

White matter microstructural integrity predicts future plasma pTau217 change

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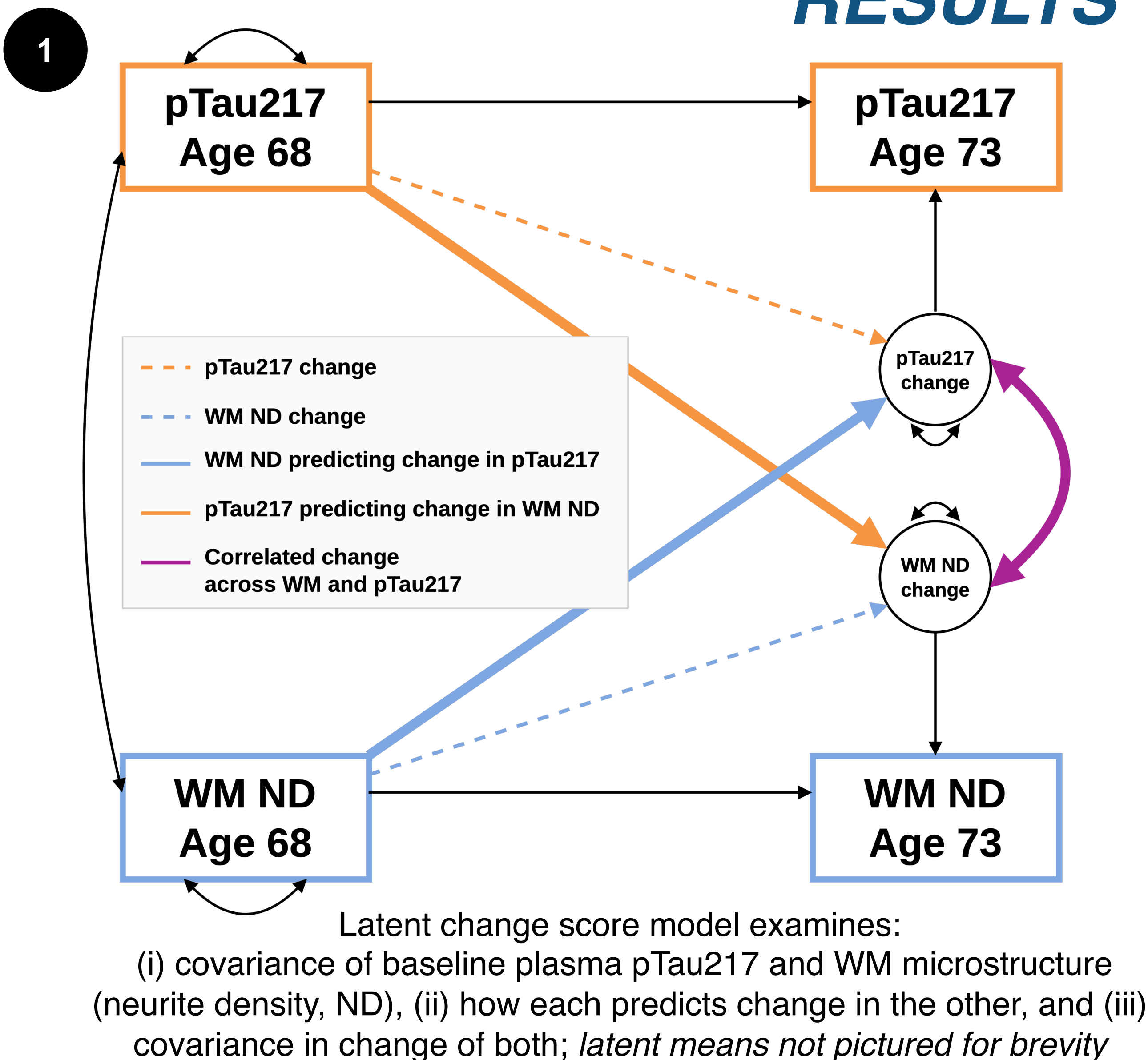
KEY FINDINGS

In a community dwelling cohort of 401 men (baseline age 68):

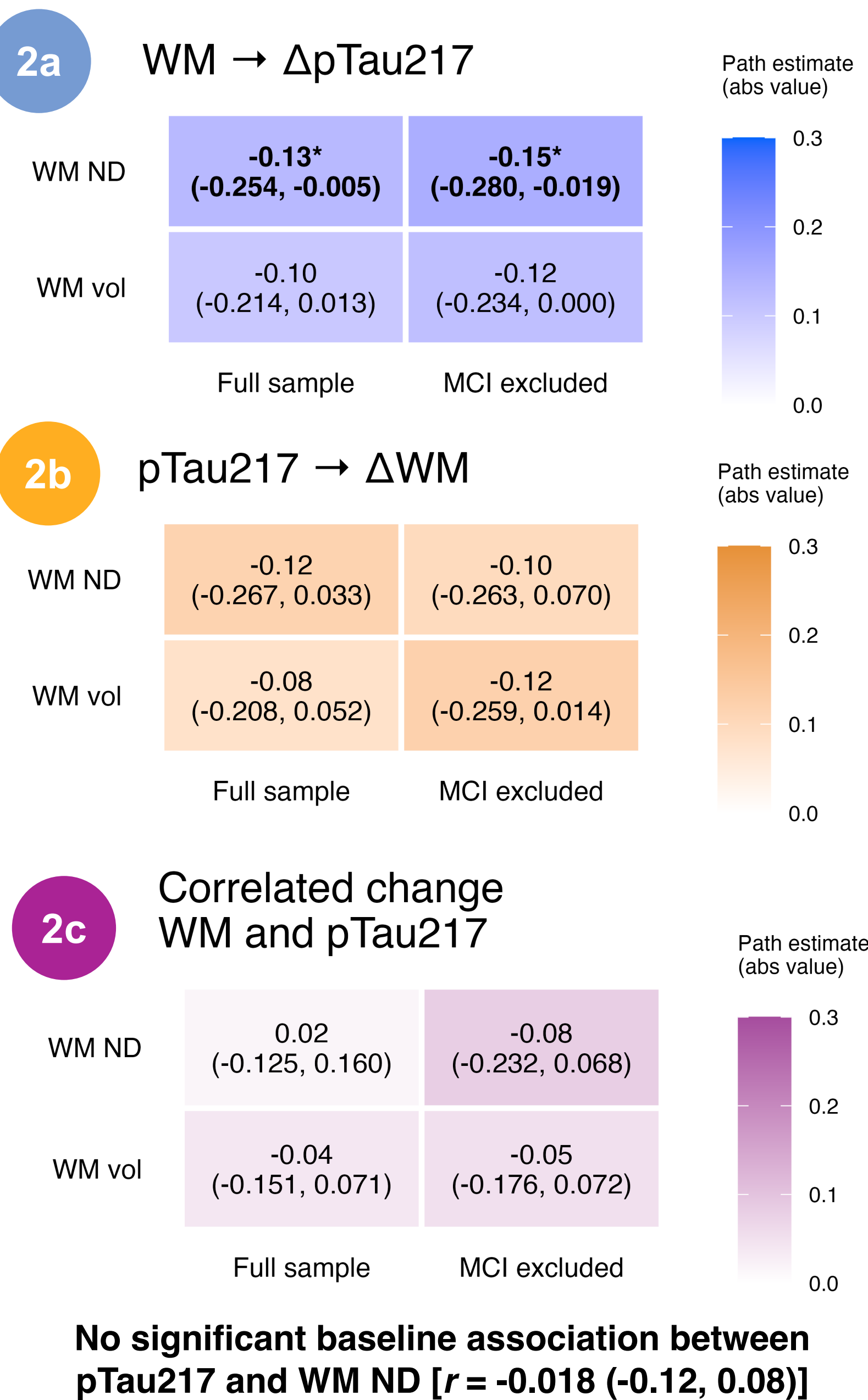
- Better white matter microstructural integrity at baseline predicts smaller increase in plasma pTau217 5.5 years later.
- Effects of baseline pTau217 on predicting change in white matter microstructure were weaker and not significant.
- Results support advanced diffusion metrics in white matter as sensitive marker of early AD-related changes.

BACKGROUND

- White matter (WM) degeneration occurs with aging and cerebrovascular disease.
- Growing evidence implicates WM degeneration in the development of Alzheimer's disease (AD), but temporal relationships between AD biomarkers and WM degeneration remains unclear.
- We examined longitudinal relationships between WM microstructural integrity (measured with diffusion MRI) and plasma phosphorylated tau-217 (pTau217) to better understand the temporal dynamics of WM degeneration and change in AD pathology in early old age.



RESULTS



METHODS

- Participants were 401 men from the Vietnam Era Twin Study of Aging (VETSA; baseline age = 67.56, SD = 2.60; timepoints were 5.5 years apart).
- Most were cognitively unimpaired at baseline (15% with mild cognitive impairment; MCI).
- Restriction spectrum imaging (RSI) model was applied to multi-shell diffusion. RSI metrics of interest included global WM neurite density (ND) across all tracts. Lower ND thought to reflect poorer microstructural integrity.
- Analyses were repeated with total WM volume, hypothesized to be a less sensitive metric of WM macrostructure compared to WM microstructure.
- Plasma pTau217 was measured with ALZpath Simoa assay (Quanterix).
- Baseline measures adjusted for age. pTau217 measures adjusted for site and storage time. WM volumes adjusted for estimated ICV.
- Latent change score model was fit to baseline and follow-up data 5.5 years later (Figure 1).

CONCLUSIONS

- **Better baseline WM microstructural integrity predicts slower change in pTau217 (Fig. 2a), which suggests slower change in brain amyloid accumulation.**
- **Baseline pTau217 showed weaker prediction of change in WM microstructure (Fig. 2b), though effect sizes suggest evidence of bidirectional effects.**
- **Sensitivity of WM predicting pTau217 was specific to WM microstructure (not volume), highlighting utility of RSI metrics.**
- **Changes in WM microstructure may be an upstream event, or diffusion measures may be more sensitive to detecting early AD-related changes than plasma pTau217.**

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