

Multi-Polygenic Risk Scores for Modifiable Factors Improve Prediction of Mild Cognitive Impairment

Ying-Cen Lin¹, Yi-Fang Chuang^{2,3}
1 Department of Medical Education, National Taiwan University Hospital, Taipei, Taiwan
2 Institute of Public Health, National Yang Ming Chiao Tung University, Taipei, Taiwan
3 Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei, Taiwan



Background & Aim

- AD PRS struggle to accurately predict early-stage cognitive decline.
- Integrate the genetic liability of the 14 modifiable dementia risk factors (2024 Lancet Commission) to construct Multi-PRS model.

Research Aims

- Identify the most informative modifiable risk PRSs for MCI
- Benchmark integrated model against base and AD PRS models
- Analyze associations between PRS composite score, specific cognitive domains, and AD biomarkers

Methods

Study population: 1,132 older adults aged 50+ (847 normal, 285 MCI)

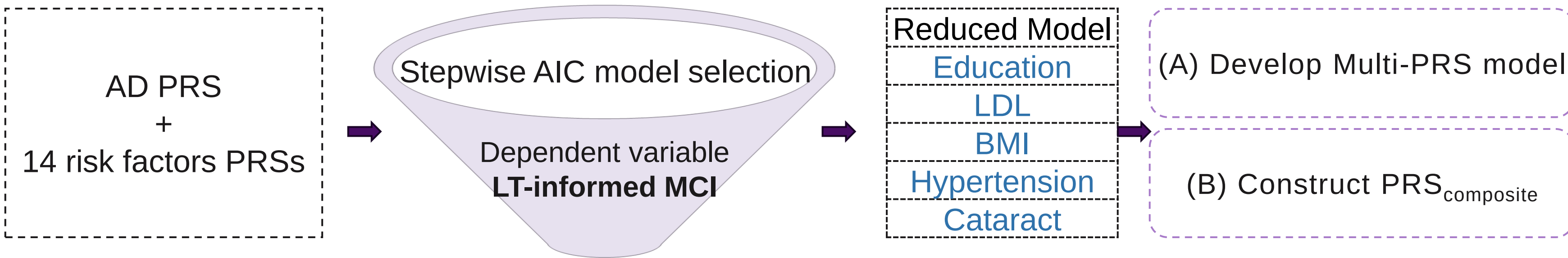
Genotyping: TWB 2.0 custom array, yielding 12,419,383 variants

PRS construction: PRS-CS / PRS-CSx (excluding the APOE region).

Statistical analysis

- Phenotype correction: A liability threshold-informed approach adjusted for age-stratified baseline prevalence, deriving an "LT-informed MCI" phenotype.
- Variable selection: Stepwise AIC selection isolated the top predictors from the 15 candidate PRSs.
- Internal validation: Leave-one-out cross-validation was utilized to weigh and derive the PRS_{composite}.

Results



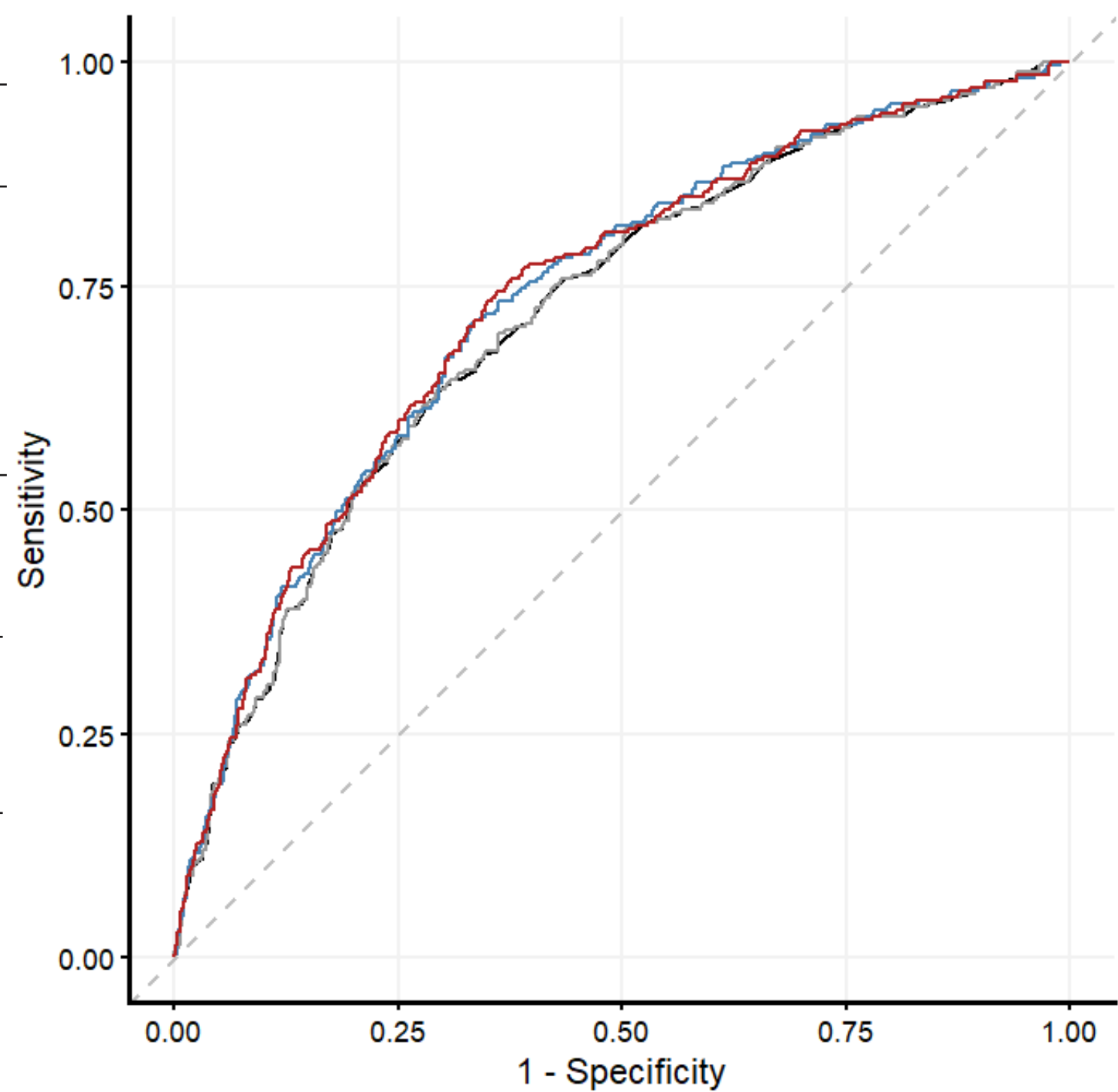
(A) Predictive performance of multi-PRS models for MCI

Model	AUC (95% CI)	P-value vs Base	P-value vs AD-PRS	P-value vs 5-PRS
— Base	0.718 (0.684, 0.752)	-	-	-
— AD-PRS	0.718 (0.684, 0.753)	0.510	-	-
— 5-PRS	0.733 (0.699, 0.766)	0.015	0.016	-
— 14-PRS	0.734 (0.700, 0.768)	0.019	0.020	0.608

(evaluated via DeLong's test)

(B) Association of PRS_{composite} on cognition and biomarkers

	Unadjusted model		Adjusted model	
	Correlation	P	age, sex, APOE ε4, top 10 PCs	
Cognition				
Attention	-0.077	0.01	-0.075	0.01
Memory	-0.069	0.02	-0.069	0.02
Executive	-0.064	0.03	-0.046	0.12
Language	-0.082	0.03	-0.082	0.03
Biomarkers				
amyloid SUVR	0.024	0.72	0.001	0.99
pTau217	0.137	0.14	0.162	0.1
pTau181	0.057	0.42	0.091	0.21



Contact
yingcen0422.md07@nycu.edu.tw
chuangy@nycu.edu.tw

Discussion & Conclusion

- Modifiable factor PRSs significantly improve MCI prediction beyond standard AD genetic risk.
- This genetic liability drives cognitive decline via pathways independent of amyloid (e.g., tau or vascular changes).