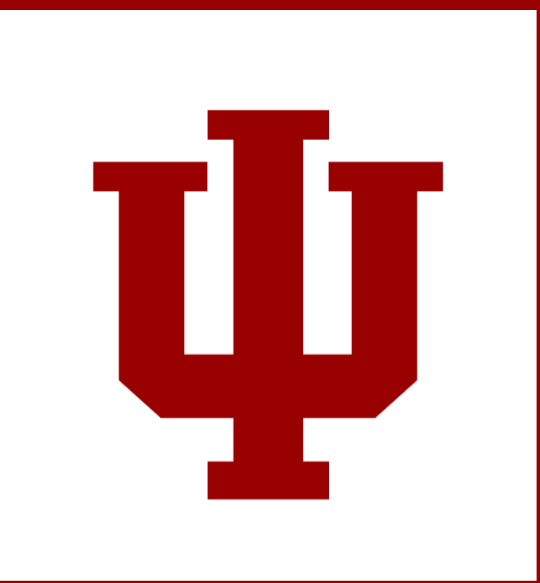




Plasma Proteins Mediate the Association between the MIND Diet and Dementia

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MIND diet adherence was associated with AD diagnosis, plasma NfL, and two plasma protein modules. Hub protein and validation analyses prioritized MCTS1 and related network proteins as candidate biological links between MIND diet and AD risk.

Background

The Mediterranean-Dietary Approaches to Stop Hypertension (MIND) diet may influence Alzheimer's disease (AD) risk through biological pathways reflected in circulating proteins¹. Weighted gene co-expression network analysis (WGCNA) can reduce high-dimensional proteomic data into biologically coherent protein modules, enabling module-level discovery followed by hub protein prioritization². We examined whether MIND diet scores were associated with AD-related outcomes and plasma protein modules, and whether candidate hub proteins showed evidence consistent with mediation and external validation.

Objective

To identify plasma protein modules and hub proteins that may link MIND diet adherence to AD diagnosis and AD-related biomarkers.

Cohorts and Workflow

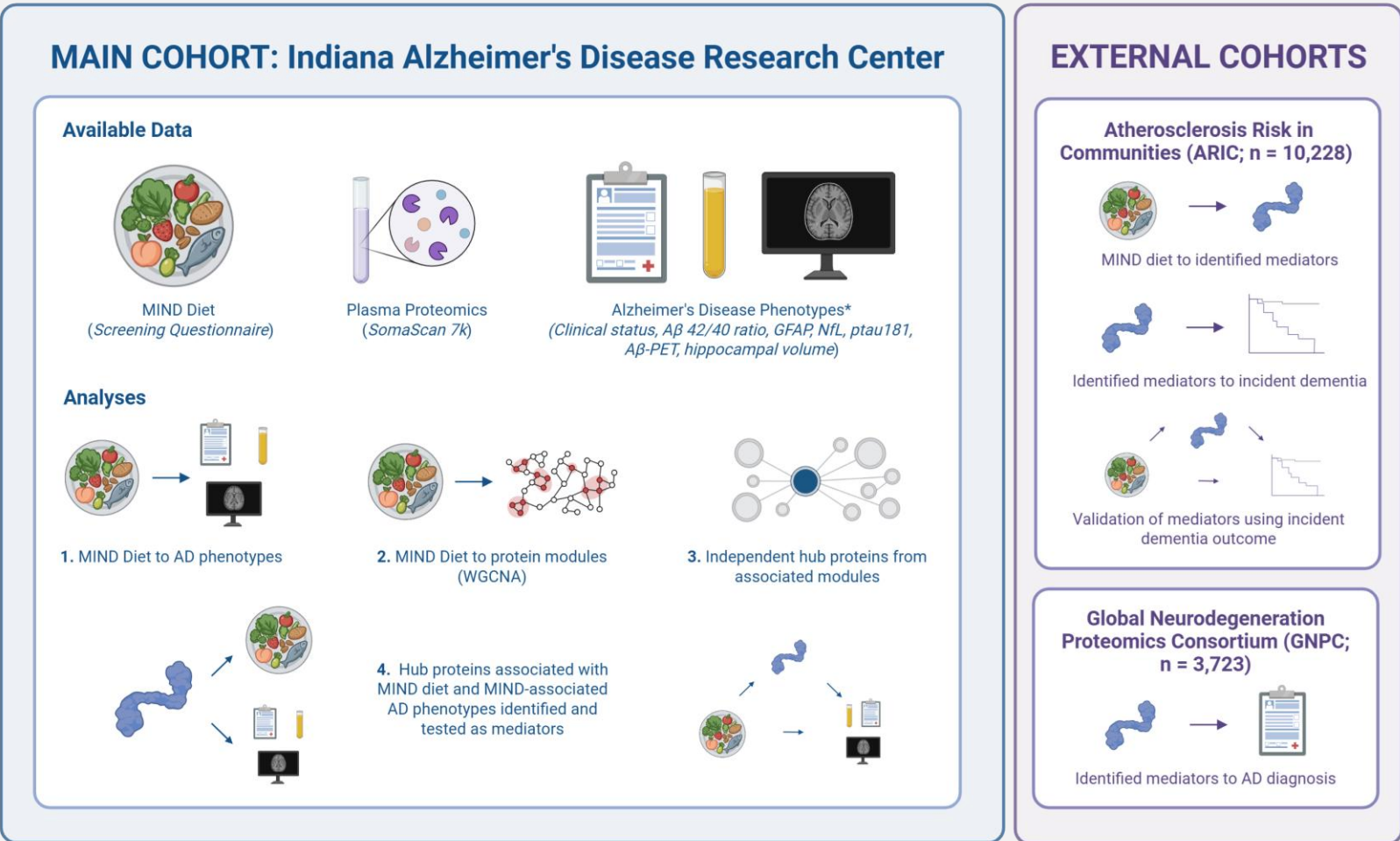


Fig 1. Study Overview. Main analyses were performed in the Indiana Alzheimer's Disease Research Center cohort using MIND diet questionnaire data, SomaScan 7k plasma proteomics, and AD-related clinical/biomarker outcomes. External validation was performed in the Atherosclerosis Risk in Communities and Global Neurodegeneration Proteomics Consortium datasets.

1. MIND Diet Associations with AD Diagnosis, Plasma NfL, and Two Protein Modules

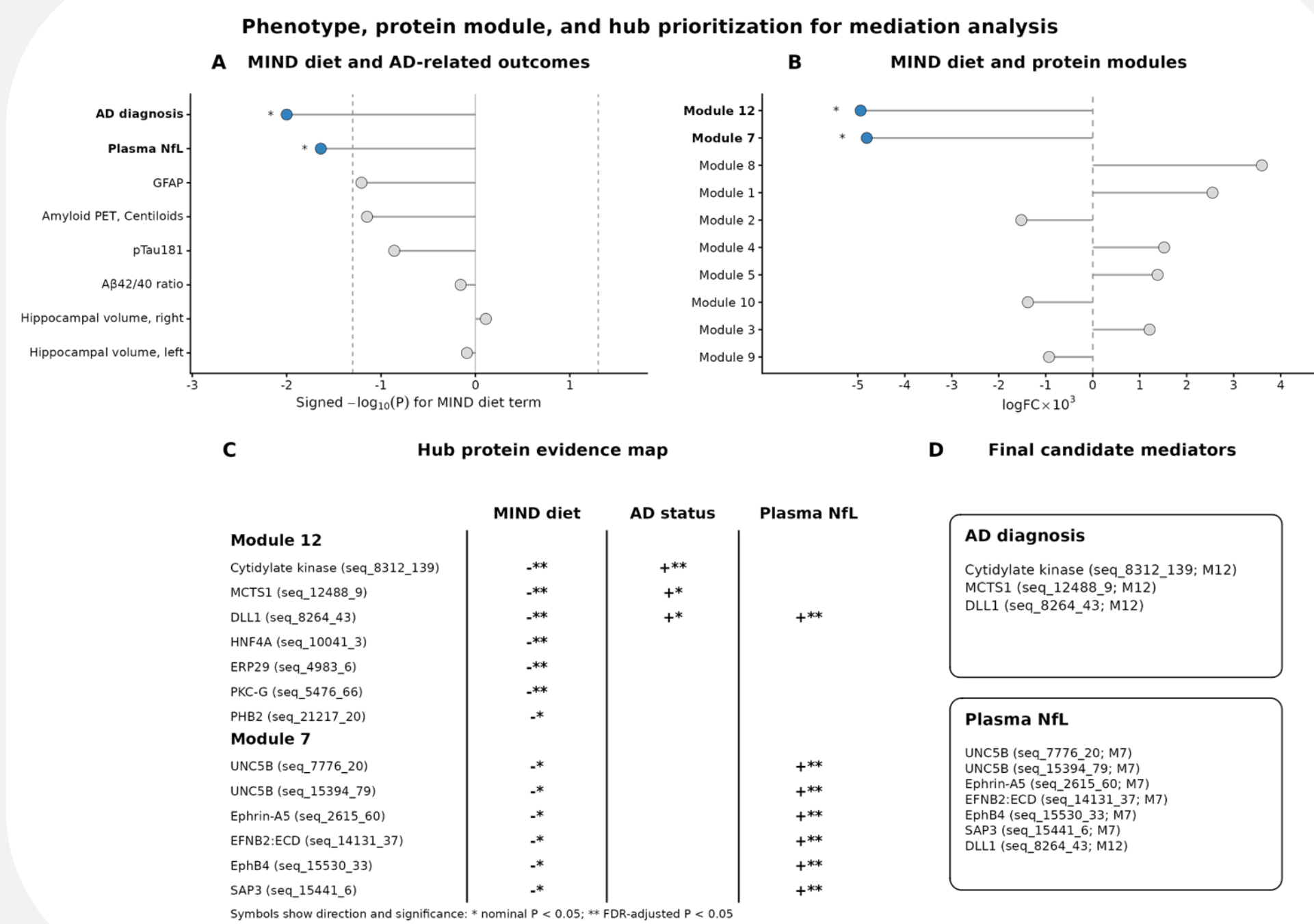


Fig 2. MIND diet was associated with AD diagnosis and plasma NfL and with Modules 12 and 7. Hub evidence maps prioritized module proteins associated with both MIND diet and MIND-associated AD outcomes

Main Findings

- MIND diet was linked to AD diagnosis and plasma NfL in the main cohort
- Previously defined plasma protein modules identified two MIND associated networks
- Hub-prioritization nominated MCTS1, DLL1, cytidylate kinase, and UNC5B/ephrin-related proteins
- Discovery analyses suggested as cytidylate kinase and MCTS1 as possible mediators of MIND—AD
- External validation provided the strongest support for MCTS1**
 - MCTS1 showed evidence of association with MIND diet in ARIC, AD classification in GNPC, incident dementia in ARIC, and mediation in ARIC.

2. Candidate Mediators Indirect Effects and External Cohort Support

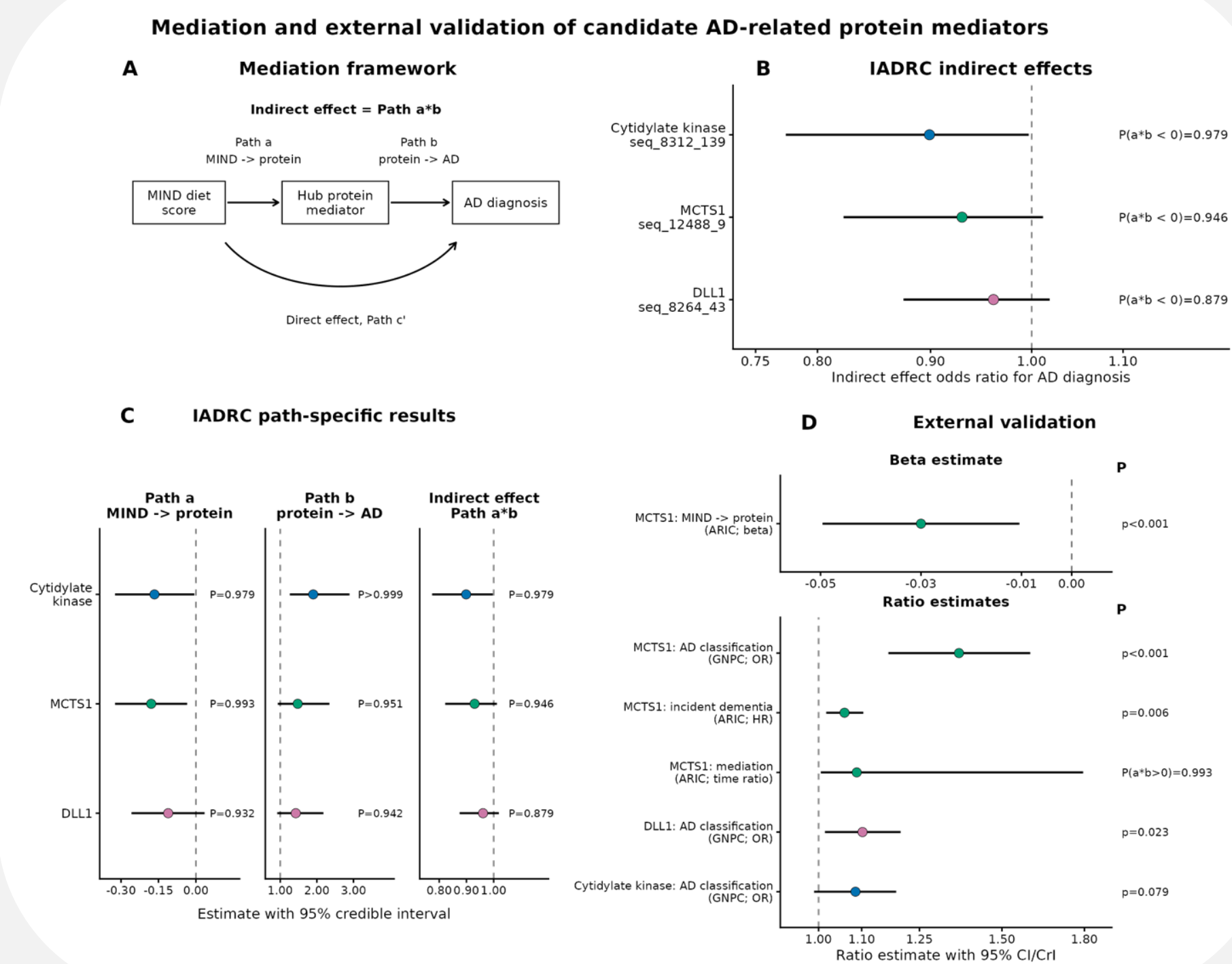


Fig 3. Indirect effect estimates for cytidylate kinase, MCTS1, and DLL1 were directionally consistent with hypothesized mediation but had wide uncertainty intervals. Only MCTS1 was available in the ARIC data and was well supported. MCTS1 and DLL1 also showed associations with AD status in GNPC

Conclusions

- Findings support plasma proteomic networks as a strategy for identifying biological pathways related to both MIND diet adherence and AD-related outcomes
- MCTS1 emerged as the protein with the most consistent signals across cohorts
 - MCTS1 has primarily been studied in oncogenic contexts but higher circulating abundance has been recently shown to be associated with increased risk of white matter hyperintensities³
- Future work should address the limitations of this study which include its cross-sectional design for primary analyses and modest sample size for some biomarker analyses

References: [1] doi.org/10.1016/j.jalz.2015.04.011, [2] doi.org/10.1002/alz.70579, [3] doi.org/10.1002/dad2.70202