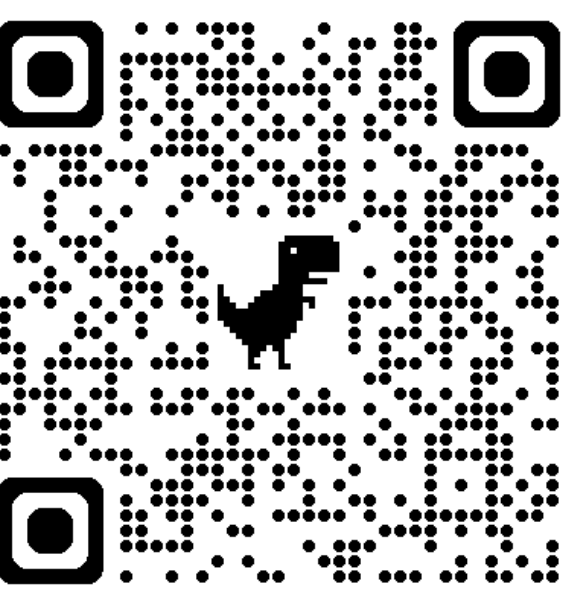




Neuroinflammatory Markers sTREM2 and YKL-40 in Association with Alzheimer's Disease Pathology: A Systematic Review and Meta-Analysis

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Highlights
 Glial biomarkers CSF sTREM2 and YKL-40 preferentially track with tau and neurodegeneration over amyloid
 Longitudinal evidence supports a potentially compensatory role of glial activation
 Glial-tau coupling weakens with disease progression → glial “exhaustion” across the AD continuum



INTRODUCTION & OBJECTIVES

- Neuroinflammation** is a core feature of Alzheimer's Disease (AD)
- Glial responses may not be uniform across the disease continuum
 - Early, compensatory responses vs. sustained & dysregulated activation
- Glial reactivity markers **sTREM2** and **YKL-40** are elevated in mild cognitive impairment (MCI) and Alzheimer's Disease (AD) compared to cognitively unimpaired (CU) individuals
 - However, it is unknown whether sTREM2 and YKL-40 are more closely linked to pathological changes in amyloid, tau, or non-specific neurodegeneration
 - Moreover, associations with pathology may evolve with disease progression

Aims

- Investigate the **cross-sectional** and **longitudinal** associations of novel neuroinflammatory biomarkers **sTREM2** and **YKL-40** with **AD pathology biomarkers**
- Examine whether these relationships **differ across the disease continuum**

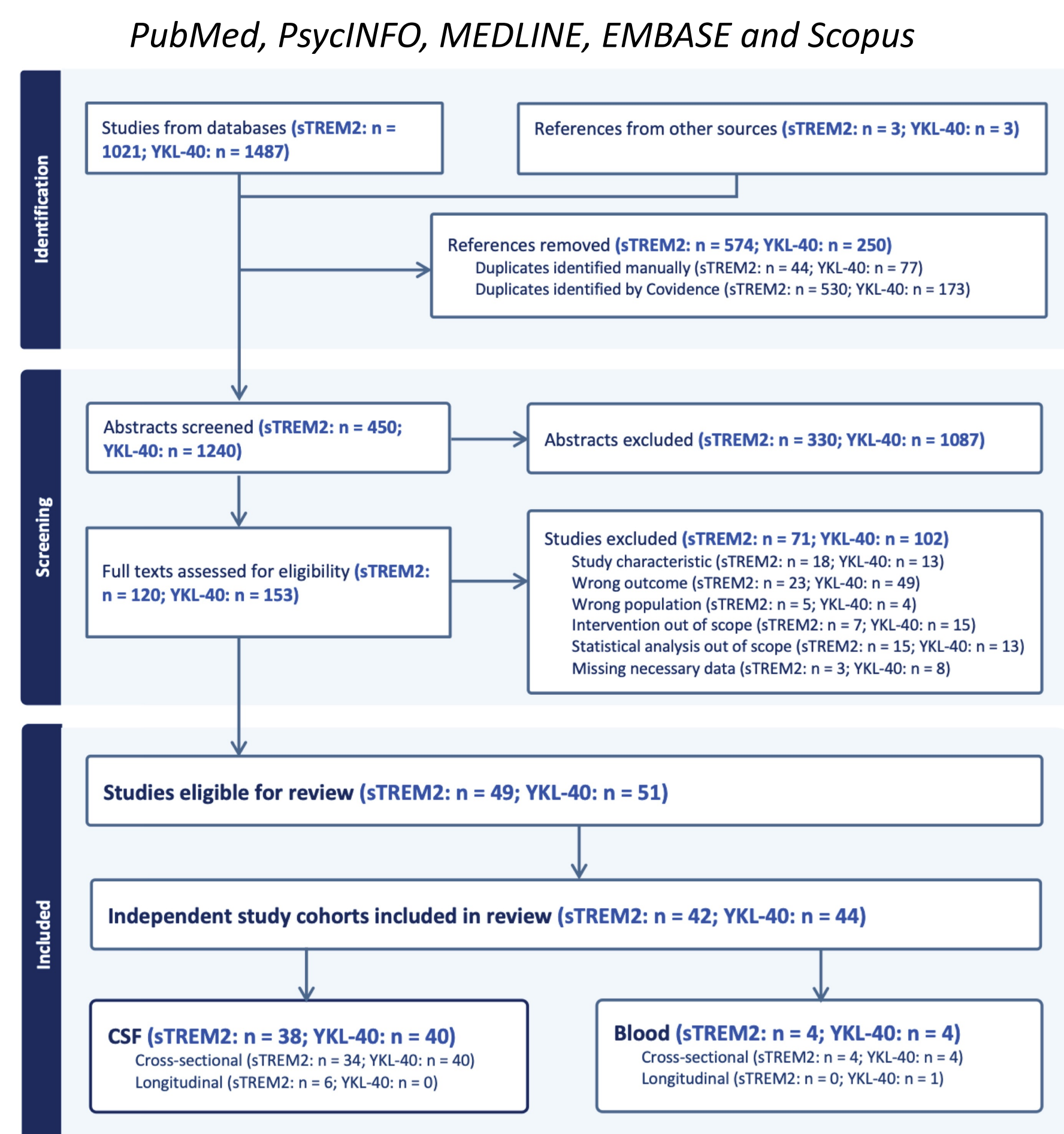
METHODS

Inclusion criteria

- ✓ Cross-sectional or longitudinal*
- ✓ Humans
 - ✗ Animal studies
- ✓ CSF or blood-based* glial markers
 - ✗ Neuropathological studies
- ✓ Community-dwelling, SCD, MCI, AD populations
 - ✗ Non-AD disease populations or non-sporadic/genetically defined AD cohorts

Final inclusion:
sTREM2: 42 studies
YKL-40: 44 studies

AD pathology outcomes



*summarised descriptively due to insufficient studies for meta-analysis

Random-effects meta-analyses estimated pooled cross-sectional effect sizes of CSF sTREM2 or YKL-40 with each AD pathology outcome

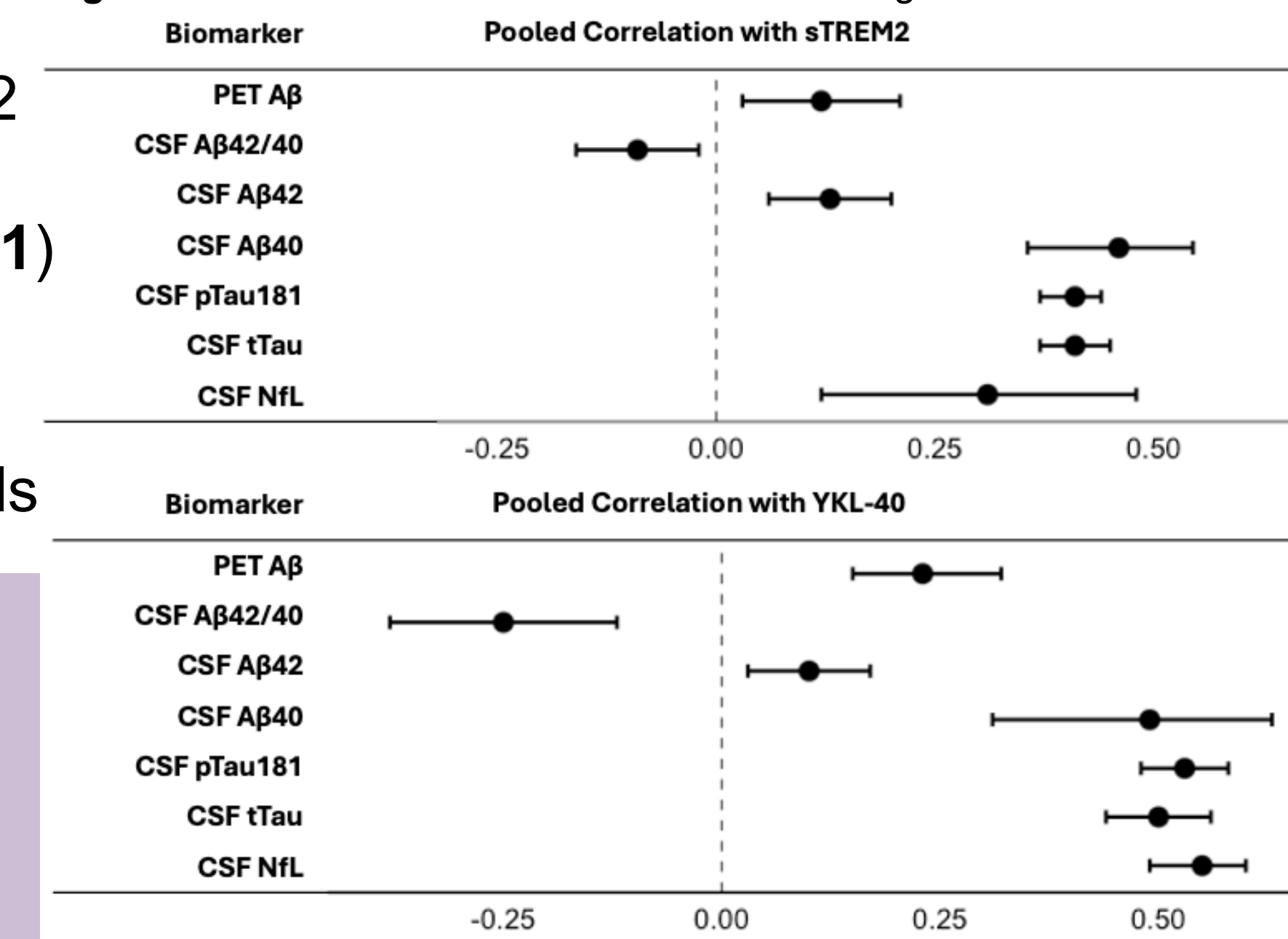
Meta-regression models in stratified samples assessed strength of associations across CU, MCI & AD

➢ Adjusted for mean age of samples

Cross-sectional associations

- Robust, consistent associations of sTREM2 and YKL-40 with CSF tau (**pTau181**) and neuronal injury markers (**tTau, NfL**) (**Fig 1**)
- Weaker relationships with **pathological amyloid (CSF Aβ42/40 and Aβ-PET)** → Non-significant in covariate-adjusted models

Fig 1. Pooled correlation coefficients between glial and AD biomarkers



Longitudinal associations

- Increased baseline sTREM2/YKL-40 associated with **increased soluble (CSF) AD pathology** (pTau181) at follow up
- But simultaneously associated with **reduced/slower rates of PET tau aggregation and PET Aβ accumulation**

→ Glial reactivity rises in response to pathology acceleration but may simultaneously exert **protective effects** by limiting their aggregation into PET-detectable insoluble deposits.

Meta-regression

Glial-tau (pTau181, tTau) coupling with both sTREM2 and YKL-40 was strongest in CU, and progressively weakened in MCI and AD (**Fig 2 & 3**).

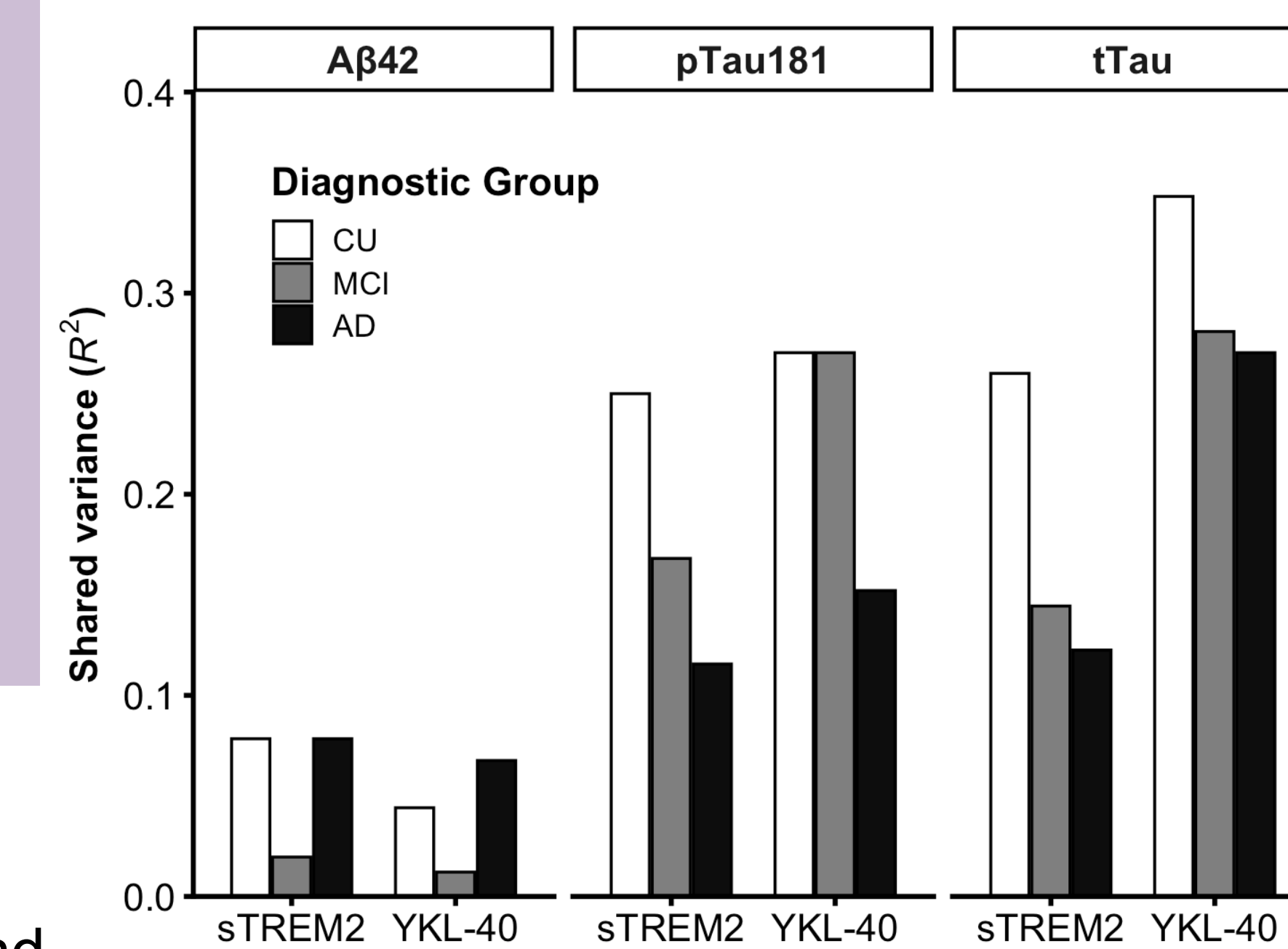
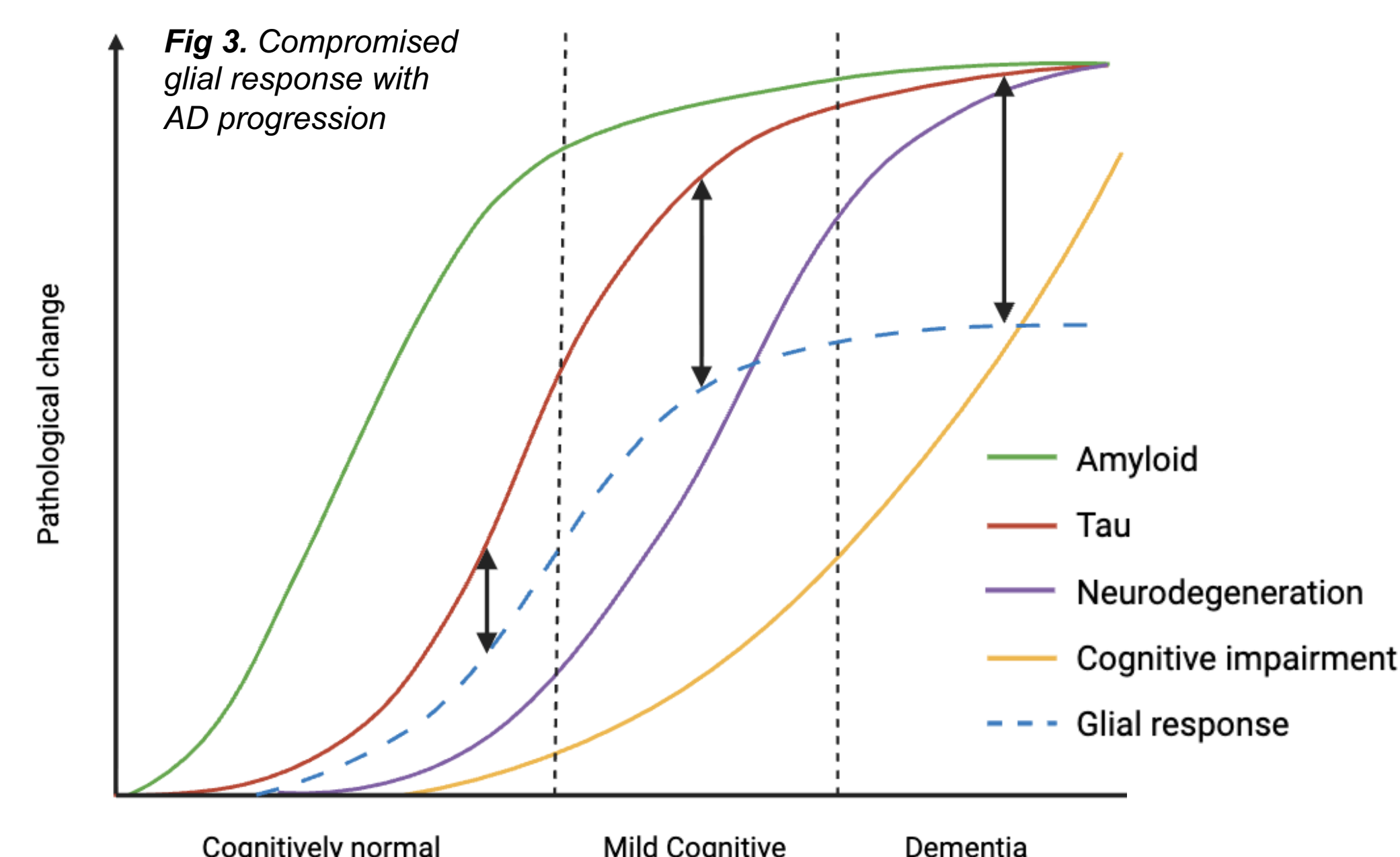


Fig 2. Pooled shared variance (R^2) of sTREM2 or YKL-40 with AD biomarkers across diagnostic subgroups



CONCLUSIONS

- sTREM2 & YKL-40 preferentially track **tau** over Aβ
- May exert **protective effects** in AD by limiting aggregation of insoluble deposits
- Glial-tau coupling weakens with disease progression (Fig 3)**
 - Inadequate response relative to burden of pathology
 - Evidence of glial “**exhaustion**” with sustained activation