In a recent commentary, Gage and Munafó argued that we should rethink the accepted role of cigarette smoking in schizophrenia: as a form of self-medication. They argue that evidence from recent genome-wide association studies suggest that Mendelian randomisation analyses could be used to test the hypothesis that cigarette smoking may play a causal role in schizophrenia. They also argue that the consistent association reported between cannabis use and schizophrenia in longitudinal studies could also be explained by the hypothesis that cigarette smoking increases the likelihood of using cannabis and developing schizophrenia.

Gage and Munafó do not fully address some important issues relating to linkages between cigarette smoking, cannabis use and psychosis. The first is the lack of neurophysiological pathways by which smoking could increase the risks of psychosis. A second issue is the lack of reports of tobacco or nicotine-induced psychoses or psychotic symptoms. This is in marked contrast to clinical reports and laboratory studies of cannabis-induced psychotic symptoms.

Gage and Munafó argue that Mendelian randomisation provides a unique method for addressing the control of non-observed confounding factors that are not addressed by conventional methods of
statistical adjustment. However, Mendelian randomisation is not the only method for controlling non-observed sources of confounding. As we have previously commented, there is an alternative approach for studying the associations between time-dynamic outcomes such as cannabis use, tobacco use and psychotic symptoms: fixed effects regression. The fixed effects regression model makes it possible to control all non-observed sources of confounding (U), both genetic and environmental, that may be correlated with a time-varying exposure variable X, and have fixed and enduring effects on a time dynamic outcome Z. We have previously used this methodology to examine the associations between cannabis use and psychotic symptoms in a New Zealand birth cohort.

We tested the hypotheses suggested by Gage and Munafó using repeated measures data collected at ages 18, 21, 25, 30 and 35 during the course of the Christchurch Health and Development Study. We used these data to examine the associations between the frequency of cigarette smoking, the frequency of cannabis use and rates of psychotic symptoms (measured by the SCL-90 at ages 18-25 and the Diagnostic Interview Schedule at ages 30-35). The fitted model included both cigarette smoking and cannabis use as fixed effects as well as a number of time dynamic covariates, including concurrent measures of: alcohol use disorder; major depression; anxiety disorder; life stress; and deviant peer affiliations. The final model fitted was a negative binomial model in which the natural logarithm of the number of psychotic symptoms at each age $Y_t$ was modelled as a linear function of: a) cigarette smoking $X_{1t}$; b) cannabis use $X_{2t}$; c) non-observed fixed sources of confounding (U); d) time-varying covariates ($Z_t$); and e) random error ($E_t$). This model was fitted to the data using Stata 12.0. The sample sizes ranged from 1025 (age 18) to 962 (age 35), representing 79% to 82% of the surviving sample at each assessment.

Table 1 shows: a) the bivariate associations between tobacco use, cannabis use and psychotic symptoms pooled over the five observation periods; and b) the model parameters for tobacco and cannabis after adjustment for fixed effects and time-dynamic covariates. The Table shows that the
frequency of both tobacco and cannabis use were significantly (p<.0001) related to rates of psychotic symptoms. After adjustment, cannabis use remained significantly related to rates of psychotic symptoms (B = .13; SE = .04; p < .001) whereas cigarette smoking did not (B = .08; SE = .05; p > .10). These findings suggest a possible causal effect of cannabis use on rates of psychotic symptoms, and imply that the associations between cigarette smoking and cannabis use are explained by the effects of: a) the associations between cigarette smoking and cannabis; b) non-observed fixed effects common to tobacco and cannabis; and c) time-dynamic covariates associated with cannabis use.

INSERT TABLE 1 HERE

These findings do not support the hypothesis that cigarette smoking plays a role in the development of psychotic symptoms. They do, however, support the hypothesis that cannabis use influences the risk of psychotic symptoms. It is important to note that the outcome measure used in our study was not a measure of schizophrenia but rather a more general measure of psychotic symptoms. This difference could explain the differences between the findings of our study and the hypotheses advanced by Gage and Munafó. Nonetheless the failure of our analysis to support the application of Mendelian randomisation to examine the linkages between smoking and schizophrenia studies suggests the need for more comprehensive analyses of data on tobacco smoking, cannabis and psychosis before we accept the premise that cigarette smoking may be a cause of psychosis and reject a causal role for cannabis use in psychosis.

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Author contributions: All authors contributed to the study design, interpretation of results and writing and editing of the manuscript. Data were analysed by JMB and LJH.
Table 1  Associations between psychotic symptoms and frequency of: a) cannabis use; and b) cigarette smoking, ages 18-35, before and after controlling for non-observed fixed effects and time-dynamic covariate factors

<table>
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<tr>
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<th>Before adjustment</th>
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<td></td>
<td>B</td>
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<tr>
<td>Frequency of cannabis use</td>
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<td>.02</td>
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<tr>
<td>Frequency of cigarette smoking</td>
<td>.30</td>
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¹ Statistically significant (p < .05) time-dynamic covariate factors included: major depression; anxiety disorder; life stress; and deviant peer affiliations.
References


