Does schizophrenia influence cannabis use? How to report the influence of disease liability on outcomes in Mendelian randomization studies

The recent *Nature Neuroscience* paper by Pasman et al entitled "GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia" (see below) provides important and novel insights into the aetiology of cannabis use and its relationship with mental health. However – in its title and elsewhere – it subtly misrepresents what the Mendelian randomization (MR) [1] analyses it presents actually show. MR analyses are increasingly being reported as demonstrating the effect of a disease (in this case schizophrenia) on the outcome, through using genome wide significant variants associated with risk of the disease on the outcome (which can be a behavior, such as cannabis smoking in the present paper, a measured trait or a second disease).

MR analyses are often carried out using summary data, where the exposure and outcome GWAS come from separate samples. In such analyses interpretation is not to apparent effects of the disease itself, but to the phenotypic effects of genetic *liability* to that disease. Typically, only a tiny proportion of participants in the outcome GWAS datasets will actually have experienced the disease – in this case particularly so given the low participation rate of people with schizophrenia in most studies in the general population. Indeed, MR studies can be carried out in datasets where there are *no* individuals with the outcome (e.g. datasets collected amongst an age group in whom the outcome will have occurred very rarely, if ever). Such analysis may reveal apparent, but impossible, effects of the disease on outcome phenotypes. To use MR analyses to investigate the causal effect of a disease on outcomes would require individual-level data with recorded disease events and subsequent follow-up. Analytical approaches to such data have, as yet, not been published.

The widespread misrepresentations of such MR studies have important implications, not just in terms of how the results are interpreted, but also how they are applied. One valuable contribution of MR studies is that they can identify modifiable exposures that can be the target of interventions. If it is recognized that what is being shown is an effect of liability to disease on an outcome, then interventions targeting the mechanisms of this liability would have benefits even in individuals who are unlikely to go on to develop the disease, including those at low risk of the disease for other reasons. For example, targeting breast cancer liability may have benefits in men if this liability influenced diseases that are common in men. If, however, it is the disease itself which has the effect, then the interventions would be targeted at those likely to develop disease: only women, in the case of breast cancer liability. It may be that schizophrenia does indeed lead to cannabis use, but the analyses reported by Pasman et al show only that *liability* to schizophrenia leads to cannabis use.

The point is a subtle one – we have both used similar language in the past in articles reporting MR analyses on which we are authors. Indeed, one of us (MM) was an author on the Pasman et al paper (and contributed principally to the MR analyses and their interpretation) but failed to suggest the correct phrasing. Fortunately, the title and discussion will be changed to address this problem so that the enduring version of the paper captures this importance nuance. However, it is a widespread and underappreciated point of interpretation in MR studies, and we feel that this presents a useful opportunity to highlight it. It also illustrates that methodologies, and the interpretation of the results they generate, continue to evolve, illustrating the need to interpret past work (including our own!) through the lens of current approaches.

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ARTICLES

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GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia

Joëlle A. Pasman[1,37], Karin J. H. Verweij[1,2,37], Zachary Gerring[3], Sven Stringer[4], Sandra Sanchez-Roige[5], Jorien L. Treur[6], Abdel Abdellaoui[2], Michel G. Nivard[7], Bart M. L. Baselmans[7], Jue-Sheng Ong[3], Hill F. Ip[7], Matthijs D. van der Zee[7], Meike Bartels[7], Felix R. Day[8], Pierre Fontanillas[9], Sarah L. Elson[9], the 23andMe Research Team[10], Harriet de Wit[11], Lea K. Davis[12], James MacKillop[13], The Substance Use Disorders Working Group of the Psychiatric Genomics Consortium[14], International Cannabis Consortium[15], Jaime L. Derringer[16], Susan J. T. Branje[17], Catharina A. Hartman[18], Andrew C. Heath[19], Pol A. C. van Lier[20], Pamela A. F. Madden[19], Reedik Mägi[21], Wim Meeus[17], Grant W. Montgomery[22], A. J. Oldehinkel[18], Zdenka Pausova[23], Josep A. Ramos-Quiroga[24,25,26,27], Tomas Paus[28,29], Marta Ribases[24,25,26], Jaakko Kaprio[30], Marco P. M. Boks[31], Jordana T. Bell[32], Tim D. Spector[32], Joel Gelernter[33], Dorret I. Boomsma[7], Nicholas G. Martin[3], Stuart MacGregor[3], John R. B. Perry[8], Abraham A. Palmer[5,34], Danielle Posthuma[4], Marcus R. Munafò[6,35], Nathan A. Gillespie[3,36,38], Eske M. Derks[3,38] and Jacqueline M. Vink[1,38*]

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