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The relationship between the predictive power of polygenic scores and the genetic ranking of individuals across PGS construction methods

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ABSTRACT:

Polygenic scores (PGS) are increasingly being used in medicine and social sciences. While their explanatory power, interpretation and limitations are widely discussed, less attention has been devoted to how their construction affects the ranking of individuals. This is particularly important for screening and personalized medicine since polygenic scores are used to target high risk individuals. How many individuals are erroneously left out of screening when a PGS is constructed on basis of a different discovery cohort, or by just including genome-wide significant SNPs? Additionally, the rank consistency of polygenic scores may have consequences for gene-environment interaction research, especially when researchers identify exposure on the basis of PGS percentiles.

In this paper, we use simulations and empirical data to study the effect of (i) GWAS discovery sample selection and (ii) polygenic score construction methods - Plink vs LDPRED and all SNPs versus genome-wide significant SNPs - on PGS rank switching. Our results suggest that different methodologies yield non-negligible rank switching. To explore potential implications of rank switching, we investigate whether PGS construction method can affect personalized cholesterol-lowering medication decisions for individual at risk of coronary artery disease. Additionally, we illustrate that the interaction between various polygenic scores and year-of-birth varies depending on the PGS construction method. Our results therefore reinforce the need for standardized PGS reporting guidelines.

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