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# Cross-disorder analysis of cannabis use disorder and schizophrenia reveals convergent and divergent genetic influences

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It has been shown that genetic liability to cannabis use disorder (CUD) is significantly associated with genetic liability to schizophrenia (SCZ), even when accounting for ever-smoked tobacco regularly, a common risk factor for both CUD and SCZ. Here, we set out to identify genetic loci that are pleiotropic for CUD and SCZ using the largest GWAS to date. First, we applied ASSET, a cross-disorder method, to identify genome-wide significant loci that are pleiotropic for CUD (N cases=42,281) and SCZ (N cases=53,386). We found 95 lead SNPs in 75 genomic risk loci showing convergent effects (same direction of effect on both CUD and SCZ) and 79 lead SNPs in 69 genomic risk loci demonstrating divergent effects (risk-increasing for one disorder and protective for the other). We also used Local Analysis of [co]Variant Association (LAVA), a method of computing local bivariate and conditional genetic correlations, to examine local partial genetic correlations between CUD and SCZ, conditioning on ever-regular smoking (N cases=311,629). We identified two genomic regions (chr18:36056933-37679127 and chr22:40378784-41722787) that showed partial genetic correlations between CUD and SCZ after conditioning on tobacco smoking. The latter region included genes implicated in cognitive ability and neuroticism (e.g., EP300), drinks per week (e.g., RANGAP1), and immunological traits (e.g., RBX1). Genetic liability for CUD is correlated with SCZ risk, even after accounting for tobacco use, but there are genomic regions and loci of both convergent and divergent effects. Still, this overall shared genetic vulnerability may partially account for the frequent comorbidity of SCZ and CUD.