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Genetic and non-genetic interplays for substance use disorders

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Background/significance/hypothesis:
Substance use disorders (SUDs) are disorders with complex mechanisms including significant environmental and genetic components, which often co-occur. GWAS has successfully identified hundreds of variants associated with SUDs. However, polygenic risk score (PRS) based on GWAS exhibits limited power for prediction in independent cohorts. As a result, the current clinical use of PRS for SUDs is not yet feasible. To improve PRS analysis, this study incorporated cross-ancestry PRS of multiple SUDs and environmental factors, to predict the risk of alcohol use disorder (AUD) in the UK Biobank.

Methods:
Cross-ancestry PRS of multiple SUDs based on the latest GWASs were calculated using a Bayesian method. The target samples include 12,787 AUD cases of European ancestry and randomly selected controls. Different models were tested between the PRS of SUDs and AUD status, correcting for covariates: 1) PRS of AUD; 2) Adding key environmental factors and the interactions; 3) Adding PRS of other SUDs. Prediction performance was measured by variances explained (pseudo-R-squared [R^2]).

Results:
The overall R^2s by different tests were small as expected, indicating the highly polygenic nature of AUD. Improved prediction performance was observed upon the inclusion of environmental factors and their interactions with genetics. Additionally, the incorporation of PRS from other SUDs further enhanced prediction.

Conclusions:
AUD is a complex and polygenic disorder with both genetic and non-genetic components, and shares genetic architecture with other SUDs. This underscores the urgent need for a new research direction that deviates from conventional analyses within this field.
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