

1. Background

- Alzheimer's disease (AD) is typically characterized by amyloid- β ($A\beta$) plaques and neurofibrillary tau tangle buildup in the brain [1–3].
- Another common pathological markers observed in the aging brain is white matter hyperintensities (WMHs) [4].
- WMHs are hallmarks of cerebral small vessel disease (CSVD) and are also associated with an increased risk of cognitive decline and development of dementia [5–6].
- What remains less clear is whether cerebrovascular pathology occurs before, after, or concurrently with the progression of $A\beta$ and tau pathology, and whether these temporal relationships differ across brain regions.
- **OBJECTIVE:** This study investigated the temporal and regional associations between PET measures of $A\beta$ and tau pathology and WMH burden in older adults.

2. Methods

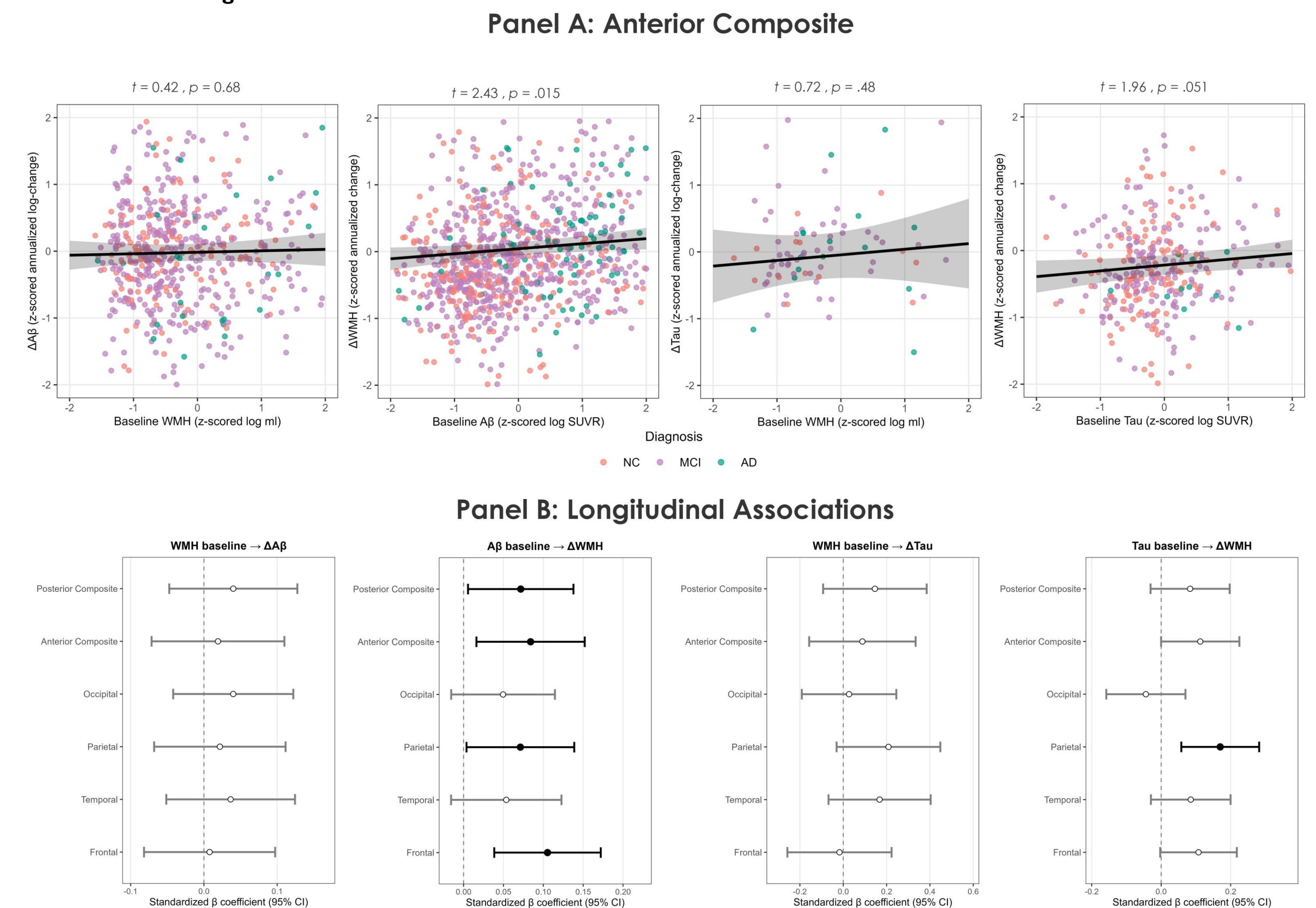
- Linear models were used to i) assess associations between baseline regional WMH and A β and tau pathology, and ii) examine whether baseline pathology in one measure was associated with change in the other measure over two years.

Table 1: Demographic and clinical characteristics for PET A β and Tau for baseline and longitudinal

Demographic Information	Baseline PET groups			Longitudinal Δ PET group compared to baseline WMH		Longitudinal Δ WMH group compared to baseline PET	
	<i>Aβ</i>	<i>Tau</i>	<i>Aβ+Tau</i>	<i>Aβ</i>	<i>Tau</i>	<i>Aβ</i>	<i>Tau</i>
N	1241	636	430	613	92	980	342
Age (baseline)	72.7 $\pm$ 7.1	71.4 $\pm$ 6.9	71.4 $\pm$ 6.8	71.9 $\pm$ 7.2	71.3 $\pm$ 7.3	72.9 $\pm$ 7.1	71.5 $\pm$ 6.8
Education	16.2 $\pm$ 2.7	16.5 $\pm$ 2.5	16.5 $\pm$ 2.6	16.5 $\pm$ 2.5	16.2 $\pm$ 2.3	16.3 $\pm$ 2.7	16.4 $\pm$ 2.6
Female Sex	588 (47.4%)	321 (50.5%)	213 (49.5%)	296 (48.3%)	51 (55.4%)	442 (45.1%)	156 (45.6%)
Diagnosis							
AD	162 (13.1%)	36 (5.7%)	17 (4.0%)	33 (5.4%)	21 (22.8%)	94 (9.6%)	12 (3.5%)
MCI	768 (61.9%)	402 (63.2%)	264 (61.4%)	423 (69.0%)	56 (60.9%)	615 (62.8%)	203 (59.4%)
NC	311 (25.1%)	198 (31.1%)	149 (34.7%)	157 (25.6%)	15 (16.3%)	271 (27.7%)	127 (37.1%)
APOE4							
0	698 (56.2%)	384 (60.4%)	267 (62.1%)	361 (58.9%)	42 (45.7%)	554 (56.5%)	218 (63.7%)
1	422 (34.0%)	194 (30.5%)	126 (29.3%)	205 (33.4%)	37 (40.2%)	342 (34.9%)	103 (30.1%)
2	106 (8.5%)	39 (6.1%)	37 (8.6%)	47 (7.7%)	13 (14.1%)	84 (8.6%)	21 (6.1%)

3. Results

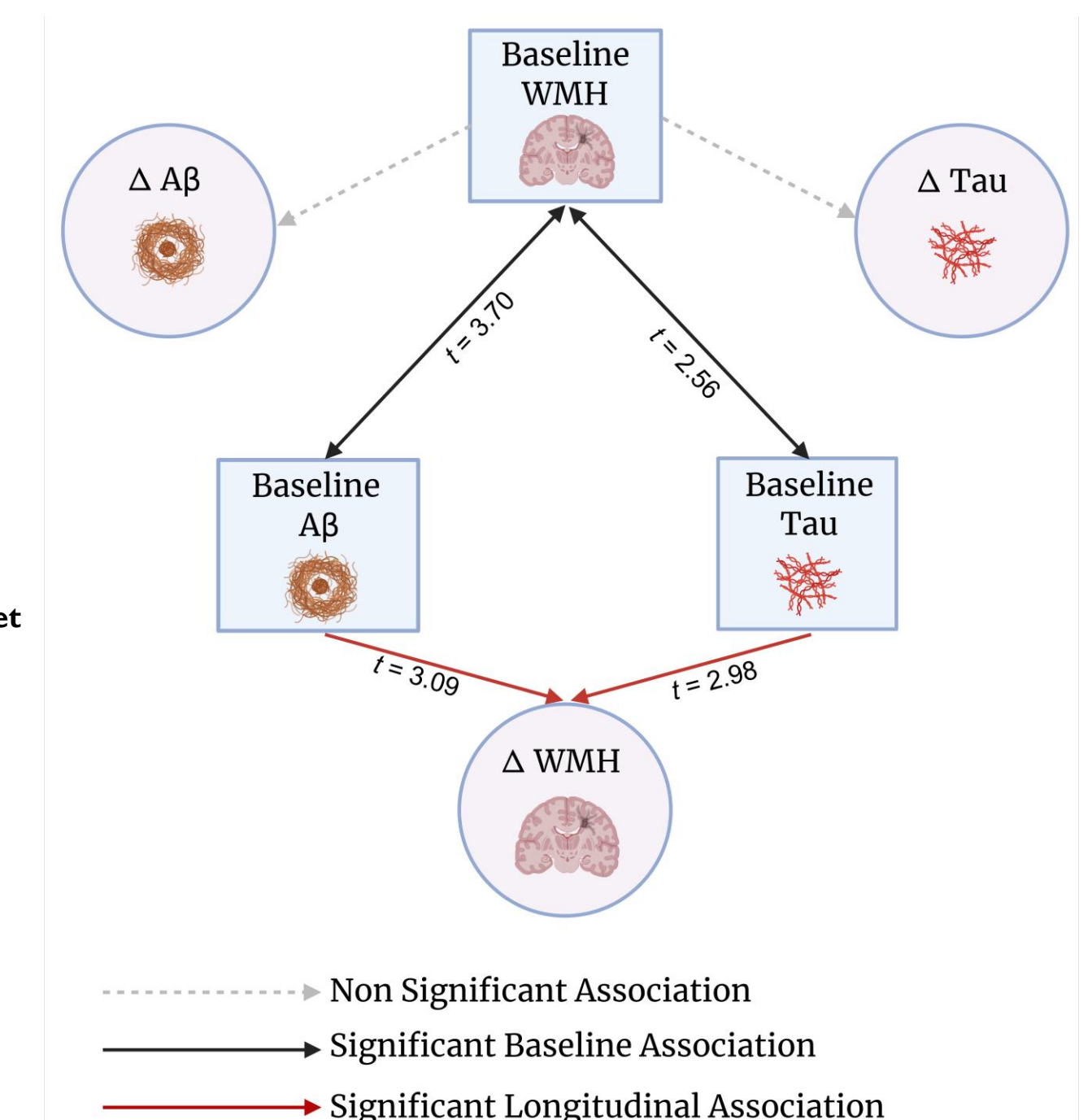
Figure 1. Panel A display scatterplots illustrating associations between z-scored baseline and longitudinal PET and WMH measures in anterior composite. Panel B summarizes model estimates as horizontal forest plots. Standardized β coefficients (95% CIs) are shown from linear models testing

Table 2: Baseline associations involving WMH with A β and Tau across brain regions

Brain Region	Aβ PET (N=1241)			Tau PET (N=636)		
	WMH → Aβ			WMH → Tau		
	<i>β</i>	<i>t</i>	<i>p</i>	<i>β</i>	<i>t</i>	<i>p</i>
Frontal	0.032	1.11	0.27	0.055	1.34	0.18
Temporal	0.064	2.29	0.022	0.043	1.1	0.27
Parietal	0.099	3.39	<0.001	0.099	2.46	0.014
Occipital	0.09	3.28	0.001	0.075	2.01	0.045
Anterior Composite	0.055	1.9	0.057	0.041	1.02	0.309
Posterior Composite	0.106	3.7	<0.001	0.101	2.56	0.011

Table 3: Baseline associations involving WMH with A β and Tau across brain regions in a common subset

Brain Region	A β PET (N=430) WMH $\rightarrow$ A β			Tau PET (N=430) WMH $\rightarrow$ Tau		
	θ	t	p	θ	t	p
Frontal	0.011	0.23	0.82	0.068	1.37	0.172
Temporal	0.06	1.29	0.199	0.041	0.85	0.397
Parietal	0.075	1.55	0.122	0.086	1.78	0.075
Occipital	0.16	3.52	<0.001	0.113	2.52	0.012
Anterior Composite	0.035	0.73	0.464	0.052	1.04	0.298
Posterior Composite	0.121	2.54	0.011	0.111	2.37	0.018



Note: Bold values indicate statistically significant associations after FDR correction. WMH = White matter hyperintensity. A β = Amyloid beta

4. Conclusion

- Amyloid and tau pathologies drive subsequent WMH accumulation rather than the reverse.
- The regional specificity of the proteinopathy effects on WMH accumulation further supports the notion that posterior WMHs and their progression are likely linked to accumulation of AD rather than vascular pathologies.