

Abstract

Background: Major depressive disorder (MDD), smoking, and drinking frequently co-occur, with evidence suggesting these relationships may differ by sex. However, the direction of causality and the extent to which these associations differ by sex remain unclear.

Methods: We investigated sex-specific genetic relationships between MDD and substance use phenotypes using genome-wide association studies (GWAS) from the UK Biobank and publicly available sex-stratified GWAS for MDD and problematic alcohol use (PAU). Causal effects were assessed using bidirectional, sex-stratified Mendelian randomization (MR). We further applied multivariable MR (MVMR) to evaluate the influence of socioeconomic status (SES).

Results: Genetic correlation analyses indicated significant shared genetic architecture between MDD and all substance use traits in the sex-combined GWAS. In sex-specific analyses, the correlation between cigarettes per day and MDD was significantly stronger in females, and drinks per week was correlated with MDD only in females. MR analyses showed that genetic liability to MDD increased risk of smoking initiation and PAU in females, and was associated with reduced alcohol drinking frequency in males. MVMR adjusting for SES attenuated the female association between MDD and smoking initiation, while the effect on weekly alcohol consumption became significant only after adjustment. The effect on PAU in females remained robust. In males, the negative association between MDD and drinking frequency became non-significant after SES adjustment.

Conclusions: These findings reveal sex-specific genetic and causal relationships between smoking, drinking, and MDD, and highlight the role of SES as a potential confounder. Incorporating sex and socioeconomic context is critical when examining the links between depression and smoking or alcohol use.