Commentaries on Hickman *et al.* (this issue)

THOUGHT EXPERIMENTS ON THE INCIDENCE AND PREVALENCE OF SCHIZOPHRENIA 'UNDER THE INFLUENCE' OF CANNABIS

If forgetting that schizophrenia was a brain disease was one of the great aberrations of 20th-century medicine [1], ignoring variations in the incidence of schizophrenia must rank as one of the great aberrations of modern epidemiology. However, recent research has provided us with data that cannot be ignored. The incidence of schizophrenia varies widely between sites [2], and varies according to a range of demographic variables such as sex, urbanicity of place of birth/residence and migrant status [3,4]. High-quality prospective cohort studies have also strengthened the case that cannabis is a risk-modifying factor for schizophrenia [5,6].

Assuming that cannabis is a causal factor for schizophrenia, what would happen to the incidence and prevalence of schizophrenia if cannabis use becomes more prevalent? To remind the reader, incidence and prevalence express disease frequencies in different ways. Incidence counts the number of new cases per given population per year (thus, it is a rate), and in models linking incidence and prevalence is called a 'flow' variable [7]. Prevalence measures the proportion of surviving individuals who manifest a disorder at a specified time (i.e. point prevalence) or during a specified period (e.g. annual prevalence, life-time prevalence). Prevalence estimates are proportions, and in modelling exercise are called 'stock' variables. Mortality and remission/recovery also need to be included in models (called 'outflow' variables). Theoretical models can be constructed that represent the hydraulics of flow, stock and outflow variables [8,9].

Hickman and colleagues [10] have explored a model that plots the incidence and prevalence of schizophrenia over time 'under the influence' of cannabis. In the model, cannabis was included as a causal agent and the prevalence of cannabis use was allowed to increase over time. As expected, the incidence and prevalence of schizophrenia also increased, as did the population attributable fraction of schizophrenia that was linked to cannabis. The results are not good news for clinicians, who are already struggling to help people with schizophrenia and their families.

The thought experiments described in the paper are based on high-quality 'flow' and 'stock' data from the United Kingdom. More complex models could also incorporate the impact of cannabis on 'outflow' variables. Cannabis use also results in an increased risk of relapse in people with established schizophrenia [11,12]. If the outcome of interest is active psychosis, increased cannabis use could increase the point prevalence of psychosis via two mechanisms. It increases the 'flow' (increased incidence) and decreases the 'outflow' (decreased remission). A higher prevalence of psychotic disorders such as schizophrenia will be translated into a greater disease burden, as measured by personal suffering, disability adjusted life-years (DALYs) and demands on services.

If the model reflects reality accurately, and the incidence of schizophrenia does increase as a result of the more widespread use of cannabis, would we be able to confirm the model empirically? Hickman and colleagues' [10] model suggests that, over a 20-year period, the incidence of schizophrenia would increase from approximately 15–18 per 100 000 person-years for men and 7–8 per 100 000 person-years for women (their Fig. 6). Researchers intending to chart the association between cannabis and schizophrenia over time need to ensure that their studies have adequate power to detect changes of this effect size.

Cannabis is not the only exposure that we need to worry about. From a broader public health perspective, we should be concerned if the prevalence of *any* candidate exposure linked to schizophrenia is increasing in prevalence. Other risk factors linked to schizophrenia are also becoming more prevalent in many societies (e.g. urbanization, paternal age, migrant status). While not widely acknowledged, the sober truth is we are not particularly good at treating schizophrenia [13]. We need a bolder research agenda that invests in primary prevention. Any candidate exposure that offers even a faint hope for the eventual primary prevention of schizophrenia should be scrutinized closely [14]. Cannabis is one such candidate.

Lulled into the false belief that the incidence of schizophrenia was invariant across time and place, the schizophrenia research community has neglected models that try to piece together the dynamics of incidence, prevalence, mortality and remission. By showing us what might happen to schizophrenia if one puts 'cannabis in the calculus', Hickman and colleagues have demonstrated convincingly the utility of these models [10].

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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

