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Advanced genetic study of problematic alcohol use in > 1 million subjects from multiple populations

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Background/significance/hypothesis:
Problematic alcohol use (PAU) is a leading cause of death and disability worldwide. Our prior GWAS for PAU in European ancestry individuals identified 29 risk loci. Despite the large sample in this and other GWAS, we lacked sufficient power in non-European populations. To improve our understanding of the genetics, biology, and relationship of PAU with other traits in multiple populations, we conducted a large cross-population meta-analysis of PAU.

Methods:
We combined Million Veteran Program (MVP) subjects with data from the UK Biobank, Psychiatric Genomics Consortium (PGC), FinnGen, and other available samples to yield a total sample of 1,041,841 individuals. We used a proxy phenotype comprising alcohol use disorder, alcohol dependence in PGC, and Alcohol Use Disorders Identification Test – Problems (AUDIT-P). We conducted within-ancestry meta-analysis for five major ancestry groups: European, African, Latin American, East Asian and South Asian, followed by cross-population meta-analysis.

Results:
In the European meta-analysis, 76 independent variants reached genome-wide significance, more than double the number in our previous study. Tissue expression analysis shows enrichments in brain tissues. Cross-ancestry genetic correlation between European and African populations is high (rg=0.81, se=0.09), indicating a shared genetic architecture between those two populations. Meta-analysis of all 5 populations yielded 105 independent variants.

Conclusions:
This updated GWAS of PAU in multiple populations fills an important gap due to the lack of missing diversity in alcohol genetic studies. These findings substantially increase our understanding of the genetic architecture of PAU, provide unprecedented power to investigate the causal relationships of PAU to other diseases.