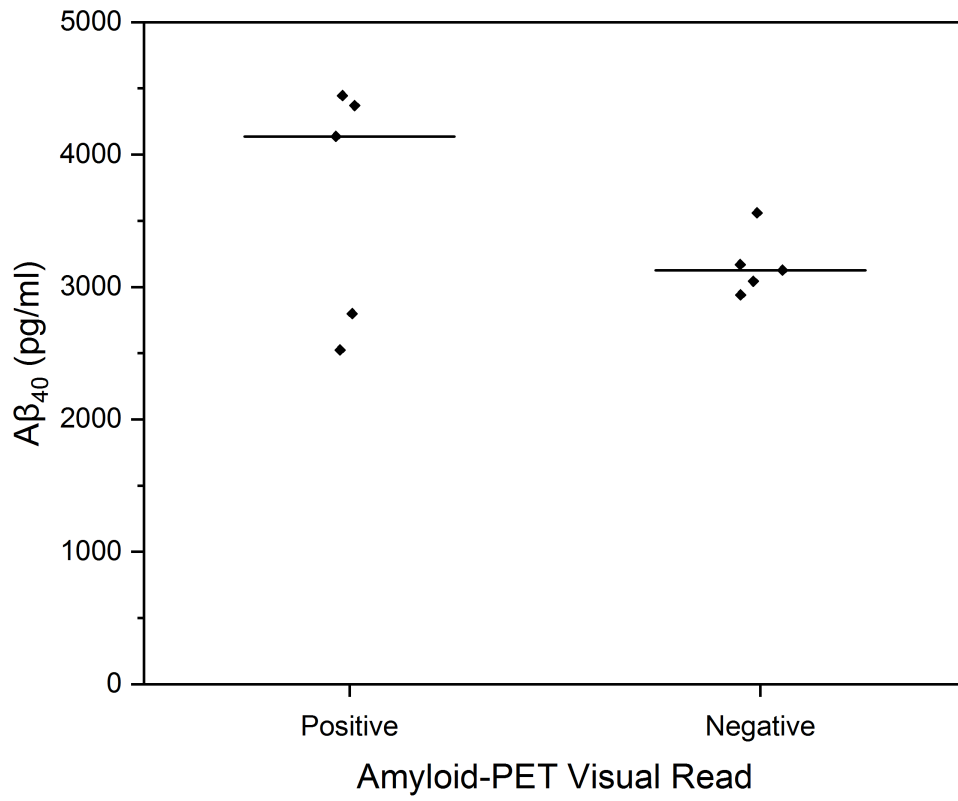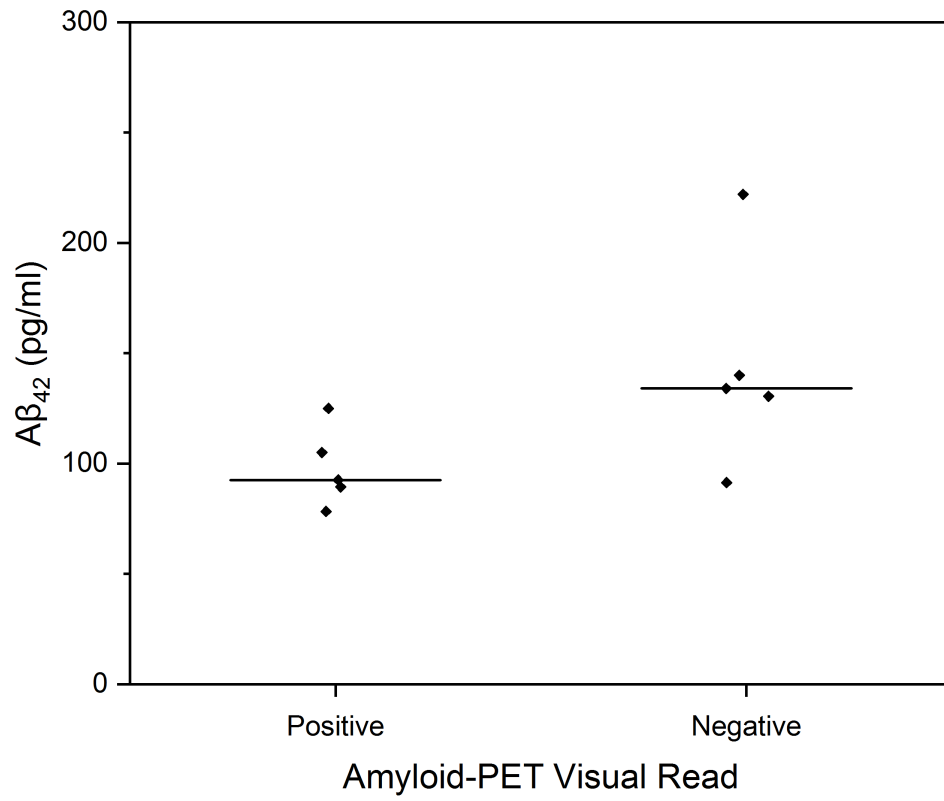
F) t-tau
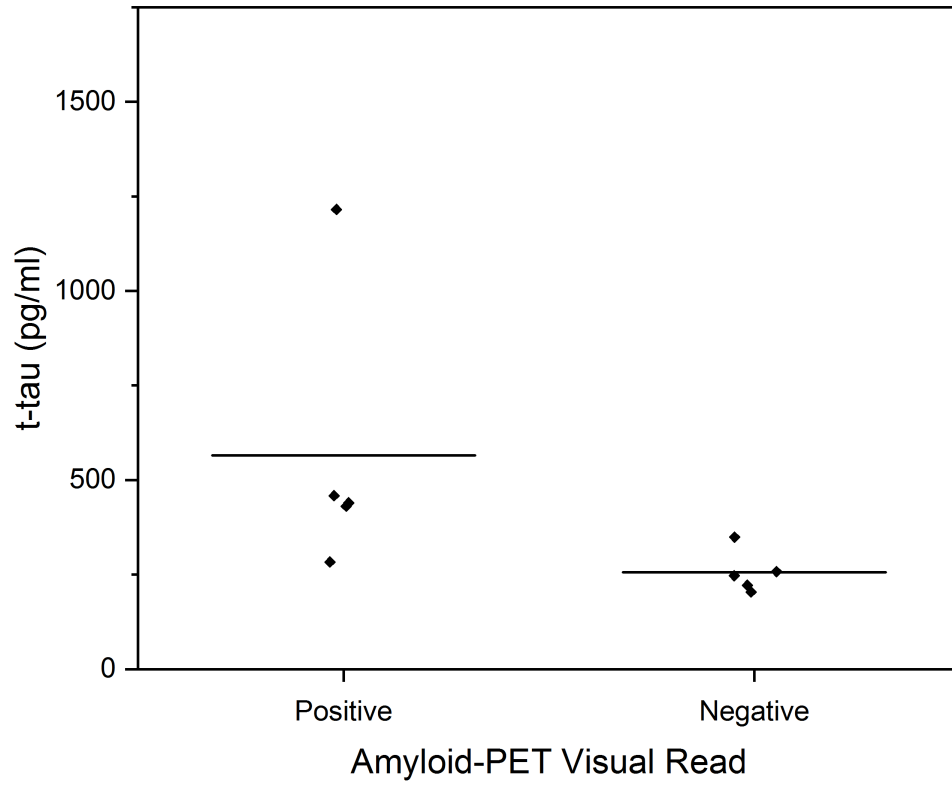
G) p-tau

H) NFL

I) sTREM2

J) Neurogranin