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Alcohol consumption vs. misuse: evidence for distinct genetic architecture

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Genome-wide association studies (**GWAS**) of alcohol use disorders (**AUD**) have identified genes that influence pharmacokinetic factors (e.g. *ADH1B*, *ADH1C*), but pharmacodynamic factors have not yet been identified. Obtaining carefully diagnosed cohorts remains challenging. Instead, we obtained quantitative measures using the Alcohol Use Disorder Identification Test (**AUDIT**) from two population-based cohorts of European ancestry: UK Biobank (UKB; N=121,630) and 23andMe (N=20,328) and performed a GWAS meta-analysis. We also performed GWAS for AUDIT items 1-3, which focus on consumption (**AUDIT-C**), and items 4-10, which focus on the problematic consequences of drinking (**AUDIT-P**). The GWAS meta-analysis of AUDIT identified 11 associated risk loci. Novel associations were localized to genes including *JCAD* and *SLC39A13*; we replicated previous signals in the genes *ADH1B*, *ADH1C*, *KLB*, and *GCKR*. The dimensions of AUDIT showed positive genetic correlations with alcohol consumption (rg=0.78-0.96) and DSM-IV alcohol dependence (rg=0.33-0.64). AUDIT-P and AUDIT-C showed different patterns of association across several traits: AUDIT-P was positively genetically correlated with schizophrenia (rg=0.22), major depressive disorder (rg=0.26), and ADHD (rg=0.23), whereas AUDIT-C was negatively genetically correlated with major depressive disorder (rg=-0.23) and ADHD (rg=-0.10). We also identified thresholds for dichotomizing AUDIT that optimize genetic correlations with DSM-IV alcohol dependence. Coding individuals with AUDIT total score of ≤4 as controls and ≥12 as cases produced a high genetic correlation with DSM-IV alcohol dependence (rg=0.82) while retaining most subjects. We conclude that AUDIT scores ascertained in population-based cohorts can be used to explore the genetic basis of alcohol consumption and AUD.