**Cannabis and psychosis: triangulating the evidence**

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Disentangling causality where complex and confounded behaviours might be impacting on even more complex mental health outcomes is notoriously challenging, and requires tackling the question in a number of different ways, to triangulate the evidence. Although observational epidemiology and experimental studies are broadly consistent in indicating a link between heavy cannabis use and risk of psychosis ([1](#_ENREF_1)), one oft-mentioned anomaly when considering the relationship is that as cannabis use has increased in certain populations the corresponding level of psychosis incidence has not. Di Forti and colleagues’ new paper ([2](#_ENREF_2)) explores this in more detail, examining detailed measures of cannabis use from 900 first-episode psychosis patients and 1200 controls across 11 sites in Europe. Additionally they used cannabis data from their control sample to assess the link between patterns of cannabis use in the region and data on psychosis incidence in that location taken from the EU-GEI project. Their results suggest that some of the variation in heaviness of use of cannabis, and type of cannabis used might be implicated in differing rates of psychosis across the different locations, going against the previously held notion.

In recent years, attention has turned to the impact of various cannabinoids on risk of poor mental health. In particular, there is some suggestion from short-term experimental intoxication studies that ratios of THC to cannabidiol could have an impact on risk of psychotic-like experiences ([3](#_ENREF_3)), with some emerging evidence even suggesting that CBD might be anti-psychotic ([4](#_ENREF_4)). Although they were unable to directly measure cannabis potency, Di Forti and colleagues created a cannabis potency variable by using self-reported type of cannabis used combined with Europe-wide data published by the EMCDDA on the concentration of THC in cannabis found in the countries under investigation. While this is subject to some uncertainty, as levels of THC are not necessarily consistent within a country or even a region ([5](#_ENREF_5)), and sample sizes are small, it is a novel and inventive way to account for levels of THC, and one which is likely to be more accurate than only asking participants to self-report the strength of their cannabis. Unfortunately data on CBD was not available in most countries so could not be accounted for in this potency variable.

All study patients were diagnosed using the same ICD-10 criteria meaning diagnoses are harmonized and therefore directly comparable across sites. The sample size is large, although when split across the 11 sites it is reduced (cases Ns ranged from 15 to 201), meaning associations within individual sites might be underpowered. The associations seen between cannabis and psychosis were largely driven by daily cannabis users, and particularly those daily users consuming high potency cannabis. In non-daily users effect sizes did not differ between the cannabis potency groups, and there was no evidence of an association between less-than-weekly cannabis use and psychosis, regardless of potency.

As well as this individual level case-control study, Di Forti and colleagues also examined the relationship between incidence rates for psychotic disorder across 11 of the different study sites, and cannabis use patterns in the control group sampled for their case-control study. They found that for almost every site in the study, prevalence of daily cannabis use in the controls, or prevalence of high potency cannabis use, was correlated with incidence rates for psychosis in the location in question, although cannabis use sample sizes were very small (37 to 302 controls per site).

Does this mean we can now be sure that (daily and high potency) cannabis use causes psychosis? Unfortunately, not all the evidence utilising different methods is consistent about causality. For example, studies using genetic data have found evidence possibly consistent with shared genetic aetiology between risk of psychosis and likelihood to use cannabis ([6](#_ENREF_6)). Di Forti’s study asks participants about their cannabis use prior to their first episode psychosis diagnosis, but it is possible that sub-clinical symptoms may have existed prior to cannabis initiation, meaning associations in the opposite direction cannot be ruled out.

It is perfectly possible that the association between cannabis and psychosis is bi-directional, as suggested by other work using genetic variables as proxies for the exposures of interest in a Mendelian randomization design ([7](#_ENREF_7), [8](#_ENREF_8)). Di Forti’s study adds a new and novel study design to the evidence available, which consistently indicates that for some individuals there is an increased risk of psychosis resulting from daily use of high potency cannabis. Given the changing legal status of cannabis across the world, and the associated potential for an uptick in use this could lead to, the next priority is to identify which individuals are at risk from daily potent cannabis use, and to develop educational strategies and interventions to mitigate this.

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