Analyzing latent propensities to addictive behaviors in a multivariate GWAS framework using GW-SEM.

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Substance Use (SU) behaviors are complex, polygenic traits with myriad genetic and environmental precursors. To date, genome-wide association studies (GWAS) are the most powerful tool for detecting genetic variants that play a role in the etiology of SU behaviors, with many notable successes. By using more sophisticated methods that integrate genomic data into more complete theoretical models, we can build on these successes, enhance our understanding of how genetic factors cause SU behaviors, and subsequently develop effective prevention and treatment programs. In the current project, we will use GW-SEM to conduct a latent variable GWAS analysis of SU propensity using three substances from the UK Biobank: cannabis (NUKB=112,109), alcohol (NUKB=379,153), and nicotine (NUKB=379,153). Preliminary CFA models suggest that a SU propensity factor drives the quantity of use for each substance. SNPs that index general addictive behaviors can be interpreted as predictors of the latent propensity to SU generally. We will follow up this analysis using the Residuals model, allowing us to explore the mechanistic associations between the substances, such as the ability detect substance specific associations that may predispose individuals to use a specific substance. Understanding the genetic factors that contribute to the general factor may be viewed as biomarkers for propensity of use of any addictive substance, while SNPs that predict the substance residuals will inform our understanding of substance specific biological risk factors. This analysis will allow genomic factors to define (and refine) our understanding of SU propensity and specific SU phenotypes.