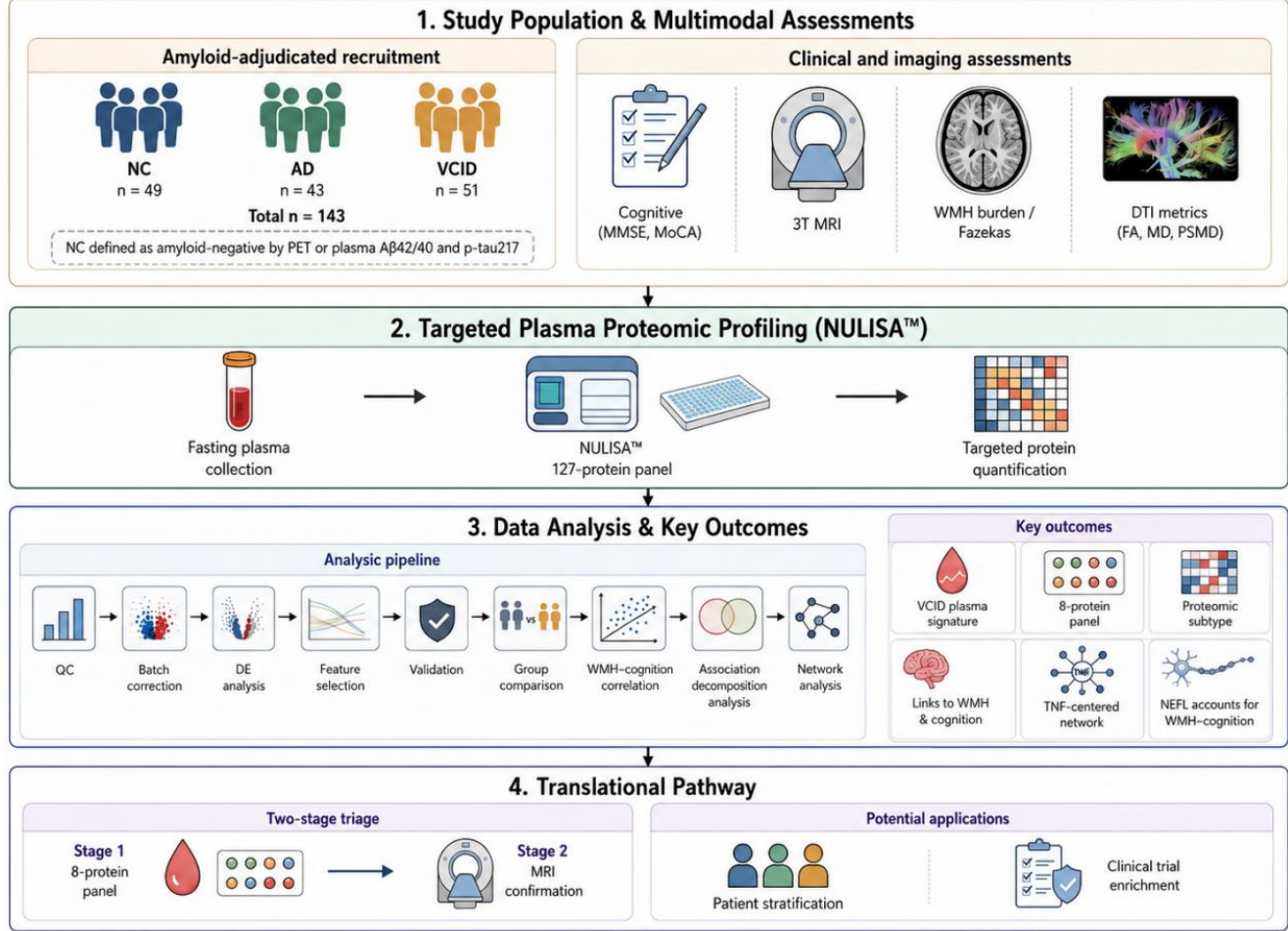
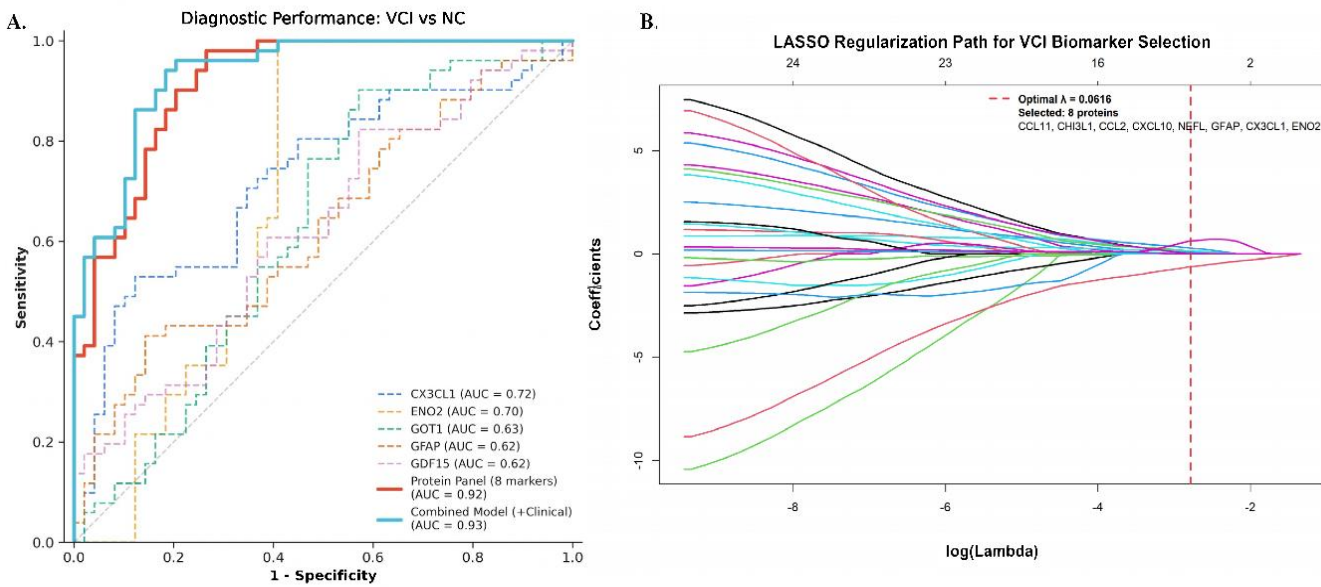
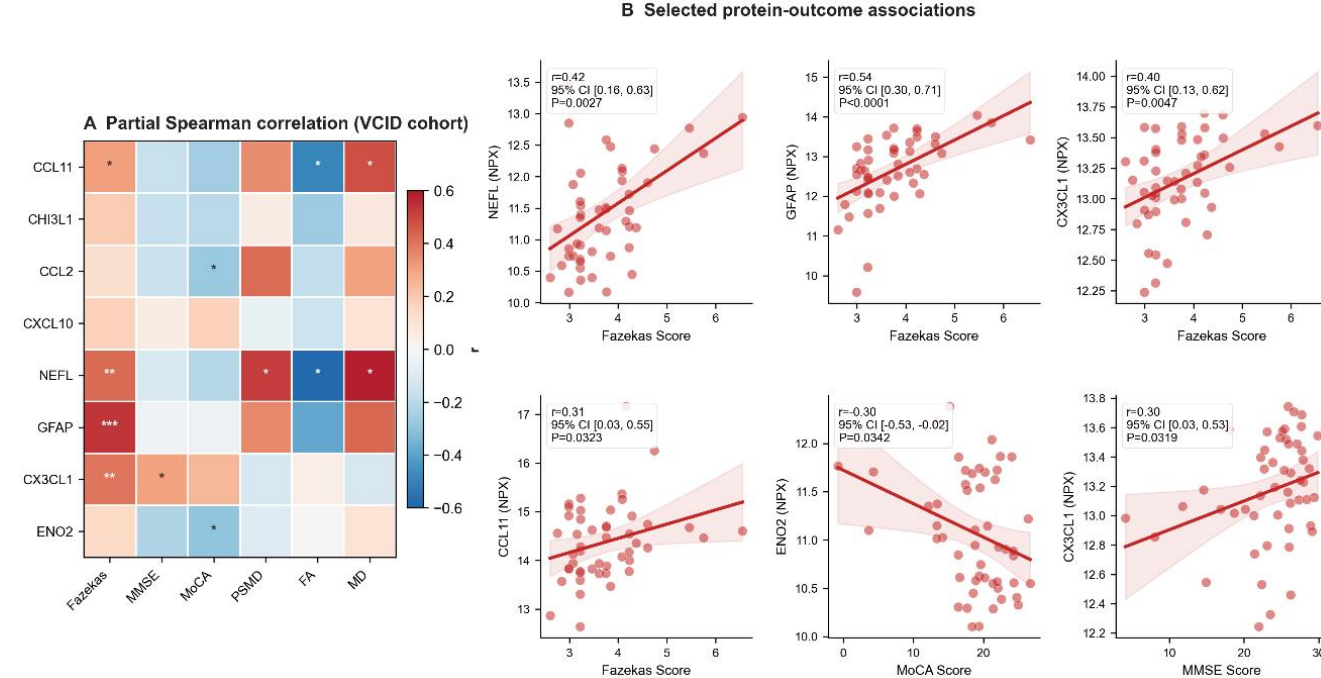


Ultrasensitive Plasma Proteomics Identifies Diagnostic and Mechanistic Signatures of Vascular Cognitive Impairment and Dementia

Abstract #4744

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Ultrasensitive NULISA plasma proteomics identified a candidate eight-protein signature that distinguished amyloid-adjudicated VCID from controls and linked inflammatory/neuroaxonal injury pathways to WMH burden and cognitive impairment.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Vascular cognitive impairment and dementia (VCID) is a major cause of cognitive decline, but clinically useful blood-based biomarkers remain limited. Interpretation is often confounded by concomitant Alzheimer’s disease (AD) pathology, and many vascular or inflammatory proteins are difficult to measure with conventional assays. We used ultrasensitive NULISA plasma proteomics in an amyloid-adjudicated cohort to identify VCID-associated proteins, derive a parsimonious diagnostic signature, and relate plasma biomarkers to white matter hyperintensity burden and cognitive performance.	We analyzed plasma from 143 amyloid-adjudicated participants: VCID (n = 51), AD (n = 43), and cognitively normal controls (n = 49). A 127-protein NULISA panel was used to identify VCID-associated proteins and derive an internally validated diagnostic signature. Signature proteins were related to MRI white matter disease, cognition, and biological pathways using adjusted correlation, cross-sectional decomposition, and enrichment analyses. 	Result 1. VCID showed a distinct plasma proteomic profile Result 2. An eight-protein signature discriminated VCID from controls Result 3. Signature proteins linked plasma biomarkers to white matter disease and cognition  	In an amyloid-adjudicated cohort, ultrasensitive NULISA plasma proteomics identified a VCID-associated protein profile and an internally validated eight-protein candidate signature. The signature discriminated VCID from controls and showed biological relevance through associations with MRI-defined white matter disease and cognition. These findings support inflammatory signaling and neuroaxonal injury, particularly NEFL-related white matter damage, as important components of VCID. External validation is needed before clinical implementation, but this plasma panel may support future VCID screening, risk stratification, and trial enrichment.	1.Raghavan S, et al. Plasma biomarkers and vascular cognitive impairment-related brain changes. <i>Alzheimers Dement</i>. 2025. 2.Gong K, et al. High-sensitivity plasma proteomics reveals disease-specific signatures in dementia. <i>Mol Neurodegener</i>. 2025. CONTACT Yi Tang, MD, PhD Department of Neurology & Innovation Center for Neurological Disorders, Xuanwu Hospital, Capital Medical University Email: tangyi@xwhosp.org ALZHEIMER'S ASSOCIATION AAIC 26