Correspondence

High-potency cannabis and incident psychosis: correcting the causal assumption

Marta Di Forti and colleagues1 claim that the frequency of cannabis use and cannabis potency are responsible for substantial variation in the incidence of psychotic disorders. The authors assume that cannabis causes psychosis or psychotic symptoms without acknowledging compelling, alternative hypotheses.2 Most reports examining associations between cannabis and psychosis have been unable to adjust for confounding that arises from correlated genetic and environmental individual differences. This oversight includes the common omission of appropriate methods for resolving causality (eg, random assignment to case and control conditions, discordant twin pairs, propensity score matching, or recently advanced genome-based restricted maximum likelihood methods). Findings of our own and others illustrate that cannabis use might be higher among individuals with a genetic liability that predisposes such individuals to cannabis use and the development of psychosis or psychotic disorders. Giordano and colleagues3 co-relative case-control design, which extrapolated data for monozygotic twin pairs, reported that a large portion of the association between cannabis abuse and schizophrenia was not causal, but instead confounded by shared familial factors. Despite increases in the prevalence of cannabis use over a 30-year period in Australia, Degenhardt and colleagues4 found no evidence of any notable increase in schizophrenia. Based on our recent meta-analysis of the largest genome-wide association study of lifetime cannabis use to date (n=184 765), we estimated a genome-wide genetic correlation of 0·25 (SE 0·03, p=0·0001) with schizophrenia risk, indicating that genetic risk factors for cannabis use and schizophrenia are positively correlated.5

This correlation could be explained by pleiotropic, causal, or reverse causal mechanisms. Mendelian randomisation is an approach that uses genetic variants associated with a modifiable exposure to estimate the causal relationship between variables. In our meta-analysis, we applied bidirectional mendelian randomisation and found a consistent pattern of evidence supporting a causal effect of schizophrenia risk on lifetime cannabis use.6 By contrast, we found little evidence for any causal effect of cannabis use on schizophrenia risk. We acknowledged the lower power of the instrumental variable for lifetime cannabis use,7 and our analyses were not based on cannabis use frequency or potency. Nevertheless, our findings strongly suggested that associations between measures of cannabis use and psychosis or psychotic disorders are far more nuanced than Di Forti and colleagues assume. In addition to correlated genetic liabilities, indirect and bidirectional processes are likely to affect the associations between cannabis use, misuse, and psychotic disorders. By not acknowledging the alternative, compelling and plausible mechanisms,3 Di Forti and colleagues’ conclusion regarding the harmful effect of high-potency cannabis use on mental health is likely to be overestimated. We declare no competing interests.

“Nathan A Gillespie, Joelle A Pasman, Jorien L Treur, Eske M Derkes, Karin J H Verweij, Jacqueline M Vink

Genetic Epidemiology, Statistical Genetics, and Translational Neurogenomics Laboratories (NAG) and Translational Neurogenomics (EMD), QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; Department of Psychiatry, Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, Richmond, VA, USA; NAG (NAG), Behavioural Science Institute, Radboud University, Nijmegen, the Netherlands (JAP, JMV); and Department of Psychiatry, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands (JLT, KJHV)


In their recent paper, Marta Di Forti and colleagues conclude that removing one environmental factor—daily high-potency cannabis use—would reduce the incidence of all psychotic disorders in Amsterdam, the Netherlands, by 50%, from 37·9 to 18·8 cases per 100 000 person-years. We think that this is very unlikely given that Sullivan and colleagues2 confirmed the heritability of schizophrenia to be about 80%. Therefore, attributing this complex multifactorial brain disorder to one environmental factor such as high-potency cannabis use seems counterintuitive, especially given that 33·6% of the patients assessed by Di Forti and colleagues had never used cannabis. The reported 50% population attributable fraction (PAF) for cannabis use in Amsterdam becomes even more questionable with a recent two-sample bidirectional Mendelian randomisation study showing that the causal direction was from schizophrenia to cannabis use and not vice versa.3 Indeed, high-potency cannabis use can lead to drug-induced psychosis and high-potency cannabis use might trigger earlier onset of psychosis in genetically vulnerable individuals who would have developed psychosis anyway.4 But these conclusions are all very different from stating that high-potency cannabis use is responsible for 50% of incident psychosis cases in Amsterdam.

So how can Di Forti and colleagues conclude that 50·3% of incident