Name: Emily Hartwell Email: emily.hartwell@pennmedicine.upenn.edu

Stratified Multi-Ancestry GWAS of Alcohol Use and Depression: Unique Genetic Architecture

Emily E. Hartwell,[1,2] Zeal Jinwala,[1,2] Sylvanus Toikumo,[1] Rachel Vickers-Smith,[3] Benjamin Voight,[1] Rachel L. Kember[1,2]

[1]Crescenz VA Medical Center, [2]University of Pennsylvania, [3]University of Kentucky

Alcohol use disorder (AUD) and major depressive disorder (MDD) are prevalent, costly, and recurrent conditions. Having one disorder increase the risk of the other four-fold and treatment is often less effective. To interrogate this comorbidity, we conducted a multi-ancestry genome-wide association study (GWAS) of AUD (N>400,000) and then a GWAS stratified by MDD status. Cases were identified in the Million Veteran Program as those with 1+ inpatient or 2+ outpatient International Classification of Diseases 9/10 codes for alcohol abuse or dependence (n=114,627; by genetically inferred ancestry: AFR = 31,552, EUR = 69,203, AMR = 13,114, EAS = 636, SAS =122). We then determined MDD status using ICD codes for depression. Controls were individuals with no instances of AUD or MDD in their electronic health record (n=288,981). Using PLINK, genome-wide association testing was performed adjusting for age, sex, and first 10 PCs and then cross-ancestry meta-analyses were conducted. Polygenic scores (PGS) were calculated using PGS-CS and phenome-wide association studies conducted in the Penn Medicine BioBank. We identified 48 genome-wide significant loci in the cross-ancestry meta-analysis of AUD, 19 in comorbid AUD+MDD, and 17 in AUD without comorbid MDD. In the stratified GWAS, 150, 93, and 42 SNPs with heterogenous effects were observed in EUR, AFR, and AMR ancestry, respectively. The AUD PGS in EUR was associated with tobacco use, alcohol-related phenotypes, other psychiatric disorders, and, notably, mood disorders. However, neither stratified PGSs were associated with non-substance use phenotypes. Results demonstrate the unique architecture of AUD with depression compared to AUD alone.