

exacerbation of positive psychotic symptoms in their schizophrenia cohort may be a product, *inter alia*, of: selection bias; the fact that the cohort already had positive symptoms (mean BPRS score at baseline 43.2): this assertion is supported by the fact that prior-month BPRS score was a much stronger predictor of increased BPRS score at each assessment point; the fact that few were using high quantities of cannabis (only a fifth using more than 3 g a week); and that they were a treated sample, so most would have been receiving dopamine blocking medication.

- (3) The symptoms that drive cannabis use in people with schizophrenia are very much the same as those that drive its use in people without schizophrenia: what we (Spencer *et al.* 2002) have called 'negative affect': so, the self-medication hypothesis is true, but self-medication is for negative rather than positive symptoms (see also Macleod, 2007).
- (4) Some individuals have a predisposition to schizophrenia but do not quite manifest positive symptoms until they are exposed to a stressor such as THC. In this small group, THC is the 'straw that breaks the camel's back' and acts as a cumulative causal factor for schizophrenia (see Arseneault *et al.* 2004): using this model, very few 'cases' of schizophrenia (estimated population attributable fraction around 8%) would actually be prevented with the global abolition of cannabis.

So, the facts appear clear, and the message must be that anyone with high psychosis proneness should avoid cannabis: the tough part is helping people with negative affect (of which those with schizophrenia have a surfeit) to find alternative ways of ameliorating those symptoms.

#### Declaration of Interest

None.

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#### Letter to the Editor

##### The coherence of the evidence linking cannabis with psychosis

Similar to the link between smoking and lung cancer, it is the level of *coherence* between observational, biological and experimental studies on the link between cannabis and psychosis that will finally inform the community about the validity and causality of any association. Macleod (Macleod, 2007) cogently argues that observational studies in psychiatry may be rich sources of bias and confounding. Therefore, no matter how many studies are conducted, one can always think of more or less plausible sources of bias and confounding. Whilst this is true, it is also true that any discussion of observational evidence is incomplete and selective if other sources are ignored. Furthermore, a discussion of observational evidence is biased if it fails to take into account important findings. For example, while Macleod agrees that the acute effects of cannabis include psychotic symptoms, he does not discuss the Danish Psychiatric Central Register follow-up of such acute intoxications, showing that the great majority were later re-diagnosed with schizophrenia (Arendt *et al.* 2005).

Macleod is selective with regard to the scope of the evidence assessing links between cannabis and psychosis. He ignores randomized experimental studies and does not discuss studies showing that the effect

of cannabis is not the same for all persons but is moderated by other factors including genetic factors. This is relevant, as classical reasoning about bias and confounding as applied to the cannabis–psychosis link by Macleod assumes that effects of cannabis are the same for everybody while it has been shown that ‘relativity of relative risks’ (Neeleman, 2003) likely underlies virtually all epidemiological findings. In other words: exposures such as cannabis are likely to have very different effects on different people in different environmental contexts and therefore uniform mechanisms of bias and confounding are unlikely to apply. For example, observational data suggest that the psychotogenic effects of cannabis may be most profound after exposure during early adolescence (Arseneault *et al.* 2002), and animal research (Schneider & Koch, 2003) is coherent in this respect. D’Souza and colleagues showed in a randomized, placebo-controlled experimental study that people with schizophrenia are more sensitive to the acute effects of cannabis than healthy controls (D’Souza *et al.* 2005). This finding, that cannot be readily explained away by bias or confounding, clearly is relevant for the finding, reported in several observational studies, that people with schizophrenia or schizophrenia vulnerability are differentially sensitive to the effects of cannabis (van Os *et al.* 2002; Verdoux *et al.* 2003; Henquet *et al.* 2005). Furthermore, Caspi and colleagues showed in a birth cohort study that differential sensitivity to cannabis, in terms of the risk of developing schizophreniform disorder, may be moderated by a functional polymorphism in the gene encoding catechol-*O*-methyl transferase that impacts on dopamine neurotransmission (Caspi *et al.* 2005). In a randomized, placebo-controlled, experimental study, the same functional polymorphism was shown to moderate the acute effects of cannabis (Henquet *et al.* 2006). Early neuro-imaging work has shown that cannabis may affect dopamine neurotransmission (Voruganti *et al.* 2001), and several studies are under way to further examine this issue.

In conclusion, the discussion on the link between cannabis and psychosis should not focus *solely* on noisy epidemiological data and all the more or less plausible mechanisms of bias and confounding that can be brought to bear on these, but on the level of coherence between epidemiological, clinical, biological and experimental findings. It is clear that main-effect observational studies have provided important insights, but reached their limit, and that more experimental, biological and observational–interactive model studies are needed. In the meantime, we have common sense to guide us. If a recreational drug was found to cause an acute increase in blood pressure or gastric acid production, how many clinicians would

want to wait until epidemiologists were finished discussing how clear the prognostic signal was in noisy observational data before advising their patients with hypertension or peptic ulcer to stop taking this recreational drug?

#### Declaration of Interest

None.

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### The Author replies

The Editor invited me to respond to three letters received by *Psychological Medicine* following publication of my commentary on the paper by Louisa Degenhardt and colleagues (2007) on the temporal relation between cannabis use and psychological symptoms amongst people with mental illness. My response to two of the letters is reasonably brief. I mostly agree with the points made by Dr Grech, in particular the need for the experimental studies he calls for to show effective ways to help patients with mental illness reduce their cannabis use and confirm that such reductions are beneficial to their overall health. Professor Castle's letter is a summary of his interpretation of the evidence around cannabis and psychosis. This interpretation is plausible though, as Professor Castle would surely agree, plausibility of itself provides a weak basis for causal inference (Hill, 1965). I am probably one of the people whose 'diffidence' about the evidence that cannabis use causes schizophrenia Professor Castle finds surprising. I will try to illustrate the reasons for my scepticism through responding to the points raised by Henquet and van Os since it is their letter that is most directly and personally critical of my own position, or what these authors perceive that position to be.

Few epidemiologists would disagree with the suggestion that the coherence of different types of evidence from different sources (or indeed their convergence) should be considered in trying to judge the strength of support for a particular causal hypothesis. What must also be carefully considered are possible non-causal explanations (bias, confounding, reverse causation) for an association between a putative cause and its possible effect. This is not some game of epidemiological pedantry; it is a crucial part of the

practice of evidence-based medicine and a hard lesson learned through experience (Davey Smith & Ebrahim, 2002; Petitti, 2004). So these steps of critical appraisal are precisely the ones that both I, and colleagues who share an interest in the aetiology of schizophrenia (along with the wider question of harmful outcomes of cannabis use) have taken (Macleod *et al.* 2004, 2006). Our scepticism probably reflects the fact that, objectively, we do not see this evidence as being as coherent or convincing as proponents of the cannabis hypothesis suggest.

The parallel Henquet and van Os draw with the tobacco and lung cancer story is interesting. The observational evidence on the causal link between smoking and lung cancer is indeed coherent. Lung cancer is an outcome that can be measured in relatively secure and objective ways. In different populations studied during different historical periods and where smoking shows markedly different social patterning (in other words where different sorts of people smoke), the association between smoking and lung cancer risk remains fairly constant, substantial and little attenuated on adjustment for possible confounding factors (Peto *et al.* 1996). In fact in the extreme situation where the normal social patterning of smoking is reversed so that smoking is associated with social advantage rather than disadvantage, patterns of lung cancer follow this distribution (Wassink, 1948). Ecological, rather than individual, level observational evidence is also compelling; when the prevalence of important causes changes in the population the prevalence of their effects follows suit. Thus, wherever they have been observed, epidemics of lung cancer have mirrored the smoking epidemics that preceded them.

Contrast this picture with the evidence to date on cannabis and schizophrenia. The most objective (i.e. unbiased) measure of schizophrenia is probably diagnosis by an experienced clinician and admission to hospital seems a reasonable proxy for this. One large observational study shows an association between cannabis use in late adolescence and a sixfold increase in risk of this outcome that is halved on adjustment for a limited number of potential confounders (Zammit *et al.* 2002). A small number of further studies (including those of Henquet and van Os) show that people who report higher cannabis use are more likely to subsequently report unusual thoughts and perceptions, particularly if at baseline they already had evidence of a tendency to report unusual thoughts and perceptions (Macleod *et al.* 2004; Moore *et al.* 2007). The size of these effects vary; however, they are generally not substantial and they are generally substantially attenuated on adjustment for whatever potential confounding factors were considered. In all

these populations cannabis use shows a similar social patterning in that it is associated with social disadvantage and pre-existing psychological symptoms. Ecological evidence does not so far suggest that epidemics of cannabis use are followed by epidemics of psychotic illness within the timescale that studies like those of Henquet and van Os would predict (Degenhardt *et al.* 2003; Hickman *et al.* 2007). Surely this evidence can only be described as 'coherent' or 'converging' in a very broad sense? Certainly, it is compatible with the possibility of a causal role for cannabis use in the aetiology of schizophrenia, an important idea that should be examined seriously and rigorously, but currently the case hardly seems compelling.

Henquet and van Os also accuse me of being 'selective' in the studies I choose to discuss and of ignoring important pieces of evidence. What they appear to mean by this is that I have sometimes failed to cite pieces of evidence that they feel are particularly convincing or relevant. Generally this is because I do not share their views on the strength or relevance of the evidence in question. For example they draw attention to a study by Arendt and colleagues showing that amongst a cohort of individuals admitted to hospital with what was labelled at the time as cannabis-induced psychosis, 44.5% (a proportion Henquet and van Os call a 'great majority') subsequently attracted a diagnosis of schizophrenia (Arendt *et al.* 2005). This finding could reflect the fact that cannabis use is common amongst people admitted to hospital with a diagnosis of psychotic illness, an observation that is not controversial and which says nothing about direction of causality. It could also reflect the inherent uncertainty in psychiatric diagnosis, and that individual diagnostic classifications often change over time. It does not, however, seem to provide key evidence on whether cannabis use causes psychosis.

I am then chided for ignoring randomized experimental studies and neglecting to discuss the issue of possible effect modification. With regard to the former charge it simply is not true. Rather than ignoring experimental studies in my commentary I discussed how they could contribute to the debate. Experimental modification of level of cannabis use by young people in the general population (say through random allocation in an intervention trial that successfully influenced level of cannabis use) could certainly provide insights into whether cannabis use causally influences risk of schizophrenia and indeed other outcomes. Unfortunately I know of no studies taking this approach and Henquet and van Os do not cite any. On the issue of effect modification I simply followed the convention of considering the strength of evidence for important main effects, before looking at the issue of

possible sub-group effects (the same convention that has been followed by all the primary, population-based longitudinal studies that have so far reported associations between cannabis use and psychosis). Effect modification has been suggested in relation to two of these studies, in one by both age of use and by genotype in the COMT functional polymorphism and in another according to whether individuals are 'psychosis prone' at baseline (whether they already reported some psychotic symptoms) (Arseneault *et al.* 2002; Caspi *et al.* 2005; Henquet *et al.* 2005). In other words evidence for effect modification is so far neither consistent nor convergent. To reassure my critics that this conclusion is not simply a reflection of my own idiosyncrasies or prejudice I refer them to a systematic review published recently in the *Lancet* (Moore *et al.* 2007). In relation to effect modification by age of use these reviewers concluded that, 'no robust evidence supports this view'; and further suggested that, 'evidence for effect modification between cannabis use and COMT variation on psychosis risk is very weak'; a view I agree with.

I am afraid that I also fail to see the relevance of arguments based on the 'relativity of relative risks' (Neeleman, 2003). In the editorial cited, Neeleman suggests that effects of social exposures on predominantly socially determined outcomes may depend on social context. This seems a reasonable suggestion, however, the discourse on cannabis and psychosis almost exclusively presents the former as a chemical exposure acting on a brain disease via neurological pathways. Social context may still conceivably have some relevance but should not be expected to be any more influential than it is in relation to the expression of the effects of tobacco use on lung cancer risk via a similarly 'biological' pathway. It is a biological explanatory model that Henquet and van Os invoke when they talk in their letter of mediation via effects on dopamine neurotransmission.

Over the last 5 years the arguments around the strength of the evidence that cannabis use causes schizophrenia have been rehearsed almost to the point of exhaustion. Proponents of the causal hypothesis appear to find it difficult to accept that some people remain sceptical, and that this scepticism is based in the scientific considerations discussed above rather than anything to do with ideology or even personal enmity. Henquet and van Os finish their letter with a rhetorical question about the advice that clinicians should give their patients around cannabis use. The answer to this question is straightforward. The public health case for prevention of cannabis use by young people is strong, irrespective of whether cannabis use causes psychotic illness (Macleod *et al.* 2006).



Prevention of cannabis use should be a public health priority, because it reinforces tobacco use. Effective ways of achieving this health benefit that do not generate disproportionate collateral costs should be found. What is also important is a consistent, critical and non-partisan scientific approach to the study of possible environmental influences on risk and prognosis of schizophrenia and other psychotic illness.

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