

Alzheimer's Polygenic Risk Scores Are Not Interchangeable: Evidence from 1,752 Models



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Alzheimer's disease polygenic risk scores are highly sensitive to methodological choices, but well-optimized models can substantially improve risk stratification beyond *APOE*.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
What is a Polygenic Risk Score (PRS)? ○ PRS aggregate all genetic risk for AD across the genome based on variant effects found through genome-wide association studies (GWAS). ○ PRS are intended to improve AD risk stratification beyond the <i>APOE</i> diplotype. Which Issues are We Trying to Resolve? ○ There are many different PRS methods (GWAS, algorithms, hyperparameters), but it is unclear which methods are the best for AD. ○ It is unclear if PRS are interchangeable and how they perform in different populations. ○ PRS have had variable practical utility in the past and past benchmarks were generally limited in size or scope.	The analytical pipeline for benchmarking 1,752 AD PRS models using the multi-ancestry ADSP R5 cohort with the GenoPred pipeline is shown above. Scores are standardized to the 1000 Genomes population.	○ Correlations between PRS models vary dramatically, ranging from moderately negative to perfectly positive. ○ Despite population standardization, individual-level PRS can have wide variability depending on the methods used for score calculation. ○ Optimal PRS methods improve AD risk stratification beyond <i>APOE</i>, yet their utility varies by population. ○ PRS thresholds can be used for AD risk stratification across <i>APOE</i> diplotypes and populations.	○ PRS methods are not interchangeable. Different approaches often produce inconsistent or contradictory risk predictions at both the population and individual levels. ○ PRS can meaningfully improve AD risk stratification beyond the <i>APOE</i> diplotype with the right methods. ○ PRS may perform best as high-risk group predictors rather than continuous linear scores.
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