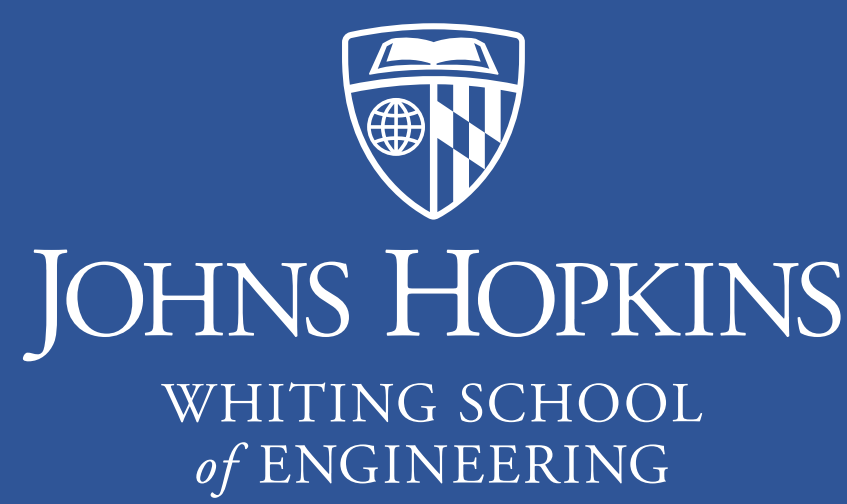


Altered T1w/T2w Ratio in White Matter Hyperintensities as an Indicator of Structural Integrity Loss: Association with Alzheimer's Disease and Vascular Dementia



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Introduction

White matter hyperintensities (WMH) are a prevalent marker of small vessel disease in older adults, present in over 90% of adults aged 65 and older. They predict increased risk of stroke, cognitive decline, and both vascular and Alzheimer-type dementia. Conventional WMH quantification focus on lesion volume, providing limited insight into the microstructural integrity of tissue. The T1w/T2w ratio is a composite marker sensitive to myelin, water content, gliosis, and tissue damage. Originally validated in multiple sclerosis, its application to aging cohorts with WMH and mixed vascular-neurodegenerative pathology has been limited. Although WMH appear similar on imaging across dementia subtypes, they invoke distinct mechanisms:

- **In vascular dementia (VD)**, WMH result primarily from chronic hypoperfusion and small vessel disease causing ischemic injury
- **In Alzheimer's disease (AD)**, WMH reflect a mixture of direct proteinopathic effects from amyloid- β toxicity alongside vascular contributions

Methods

Study Population (BICWALZS): a multicenter study across 7 university-affiliated hospitals in South Korea. N = 576 participants (from an initial cohort of 668): SCI (N=71), MCI non-amnesic (N=74), MCI amnesic (N=196), AD (N=125), VD (N=88), Other (N=22).

MRI Acquisition: 3 Tesla MRI (GE, Siemens, Philips); 3D T1-weighted MPRAGE; T2-weighted FLAIR sequences

WMH Segmentation: LST-AI (ensemble of three 3D U-Net models) applied to FLAIR sequences. FreeSurfer v7.1.1 used to define normal-appearing white matter (NAWM).

T1w/T2w Ratio Calculation:

1. T2w co-registered to T1w using ANTs
2. Bias field correction applied to both sequences
3. Normalization to MNI space with histogram matching
4. Voxel-wise T1w/T2w ratio computed (MPRAGE $\div$ FLAIR)

Residualization: WMH regressed against NAWM T1w/T2w ratios

Statistical Analyses:

- **Linear regression** models with age, sex, education, site, and MRI-to-visit interval as covariates
- Multiple Imputation by Chained Equations (**MICE**) with Random Forest; estimates pooled via Rubin's rules
- Structural Equation Modeling (**SEM**) via lavaan for causal mediation analyses.

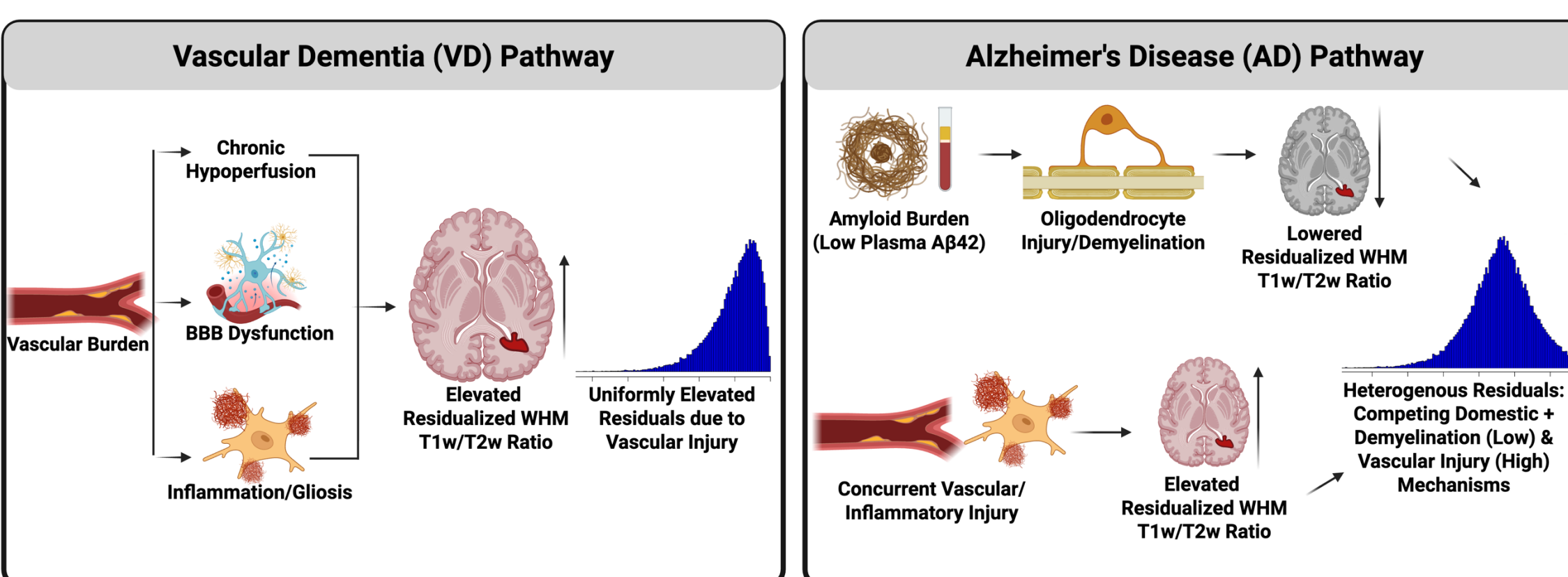


Figure 1. Conceptual model of divergent mechanisms underlying WMH microstructural signatures in vascular dementia and Alzheimer's disease

Results

Participant Characteristics: Mean age 72.4 years (SD 7.6); 66.8% female; 30.6% APOE ϵ 4 carriers; 32.1% amyloid-PET positive.

T1w/T2w Ratio Associations:

- **Age:** Greater age was associated with higher residualized T1w/T2w ratio (Figure 2A)
- **Diagnosis:** Both AD and VD groups showed significantly elevated T1w/T2w ratios relative to SCI (Figure 2B)
- **Plasma A β 42:** Lower plasma A β 42 (indicating greater amyloid burden) was associated with lower T1w/T2w ratio (β = 0.093–0.10, p < 0.05; Figure 2C)
- **Vascular Risk:** ≥ 3 vascular risk factors independently associated with higher T1w/T2w ratio (β = 0.437–0.445, p = 0.001)

Mediation Analyses (Figure 3):

AD $\rightarrow$ A β 42 $\rightarrow$ T1w/T2w: Plasma A β 42 partially mediated the association between AD diagnosis and T1w/T2w ratio (indirect effect B = –0.0081). AD participants showed lower plasma A β 42 (greater amyloid burden), and lower A β 42 predicted lower T1w/T2w ratio (Figure 3C–D)

AD $\rightarrow$ A β 40 $\rightarrow$ T1w/T2w: No significant mediation (B = –0.0047, p = 0.16)

VD $\rightarrow$ Vascular Risk (3+) $\rightarrow$ T1w/T2w: Vascular comorbidity burden partially mediated the relationship between VD diagnosis and T1w/T2w ratio (indirect effect B = 0.0099, p < 0.05; Figure 4A)

High vascular burden did not mediate the association between AD and T1w/T2w ratio

Figure 2. Association of residualized T1w/T2w ratio with age, cognitive diagnosis, and plasma A β 42

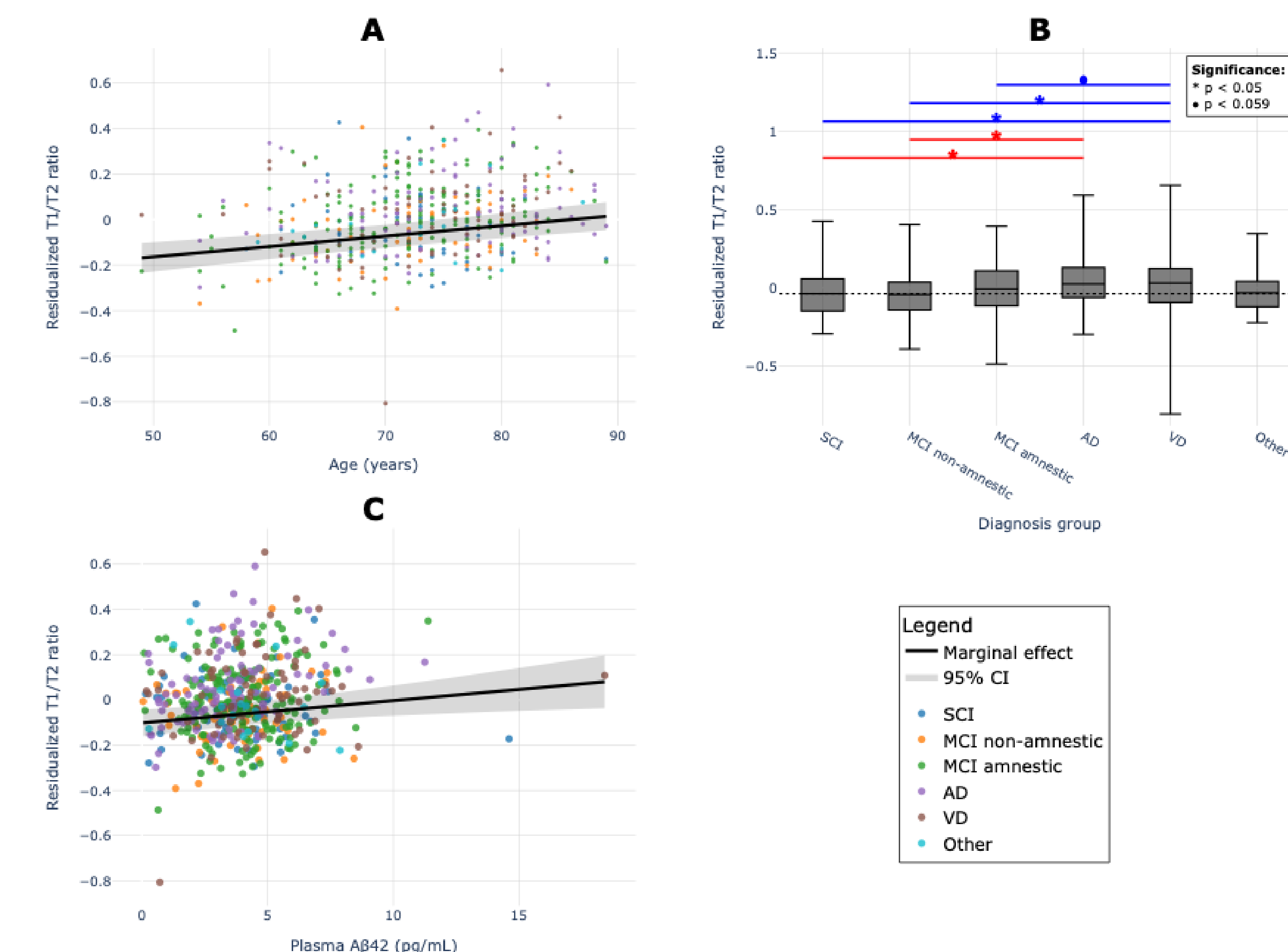


Figure 3. Mediation analysis of Alzheimer's disease diagnosis on T1w/T2w ratio via plasma amyloid biomarkers

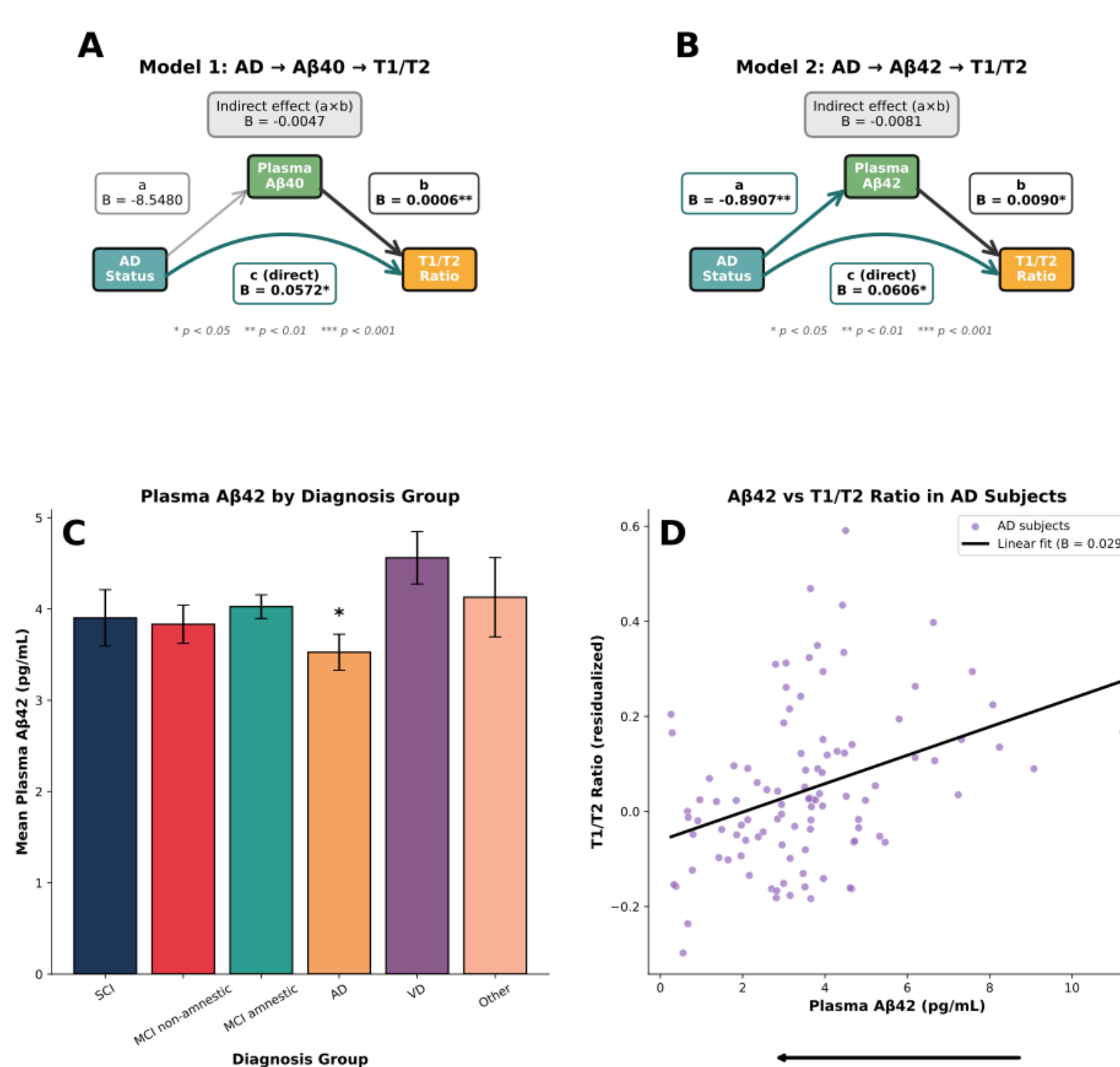


Figure 4. Mediation analysis of vascular dementia diagnosis on T1w/T2w ratio via vascular risk burden

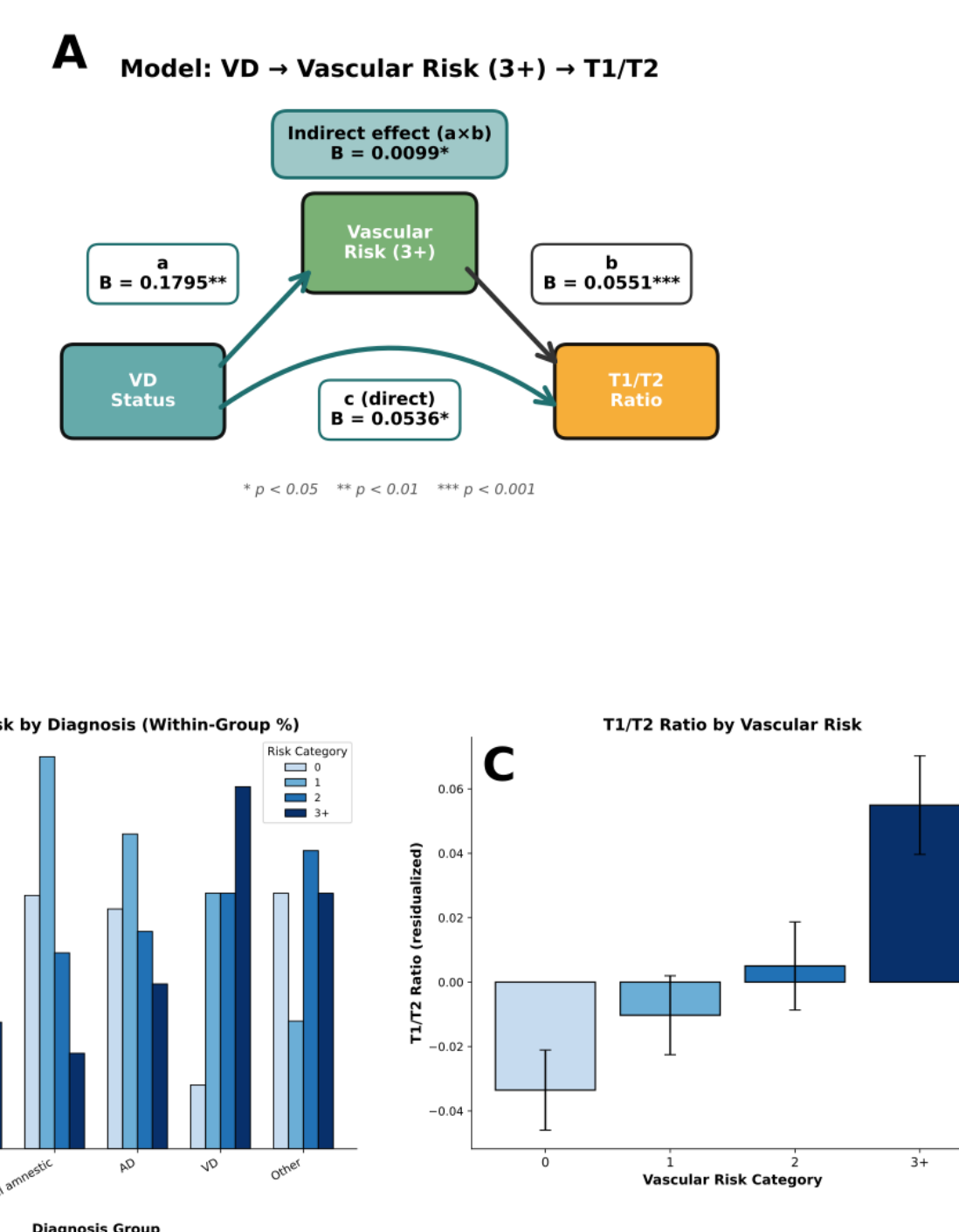
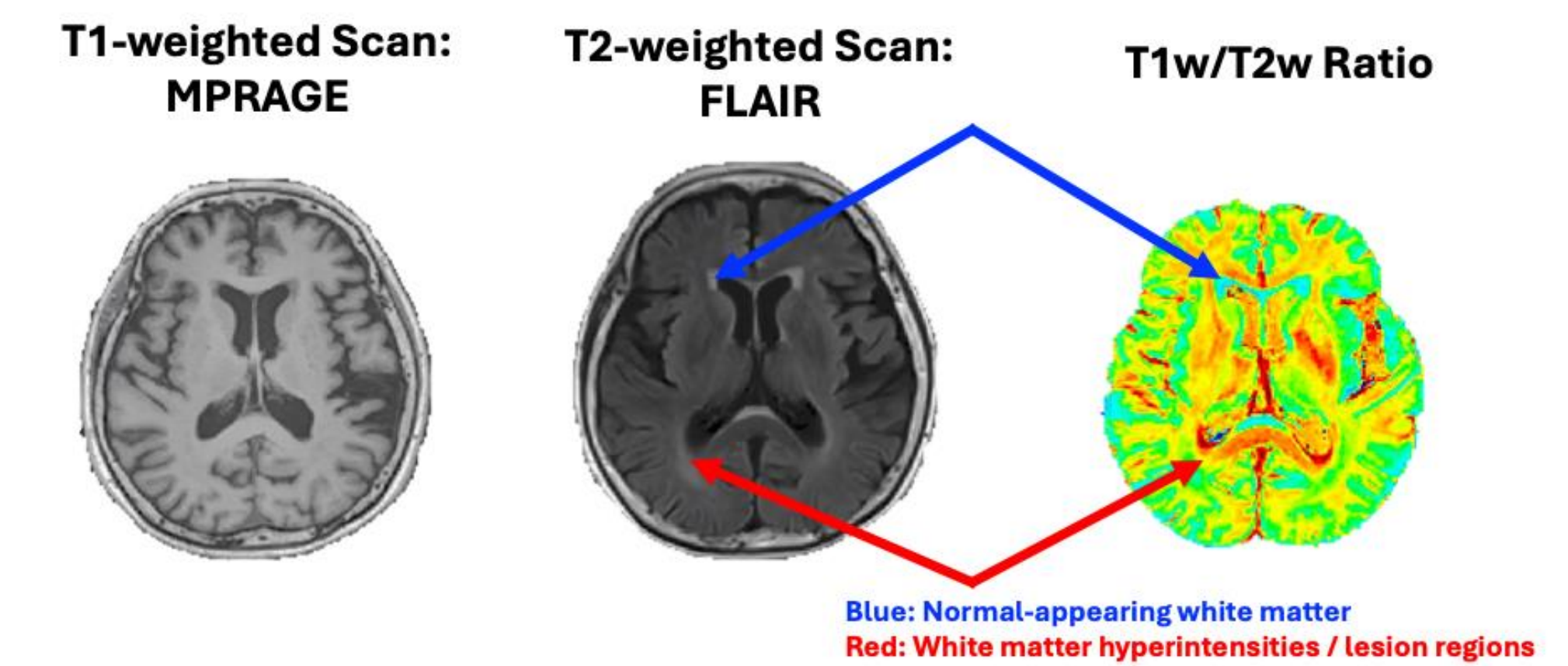


Figure 5. T1w/T2w Ratio Computation from Structural MRI



Discussion

- Residualized WMH T1w/T2w ratio captures microstructural heterogeneity within white matter lesions that is not visible through conventional volumetric measures
- **Both AD and VD show elevated WMH T1w/T2w ratios relative to SCI, but through divergent mechanisms**
- **In AD, lower plasma A β 42 (greater amyloid burden) partially mediates lower T1w/T2w ratios**, suggesting amyloid-driven demyelination as a contributing pathway
- **In VD, greater vascular comorbidity burden partially mediates higher T1w/T2w ratios**, consistent with ischemic-inflammatory injury
- These distinct pathological signatures – detectable from routine T1w and T2w/FLAIR MRI – may improve mechanistic subtyping and diagnostic precision in mixed-pathology dementia
- The T1w/T2w ratio can be **derived from standard clinical MRI sequences** already acquired in routine dementia evaluations, requiring no additional scanning time, specialized protocols, or expensive biomarker assays – **making it broadly accessible for clinical translation.**
- Future longitudinal studies are needed to establish temporal precedence and test whether this measure improves ARIA risk stratification in anti-amyloid therapy

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