Improving transferability of polygenic risk scores across Dutch ethnic groups: the case of lifetime depression in the HELIUS study

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BACKGROUND

PRS
- Sum of the weighted effects of many genetic variants as determined by Genome-Wide Association Studies (GWAS), represents an individual's genetic risk
- Useful for: research + clinical practice/personalized medicine

Limitations of the GWAS results also **transfer** to the PRSs! e.g. Lack of generalizability (Eurocentric bias) → **Aggravation of pre-existing health disparities!**

What to do?
- Increase ethnic representation in cohorts (long-term goal)
- Leverage statistical methods to improve polygenic risk predictions across populations (short-term solution)

Aim of the study: Improve the transferability of depression polygenic risk across Dutch ethnic groups of different ancestries

METHODS

Case definition

sadness AND/OR anhedonia
AND
impairment

QC

- Base (GWAS) data
- Target (HELIUS) data

PRS calculation

1) Single-ancestry *
2) Multi-ancestry *
3) Cross-ancestry (PRS-CSx)

**single-discovery methods*

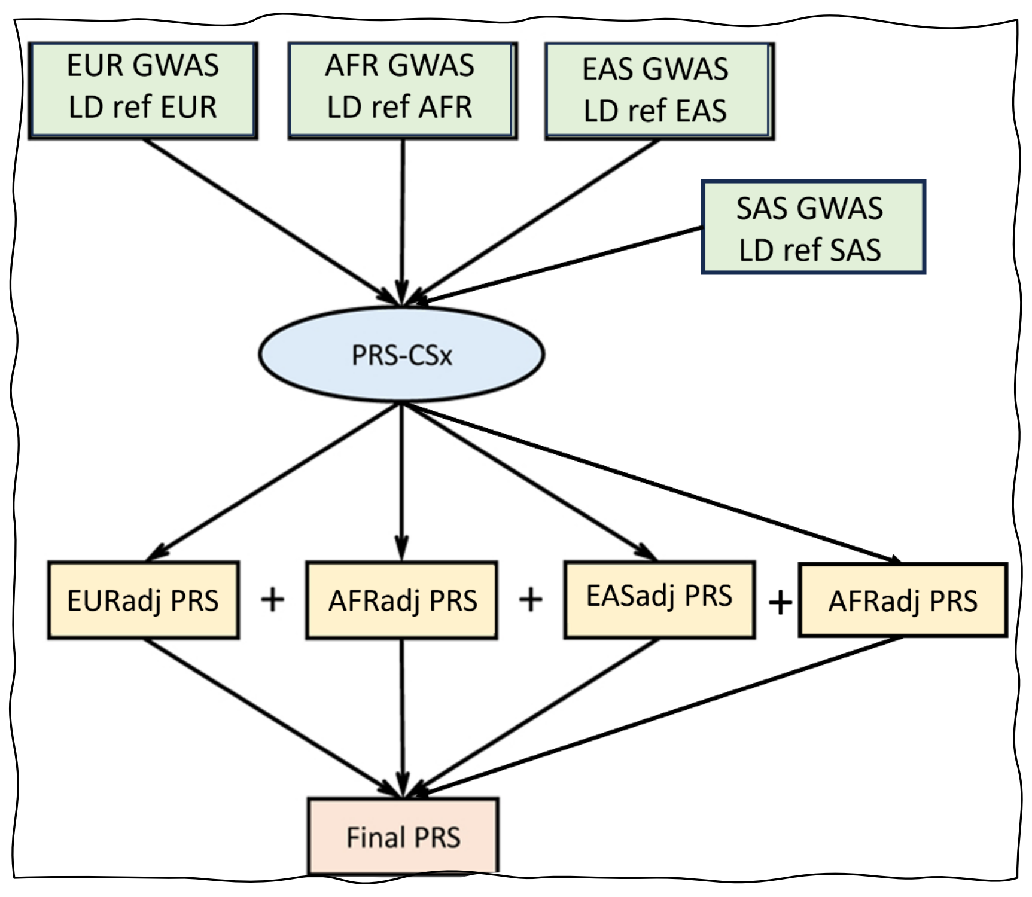
Model fitting

- base glm (β_0)
covariates: age, sex, 10 first technical PCs
- full glm= β_0 + **PRS**

ANOVA

R^2_{full} vs R^2_{base}

Has the addition of PRS to the glm **significantly improved** model performance?

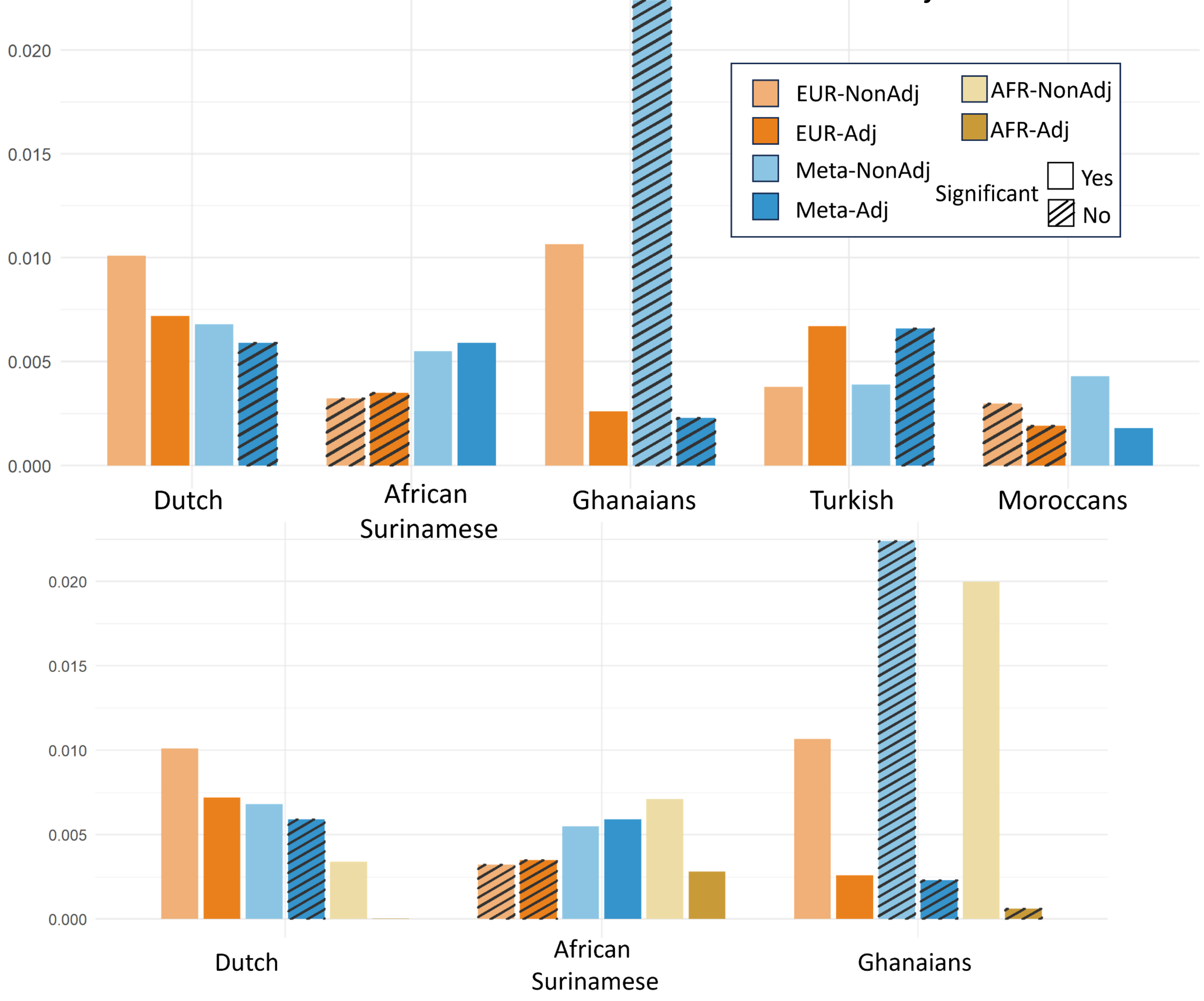


Adjusted from Ruan et al. (2022)

RESULTS

Variance explained by the PRS

$(R^2_{PRS} = R^2_{full} - R^2_{base})$



EUR-NonAdj: The standard, single-ancestry PRS based on European-only GWAS data[3]

EUR-Adj: cross-ancestry PRS based on PRS-CSx-adjusted European GWAS data[3]

Meta-NonAdj: multi-ancestry PRS based on EUR, AFR, EAS, SAS and HIS participants[4]

Meta-Adj: cross-ancestry PRS based on meta-analyzed, individually-adjusted GWAS data from EUR, AFR, EAS and SAS populations[4]

AFR-NonAdj: single-discovery PRS based on African-only GWAS data[4]

AFR-Adj: PRS based on PRS-CSx-adjusted African GWAS data[4]

PRELIMINARY CONCLUSIONS

- **Each population exhibits distinct patterns of PRS method performance**

e.g.
-***European Dutch***: performance **declines** with increased diversity-complexity
-***Afr. Surinamese***: performance **increases** with increased diversity-complexity

- **Ancestry-specific data as the base GWAS performed better than European-based or even multi-ancestry-based methods**
(despite their respective 12-fold and 2-fold larger sample sizes)
- **The PRS-CSx adjustment shows poor performance in underpowered GWASs** (e.g. African GWAS)

There is no one-size-fits-all solution

NEXT STEPS

- Examine other phenotypes (preferably measures of current depression)
- Impute phenotypic data to handle missingness
- Run the analyses also for the South Asian Surinamese participants of HELIUS
- For populations of interest: perform other cross-ancestry methods like **BridgePRS** (outperforms PRS-CSx in cases of high uncertainty)

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