

Developing A Blood-based DNA Methylation Index Of Cognitive Ability

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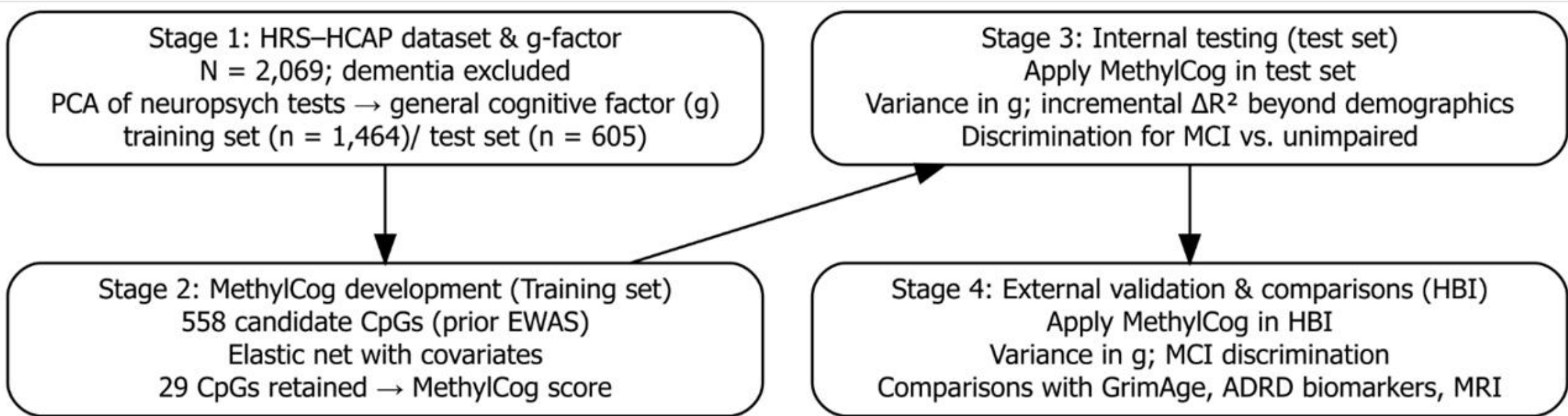
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Background

- Cognitive aging varies substantially and contributes to AD risk.
- Current epigenetic clocks capture biological aging, not cognition.
- We developed and externally validated **MethylCog**, a **29-CpG DNAm** index of general cognitive ability.

Methods



Final model: 29 CpGs selected from 558 candidates.

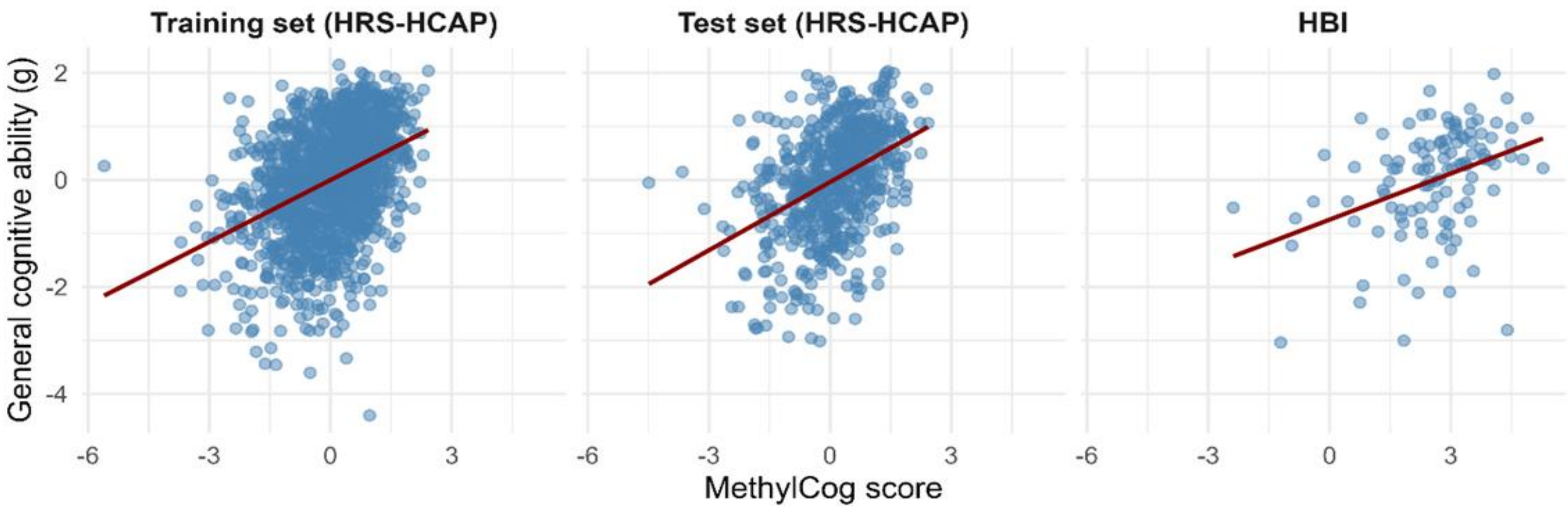
Cohorts	HRS (HCAP)		HBI
	Training Set (n = 1,464)	Test Set (n = 605)	External Validation (n = 112)
Age, years Mean (SD)	75.2 (7.0) 65–98	75.2 (7.1) 65–96	68.4 (10.4) 46–89
Education, years Mean (SD)	12.8 (3.1) 0–17	12.9 (3.0) 0–17	16.2 (2.1) 11–20
Female n (%)	828 (56.6%)	345 (57.0%)	78 (69.6%)
MCI n (%)	348 (23.8%)	141 (23.3%)	37 (33.0%)
APOE ε4 n (%)	318 (23.3%)	131 (23.0%)	32 (29.0%)

Race/ethnicity: HRS-HCAP training/test: White 79.6%/84.8%, Black/AA 14.6%/12.4%, Hispanic 10.7%/9.6%. HBI: White 85.7%, Hispanic 8.9%.

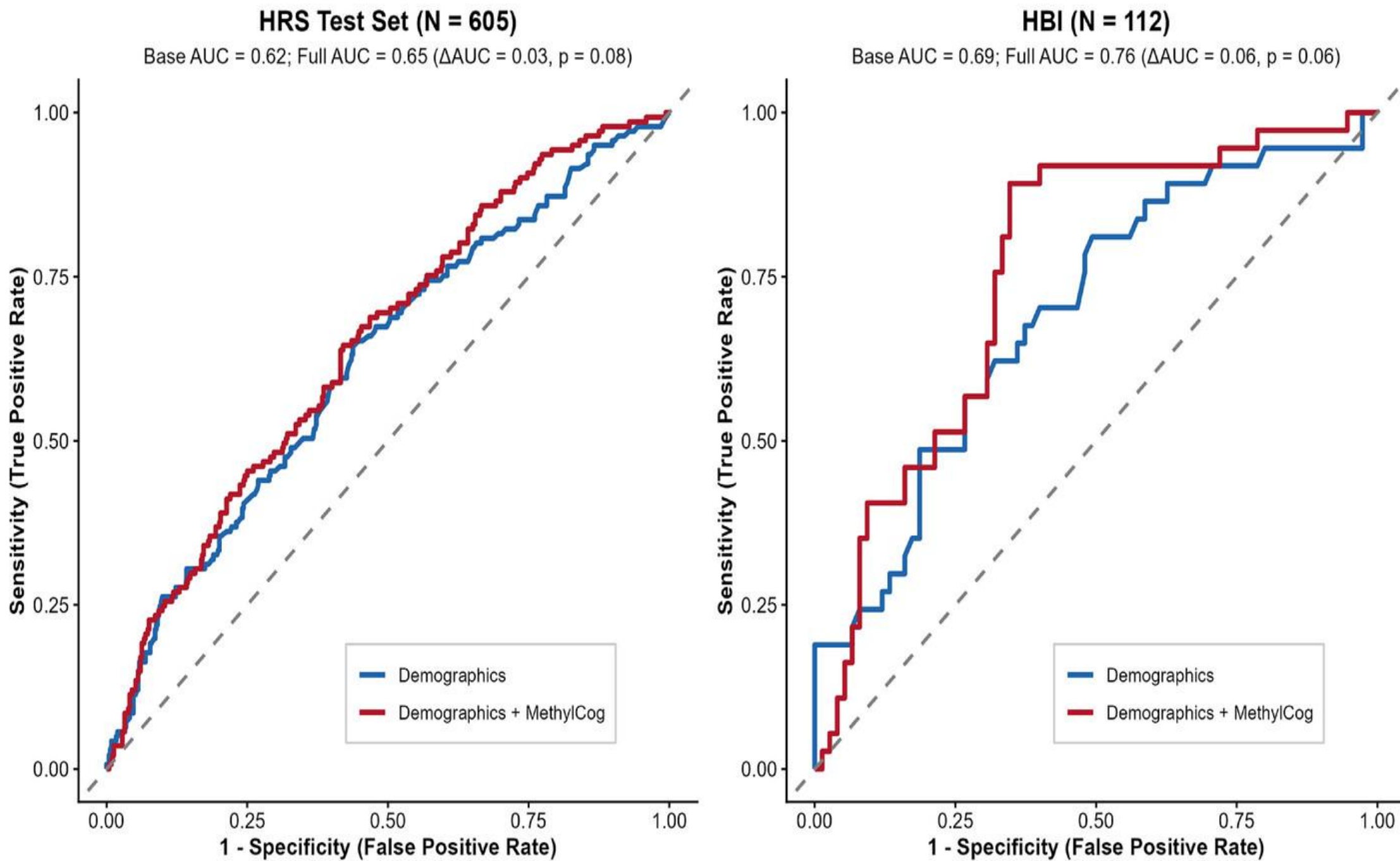
Results

MethylCog generalized across cohorts and improved MCI discrimination

Relationship between MethylCog and g across datasets



Diagnostic Discrimination of MethylCog for Mild Cognitive Impairment



Key Findings

- 17% Variance explained (HRS)
- 13% External validation (HBI)
- 11% Beyond demographics (HBI)
- OR 0.74 / 0.67 Lower MCI odds (HBI,HRS)
- AUC 0.69→0.76 Improved discrimination (HBI)

Reference

O'Shea, D. M., Wang, L., Lukacsovich, D., Dhanekula, D., Zhang, W., Galvin, C., Besser, L & Galvin, J. E. (2026). Development and validation of MethylCog, a blood DNA methylation proxy for cognition. *Alzheimer's & Dementia*, 22(5), e71421.

Support



1K12TR004555

Financial Disclosure
Nothing to disclose

Conclusions

- 29-CpG DNAm biomarker of general cognitive ability.
- Generalized across independent cohorts. Added predictive value beyond demographics.
- Distinct from biological aging.
- Potential for cognitive phenotyping in large epidemiologic studies.