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

Emma C Johnson, Alexander S Hatoum, Joseph D Deak, Renato Polimanti, Robin Murray, Howard J Edenberg, Joel Gelernter, Marta Di Forti, Arpana Agrawal

Background: The relationship between heavy cannabis use and schizophrenia (SCZ) is one of psychiatry's enduring controversies, with increased importance given recent legalization of cannabis in many jurisdictions. Recent genome-wide association studies (GWAS) have found modest but significant genetic correlations between SCZ and cannabis ever-use (Pasman et al., 2018), and between SCZ and cannabis use disorder (CUD; Johnson et al., 2020). No study has yet systematically examined the genetic loci that are associated with both CUD and SCZ liability.

Methods: Using the largest GWAS datasets available (Ns from 46,213 - 632,802), we set out to disentangle the relationships between genetic liability for cannabis use (ever-use and CUD) and SCZ. Because tobacco smoking is phenotypically and genetically correlated with both CUD and SCZ, we also estimated its role in this association. First, we used genomic structural equation modelling to investigate the relationship between genetic liability for cannabis ever-use and CUD, ever-smoking, Fagerström Test for Nicotine Dependence (FTND) scores (which reflect nicotine dependence), and SCZ. Second, we used ASSET, a genome-wide cross-disorder method, to identify specific genetic loci that are associated with both CUD and SCZ and to examine whether those loci have convergent or divergent directions of effect.

Results: When all four substance phenotypes were modeled as simultaneous predictors, cannabis ever-use, CUD, and FTND were significantly positively associated with SCZ, while ever-smoking showed an inverse relationship with SCZ. The strongest association was between CUD and SCZ. We found 121 independent genome-wide significant loci pleiotropic for CUD and SCZ, with a particularly strong signal at a previously identified chromosome 8 locus that contains the genes *EPHX2* and *CHRNA2*.

Discussion: Our multivariate analysis shows that genetic risk for CUD is associated with genetic liability for SCZ, above and beyond the contributions of cannabis ever-use and tobacco smoking. Our findings strengthen the existing evidence that the chromosome 8 locus may be a point of shared genetic vulnerability for CUD and SCZ.

References: Johnson, E. C. *et al.* A large-scale genome-wide association study meta-analysis of cannabis use disorder. *The Lancet Psychiatry* (2020). doi:10.1016/S2215-0366(20)30339-4; Pasman, J. A. *et al.* GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat. Neurosci.* **21**, 1161–1170 (2018).

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