

Proteomic signatures of global cognitive trajectories and incident cognitive impairment and dementia: The Multi-Ethnic Study of Atherosclerosis (MESA)

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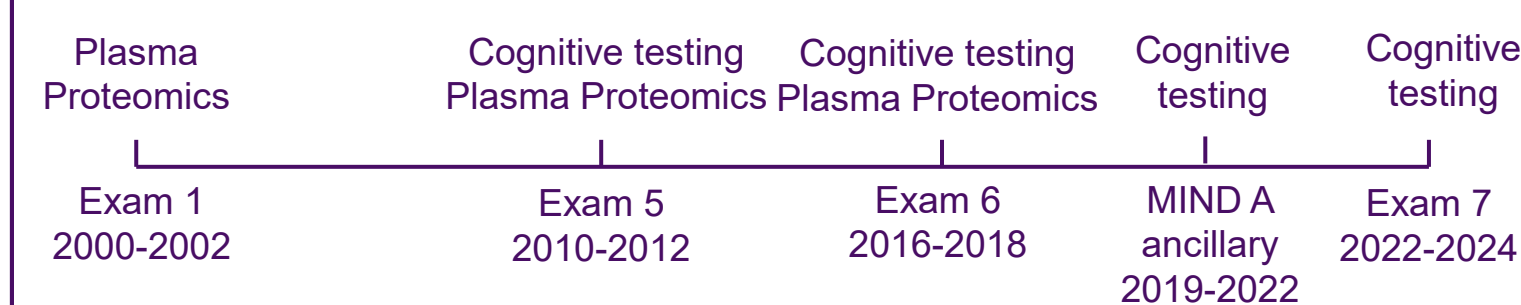
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- Cognitive aging is heterogeneous
- A 376-protein signature identified participants at higher risk of adverse cognitive aging
- Longitudinal increases in proteomic risk were associated with future dementia

INTRODUCTION

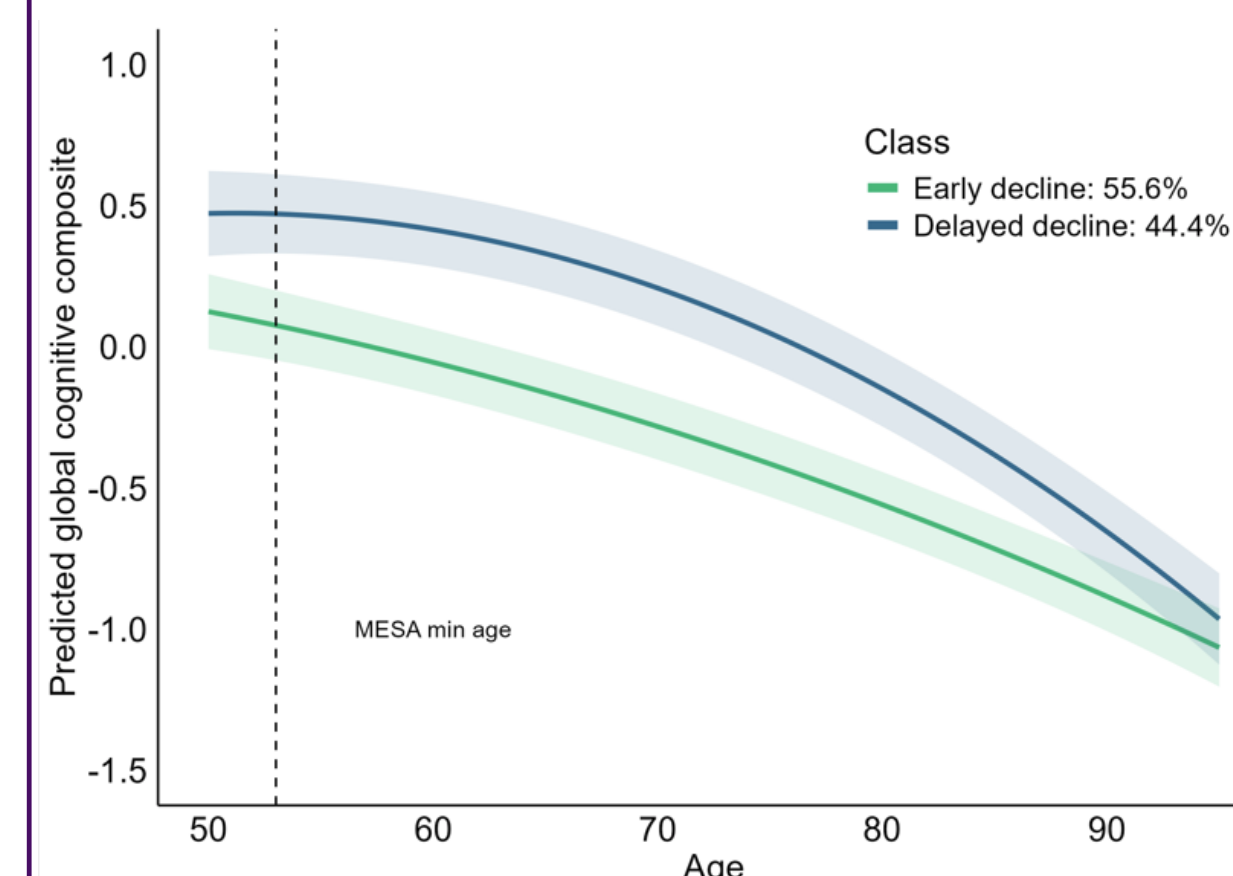
- Cognitive function declines with age, but individuals follow distinct trajectories
- The molecular mechanisms underlying different cognitive aging trajectories remain poorly understood
- We used longitudinal plasma proteomics to identify signatures of early cognitive decline and evaluate their relationship with future mild cognitive impairment (MCI) and dementia

METHODS

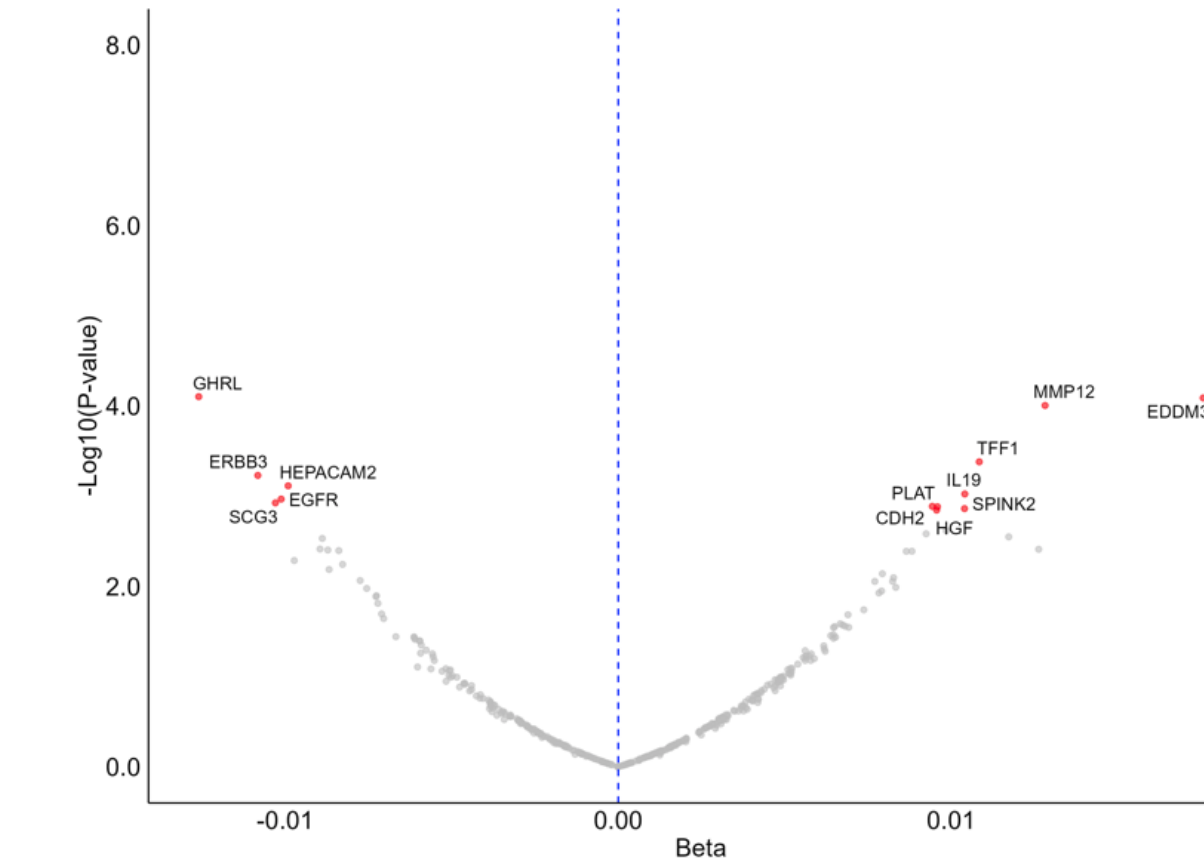


- Latent class mixed models to identify longitudinal cognition trajectories in MESA (N=4,031, 2010-2024)
- Plasma proteomics (2,882 **proteins**) measured at Exam 1, 5 and 6 with the Olink platform
- Elastic-net regression to predict probability of early cognitive decline with Exam 5 proteomics
- Proteomic scores derived at Exam 1 and 5
- Cox proportional hazards models to assess associations of proteomic score at Exam 5 and its change from Exam 1 to 5 with incident MCI/dementia
- MCI/dementia combines the ICD codes and the adjudicated cognitive status
- 848 incident MCI/dementia over a median follow-up of 10.4 years

RESULTS



- A 376-protein model predicting early cognitive decline, with $R^2=0.47$ in training/testing sets
- Inflammation, 103 proteins;
Cardiometabolic, 98 proteins; Oncology, 91 proteins; Neurology, 84 proteins



- 12 proteins significantly associated with early cognitive decline after false discovery rate correction
- Associated with higher probability of early decline: HGF, SPINK2, IL19, CDH2, PLAT, TFF1, MMP12, EDDM3B
- Lower probability: ERBB3, SCG3, HEPACAM2, GHRL, EGFR

Table. The risk of MCI/dementia

Model	HR (95% CI)
	Per SD increment
Proteomic score at Exam 5	
+ Covariates	1.28 (1.14-1.45)
+ Covariates and Exam 5 cognition	1.07 (0.94-1.22)
Annual change rate of the proteomic score from Exam 1 to 5	
+ Covariates + time interval between Exam 1 to 5	1.16 (1.08-1.24)
+ Covariates + time interval between Exam 1 to 5 and Exam 5 cognition	1.12 (1.04-1.20)
Covariates include age, gender, race/ethnicity, education level, language use, and APOE-ε4	

CONCLUSIONS

- A trajectory-derived proteomic score predicted future MCI/dementia independent of cognitive performance
- Longitudinal changes in proteomic risk may identify individuals at elevated risk years before clinical impairment.

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