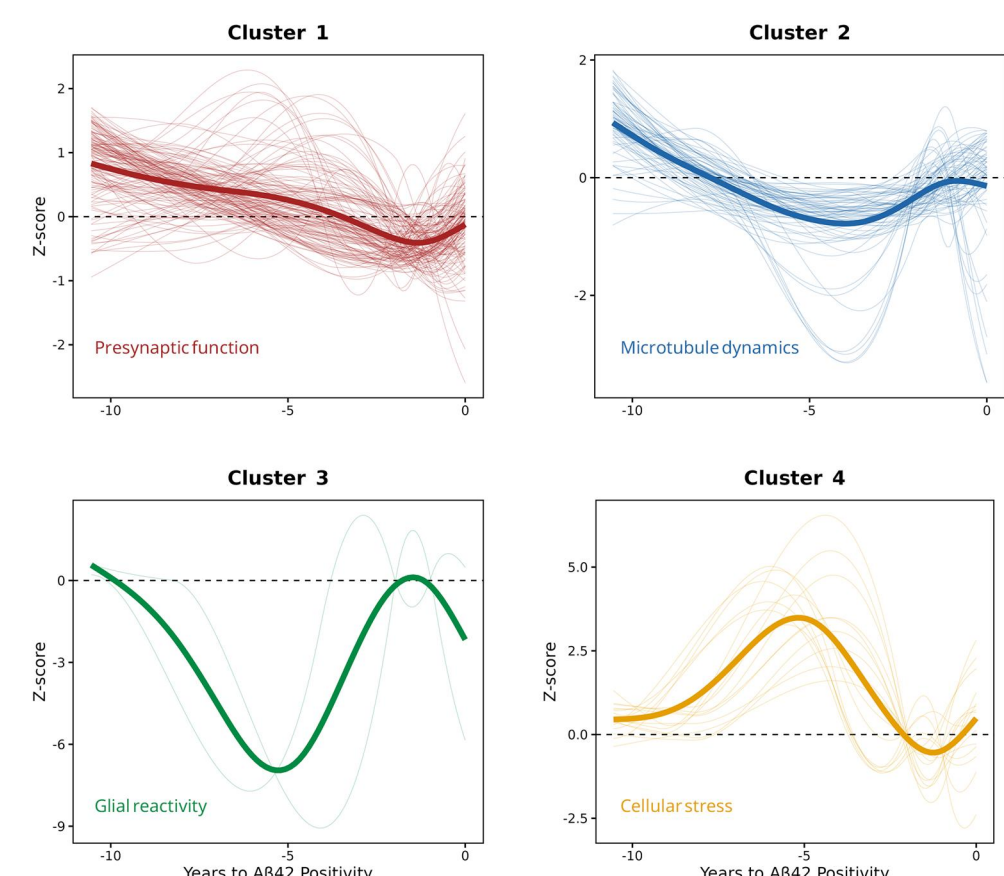
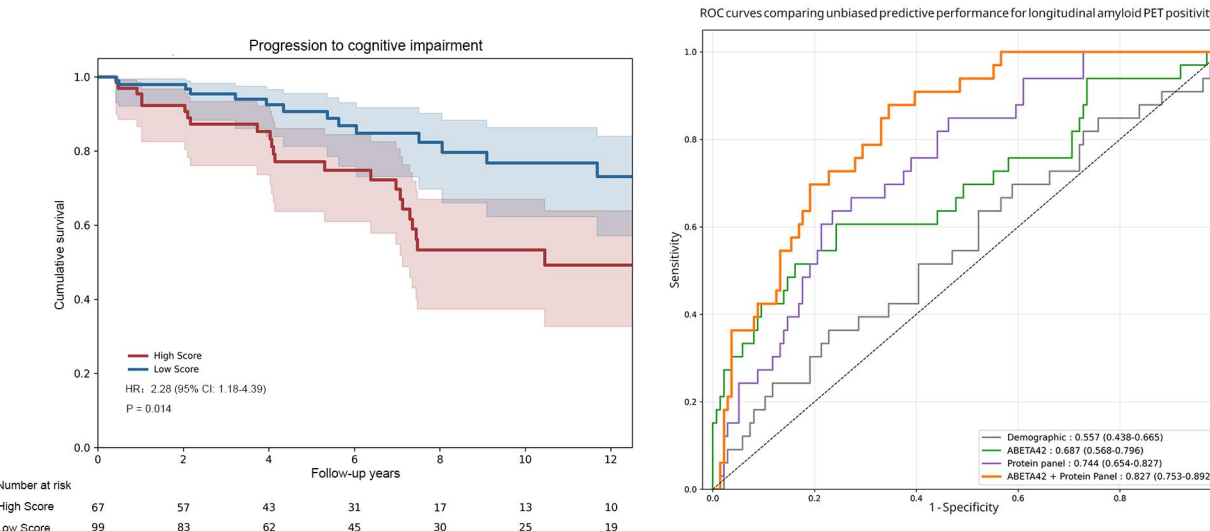


Early cerebrospinal fluid proteomic signatures preceding amyloid accumulation predict Alzheimer's disease progression

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In amyloid-PET negative individuals, the proteomic features correlated with longitudinal CSF Aβ42 dynamics were mainly enriched in synaptic function–related pathways. On the basis of current biomarkers, these observations hold potential for predicting future amyloid PET positivity conversion and clinical progression.

INTRODUCTION	RESULTS	Results	CONCLUSIONS	REFERENCES
CSF Aβ42 dysregulation begins decades before AD symptoms. However, the proteomic landscape preceding amyloid pathology remains largely unexplored, limiting early risk stratification. METHODS We profiled over 6,000 CSF proteins in 201 non-demented, amyloid PET-negative ADNI participants. LME models identified proteins associated with longitudinal Aβ42 change, followed by pseudo-temporal trajectory modeling. Nested LOOCV evaluated the predictive performance for future amyloid PET positivity.	We identified 235 proteins associated with longitudinal Aβ42 decline, revealing four potential pseudo-trajectory patterns enriched for synaptic, microtubule, glial, and stress-related pathways. 	These proteomic features improved prediction of amyloid PET conversion when combined with Aβ42 (AUC = 0.827). Applying the derived 10-protein panel, we found that a higher risk score was significantly associated with accelerated progression from CN to aMCI or AD (HR = 2.28, 95% CI 1.18-4.39, P = 0.014), as well as with longitudinal cognitive decline. 	The phase preceding amyloid accumulation is a biologically active period characterized by orchestrated, multi-pathway molecular remodeling. Integrating early CSF proteomic signatures with Aβ42 provides a practical approach to identifying high-risk individuals before irreversible amyloid deposition, offering a molecular window for timely preventive intervention.	Guo Y, Chen SD, You J, et al. Multiplex cerebrospinal fluid proteomics identifies biomarkers for diagnosis and prediction of Alzheimer's disease. <i>Nat Hum Behav.</i> 2024;8(10):2047-2066. doi:10.1038/s41562-024-01924-6 Ali M, Timsina J, Western D, et al. Multi-cohort cerebrospinal fluid proteomics identifies robust molecular signatures across the Alzheimer disease continuum. <i>Neuron.</i> 2025;113(9):1363-1379.e9. doi:10.1016/j.neuron.2025.02.014 CONTACT We welcome further discussion and exchange of ideas. Ting Yang: yt_ginny@163.com Dandan Sheng: shengdd2017@gmail.com 