Name: Jeanne Savage Email: j.e.savage@vu.nl

Genetic Heterogeneity Across Dimensions of Alcohol Use Behaviors

Jeanne Savage[1], Peter Barr[2,3], Tanya Phung[1], Younga Lee[4,5,6], Yingzhe Zhang[4,6,7], Vivia McCutcheon[8], Tian Ge[4,5,6,9], Jordan Smoller[4,5,6,9], Lea Davis[10], Jacquelyn Meyers[2,3], Bernice Porjesz[2], Danielle Posthuma[1,11], Travis Mallard[4,5,6], Sandra Sanchez-Roige[10,12,13]

[1]Department of Complex Trait Genetics, Vrije Universiteit Amsterdam; [2]Department of Psychiatry and Behavioral Sciences, SUNY Downstate Health Sciences University; [3]Veterans Administration New York Harbor Healthcare System; [4]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital; [5]Department of Psychiatry, Harvard Medical School; [6]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard; [7]Department of Epidemiology, Harvard T.H. Chan School of Public Health; [8]Department of Psychiatry, Washington University School of Medicine; [9]Center for Precision Psychiatry, Massachusetts General Hospital; [10]Department of Medicine, Vanderbilt University Medical Center; [11]Department of Child and Adolescent Psychology and Psychiatry, Amsterdam University Medical Center; [12]Department of Psychiatry, University of California San Diego; [13]Institute for Genomic Medicine, University of California San Diego

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.

DRAFT