

Predicting Alzheimer's disease through a composite genetic risk score reflecting multiple pathophysiological pathways

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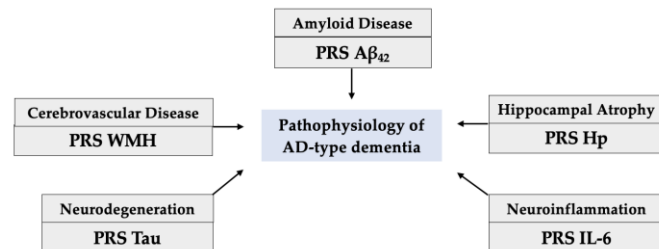
INTRODUCTION

- Complex genetic risk scores for Alzheimer's disease (AD) combine multiple polygenic risk scores (PRS)
- These scores have not yet provided additional predictive power beyond disease-specific PRSs

METHODS

- We calculated a composite genetic risk score for AD-type dementia (*Meta-GRS*) integrating 5 distinct PRSs specific for pathophysiological pathways
- We used machine learning models (*elastic-net logistic regression* with 10-fold cross-validation) to account for overlapping genetic contributions
- The Meta-GRS was compared with a disease-specific PRS specific for late-onset AD (PRS-AD)

Figure 1. PRSs included in the Meta-GRS



$$\text{Meta-GRS} = \beta_1 * \text{PRS } A\beta_{42} + \beta_2 * \text{PRS } \text{Tau} + \beta_3 * \text{PRS } \text{WMH} + \beta_4 * \text{PRS } \text{Hp} + \beta_5 * \text{PRS } \text{IL-6}$$

- Data were drawn from HELIAD : a community-dwelling cohort of Greek individuals over 64 years of age
- 597 unrelated participants were included: without dementia at baseline (mean follow up of 2.9 years)

Figure 2. Flowchart of study participants

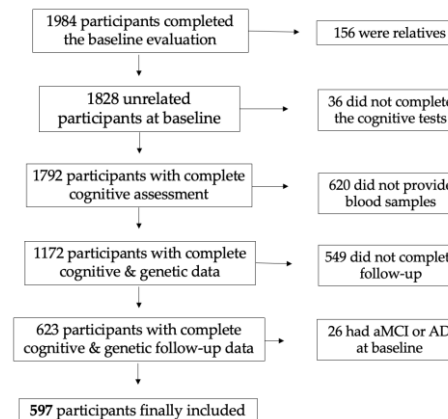
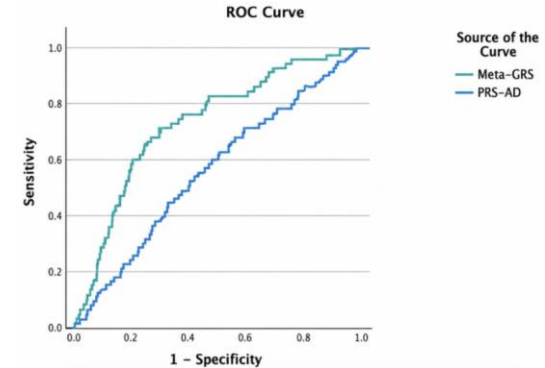


Figure 3. ROC curves for aMCI / AD risk



Explained Variability (pseudo-R²)

The Meta-GRS accounted for 9.8% of the variance in amnesic MCI (aMCI) /AD risk, which exceeded the proportion explained by the PRS-AD (R² = 6.1%)

CONCLUSIONS

- A Meta-GRS combining PRSs specific for biological pathways may improve risk prediction beyond disease-specific PRSs
- The selection of included PRSs is crucial for generating more accurate genetic risk scores

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RESULTS

COX proportional hazards models with amnesic MCI / AD as outcome

	Hazards Ratio (HR)	CI 95%	P-Value
Meta-GRS	1.996	1.545, 2.580	<0.001
PRS-AD	1.524	1.053, 1.995	<0.001

Models adjusted for age, sex, education years and APOE genotype

Discriminative Ability (AUC)

The Meta-GRS showed superior discriminative ability (AUC=0.791) than the PRS-AD (AUC=0.742)