

Clinical and Polygenic Risk Show Independent Associations with Cognitive Decline

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BACKGROUND

- Clinical and genetic risk factors are associated with cognitive decline and Alzheimer's disease (AD).
- Integrating clinical and genetic risk may improve characterization of cognitive decline and dementia risk.
- The combined contribution of these risk domains to longitudinal cognitive outcomes remains incompletely understood.

Objective

- Evaluate the independent and joint associations of a dementia clinical risk score (CRS) and AD polygenic risk score (PRS) with cognitive decline and incident dementia.

Hypothesis

- Higher CRS and PRS are associated with accelerated cognitive decline and increased dementia risk.

METHODS

Data

- National Alzheimer's Coordinating Center. [1] Participants with genetic data and longitudinal cognitive assessments (NACC, N=11,531; aged 73 ± 8 years; 56% female; 40% *APOE** ϵ 4)

Exposures

- Clinical Risk Score (CRS): modified CAIDE score (age, sex, education, obesity, hypertension, and hypercholesterolemia. [2])
- Polygenic Risk Score (PRS): PRS-CSx cross-ancestry AD PRS. [3]

Outcomes

- Harmonized memory, executive function, and language domain scores (ADSP-PHC). [4]
- Secondary: Incident MCI or dementia.

Statistical Analysis

- Linear mixed-effects models with age as the time scale. Models adjusted for *APOE* ϵ 4 and genetic PCs.
- Predicted trajectories and contrasts estimated at low (−1 SD), mean, and high (+1 SD) CRS and PRS.
- Secondary: Cox proportional hazards models for incident MCI or dementia.

CONCLUSIONS

Clinical and genetic risk were independently associated with cognitive decline and dementia risk. Joint consideration of these risk domains identified consistent gradients of risk across cognitive and clinical outcomes, supporting the value of integrating clinical and genetic information when characterizing disease susceptibility. Findings were largely consistent with additive effects of CRS and PRS, with limited evidence for multiplicative interaction. Future studies leveraging larger and more diverse populations, earlier longer follow-up, and joint modeling of cognitive trajectories and clinical conversion may further clarify how clinical and genetic risk jointly influence disease progression.

REFERENCES:

[1] Beekly DL, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. Alzheimer Dis Assoc Disord. 2007 Jul-Sep;21(3):249-58. doi: 10.1097/WAD.0b013e318142774e. [2] Tolea MI, et al. A Modified CAIDE Risk Score as a Screening Tool for Cognitive Impairment in Older Adults. J Alzheimers Dis. 2021;82(4):1755-1768. doi: 10.3233/JAD-210269. [3] Ruan Y, et al. Improving polygenic prediction in ancestrally diverse populations. Nat Genet. 2022 May;54(5):573-580. doi: 10.1038/s41588-022-01054-7. Epub 2022 May 5. Erratum in: Nat Genet. 2022 Aug;54(8):1259. doi: 10.1038/s41588-022-01144-6. PMID: 35513724; PMCID: PMC9117455. [4] Hohman, T.J. (2023), ADSP Phenotype Harmonization Consortium. Alzheimer's Dement., 19: e077713. doi: 10.1002/alz.077713
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Clinical and Genetic Risk Independently Contribute to Cognitive Decline

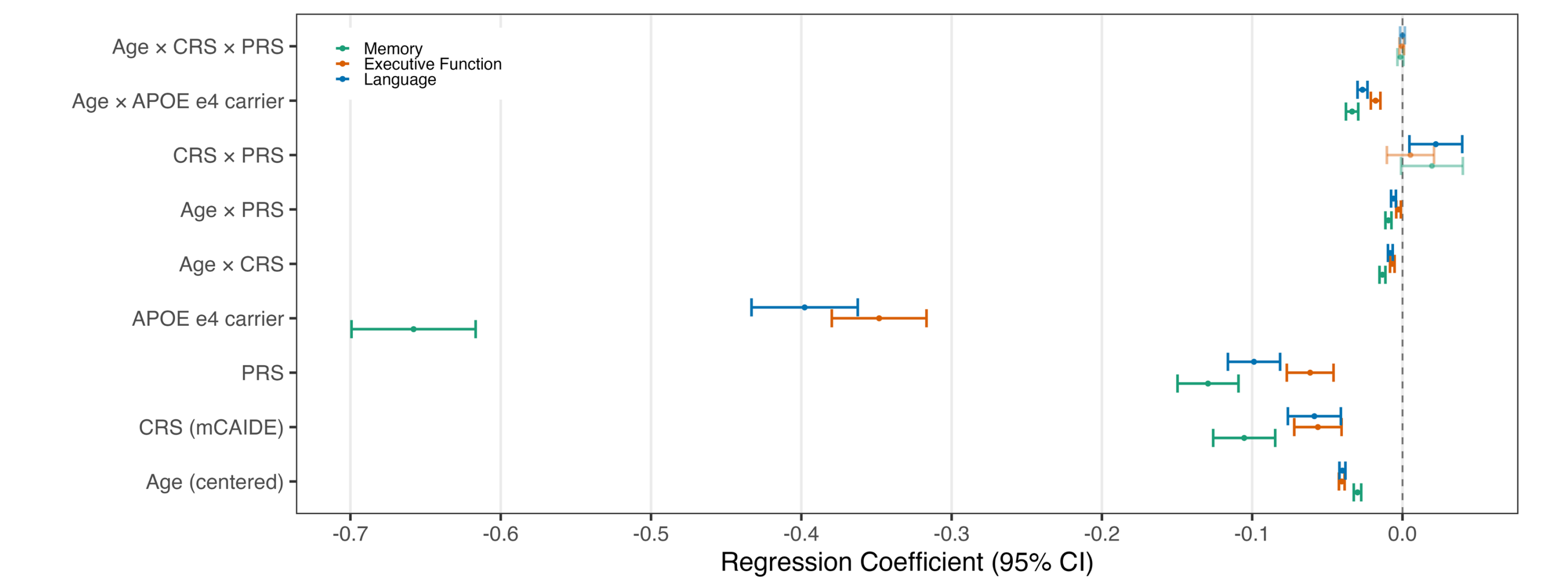


Figure 1: Standardized fixed-effect estimates (95% CIs) from linear mixed-effects models for memory, executive function, and language. Adjusted for *APOE** ϵ 4 status, genetic principal components.

Memory Trajectories Worsen With Increasing Combined Clinical and Genetic Risk

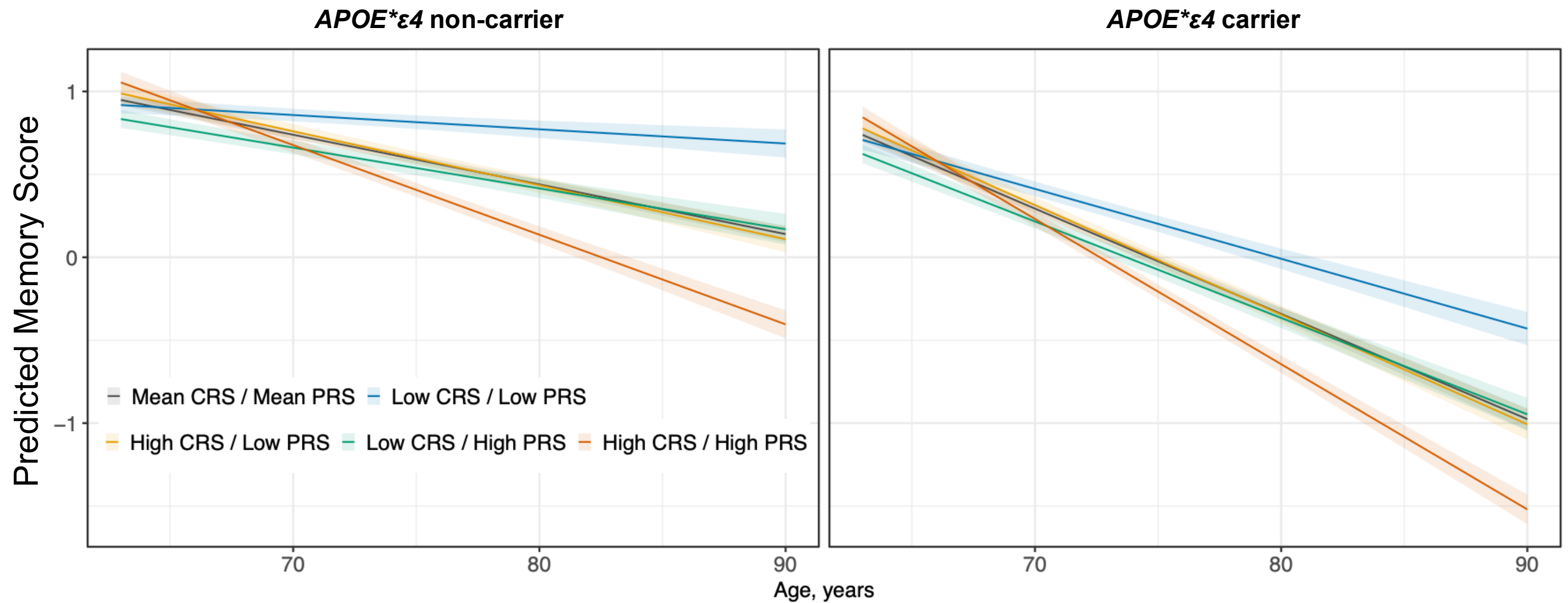


Figure 2: Predicted memory trajectories from the linear mixed-effects model across combined clinical risk score (CRS) and polygenic risk score (PRS) profiles defined at ±1 SD and the mean.

Higher Clinical Risk Is Associated With Reduced Dementia-Free Survival Across Polygenic Risk Levels

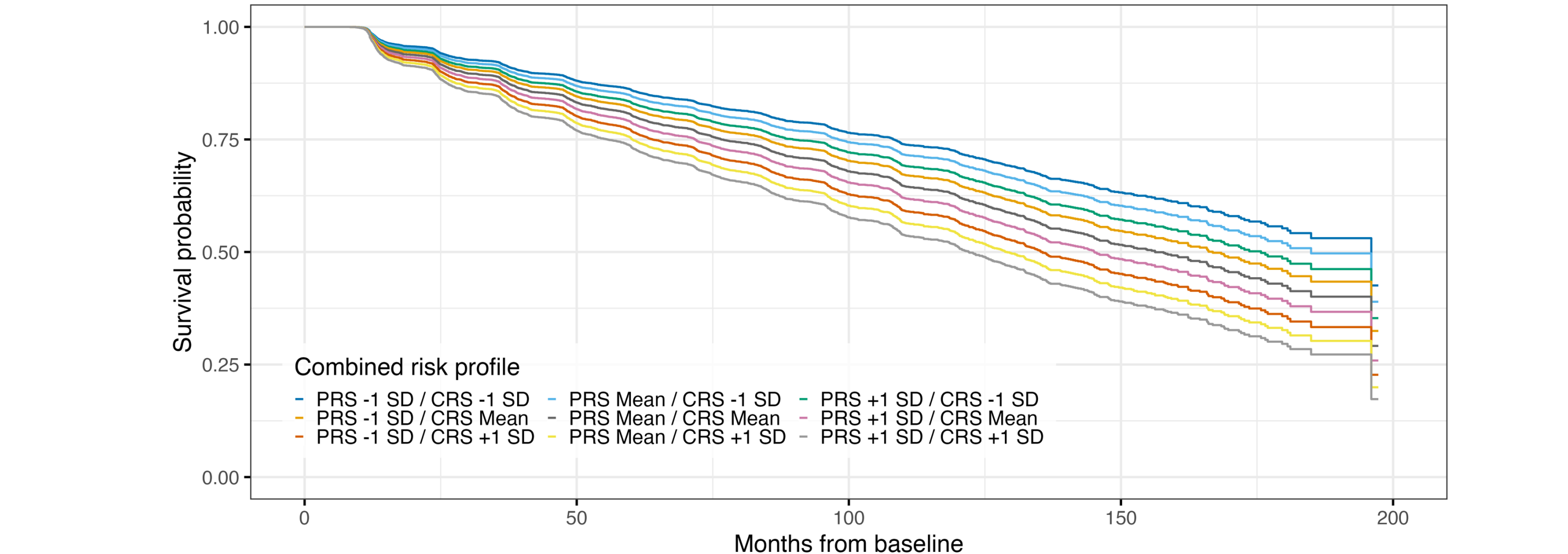


Figure 3: Model-based dementia-free survival curves estimated from the Cox proportional hazards model for representative combinations of standardized CRS and PRS values, adjusted for *APOE** ϵ 4 status and genetic principal components.