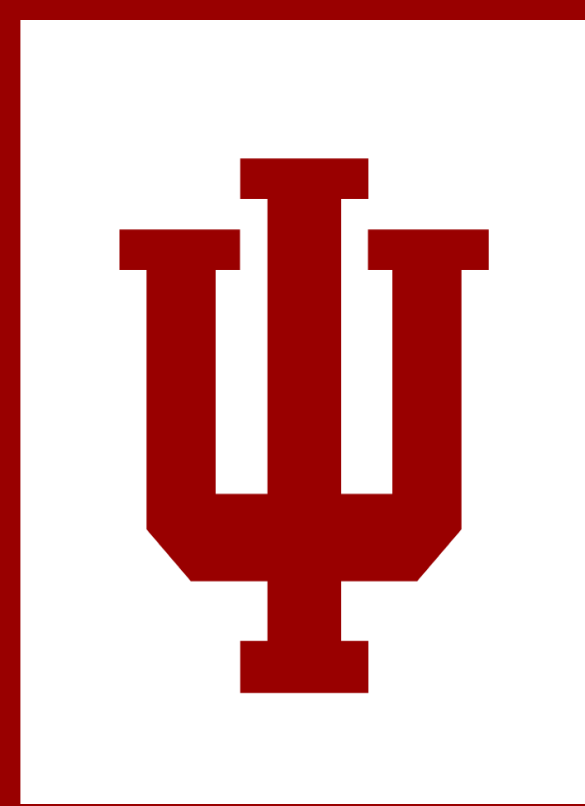




Cardiovascular-Kidney-Metabolic Syndrome and White Matter Hyperintensity Burden in Alzheimer's Disease

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Introduction

- AD is a heterogeneous pathophysiology that is heavily influenced by modifiable cardiometabolic risk factors.
- Cardiovascular-Kidney-Metabolic (CKM) syndrome captures the interdependence of these cardiovascular, renal, and metabolic risks on a continuous spectrum.¹
- White matter hyperintensities (WMH) on T2-weighted MRI are strongly associated with cognitive impairment and may signify a complex pathological process that intersects with and modifies classical AD biomarker trajectories.²
- Current large-scale epidemiological studies linking advanced CKM stages to probable AD dementia are heavily limited by their reliance on administrative ICD-10 codes.³
- The role of CKM syndrome in predicting baseline and longitudinal WMH burden across the AD continuum remains incompletely understood in patients with a strictly defined AD diagnostic criteria.

Methods

- We analyzed 646 participants (201 CN, 310 with MCI, and 135 with probable AD) from the Alzheimer's Disease Neuroimaging Initiative.
- Participants were staged according to the American Heart Association (AHA) CKM syndrome staging framework (Stages 0 through 4). CKM syndrome is categorized into five stages that reflect progressively increasing cardiometabolic risk. AHA defines staging in the following format: CKM stage 0 as "no risk factors," CKM stage 1 as "excess adiposity," CKM stage 2 as "metabolic risk factors and chronic kidney disease," CKM stage 3 as "subclinical cardiovascular disease" and stage 4 as "clinical cardiovascular disease"
- Cross-sectional models examined the association of baseline CKM stages with baseline WMH.
- Longitudinal models examined the association of baseline CKM stages with longitudinal WMH (n= 625, total observations = 2,796). Missing data accounted for by linear mixed models.
- Covariates included age, sex, APOE ε4 status, education, machine manufacturer, total intracranial volume.

Baseline WMH Burden Across CKM Stages

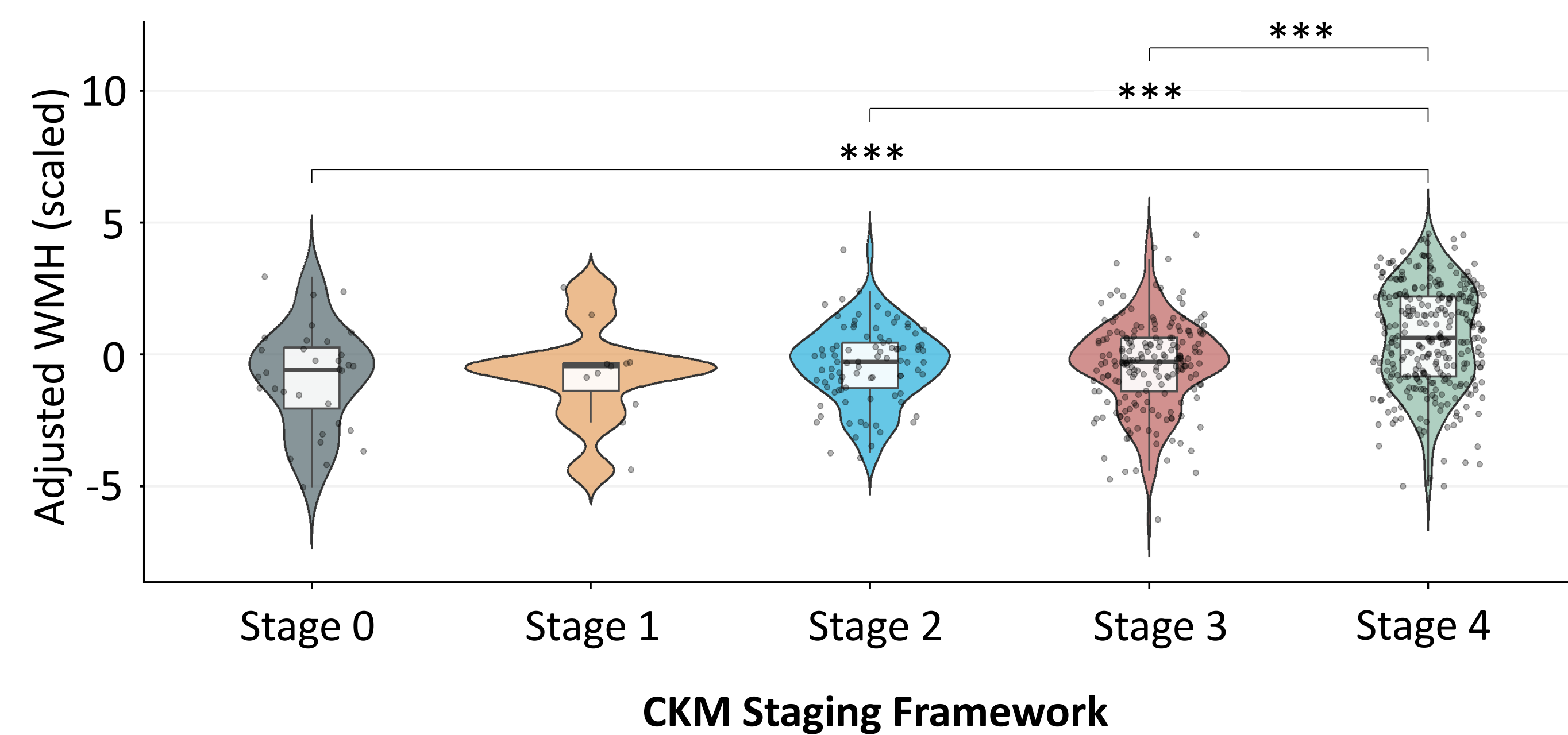


Figure 1. A generalized linear regression model performed to assess association between WMH and CKM stages. The Y axis represents log-transformed WMH values, while the x-axis represents CKM stages. ***p < 0.001

Findings: The model demonstrated that CKM staging was a significant independent predictor of baseline WMH, where the higher risk CKM stage 4 was significantly associated with increased WMH burden at baseline compared to earlier CKM stages.

Cross-sectional Association between CKM Stage and WMH Burden stratified by Diagnostic Group

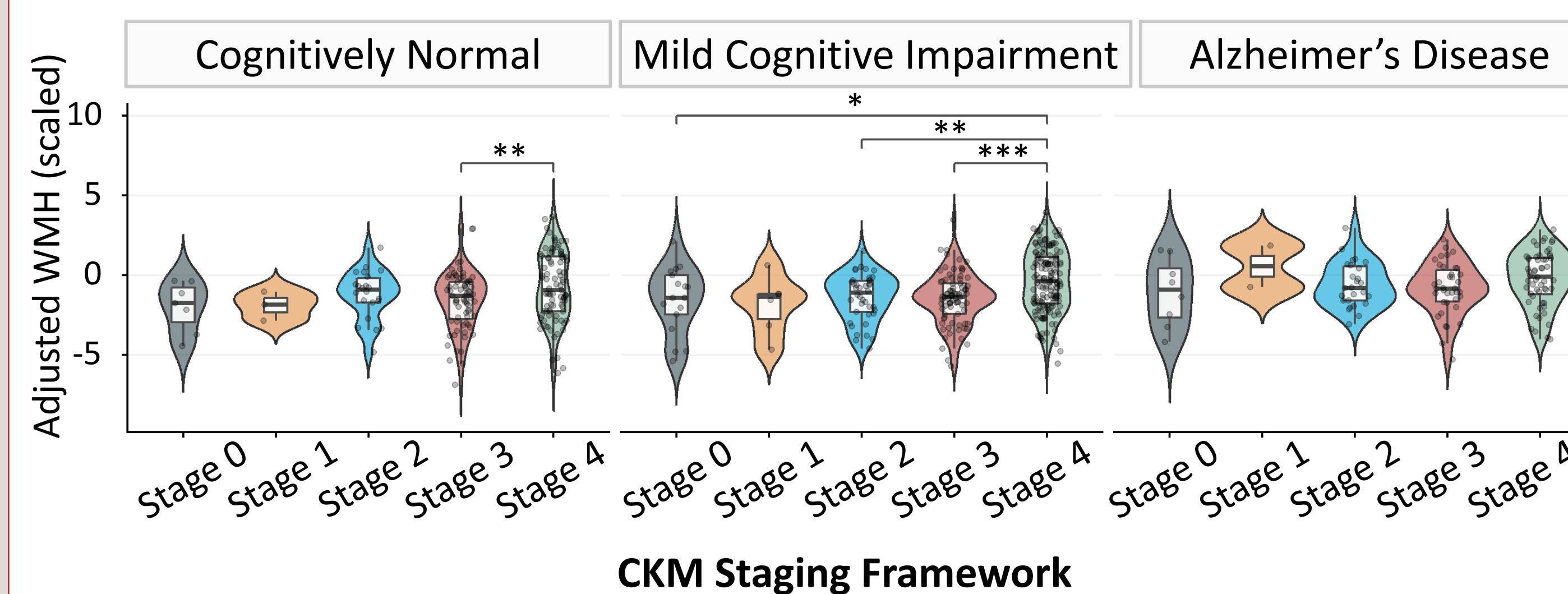


Figure 2 A generalized linear regression model performed across diagnostic groups to assess association between WMH and CKM stages. The y-axis represents log-transformed WMH values, while the x-axis represents CKM stages. ns > 0.05, *p<0.05, **p<0.01, ***p <0.001.

Findings: CKM stage was significantly associated with baseline WMH burden within CN and MCI cohorts, but no significant associations were observed within the probable AD diagnostic group.

Longitudinal WMH Accumulation by Baseline CKM Stage

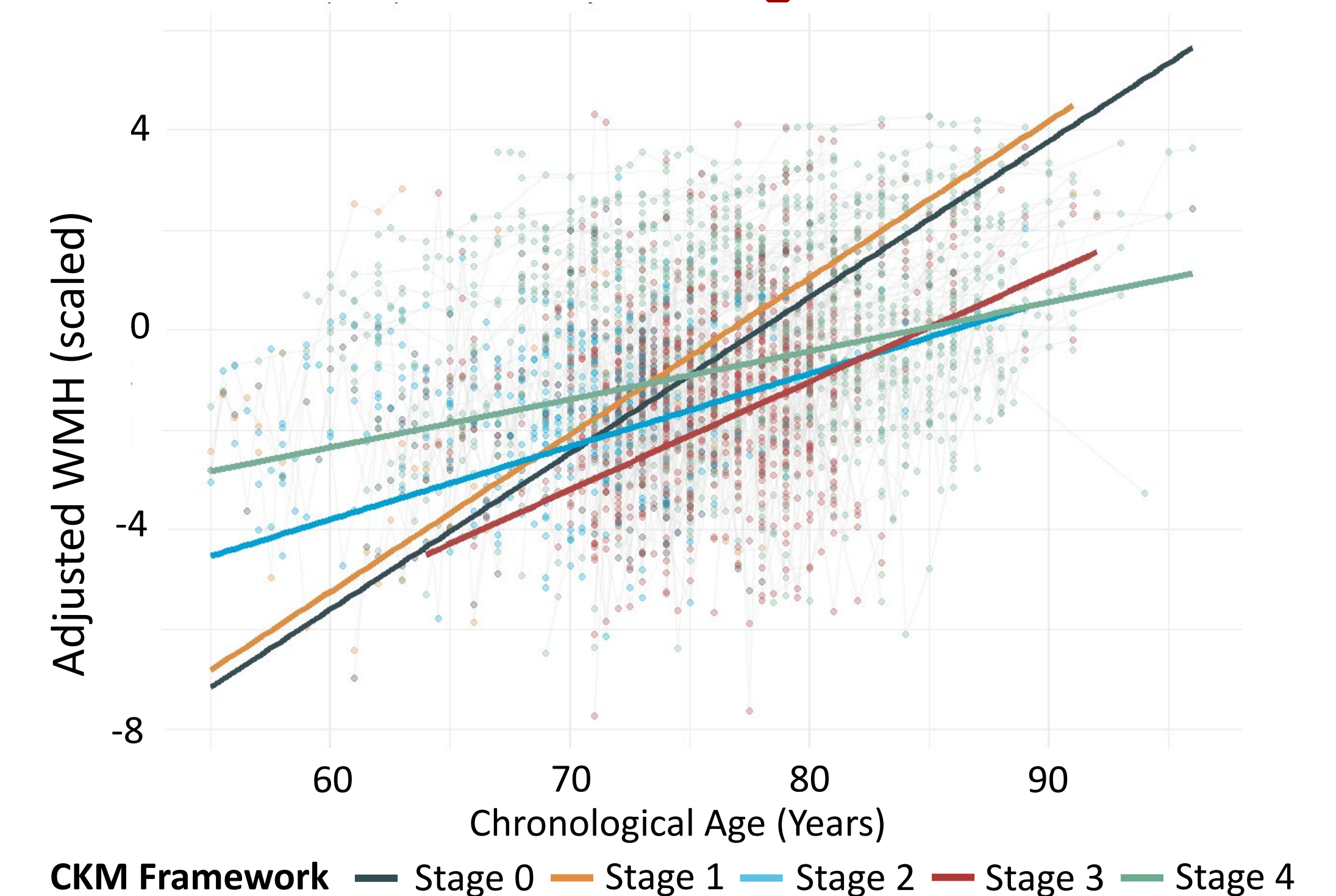


Figure 3 A mixed linear regression model performed to assess association between longitudinal WMH and baseline CKM stages. The y-axis represents log-transformed WMH values, x-axis is age in years.

Findings: In a longitudinal assessment, a significant association was found between baseline CKM stage with longitudinal WMH accumulation. Specifically, longitudinal trajectory analysis revealed that the slope of CKM Stage 4 for WMH accumulation was significantly slower than Stage 0 (p-value < 0.001), CKM stage 1 (p-value = 0.0097), and CKM stage 3 (p-value < 0.001).

Conclusions

- CKM stage 4 was strongly associated with increased WMH burden at baseline, but a slower accumulation of WMH volume over time compared to earlier CKM stages.
- The association between CKM stage 4 and greater WMH burden was most evident among CN and MCI participants, but not among participants with probable AD.
- The CKM framework may enhance the identification of older adults at elevated risk for vascular-driven neurodegeneration before advanced clinical dementia manifests.

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