

Extreme Polygenic Risk Scores Are Uncommon But Strong Indicators Of Alzheimer’s Disease Risk



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Rare extreme polygenic risk scores identify a small subset of individuals with significantly elevated Alzheimer’s disease risk independent of *APOE* diplotype, which could improve pre-symptomatic clinical trial stratification and interventions for at-risk individuals.

INTRODUCTION

What is a Polygenic Risk Score (PRS)?

- Combines the small individual effects of many common variants into a single score reflecting overall genetic risk for disease.
- A small subset of individuals have very high “extreme” scores.

What issues can extreme PRS address?

- Alzheimer’s disease (AD) neuropathological changes begin 15-20 years before clinical symptoms.
- PRS are currently good at population-level predictions but often fall short at individual-level risk predictions.
- We need reliable tools to identify high-risk individuals long before symptom onset so that clinical interventions can prevent memory loss before it starts.
- Extreme PRS thresholds offer a promising way to identify individuals at the highest genetic risk for AD before symptom onset.
- Extreme PRS could be used for pre-symptomatic enrichment of high-risk individuals for future clinical trials.

METHODS

The pipeline starts with the ADSP R5 Dataset (11,200 Cases (AD + MCI), 19,321 Controls) and GWAS Summary Statistics (Kunkle et al. (2019), Jansen et al. (2019), Bellenguez et al. (2022)). Both are pre-processed. The Target Cohort is then processed with 9 Algorithms (584 hyperparameter combinations) to generate 1,752 PRS. These are used in Statistical Analyses (All analyses stratified by genetic ancestry), followed by Correlation Reduction (26-43 unique PRS (p < 0.5)), Identification of Extreme High-Precision Thresholds, and finally Rules-Based Risk Stratification.

Analytical pipeline for PRS computation and identification of extreme high-precision AD thresholds in the ADSP cohort.

RESULTS

Four line plots showing % AD Cases vs. Optimal PRS z-score for different ancestries. Each plot includes a legend for Average (blue), APOE ε3/ε3 (red), APOE ε3/ε4 (green), and APOE ε4/ε4 (orange). Horizontal dashed lines indicate average AD risk per APOE diplotype. Open dots show AD risk by PRS decile, stratified by APOE diplotype. Solid dots show extreme low/high PRS (n ≥ 10).

Two bar charts showing % AD Cases for different genetic ancestries. (A) Top Performing J/rip Rules Including APOE ε3/ε4. (B) Top Performing J/rip Rules Independent of APOE. Each chart compares the Overall ancestry baseline (light blue) with the Top J/rip rule (dark blue).

Genetic Ancestry	# of PRS (p < 0.5)	Optimal GWAS source and PRS	Optimal Z-score threshold	# Cases	# Controls	# of individuals per APOE diplotype	P-value corrected by independent PRS
African	43	Bellenguez et al., 2022 LassoSum	0.485	12	0	ε2/ε3: 0 ε3/ε3: 4 ε3/ε4: 6 ε4/ε4: 2	0.004827
Admixed American	32	LDpred2 non-spars model P=0.018 h2=0.05	0.543	11	1	ε2/ε3: 1 ε3/ε3: 5 ε3/ε4: 6 ε4/ε4: 0	0.02727
East Asian	36	Kunkle et al., 2019 LassoSum	0.398	12	1	ε2/ε3: 0 ε3/ε3: 8 ε3/ε4: 4 ε4/ε4: 1	0.02824
European	26	Kunkle et al., 2019 LassoSum	0.619	42	0	ε2/ε3: 1 ε3/ε3: 11 ε3/ε4: 24 ε4/ε4: 6	2.3068 x 10 ⁻¹³

Thresholds that maximize precision (≥10 individuals), reaching 100% in African and European ancestries.

CONCLUSIONS

- Extreme PRS thresholds identify individuals with near-perfect precision for AD, largely independent of *APOE* diplotype.
- Although rare, these extreme scores provide high-confidence identification of individuals at exceptionally elevated AD risk.
- Exceptionally low PRS should not be interpreted differently than low PRS.

CONTACT

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Questions?
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