## **Genetic Heterogeneity Across Dimensions of Alcohol Use Behaviors**

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Background, Rationale/significance, hypothesis: Increasingly large genome-wide association studies (GWASs) of alcohol use behaviors (AUBs) have led to an influx of associated genes, yet their clinical and functional understanding remains low. This may be because most GWASs do not account for the complex and varied manifestations of AUBs. This study applied a multidimensional framework to investigate the latent genetic structure of AUBs obtained from self-reports, medical interviews, and electronic health records, hypothesizing that heterogeneous genetic influences underlie these measures.

Results: We performed a GWAS and genomic structural equation modelling of 18 AUBs in approximately 400,000 UK Biobank participants. Four latent factors were identified: severe/chronic alcohol Problems, frequency and quantity of Consumption, a pattern of decreasing alcohol consumption in later life with a preference for beer (BeerPref), and a preference for fortified wine and spirits (AtypicalPref). Thirty-five novel loci were identified, largely driven by BeerPref. The latent factors were moderately correlated (rg= .12-.57) and had distinct patterns of associated genes, brain regions, and cell types. Factor-associated genetic variants predicted alcohol and substance use disorders in multiple independent samples.

Discussion: Deep phenotyping is an important next step to improve understanding of the genetic etiology of AUBs, in addition to increasing sample size. Additional measures beyond total consumption levels and lifetime alcohol use disorder diagnoses carry genetic information that is relevant to individual risk. Further effort is required to uncover the genetic heterogeneity underlying AUBs using methods that account for their multidimensional nature.