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Background

- Central arterial stiffness has been linked to Alzheimer's disease (AD) and related dementias, particularly through cerebrovascular disease and dysregulation. However, the extent to which vascular risk and AD neuropathology jointly influence cerebrovascular injury, particularly across distinct pathways, remains unclear.
- We investigated whether AD biomarker status modifies aortic stiffness associations with cerebrospinal fluid (CSF) measures of cerebrovascular structural integrity.

Methods & Analysis Plan

- Vanderbilt Memory and Aging Project participants (n=145, 72±6 years, 66% male; **Table 1**) underwent cardiac magnetic resonance imaging (MRI) to quantify pulse wave velocity (PWV) for aortic stiffness assessment at baseline.
- Serial CSF collection (mean follow-up=4.1±1.4 years) was also completed, including assay-based quantification of CSF/serum albumin quotient (QA1b; blood-brain barrier permeability), platelet-derived growth factor receptor beta (PDGFRβ; pericyte injury), fms-like tyrosine kinase 1 (FLT-1; angiogenesis), and matrix metalloproteinases (MMP; extracellular matrix remodeling) -2 and -9. AD neuropathology was also quantified using assays for CSF phosphorylated tau 181 (p-tau₁₈₁) and CSF amyloid-beta 42 to 40 ratio (Aβ_{42/40}), with biomarker status positivity defined as p-tau₁₈₁≥50.2 ng/L and Aβ_{42/40}≤0.07.
- Linear mixed-effects models evaluated Aβ_{42/40} × PWV × time or p-tau₁₈₁ × PWV × time interactions on longitudinal CSF biomarker trajectories, adjusting for age, sex, race/ethnicity, education, cognitive status, modified Framingham Stroke Risk Profile, *Apolipoprotein* ε4 status, and follow-up time. Follow-up models were stratified by AD biomarker status.

Results

- Aβ_{42/40} status modified PWV associations with MMP-2 (p=0.03; **Figure 1**), such that higher PWV marginally related to slower increases in MMP-2 among amyloid-negative (β=-44.12, p=0.09) but not amyloid-positive individuals (β=35.56, p=0.13). Aβ_{42/40} status also modified PWV associations with QA1b (p=0.03; **Figure 1**); stratified findings were null (p-values>0.19) but showed similar directional patterns.
- p-tau₁₈₁ status modified PWV associations with MMP-9 (p=0.01; **Figure 2**), such that higher PWV related to increasing MMP-9 among tau-positive (β=0.24, p=0.03) but not tau-negative individuals (β=-0.08, p=0.65).

Table 1. Participant Characteristics

	Baseline Sample (n=145)	p-tau ₁₈₁ Positive (n=55)	p-tau ₁₈₁ Negative (n=90)
Age, years	72±6	74±6	71±7
Sex, % male	66	62	69
Race/ethnicity, % White non-Hispanic	93	98	90
Education, years	16.0±2.8	16.1±2.4	16.0±3.0
Cognitive status, % cognitively unimpaired	54	44	61
APOE-ε4 carriers, %	31	49	20
FSRP score, total	11.6±3.8	12.1±4.0	11.2±3.7
PWV, m/s	7.9±2.6	7.9±3.1	7.9±2.3

Note. Values denoted as mean±standard deviation or frequency. Framingham Stroke Risk Profile (minus age) scores used for analytical purposes were 5.8±2.7 for the combined cohort, reflecting baseline composite cardiovascular risk factors of systolic blood pressure (140±16 mmHg), anti-hypertensive medication usage (46%), diabetes (17%), smoking (1%), left ventricular hypertrophy (3%), and prevalent cardiovascular disease (3%) or atrial fibrillation (4%). Cognitive status included 54% cognitive unimpaired, 9% ambiguous at risk, and 37% mild cognitive impairment. APOE=apolipoprotein E; FSRP=Framingham Stroke Risk Profile; p-tau=phosphorylated tau; PWV=pulse wave velocity.

Table 2. Annual Change in CSF Biomarkers

CSF Biomarker	Annual Change (n=118)
PDGFRβ, pg/mL	0.5±28.1
QA1b	0.2±0.5
Flt-1, pg/mL	-1.6±8.3
MMP-2, pg/mL	225±732
MMP-9, ng/mL	0.1±3.5

Note. Values denoted as mean ± standard deviation or frequency. FLT-1=fms-like tyrosine kinase 1; MMP=matrix metalloproteinase; PDGFRβ=platelet-derived growth factor receptor beta; QA1b=cerebrospinal fluid/serum albumin quotient.

Figure 1. PWV × Aβ_{42/40} Status and CSF Biomarkers

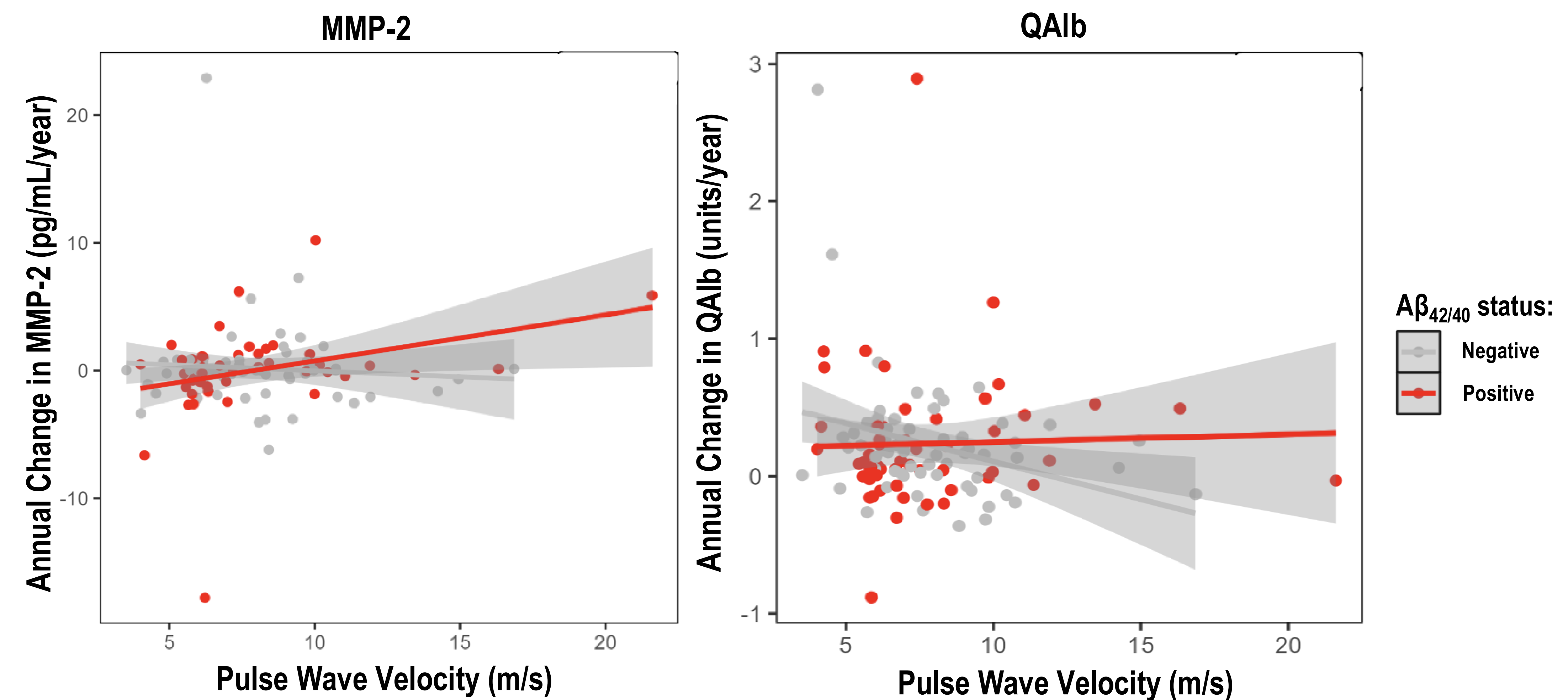
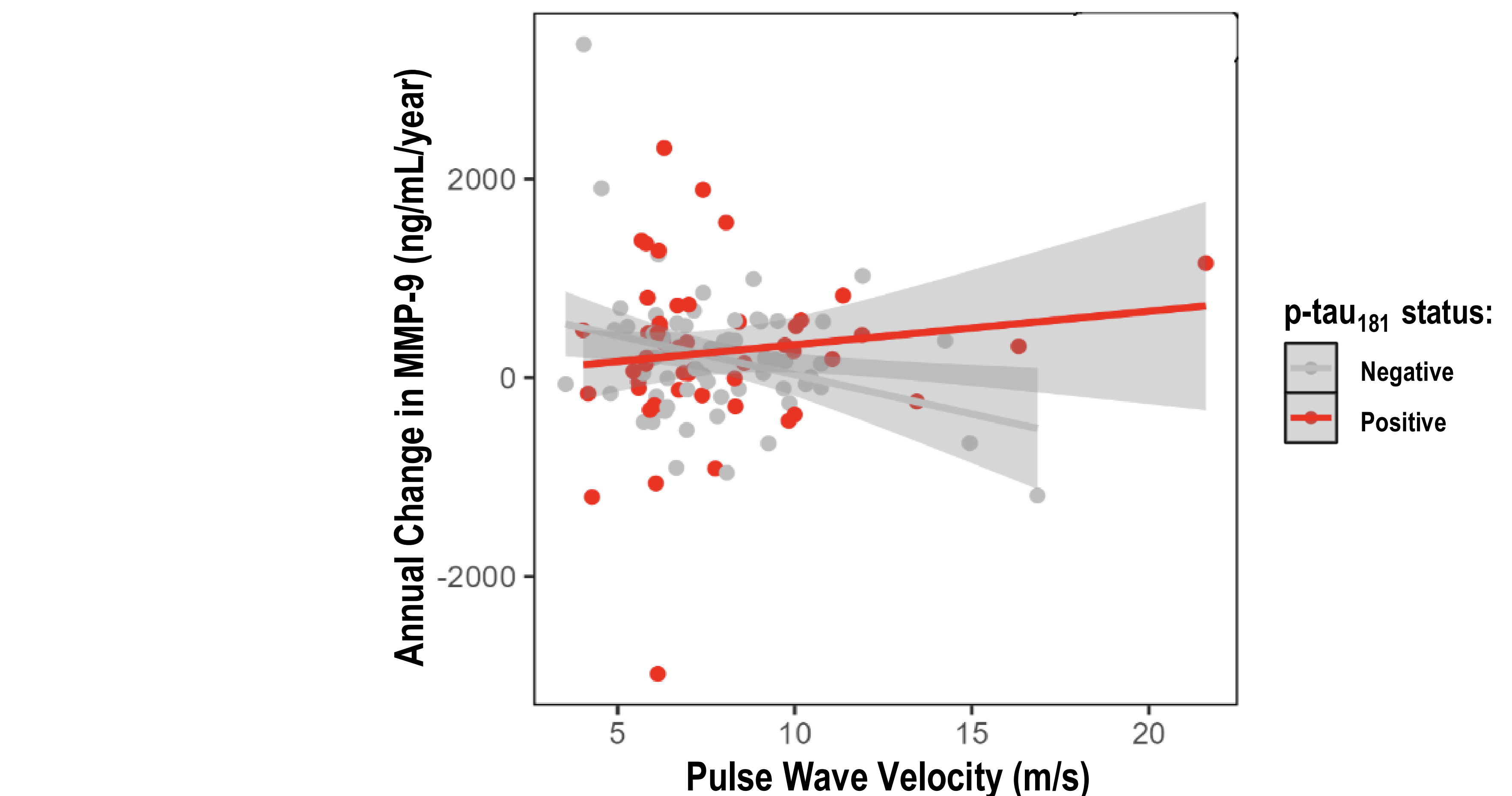


Figure 2. PWV × p-tau₁₈₁ Status and CSF Biomarkers



Conclusions

- Findings suggest that the impact of central arterial aging on cerebrovascular remodeling biomarkers over time depends on underlying AD pathology.
- In the absence of amyloidosis, aortic stiffness relates to attenuated longitudinal increases in extracellular matrix remodeling pathways often linked to constitutive vascular maintenance and remodeling (MMP-2). Directionally similar patterns emerged for blood-brain barrier permeability (QA1b).
- In the presence of tauopathy, aortic stiffness relates to greater longitudinal increases in extracellular matrix remodeling pathways often linked to active neuroinflammation and tissue injury (MMP-9).
- Future work should replicate findings with complementary measures of cerebrovascular structural integrity (e.g., functional imaging techniques) to determine whether similar modification patterns persist.