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Cannabis and psychosis

Marta Di Forti and colleagues¹ report that the use of herbal cannabis (skunk), but not resin (hash), is associated with increased risk of psychosis. They make the reasonable assumption that cannabis type is a proxy for strain potency and predominant cannabinoid present. Their findings are broadly consistent with recent experimental studies showing a psychomimetic effect of tetrahydrocannabinol (THC), and a potential antipsychotic effect of cannabidiol.²

At first glance, these findings suggest skunk use is hazardous to mental health whereas hash use is relatively safe in this context. This finding would have great implications for public health. However, it is important to consider whether this association is likely to be causal. Although there is largely consistent evidence that cannabis use is associated with psychotic symptoms, the strongest evidence for an effect on risk of clinical psychosis derives from populations in which most cannabis use would have been either resin cannabis or relatively low-potency herbal strains.³ Moreover, findings from previous studies generally suggested a dose-response relation, with the strongest association being noted in the heaviest users, and little or no association noted in those who use infrequently.³ Di Forti and colleagues¹ found this pattern in skunk users but not hash users. These earlier findings of a dose-dependent relation

have been used in support of claims that cannabis use is causally associated with psychosis risk.⁴

This discrepancy with previous studies suggests an alternative interpretation of the data. Specifically, it is possible that the association reported by Di Forti and colleagues¹ does not represent a biological effect, but rather some other predisposing risk factor for psychosis that could also lead people to select the most potent drug available to use. When associations depend on where an exposure lies in a distribution (rather than its absolute level), this pattern suggests confounding rather than a causal relation. For example, low concentrations of cholesterol predict negative non-vascular health outcomes in both European and east Asian populations, despite absolute cholesterol concentrations at the low end of the distribution in European populations being in the middle of the distribution in east Asian populations.⁵ The similarity in the shape of risk curve between the two populations indicates that the observed association does not indicate a biological effect of low cholesterol on increased mortality, but rather that various confounding factors (including illness-induced reductions in cholesterol concentrations) give rise to the association.

We took the figures from the study by Di Forti and colleagues and combined the hash and skunk groups. The resulting effect size (OR 1.92, 95% CI 1.35–2.73) is similar to that reported in the meta-analysis by Moore and colleagues³ (ever use 1.41, 1.20–1.65, heavy use OR 2.09, 1.54–2.84). In other words, the basic association between cannabis use and risk of psychosis was noted in populations where skunk use was uncommon. When skunk became available, a subgroup already at high risk of psychosis might have selected to use this form of cannabis. Therefore, although it is certainly plausible that use of skunk could be causally associated with psychosis, it is important to consider alternative explanations for the associations

noted. Moreover, any message that hash is comparatively safer than other forms of cannabis might have negative public health consequences, given its potential effect on respiratory health.⁶

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- 1 Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry* 2015; **2**: 233–38.
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Marta Di Forti and colleagues' retrospective case-control study¹ distinguished between self-reported use of high-potency (skunk) versus lower potency (hash) cannabis. Scaremongering headlines in the media predictably followed. The *Daily Mail* screamed "Scientists show cannabis TRIPLES psychosis risk: Groundbreaking research blames 'skunk' for 1 in 4 of all new serious mental disorders." Undoubtedly, politicians and policy makers who have already made up their minds about regulation of cannabis will seize on the study as support for their views.

The authors must share some of the blame for misinterpretations of their results. They were pre-committed to causal language and failed to acknowledge important limitations

of their study. An earlier report² by the authors concerning the same cases but not cited in the present one¹ declared “Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users”. The title of the present Article announces “psychosis attributable to use.” The abstract reports a “population attributable fraction”, with obvious interest to journalists and politicians who will not recognise the inferential leap. Population attributable fraction or risk is a term that should be reserved for associations for which causality has been more firmly established and appropriate caveats should indicate uncertainty about its applicability.³

Both cases and controls were selected from South London. The area’s distinctive character limits generalisability to other areas of the UK or the world. Cases and controls were poorly matched. Half of the cases were black individuals and only a third were white, with these proportions reversed among controls. There are also highly significant differences in gender, education, and ever being employed. Such differences cannot be overcome in analyses with inclusion of an incomplete selection of crudely measured control variables. Frequency of use of cannabis was established by retrospective self-report and the key distinction of skunk versus hash was not one that participants might be able to reliably make.

Results could conceivably be explained by protopathic bias, with people who developed psychosis using cannabis or skunk to self-medicate early symptoms. Note the doubling of probability of psychosis for “never” as compared with “less than once a week”.¹ Confounding by indication⁴ is suggested by the profound disorientation that daily use of skunk entails and the likelihood that people who are not already dysfunctional would find it aversive and intolerable.

Causal inferences from case-control studies are always hazardous, particularly with poor matching and

incomplete specification and imprecise measurement of possible confounds. The unwanted influence of relevant group differences, whether measured or left unmeasured, might only be compounded by brute application of statistical controls. Awareness of the obvious political and policy implications of results, and the likely misuse to which they could be put, apparently failed to discourage the authors from inappropriate causal inferences and ignoring of obvious limitations of their study. This failure can only serve to distract readers from the important message concerning the need for a distinction between higher and lower potency forms of cannabis, even if it should be made with greater precision and in the context of a prospective study.

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In a 15-year follow-up study of 45 570 conscripts in the Swedish army, Sven Andréasson and colleagues¹ found 21 cases recorded subsequently as suffering from schizophrenia among those 752 individuals who had taken cannabis more than 50 times. This finding represents a relative risk of 6.0 times that in the cohort as a whole. None of these 21 individuals had been diagnosed with schizophrenia when seen at age 18 years, although they were 3.1 times at risk of other psychiatric diagnosis. Andréasson and

colleagues interpreted the association as causal—ie, that cannabis is a cause of schizophrenia (Hypothesis 1)—although they also acknowledged the postulate that personality or other characteristics that precede the onset of schizophrenia are associated with increased likelihood of cannabis use (Hypothesis 2).

Notwithstanding absence of significant differences between cases and controls in whether their subjects had ever taken cannabis, or in age at first use, Marta Di Forti and colleagues² claim support for Hypothesis 1 on the basis that 218 (53%) of the 410 individuals with a first episode of psychosis compared with 70 (19%) of the 370 people in the control group used high-potency cannabis (skunk). But of those who smoked traditional cannabis (or hash) only 57 (14%) individuals with a first episode of psychosis did so compared with 162 (44%) of controls. By the logic adopted by these authors, so-called traditional cannabis must be assumed to protect an individual against schizophrenia! But skunk was not available in Sweden in the 1970s. To suppose that traditional cannabis was a significant cause of schizophrenia in Sweden in the 1960s and 1970s but now protects the population of South London that has meantime become selectively susceptible to a modified chemical form (skunk) is implausible; hypothesis 1 is untenable. The proportion of skunk plus hash in the two groups is similar—67% overall users in the first episode of schizophrenia group (53% skunk plus 14% hash), and 63% overall users in the controls (19% skunk plus 44% hash). The data are readily accommodated by hypothesis 2—that the population of individuals with or predisposed to a diagnosis of schizophrenia includes some who are inclined to seek out some addictive substances (such as tobacco and cannabis). When such substances are available, these individuals are disposed by their illness to consume more or stronger forms.

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