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-

ing a causal relation of the magnitude suggested by the only large prospective general population study to estimate this effect in individuals [3]. Our projections of 'expected' schizophrenia cases in the near future can now be compared with those observed. Any causal inference made from this comparison will inevitably be subject to the dangers of ecological fallacy [4]. Nevertheless, we hope to add to the jigsaw around the aetiology of the 'leading unsolved disease afflicting humans' [5].

The key public health issue in the current epidemiological debate is whether cannabis use causes clinically significant and enduring psychosis in individuals who would not otherwise have become psychotic. That cannabis use can precipitate transient 'psychotic' symptoms or may exacerbate symptoms in individuals with existing psychosis is not controversial, and we agree with McGrath & Saha [6] that the latter could usefully be added to a future model of schizophrenia. None the less, we believe these questions are subsidiary to the main issue. Anthony & Degenhardt [7] seem sceptical as to whether current evidence supports strongly the hypothesis that a substantial proportion of clinically important psychosis is attributable primarily to cannabis use. We share this scepticism; indeed, we have expressed it in detail elsewhere [8–10]. Yet several prominent, credible commentators writing in widely read, mainstream journals have suggested recently that up to 50% and probably a little less than 10% of psychosis in the population is attributable to cannabis use [11–13]. Our 'thought experiment' was to ask what are the implications if this is true, given what we know about rates of cannabis use and psychosis in the population?

We agree wholeheartedly with Anthony & Degenhardt's [7] point that the fundamental weakness of observational epidemiology relates to the non-random distribution of many environmental exposures (and potential confounders) in the population, although clearly this in not unique to the study of consequences of drug use, nor a reason to abandon observational epidemiology [14]. The genetic dimension is another question, and twin studies offer one way to investigate this. However, as Anthony & Degenhardt [7] argue, twin studies also have their drawbacks, and are not likely to be entirely unconfounded by environmental factors. The importance of such confounding varies according to the study question. For example, our commentators cite the ingenious discordant twin design, where monozygotic twins discordant for the exposure of interest are studied. This design can still be confounded by environmental factors underlying the discordance on which the comparison is based [15]. In monozygotic twins, environmental discordance is more likely in adolescence than very early life. It therefore follows that monozygotic twins discordant for a cannabis use phenotype are probably a more useful design to clarify the role of confounding by very early life factors, such as may be relevant to associations between cannabis use and serious mental illness [16]. For associations where possible confounding by adolescent factors is probably more of an issue, those between cannabis use and use of other drugs, for example, discordant twin designs may be less informative [15].

The bottom line is that if the question of the nature of the association between cannabis use and serious enduring psychosis is important then we need better evidence to help us to answer it. We have suggested various strategies to generate such evidence [11–13]. One strategy relates to McGrath & Saha's [6] well-made point about the importance of pursuing primary prevention of psychosis, in view of the limited effectiveness of treatment [17]. Cannabis use is one candidate for such prevention. It may not be the most promising candidate; however, this consideration should be balanced against the fact that the reduction of cannabis smoking by young people has a strong public health justification, irrespective of the effect of cannabis use on psychosis [18]. Evaluation of such prevention should be subject to the normal conventions of health technology assessment—that is, it should be cost-effective, acceptable to the people receiving it and should not generate substantial collateral harms [19]. We think it is unlikely that the more vigorous criminal justice-based approach Anthony & Degenhardt [7] are afraid our paper will precipitate would fulfil these criteria.

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