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**Prediction of alcohol and other substance use disorders using a polygenic score for broader externalizing risk.**

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Polygenic scores (PRS) for alcohol and other substance use disorders (SUD) continue to predict small portions of the variance in these traits. In this analysis, we use results from a multivariate GWAS to determine whether modeling shared genetic risk improves predictive power of PRS for SUDs. Research from twin and family data reveal that substance use disorders, other non-clinical behaviors, and personality traits characterized by behavioral disinhibition load on to a single, highly heritable (~80%) underlying latent factor often referred to as Externalizing. Using a set of well-powered GWAS summary statistics of phenotypes across the externalizing spectrum, we performed a multivariate GWAS using Genomic SEM to model the latent factors driving the genetic correlations across the externalizing spectrum (alcohol problems, N = 150,640; lifetime cannabis use, N = 186,875; ever smoker, N = 1,251,809; general risk tolerance, N = 390,934); ADHD, N = 53,293; age at first sexual intercourse, N = 357,187; and number of sexual partners, N = 336,121). Results from the Genomic SEM model reveal a single underlying factor for externalizing psychopathology (effective N ~1.5 million) with ~620 independent genome-wide significant loci. We derive polygenic scores from this latent factor to predict alcohol use disorder, cannabis use disorder, other illicit drug use disorders, and correlated psychiatric phenotypes in two independent samples: The National Longitudinal Study of Adolescent to Adult Health (Add Health); and the Collaborative Study on the Genetics of Alcoholism (COGA).