

Submitter Name: Roseann E. Peterson
Submitted email: peterson.roseann@gmail.com

**Cross-ancestry Genome-wide Analyses of Substance Use Behaviors in Schizophrenia:
Findings from the Genomic Psychiatry Cohort.**

Roseann E. Peterson¹, Tim B. Bigdeli², Jacquelyn Meyers², Giulio Genovese³, GSCAN Consortium, Genomic Psychiatry Cohort, Michele Pato², Carlos Pato², Ayman H. Fanous².

¹Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University;

²Department of Psychiatry & Behavioral Sciences, State University of New York Downstate Medical Center; ³Department of Genetics, Harvard Medical School.

Alcohol and drug dependence have been found to be more than twice as common in those with a psychotic disorder. Despite numerous associations between substance use and schizophrenia spectrum disorders, there has been limited research on shared genetic liability, particularly in non-European cohorts. Here, we used the latest results from the Genomic Psychiatry Cohort (GPC) to dissect genetic overlap between schizophrenia (SCZ) and substance use behaviors including heavy alcohol use, lifetime smoked 100 cigarettes, and cannabis use. The GPC is a clinically-assessed, multi-ethnic sample (African-admixed, Latino, European ancestry) collected by 12 collaborative US sites (n=13,432 SCZ/SAD cases, n=11,542 screened controls). As expected, SCZ cases had significantly elevated rates of heavy alcohol use, smoking initiation, and cannabis use compared to controls across all ethnic strata. Polygenic risk scores (PRS) constructed from results of large-scale genome-wide association studies of alcohol, tobacco, and cannabis use (GSCAN, ICC) significantly predicted SCZ case status but results attenuated across ancestry. Conversely, however, PGC-SCZ PRS did not significantly predict substance use behaviors in SCZ-cases or controls. Additionally, we report on the first cross-ancestry genome-wide association studies of substance use behaviors among schizophrenia cases, which yielded two novel genetic risk loci for cannabis use. Results support a partially shared genetic liability between SCZ and substance use and suggest population differences in genome-wide pleiotropic effects. Future research needs to address causal mechanisms underlying associations between SCZ and substance use.