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PROJECTING THE IMPACT OF CHANGES IN CANNABIS USE UPON SCHIZOPHRENIA IN ENGLAND AND WALES: THE ROLE OF ASSUMPTIONS AND BALANCE IN FRAMING AN EVIDENCE-BASED CANNABIS POLICY

In this issue, Hickman and colleagues [1] present estimates from a simulation exercise to project the impact of cannabis use upon the future incidence of schizophrenia in England and Wales. The projections are based upon an assumption (which the authors disclose) that cannabis smoking causes newly incident cases of schizophrenia that would never appear in the absence of cannabis smoking. It is important to remember here that the projection exercise refers to the generally serious and long-term disabling condition of schizophrenia. This is not about cannabis intoxication complicated by very transient psychosis-like clinical features that remit soon after cessation of cannabis smoking.

The authors make it clear that the study's findings are hypothetical, tentative and limited. No other sorts of relationships between cannabis and psychosis were modeled (such as the possibility that cannabis use might exacerbate the course of schizophrenia among those who had already developed schizophrenia, or the counterfactual possibility that the effect of cannabis is to trigger a schizophrenia solely among individuals who would have developed the disorder eventually regardless). The value of the hypothetical projections rises and falls with a belief that cannabis causes long-term disabling psychoses that would not be occurring in the absence of cannabis.

Should any reader now hold a firm belief that cannabis generally and inevitably causes long-term disabling psychoses that would not be occurring in the absence of cannabis? We think not. The current items of evidence on the linkage between cannabis smoking and psychosis now favor the idea that genetic susceptibility traits are involved, but the evidence remains far from definitive in nature. Indeed, the evidence base still has the character of grains of sand. Originating first in anecdotes and clinical case reports, the evidence has grown to include several implicative but non-definitive epidemiological studies. As we outline below, the quality of evidence from published observational studies of population cohorts remains constrained by the nature of their comparison groups.

Perhaps the most serious defect in the epidemiological studies involves the choice of comparison groups of individuals who do not smoke cannabis. At first glance, it might seem that valid estimates of cannabis-associated relative risk of psychosis might be derived by comparing all cannabis users with non-users in an epidemiological sample. However, cannabis smoking is not distributed randomly throughout epidemiological samples.

This point might become more clear with an example. Consider a paradigmatic (but hypothetical) study of monozygotic (MZ) male twins, who are discordant for cannabis smoking during the adolescent years, and who are followed-up through the age interval during which the risk of developing psychosis reaches its peak. Because this type of study can hold constant the genes shared in common (including just-mentioned genetic susceptibility traits), as well as many shared aspects of intrauterine and later rearing environments, it might be thought to give a

very clear picture of the effects of cannabis smoking in adolescence on the later risk of developing psychosis. The fly in the ointment is that something of importance must predate both the cannabis smoking and any subsequently observed psychosis, causing one of the twins to smoke cannabis when the other cotwin does not. As such, the relative risk of newly incident psychosis for a cannabis-smoking MZ twin versus the non-smoking co-twin is confounded by the still-imbalanced causal determinant of why one twin started cannabis smoking whereas the other did not.

Our theories about what causes adolescents to smoke cannabis are growing stronger, but they are not at all complete. As such, we cannot ensure complete specification of the study designs, to know what to measure and how to measure the confounders and to take these confounding variables into account in the study designs. This hypothetical MZ twin study illustrates the general problem that also besets epidemiologically credible samples used to make contrasts of psychosis risk for cannabis smoking and non-smoking individuals, which—importantly—have not yet had the benefit of holding all genetic influences constant.

It would be a little unkind for any reviewer to wave hands in the direction of a hypothetical confounding variable without specifying what that confounding variable might be. A plausible confounding variable that has not yet been addressed in prior epidemiological studies of the cannabis–psychosis association is linked to the illegal status of cannabis smoking in most jurisdictions. That is, in virtually every country of the world, the act of smoking cannabis is an illegal behavior, often subject to serious social (and legal) sanctions. The propensity to engage in illegal and socially discouraged behaviors (such as cannabis smoking) might be an independent causal determinant of (a) early cannabis smoking and also (b) later newly incident psychosis. To the extent that this theoretically plausible confounding characteristic is actually functioning to confound the estimates of the cannabis–psychosis association, it must be held constant one way or the other. Regrettably, the estimates of relative risk applied in the projections made by Hickman and colleagues do not take this type of potential confounding characteristic into account.

A simulation exercise of the type reported by Hickman and colleagues [1] is not irrelevant. It conveys information of potential future utility. None the less, it is hypothetical, and we join Hickman and colleagues in urging caution in any interpretation and future practical application of these projections [1]. The projections depend very heavily upon the validity of the cannabis–psychosis relative risk estimates that the authors themselves characterize as somewhat tentative in character. There are now recent studies showing no excess psychosis risk for cannabis smokers who lack genetic susceptibility traits.

Alas, in such a context policy makers might come to cite these research results as reason to increase the degree of formal social control over cannabis smoking (e.g. jail time; increased fines) in anticipation of hypothesized deterrent effects, reduced cannabis smoking or prevention of future smoking. In our judgment, evidence-based policy decisions will be guided by estimates of the harms induced when cannabis smokers are made into criminals, in complement with simulation exercises and projections of cannabis-induced harms illuminated by the best possible epidemiological investigations.

Hickman and colleagues [1] clearly have a flair for simulation exercises based upon projected future harms that otherwise might not occur if cannabis smoking were to be eliminated. We wonder whether this flair might now turn in the direction of projecting future harms that otherwise might not occur if criminal penalties for simple possession and use of cannabis were to be eliminated. Even-handed evidence-based cannabis policy will be guided by a clear appraisal of the harms thought to be caused by imprisonment or other criminalization of otherwise law-abiding cannabis smokers in balance with a clear appraisal of the harms caused by cannabis smoking *per se*, including the now clear possibility of cannabis-induced schizophrenia.

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RESPONSE TO THE COMMENTARIES

In our paper [1], we essentially took an ecological approach to the empirical question of whether cannabis use causes schizophrenia. In so doing we took our lead, partly, from a recent paper by one of our commentators [2]. Using the best data available to us, and acknowledging the imperfections in this evidence, we related changes in levels of cannabis use since the early 1970s to incidence of schizophrenia in the late 1990s and modelled the subsequent impact of the former on the latter, assum-

