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# Sex-Specific Genetic Effects in Substance Use Disorders: A Meta-Analysis of Sex-Stratified GWAS Across Over 2 Million Individuals

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Substance use disorders present sex-specific patterns in prevalence, progression, and response to treatment, yet the underlying factors contributing to these differences remain unclear. It has been hypothesized that certain genetic variants may have sex-specific effects, driving variations in hormonal regulation, metabolism, and gene-environment interactions. However, due to the lack of sufficiently large and diverse datasets, no study has been sufficiently powered to comprehensively examine sex-specific genetic effects across multiple substances, nor to do so across multiple ancestries. In the present study, we are combining data on alcohol, nicotine, cannabis, cocaine, and opioid use and use disorders across over 20 cohorts, for a total sample size of over 2.13 million individuals. With this sample, we will conduct a meta-analysis using of sex-stratified genome-wide association studies (GWAS) to investigate sex-specific genetic variants associated with effects on substance use and use disorders. Rigorous quality control measures and harmonization of phenotypic definitions will be applied to ensure consistency across cohorts. By leveraging a sample of unprecedented size and diversity, this study seeks to pinpoint sex-specific variants, assess the degree of overlap in the genetic risk between sexes, to identify potential sex-differentiated biological pathways involved in substance use behaviors, and to explore gene-environment interactions and their potential role in modulating these sex-specific effects. Understanding the sex-differentiated pathways involved in the etiology of SUD may contribute to the development of tailored prevention and treatment approaches, and provide insights into the role of sex in moderating the heritability and genetic risk factors associated with substance.