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## Identifying Shared and Specific Genetic Risks for Substance Use Disorders

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Substance use disorders (SUDs) frequently co-occur. Much of the genetic influence on SUDs is shared, operating through a shared liability, often termed *externalizing*. Individual SUDs also show substance specific genetic risk unique to that particular substance/disorder. Multivariate GWASs allow us to tease apart these shared versus specific influences in order to better understand pathways of risk for any one disorder. We illustrate this using problem alcohol use (ALCP), separating out variance for AUDs due to shared externalizing risk (EXT) from the residual variance specific to problematic alcohol use (ALCP-S). We compare the results from the univariate GWAS of ALCP (N ~ 160,000) to the multivariate GWAS results that separate variance into EXT and ALCP-S (N ~1.5 million). These 3 GWAS show differing patterns of genetic correlations with other substance use, impulsivity, and psychiatric disorders. Associations between ALCP with impulsivity and other substance use disappear once we partial out EXT. Polygenic scores for ALCP and EXT are associated with other substance use and SUDs. However, polygenic scores for ALCP-S are only associated with alcohol phenotypes. Finally, in longitudinal models, polygenic scores for ALCP-S and EXT are differentially associated with alcohol misuse across development. Those with greater EXT polygenic scores engage in more alcohol misuse in adolescence, and this increased misuse continues across the early life course. Those with higher levels of the ALCP-S polygenic score increase their misuse more rapidly over time. Our results demonstrate the utility of teasing apart genetically influenced pathways of risk for SUDs.