

The effect of α -synuclein and cerebral amyloid angiopathy on the associations between AD-related plasma biomarkers and postmortem AD pathology

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BACKGROUND

- P-tau217, A β 42/40, GFAP, and NfL are increasingly used in the context of Alzheimer's disease diagnosis, but most validation comes from clinically "pure" cohorts.
- Real-world memory-clinic and autopsy populations carry frequent co-pathologies^{1, 2} and these may alter how plasma biomarkers relate to underlying AD pathology.

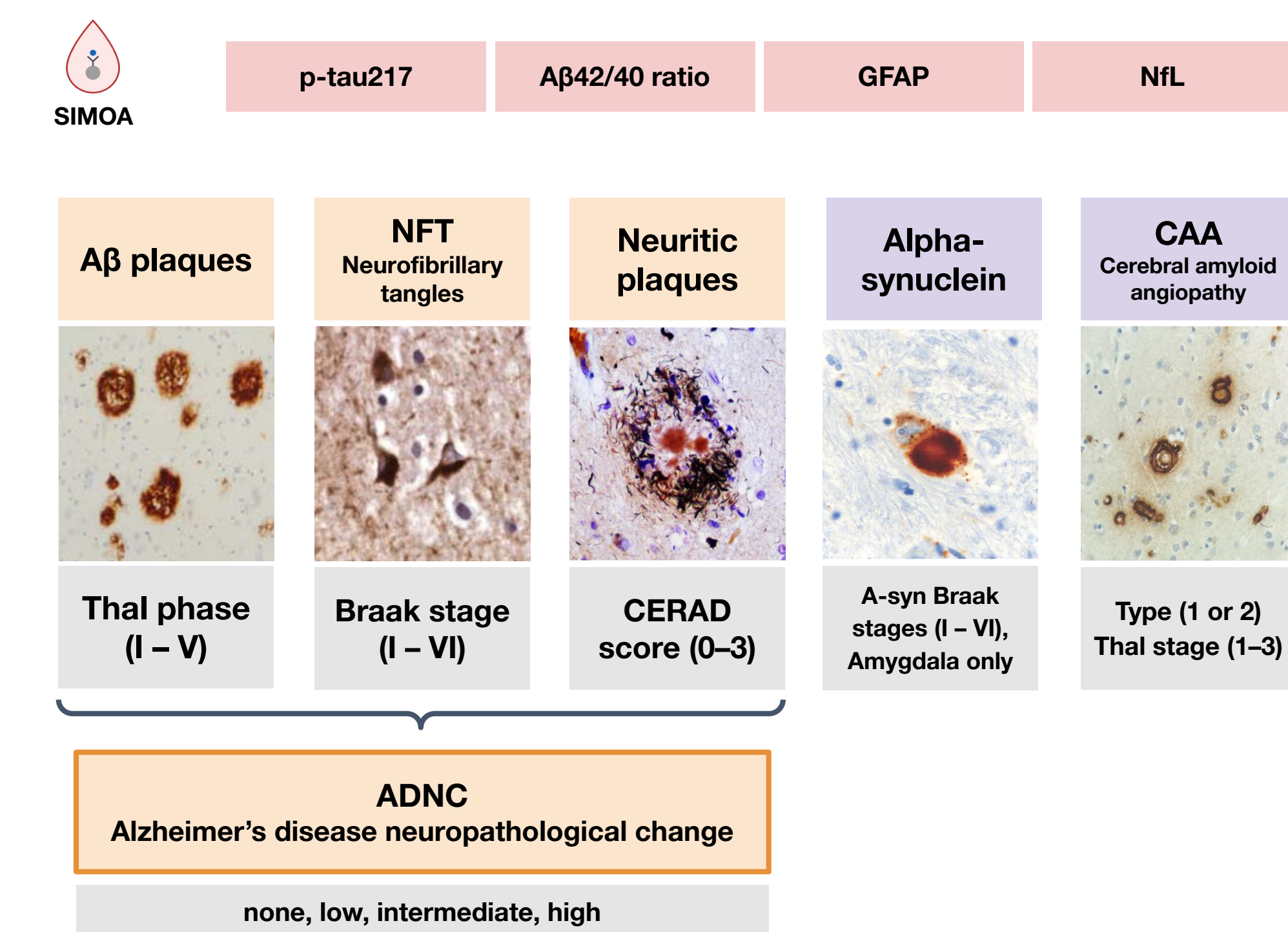
AIM

Do CAA and α -synuclein pathologies change the associations between postmortem AD neuropathology and AD plasma biomarker levels?

METHODS

Memory clinic population: Amsterdam Dementia Cohort with matching Netherlands Brain Bank report

Pathological diagnosis	AD	LBD	4R Tauopathies*	FTLD-TDP	Other†
Total, n=98	45	17	13	11	12
Age at death, median [IQR]	68 [65–74]	74 [68–80]	73 [68–79]	70 [67–72]	69 [62–73]
Female, n (%)	13 (29%)	1 (6%)	6 (46%)	4 (36%)	3 (25%)
Time blood collection to death, yrs, median [IQR]	5.0 [3.4–8]	4.6 [3.5–6.8]	5.9 [2.6–6.8]	4.0 [2.8–6.5]	4.6 [2.6–7.6]



Linear regression (Fig. 3)

Does [plasma biomarker] track [AD pathology stage] independently of co-existing [other pathology]?

Plasma biomarker	~	covariates	+	AD pathology stage	+	Other pathologies
p-tau217 A β 42/40 ratio GFAP NfL		Age Sex Blood-draw-to-death time		ADNC Thal phase (A β) Braak stage (NFT) CERAD (neuritic plaques)		CAA Thal stage Alpha-syn Braak stage or both

RESULTS

1 P-tau217 and GFAP distinguish AD from non-AD dementias

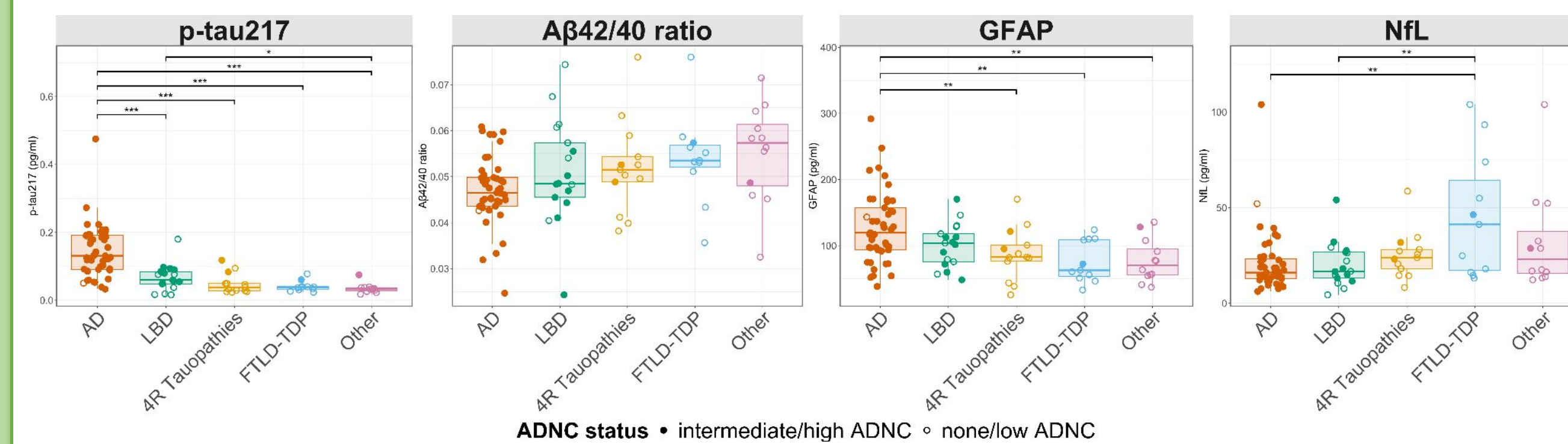


Fig 1. Plasma biomarkers by neuropathological diagnosis. Boxplots show median and IQR; each point is one participant, denoted by their ADNC level; BH-adjusted pairwise differences (covariate-adjusted for age, sex, and time blood collection to death ; *p<0.05, **p<0.01, ***p<0.001)

2 P-tau217, A β 42/40 and GFAP track AD neuropathologic change (ADNC score)

3 P-tau217, A β 42/40 and GFAP distinguish CAA presence (but not type) and track with CAA stage

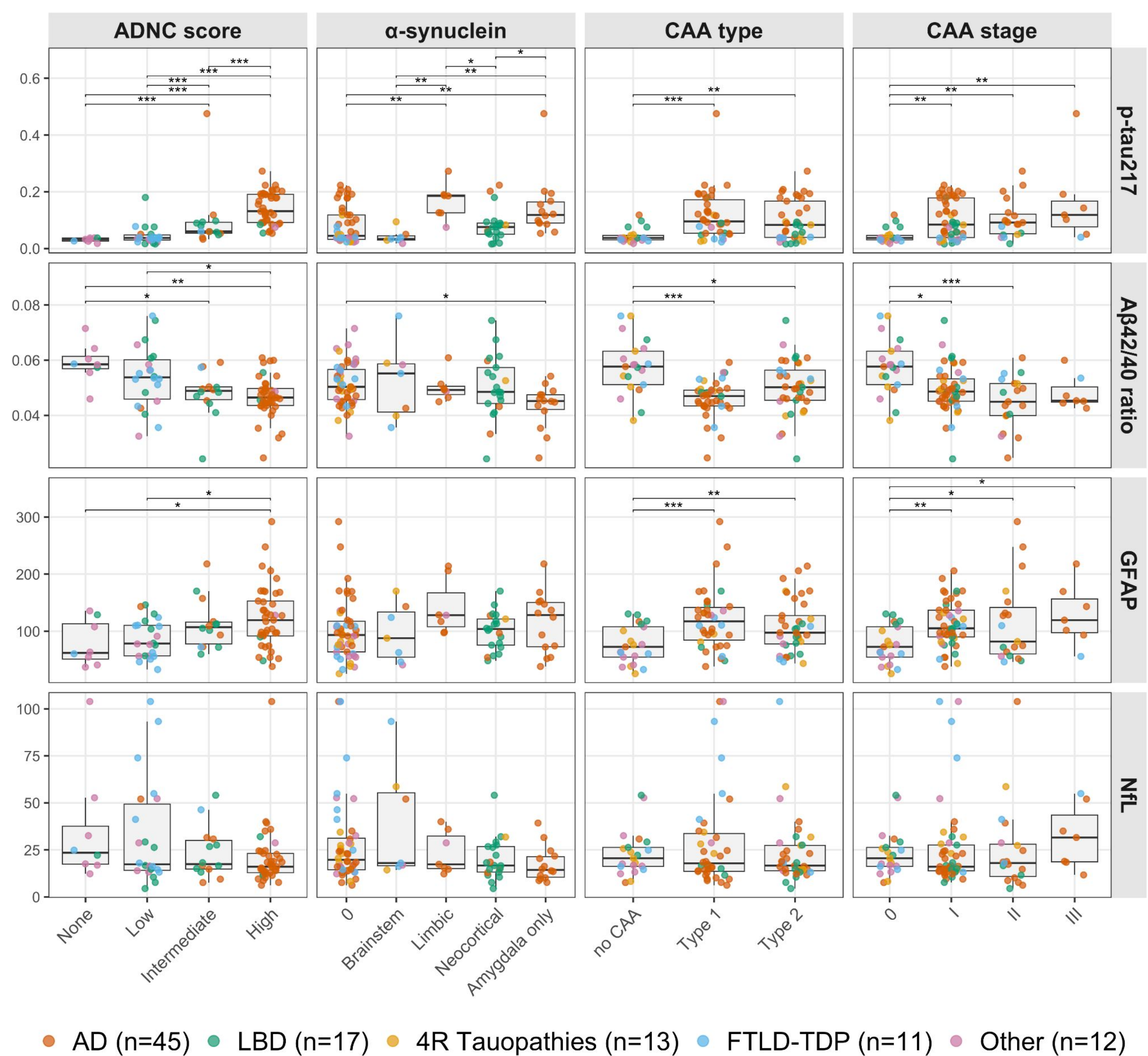


Fig 2. Plasma biomarkers across AD, α -synuclein and CAA neuropathology measures. Points coloured by diagnosis group. 4R-Tauopathy group excluded for ADNC score comparisons since AD-style tau-based staging is unreliable for group. BH-adjusted pairwise differences (covariate-adjusted for age, sex, and time blood collection to death ; *p<0.05, **p<0.01, ***p<0.001)

RESULTS

4 CAA and α -synuclein do not change p-tau217 or GFAP associations with ADNC

5 A β 42/40 additionally reflects CAA and α -synuclein co-pathology (when captured by A β Thal)

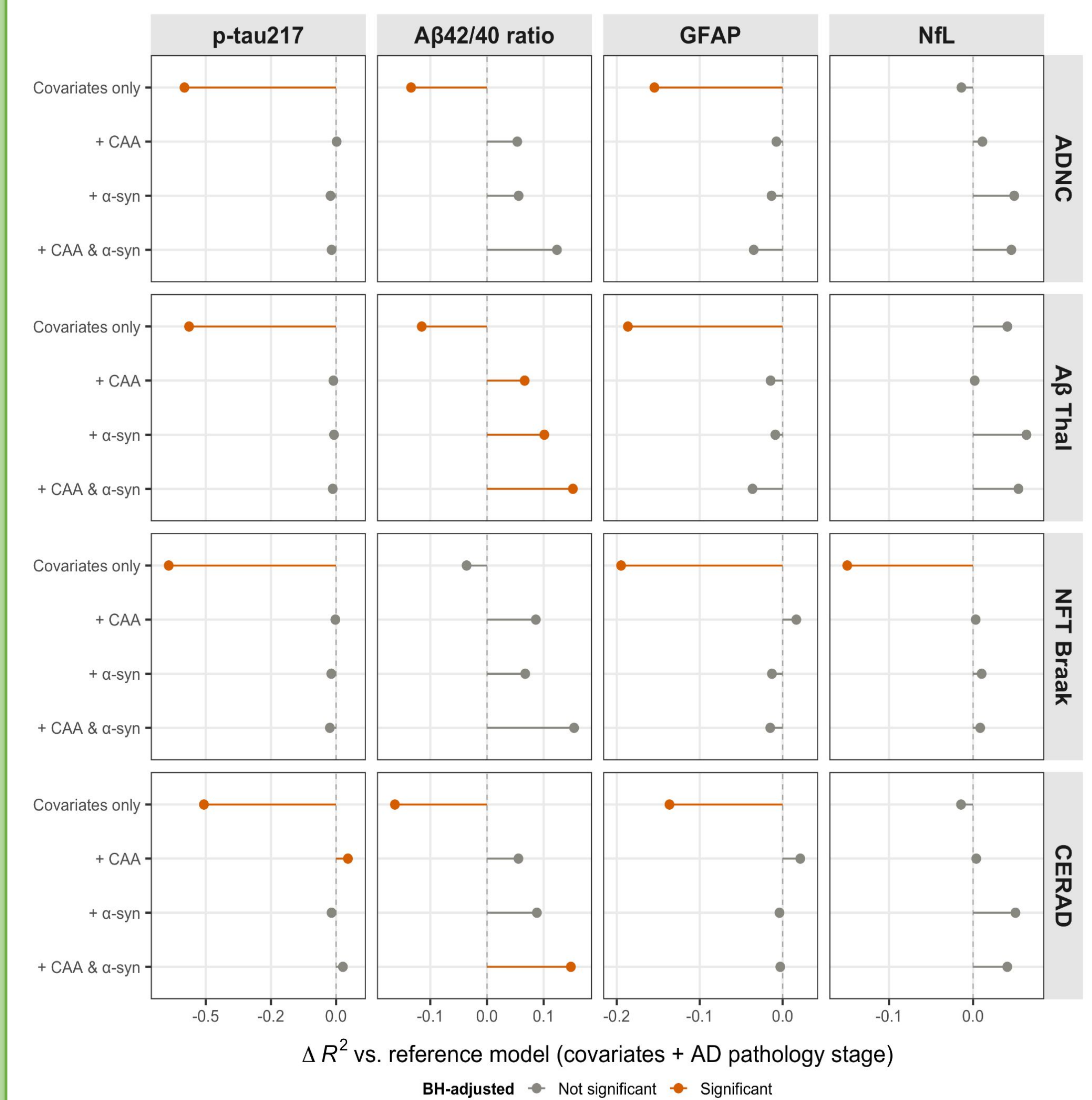


Fig 3. Incremental explained variance when adding α -synuclein and/or CAA co-pathology. Change in adjusted R^2 when adding CAA stage and/or α -synuclein stage to a reference model (demographic covariates + the AD-pathology measure), depicted as dashed line. n = 80; 4R-Tauopathy group excluded since AD-style tau-based staging is unreliable for group.

CONCLUSION

- P-tau217 and GFAP associations with AD neuropathology are robust to co-existing CAA and α -synuclein, supporting their interpretation even in mixed-pathology populations.
- A β 42/40 ratio additionally reflects co-existing vascular amyloid (CAA) and α -synuclein burden, so it should be interpreted with caution.
- NfL remains a nonspecific marker of axonal injury, showing no association with AD neuropathology, CAA or α -synuclein.