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The relationships between cannabis, tobacco, and schizophrenia: a genetically informed perspective

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While recent genome-wide association studies (GWAS) have found modest but significant genetic correlations between SCZ and cannabis use disorder (CUD), no study has systematically examined the genetic loci that are associated with both CUD and SCZ liability. Using the largest GWAS available (Ns from 46,213 - 632,802), we set out to disentangle the relationships between genetic liability for cannabis use (ever-use and CUD), tobacco smoking (which is correlated with both CUD and SCZ), and SCZ. First, we used genomic structural equation models to investigate the relationship between genetic liability for cannabis ever-use and CUD, ever-smoking, Fagerström Test for Nicotine Dependence (FTND) scores, and SCZ. When all four substance phenotypes were modeled as simultaneous predictors, the strongest association was between CUD and SCZ. CUD, cannabis ever-use, and FTND were significantly positively associated with SCZ, while ever-smoking showed an inverse relationship with SCZ. Next, using a genome-wide cross-disorder method, we found 121 independent genome-wide significant loci pleiotropic for CUD and SCZ, with a particularly strong signal at a chromosome 8 locus containing the genes *EPHX2* and *CHRNA2*. The genetic covariance between CUD and SCZ appeared to be concentrated in genes related to the brain ($p = 0.01$); the strongest association was in the frontal cortex (using GTEx data; $p = 1.8e\text{-}11$), but all brain regions were significantly associated. Our multivariate analyses show that genetic risk for CUD is associated with genetic liability for SCZ, above and beyond the contributions of cannabis ever-use and tobacco smoking.