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27. SEX-SPECIFIC GENETIC ARCHITECTURE AND COMORBIDITIES OF ALCOHOL USE BEHAVIORS

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($n = 734$), SDS was lower after trauma (mean difference = -0.19 , $p = 3.1 \times 10^{-12}$).

Height PGS explained 18.6% of SDS variation in children and 33.9% in adults and was significantly associated with height in both groups. No interaction was found between ACE exposure and PGS.

Discussion: Childhood trauma is associated with shorter height during development, independent of genetic and socioeconomic factors. This suggests that early adversity may be associated with developmental growth delays during sensitive periods. In adults, childhood trauma is associated with slightly lower height, but this is explained by lower average height PGS among ACE-exposed individuals. These findings suggest that childhood trauma has a direct impact on growth in children, while adult height differences more likely reflect inherited variation. By incorporating genetic data, we can better distinguish between environmental and genetic influences on height and growth.

Disclosure: Nothing to disclose.

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TUESDAY, OCTOBER 21, 2025

Oral Session: Genomics of Addiction and Substance Use Disorders
1:00 p.m. - 2:30 p.m.

25. ABSTRACT WITHDRAWN

doi: [10.1016/j.euroneuro.2025.08.130](https://doi.org/10.1016/j.euroneuro.2025.08.130)

26. X, Y, AND WHY: UNPACKING SEX DIFFERENCES IN ALCOHOL USE AND DEPRESSION

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Background: Alcohol use disorder (AUD) and major depressive disorder (MDD) commonly co-occur. These recurrent conditions are costly and marked by higher rates of morbidity and mortality. Having one of these disorders increases the risk for the other four-fold and may make treatment less effective.

Methods: To investigate this comorbidity, we conducted a multi-ancestry genome-wide association study (GWAS) of AUD ($N > 590,000$, 91% male) and then stratified by MDD. Using the Million Veteran Program, we identified those with 1+ inpatient or 2+ outpatient International Classification of Diseases 9/10 codes for alcohol abuse or dependence ($n=114,627$; genetically inferred ancestry: AFR=31,552, EUR=69,203, AMR=13,114, EAS=636, SAS=122). We then determined MDD status (68% of those with AUD also had MDD, i.e. AUD+/MDD+) using ICD codes for depression. Controls were individuals with no instances of AUD or MDD in

their electronic health record ($n=288,981$). Using PLINK, genome-wide association testing was performed adjusting for age, sex, and first 10 PCs, then cross-ancestry meta-analyses were conducted, and lastly by sex. We then performed tissue enrichment analysis for all groups.

Results: We identified 48 genome-wide significant loci in the cross-ancestry meta-analysis of AUD, 19 in comorbid AUD+/MDD+, and 17 in AUD+/MDD-. In the stratified GWAS, 150, 93, and 42 SNPs with heterogeneous effects were observed in EUR, AFR, and AMR ancestry, respectively. In the sex-stratified analyses, we found 12, 1, 1 significant loci in EUR, AFR, AMR males, respectively, with AUD+/MDD+ versus 7, 1, 1 in AUD+/MDD-. In females, there were 0, 0, 1 significant loci in EUR, AFR, AMR ancestries, respectively, in AUD+/MDD+, versus 6, 7, 3 in AUD+/MDD-. In males with AUD+/MDD+, significant brain enrichment was observed in several regions in the AFR group including the basal ganglia, hippocampus, and hypothalamus, and the nucleus accumbens in the EUR group. In AMR females with AUD+/MDD-, we found significant enrichment in the cortex and ACC.

Discussion: Results demonstrate not only the unique genetic architecture of AUD with depression compared to AUD alone, but also the differential architecture by sex.

Disclosure: Nothing to disclose.

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27. SEX-SPECIFIC GENETIC ARCHITECTURE AND COMORBIDITIES OF ALCOHOL USE BEHAVIORS

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Background: Sex differences in alcohol use-related behaviors are well established: males typically engage in heavier drinking and exhibit externalizing behaviors, while females transition more rapidly to dependence and present more internalizing symptoms. However, the underlying biological mechanisms that underpin these differences remain relatively unknown.

Methods: We investigated the sex-specific genetic architecture across a spectrum of alcohol use phenotypes by leveraging published sex-stratified genome-wide association studies (GWAS) for 10 alcohol use behaviors from UK Biobank, problematic alcohol use (PAU), and a new sex-stratified GWAS of Alcohol Use Disorder Identification Test (AUDIT) total ($N = 40,335 - 613,148$). We calculated genetic correlations (rg) with 120 alcohol-related traits (e.g., externalizing, internalizing and socioeconomic traits), and es-

timated polygenic scores (PGS) associations with ~1,817 medical comorbidities via phenome-wide association studies (PheWAS) across two clinical populations ($N \sim 95,875$). **Results:** Between-sex genetic correlations across alcohol phenotypes ranged from 0.68 ± 0.07 to 0.89 ± 0.04 , with spirit, beer and white wine quantity showing the lowest values ($rg < 0.80$). In addition, SNP heritability estimates were significantly higher ($p < 0.05$) in males for beer quantity ($9.73 \pm 0.66\%$ vs. $3.13 \pm 0.33\%$), AUDIT-problems ($6.64 \pm 0.93\%$ vs. $3.63 \pm 0.68\%$) and PAU ($8.36 \pm 0.41\%$ vs. $4.50 \pm 0.55\%$). Genetic correlations revealed sex-specific patterns. In males, we identified stronger positive genetic correlations with externalizing behaviors (e.g., $rg-M = 0.58 \pm 0.03$ vs. $rg-F = 0.42 \pm 0.05$ between beer quantity and general addiction) and negative genetic correlations with cognitive traits (e.g., $rg-M = -0.46 \pm 0.02$ vs. $rg-F = -0.20 \pm 0.03$ between beer quantity and educational attainment). In females, we identified stronger positive genetic correlations with internalizing traits (e.g., $rg-F = 0.39 \pm 0.11$ vs. $rg-M = 0.07 \pm 0.07$ between beer quantity and self-harm) and negative genetic correlations with cognitive traits (e.g., $rg-F = -0.50 \pm 0.03$ vs. $rg-M = -0.15 \pm 0.03$ between spirit quantity and educational attainment). Overall, sex differences varied by alcohol phenotype: they were more pronounced for quantity measures, but less evident for frequency measures or alcohol misuse. PheWAS further showed that while sex-matched PGS did not improve AUD prediction in clinical samples compared to sex-combined PGS (e.g., combined PGS $OR_m = 1.57$ [1.42,1.73] vs. male PGS $OR_m = 1.47$ [1.34, 1.62] for drinking quantity), they uncovered sex-specific medical comorbidities that were obscured in the sex-combined analyses. For example, bone-related disorders were only significant in females when using female-specific PGS (e.g., $OR_f = 1.07$ [1.03,1.12] vs. $OR_m = 0.98$ [0.93,1.04] for osteoarthritis and drinking quantity PGS), while associations with substance use disorders and related conditions, including hepatitis, liver diseases, and respiratory disorders, were higher or only significant in males irrespective of the male-specific or combined PGS (e.g., $OR_m = 1.37$ [1.24,1.51] vs. $OR_f = 1.05$ [0.975,1.141] for viral hepatitis and beer quantity PGS).

Discussion: This work provides one of the most comprehensive genomic characterizations of sex differences in alcohol use behaviors to date. It underscores the need of modeling sex as a biological variable to guide future sex-informed preventative and personalized treatment approaches for alcohol use disorder.

Disclosure: Nothing to disclose.

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28. THE INTERNATIONAL CANNABIS CONSORTIUM: NEW FINDINGS FROM THE LARGEST GWASS ON EVER USE AND FREQUENCY OF USE

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Background: Cannabis is one of the most widely used psychoactive substances worldwide, and genetic factors play a significant role in individual differences in cannabis use. Twin studies report moderate heritability for both lifetime cannabis use and frequency of use, and somewhat higher estimates for cannabis use disorder.

To date, large-scale genome-wide association studies (GWASs) on cannabis use have focused primarily on ever use or cannabis use disorder, with most studies limited to individuals of European ancestry. Here, we present the first well-powered GWAS of cannabis use frequency ($N=269,160$ cannabis users), along with an updated GWAS meta-analysis of lifetime cannabis use, more than doubling the sample size of previous efforts and adding the first trans-ancestry findings ($N=467,889$ European ancestry; $N=122,224$ non-European ancestry).

Methods: GWASs were conducted on various cannabis use phenotypes—ever use, frequency of use (lifetime maximum and recent use)—using data from > 24 cohorts. Meta-analyses were performed with METAL and GENESIS, allowing for both ancestry-specific and cross-ancestry analyses. Using a set of functional annotation methods, we identified likely causal genes and implicated brain cell types. Genomic structural equation modeling (Genomic SEM) and Genetic Network Analysis (GNA) were used to examine shared liability across different cannabis use phenotypes.

We estimated SNP-based heritability and calculated genetic correlations with a broad range of phenotypes, including cognitive function, socioeconomic status, psychiatric disorders, personality traits, and other substance use, using LD Score Regression. Out-of-sample polygenic scores were generated in the Swedish Twin Registry ($N=32,033$) to examine associations with a range of outcome measures. Mendelian Randomization was applied to test potential causal links with key mental health traits.

Results: Preliminary results identified 3 independent genome-wide significant SNPs for cannabis use frequency ($SNP-h^2=2.3\%$) and 32 loci for ever use in European ancestry samples ($SNP-h^2=7.0\%$). Additional findings for non-European ancestry groups will be presented. *CADM2* emerged as a high-confidence gene across multiple analytic methods. The different cannabis use traits clustered together, with frequency showing a stronger overlap with cannabis use disorder than ever use. Significant genetic correlations were observed between cannabis use (ever use and frequency) and a range of psychiatric, cognitive, personality, and risk-related traits, with some interesting opposing associations for ever use and frequency. MR analyses suggest putatively causal associations between cannabis use and mental health outcomes, with both ever-use and frequency showing causal effects across seven psychiatric conditions, and frequency of use demonstrating robust associations with ADHD, anxiety, and schizophrenia.

Discussion: This study provides new insights into the genetic and biological underpinnings of cannabis use, particu-