Name: Kazi Tanvir Hasan, Ph.D. Email: kazitanvir.hasan@yale.edu

Leveraging phenome-wide data in the Million Veteran Program: Genomic relationships between substance use disorders and a broad spectrum of health indicators and medical conditions

Substance use disorders (SUDs) occur alongside an array of health problems; however, few studies have systematically examined the relationship between SUDs and a comprehensive set of clinical outcomes. Here, we leverage GWASxPheWAS data from the Million Veteran Program (MVP) to examine the genetic relationship between different SUDs and their clinical correlates across 26 medical domains.

We built a large-scale analysis pipeline using summary statistics from the previously published MVP GWAS×PheWAS (PMID:39024449). This allowed for a series of LD Score Regression (LDSC) analyses to examine phenome-wide genetic correlations. We applied this method to multiple SUDs using European (EUR) ancestry summary statistics including: cannabis use disorder (CanUD)(PMID: 37985822), opioid use disorder (OUD)(PMID:35879402), problematic alcohol use (PAU)(PMID:38062264), and tobacco use disorder (TobUD)(PMID:38632388). Data from the MVP GWASxPheWAS included 1,669 EUR traits spanning 26 medical domains. Bonferroni significance was set at $P<4.62\times10^{-5}$ accounting for correlated traits.

We identified 1,112 significant genetic correlations (rg) between the examined SUDs and PheWAS traits spanning 22 medical domains. The number of significant genetic correlations across the phenome was: CanUD (n=368), OUD (n=110), PAU (n=267) and TUD (n=367). The most significant correlation found was between TobUD and chronic airway obstruction (rg=0.76;p<1.00x10-300). CanUD was most significantly correlated with smoking at least 100 lifetime cigarettes (rg=0.55;p=6.67x10-153). 'Viral Hepatitis and Hepatitis C' was the most significant correlation for OUD (rg=0.91;p=6.83x10-35) and PAU (rg=0.67;p=1.32x10-121), and was also significantly correlated with CanUD (rg=0.88;p=1.76x10-152) and TobUD (0.64;p=9.55x10-94). All SUDs were also significantly correlated with 'Diseases of the Teeth' (rg-range=0.42-0.63; p-range=3.77x10-16-7.71x10-73) and 'Nonspecific Chest Pain' (rg-range=0.27-0.43; p-range=4.55x10-08-5.74x10-45). Many additional novel findings with etiologically-relevant conditions were also identified.

Findings from the current study demonstrate that SUDs are related to health consequences impacting many bodily systems. This analysis framework provides promise for further research into causal relationships and identifying mechanistic pathways linking SUDs and medical comorbidities.

Authors:

Submitter: Kazi Tanvir Hasan, Postdoctoral Associate, Yale School of Medicine, New Haven
Joseph Deak, PhD, Yale School of Medicine
Joel Gelernter, MD, Yale School of Medicine

DRAFT