High-potency cannabis and incident psychosis

I declare no competing interests.

Clas Linnman
clinnman@partners.org

Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA

1 Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 2019; **6:** 427–36.

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Authors' reply

We are grateful for the opportunity to respond to the letters published in response to our Article.[1] We do not believe—nor do our findings imply—that the cause of psychotic disorder is simple and attributable to one factor; rather, we acknowledge that multiple factors combine to cause it. A complex pathway underlying psychotic disorder might involve predisposing genes, exposure to prenatal complications, and use of high-potency cannabis. Removing any one of these factors would prevent all cases of the disorder attributable to this complex set of factors. In this way, population attributable fractions can add up to more than 1 (100%), because some individuals with more than one risk factor can have disease onset prevented in more than one way.[2] Therefore, we respond to Iris Sommer and Wim van den Brink by highlighting that our paper shows, assuming complex causality, that removing high-potency cannabis use—as one component cause among others—could prevent up to 50% of new cases of psychotic disorder in Amsterdam, the Netherlands. Thus, our proposal that high-potency cannabis use accounts for a sizeable proportion of incident cases of psychosis is neither implausible nor inconsistent with what is known about the genetics of multifactorial disorders such as psychosis. Furthermore, in estimating heritability, gene–environment interactions are typically attributed to the genetic component, leading the unwary to underestimate the effect of the environment.[3] The comments of Sommer and Van den Brink on the characteristics of our control sample reflect low familiarity with epidemiological case-control designs, which, as we clearly explain in the paper, require controls representing the population at risk of developing the target disorder, rather than controls with other diseases, to produce robust findings.

We agree with Clas Linnman that pollution and tobacco smoking might have a causal role in psychotic disorder, although the evidence is much less substantial than that for heavy cannabis use; nor did they explain the excess of psychotic disorder cases we found in northern European cities, compared with case numbers in Spain and Italy. Firstly, we controlled for cigarette smoking. Secondly, although, as Linnman points out, we found an effect of tobacco smoking on the odds ratio for psychotic disorder in the overall sample, this effect was mostly driven by cities in Spain and Italy, where the prevalences of tobacco smoking were among the highest in all of our European sites, both in cases and controls. In our study, the proportions of controls smoking more than 10 cigarettes per day were highest in Madrid (16%) in Spain and Bologna (14%) in Italy, which were around double those in Amsterdam (7%) and London, UK (5%; unpublished). Thirdly, in relation to pollution, the data from the European Environmental Agency referenced by Linnman indicate that Madrid was one of the cities with the highest NOx pollution in Europe during the years preceding illness onset in our patient group. Finally, we agree with Linnman that Δ^9-tetrahydrocannabinol is not the only cannabinoid contained in cannabis; however, it is the one consistently linked to psychosis and the one used by international agencies to indicate cannabis potency.

Nathan Gillespie and colleagues appear unaware of the large body of evidence from epidemiological, experimental, and neuroimaging studies supporting a causal link between cannabis use and psychosis. Nor do they refer to the study of Boydell and colleagues,[4] which provides evidence of an increase in the incidence of psychosis alongside increases in the prevalence of cannabis use.[4] Gillespie and colleagues quote findings from Degenhardt et al showing that psychosis incidence in Australia goes against patterns of cannabis use; however, these findings were generated by modelling trends on the basis of assumptions that even Degenhardt and colleagues accept might not be accurate. Although we controlled for the potential effect of other risk factors and used incidence values already adjusted for age and migration, Degenhardt and colleagues assumed that changes in prevalence of cannabis use alone might explain the incidence of psychosis; however, changes in other risk factors that they do not estimate could have also led to decreased cases of psychosis.

The Mendelian randomisation studies published to date on the direction of causality between cannabis use and schizophrenia[5] do not come to the same conclusions as the Pasman et al study referenced by Gillespie and colleagues. Pasman and colleagues report a causal effect of schizophrenia risk genes on cannabis use, but their study only has data relating to what they define as

cannabis initiation (ie, having ever used cannabis, yes or no). However, having used cannabis once is no more useful as a measure of psychosis risk than is a single event of alcohol consumption as a measure of liver disease risk. Thus, the phenotype they use is not comparable to the detailed measures of patterns of use, daily use, and use of high-potency cannabis that we found to affect the incidence of psychotic disorder.

In response to Carey Clark, the types of high-potency cannabis available across our European sites were unlikely to be contaminated by the same pesticides or have the same concentrations of metals. We also did control in all our analyses for the potential confounding effect of all of the drugs to which Clark refers.

To conclude, most importantly, we found that heavy cannabis use is a modifiable risk factor for psychotic disorders and, as such, a potential target of preventive efforts that might reduce the number of individuals who develop these devastating disorders.

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Marta Di Forti, Craig Morgan, Jean-Paul Selten, Michael Lynskey, Robin M Murray
marta.diforti@kcl.ac.uk

Social, Genetic and Developmental Psychiatry Centre (MDF), Department of Health Service and Population Research (CM), Department of Addiction (ML), and Department of Psychosis Studies (RMM), Institute of Psychiatry, Psychology and Neuroscience, King's College London, London; South London and Maudsley NHS Mental Health Foundation Trust, London, UK (MDF); and Rivierduinen Institute for Mental Health Care, Leiden, Netherlands (J-PS)

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Prevalence of mental disorders in China

Yueqin Huang and colleagues[1] reported the findings of the China Mental Health Survey, in which they found that the lifetime prevalence of any psychiatric disorder was 16·6% and the 12-month prevalence was 9·3% in the general population of China based on a two-stage sampling study. As the authors discussed, their findings differ from the figures reported by earlier studies. For example, the 1-month prevalence of any psychiatric disorder in four provinces in China was 17·5%.[2] Huang and colleagues[1] suggested that their findings were not comparable with previous results because of differences in diagnostic criteria, instruments, survey methods, investigated disorders, and sampled populations. We propose other methodological limitations in Huang and colleagues' survey that might also have affected their findings.

In the China Mental Health Survey, psychiatric diagnoses, except for psychotic disorders and dementia, were established with the highly structured Composite International Diagnostic Interview-3.0 (CIDI-3) by lay interviewers. The CIDI-3 cannot be administered in a flexible manner, which is particularly important for illiterate or poorly educated participants who might require explanations. China has 56 ethnic groups who speak hundreds of regional dialects.[3] In the Huang et al. study,[1] the training courses on the application of diagnostic instruments were delivered in Mandarin.[4] Although local interviewers were hired and the Chinese technical terms of the CIDI-3 were modified to help lay interviewers understand the interview content,[5] we think that some dialect-speaking participants were likely unable to fully understand the standardised questions without a flexible explanation or rephrasing of the questions. Huang and colleagues reported that the wording of the diagnostic instruments was translated and back translated from Mandarin to local dialects. However, the hundreds of dialects in China would have made it logistically very difficult, because even in the same area, many different dialect speakers cannot understand each other well: it is not clear from the Huang and colleagues' study how they overcame this problem. Furthermore, the psychometric properties of the instruments might be affected by translations from Mandarin to local dialects. We propose that validated semistructured diagnostic instruments, such as the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) with additional probes, would be more appropriate for epidemiological surveys.

Second, the quality of the interviews and proper use of the diagnostic instruments were assessed by 147 quality control staff in stage 1 and 15 staff from Beijing and Tianjin in stage 2 by listening to the audio records.[4] This procedure could also have been considerably affected by the numerous dialects used in the interviews because the quality control staff were unlikely to consistently understand these dialects in the audio records.

Third, essentially no psychiatric diagnosis can be reliably established only by a structured interview without probing questions by an experienced clinician. Structured interviews administered by a lay person would yield only a rough estimate at best. For example, Kessler and colleagues[6] found that the CIDI-SCID concordance—ie, an interview done by a clinician compared with a lay person's diagnostic estimate with a highly structured interview schedule—was low for bipolar 2 disorder.