

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=184765), 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.⁵ 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,⁵ 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.

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1 Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 2019; **6**: 427–36.

- 2 Minozzi S, Davoli M, Bargagli AM, Amato L, Vecchi S, Perucci CA. An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results. *Drug Alcohol Rev* 2010; **29**: 304–17.
- 3 Giordano GN, Ohlsson H, Sundquist K, Sundquist J, Kendler KS. The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. *Psychol Med* 2015; **45**: 407–14.
- 4 Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend* 2003; **71**: 37.
- 5 Pasman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci* 2018; **21**: 1161–70.

In their recent paper, Marta Di Forti and colleagues¹ 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

psychosis cases in Amsterdam are attributable to high-potency cannabis? The answer is simple: they calculated PAFs from the observed odds ratios (ORs) “assuming causality”—ie, that the observed OR is 100% causal. However, case-control studies such as theirs generally suffer from considerable confounding. Moore and colleagues,⁵ in reviewing studies about the association between cannabis use and psychosis, showed that 10–85% of the observed risk was due to confounding. Di Forti and colleagues tried to adjust their observations for confounding, but it is very likely that their adjusted ORs and thus their PAFs were still subject to considerable residual confounding due to unmeasured differences between cases and controls in—among other factors—genetic vulnerability for mental disorders and, more specifically, for psychosis. Furthermore, their study used a fairly undefined control group of local individuals without any psychiatric history, instead of healthy siblings or patients with a mental disorder other than psychosis. As a consequence, the ORs and the associated PAFs are very likely to be seriously overestimated.

The authors’ data already show this overestimation: Gouda and Voorburg, other Dutch cities close to Amsterdam with access to high-potency cannabis that is very similar to that in Amsterdam, together had a much lower OR (1.5 vs 3.6) and PAF (12.2 vs 50.3%) for high-potency cannabis use. Thus, taking actions to prevent incident psychosis is certainly a good idea, but prohibition of high-potency cannabis is unlikely to substantially reduce new cases of psychosis.

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- 1 Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 2019; **6**: 427–36.
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Marta Di Forti and colleagues¹ found that daily cannabis consumers have increased odds of developing a psychotic disorder (odds ratio [OR] 3.2), with even higher risk for high-potency cannabis users (OR 4.8), suggesting that Δ^9 -tetrahydrocannabinol (THC) is a causal factor.

Although THC has well documented psychoactive properties, it is not the only component in cannabis smoke. In Europe, cannabis is typically mixed with tobacco, and Di Forti and colleagues¹ also found that smoking more than 10 tobacco cigarettes per day had a 2.5 OR for psychotic disorders (reported on p 10 of their appendix). Across regions represented in the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) data, the prevalence of psychotic disorders ranged from 6 cases per 100 000 person-years to 46 cases per 100 000 person-years,² with higher prevalence in larger cities. Previous studies indicate that frequent cigarette smoking and urban living each approximately double the risk of psychosis.^{3,4} Therefore, the question arises as to whether urban living, cannabis smoke, and tobacco smoke have a common factor that can cause psychosis.

Newbury and colleagues⁵ reported this year that moderate air pollution (33.0 $\mu\text{g}/\text{m}^3$ of nitrogen oxide [NOx],

equivalent to a daily exposure of 330 μg) was associated with a 1.7 OR for psychotic disorders in adolescence (12–18 years) in England and Wales. I conceptually replicated this finding with the EU-GEI data: the mean nitrogen dioxide concentrations (for 2010–15, using public data from the European Environmental Agency) in the 17 regions included in the EU-GEI dataset^{1,2} were related to regional incidence of psychotic disorders. I found a significant positive correlation ($r=0.64$, $p=0.006$), confirming the association between NOx and psychosis reported by Newbury and colleagues, albeit with a crude analysis (unpublished).

The NOx content of mainstream smoke from a typical tobacco cigarette is 68 μg .⁶ Smoking 10 cigarettes per day (breathing 680 μg NOx) is associated with a 3.7 hazard ratio for schizophrenia,³ or, in Di Forti and colleagues’ study, with a 2.5 OR for psychotic disorders.¹ With typical forceful inhalation, the NOx content of a single marijuana joint is around 690 μg .⁶ Assuming that daily cannabis users smoke one joint per day, their exposure to NOx from cannabis smoke, and their increased risk of psychosis, would thus be of the same magnitude as the risks and NOx exposure from urban air pollution or 10 cigarettes per day. The effects of cannabis potency on smoke NOx content are not known, although high THC cannabis typically produces more alkaline smoke. A limitation of this alternative explanation is that intravenously administered THC, and edible cannabis products, have been associated with acute psychosis-like experiences.

In summary, NOx exposure—from all types of smoke—might be a more ubiquitous explanation for the reported link between cannabis and psychosis. Until causal mechanisms are established, limiting exposure to NOx from exhausts and cigarette and cannabis smoke could be an effective and perhaps minimally controversial method to reduce harm.

For more on air quality statistics from the European Environmental Agency see <https://www.eea.europa.eu/data-and-maps/dashboards/air-quality-statistics>