Association Between Continued Cannabis Use and Risk of Relapse in First-Episode Psychosis
A Quasi-Experimental Investigation Within an Observational Study

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➕ Supplemental content

IMPORTANCE Cannabis use after first-episode psychosis is associated with poor outcomes, but the causal nature of this association is unclear.

OBJECTIVE To examine the precise nature of the association between continued cannabis use after the onset of psychosis and risk of relapse of psychosis.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study followed up for at least 2 years after the onset of psychosis 220 patients who presented to psychiatric services in South London, England, from April 12, 2002, to July 26, 2013, with first-episode psychosis. Longitudinal modeling (fixed-effects analysis, cross-lagged path analysis) was used to examine whether the association between changes in cannabis use and risk of relapse over time is the result of shared vulnerability between psychosis and cannabis use, psychosis increasing the risk of cannabis use (reverse causation), or a causal effect of cannabis use on psychosis relapse.

INTERVENTIONS Exposure to cannabis within the first and second years after onset of psychosis.

MAIN OUTCOMES AND MEASURES The main outcome measure was relapse of psychosis, defined as subsequent hospitalization for psychosis. Effect of cannabis use status in the first year (C_{t1}) and second year (C_{t2}) and pattern of cannabis use continuation in the first year and second year were modeled for risk of relapse in the first year (R_{t1}) and risk of relapse in the second year (R_{t2}) after psychosis onset.

RESULTS A total of 220 patients with first-episode psychosis were included in the analysis (mean [SD] age, 28.62 [8.58] years; age range, 18-65 years; 90 women [40.9%] and 130 men [59.1%]). Fixed-effects models that adjusted for time-variant (other illicit drug use, antipsychotic medication adherence) and time-invariant (eg, genetic or premorbid environment) unobserved confounders revealed that there was an increase in the odds of experiencing a relapse of psychosis during periods of cannabis use relative to periods of no use (odds ratio, 1.13; 95% CI, 1.03-1.24). Change in the pattern of continuation significantly increased the risk (odds ratio, 1.07; 95% CI, 1.02-1.13), suggesting a dose-dependent association. Cross-lagged analysis confirmed that this association reflected an effect of cannabis use on subsequent risk of relapse ($C_{t1} \rightarrow R_{t2}$: $\beta = 0.44$, $P = .04$) rather than an effect of relapse on subsequent cannabis use ($R_{t1} \rightarrow C_{t2}$: $\beta = -0.29$, $P = .59$).

CONCLUSIONS AND RELEVANCE These results reveal a dose-dependent association between change in cannabis use and relapse of psychosis that is unlikely to be a result of self-medication or genetic and environmental confounding.

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U nderstanding the nature of the association between cannabis use and psychotic disorders is crucial for the formulation of evidence-based health policies concerning cannabis, especially in light of changing public attitudes and legalization of cannabis use in several states in the United States and other countries.[1-4] This understanding is particularly important because psychotic disorders, such as schizophrenia, cause the most severe health loss of all human disorders[5,6] and are associated with considerable financial burden.[7,8] Psychotic disorders are also associated with a high rate of comorbid abuse of cannabis,[9,10] the most commonly used illicit drug worldwide.[11]

Cannabis use typically continues after the onset of psychosis, and meta-analytic evidence[12] from studies of more than 16 500 patients suggests that continued cannabis use after the onset of psychosis is associated with increased relapse rates, length of hospitalizations, and severity of symptoms of psychosis. However, methodologic questions remain,[13,14] including the concern that the association between cannabis use and psychosis relapse may reflect the effect of shared genetic and environmental risk and the possibility of reverse causation[13] (ie, psychosis that leads to cannabis use rather than cannabis use that leads to relapse of psychosis). Studies that have examined the issue of reverse causation in those with preexisting psychosis report a bidirectional association between cannabis use and symptom severity[15] or that frequency of cannabis use predicts an increase in subsequent symptoms of psychosis but not vice versa.[16,17] However, such evidence does not rule out the possibility that systematic differences between cannabis-using and non–cannabis-using patients with psychosis, such as a genetic predisposition that influences psychosis and cannabis use,[18] may underlie the association between cannabis use and relapse of psychosis.

The criterion standard of evidence for establishing that cannabis use is causally linked to a risk of relapse in those with preexisting psychotic disorder would be a randomized clinical trial that involves experimental cannabis administration, which is unlikely to be realized because of ethical reasons. Short of that, a quasi-experimental approach that involves the assessment of within-individual changes in cannabis use over time provides a compelling alternative that is considered only second best to a randomized clinical trial when examining causality.[19] The application of such a design, also called fixed-effects analysis of longitudinal panel data,[20,21] allows for the control of the effects of unobserved time-invariant confounding factors, such as shared genetic and environmental factors that do not change over time,[13,14] and those observed potential confounding factors that change over time. This design has been used to establish an association between cannabis use and increased risk of symptoms of psychosis in the general population[22] and independently in long-term methamphetamine users without a comorbid diagnosis of psychosis.[21] Studies[21-23] also suggest a dose-response relationship between frequency of cannabis use and symptoms of psychosis when controlling for preexposure confounding factors, an important criterion when establishing causality.[24] These methodologic approaches strengthen the argument for causality and have been used in investigations conducted in the general

Key Points

Question Is the association between continued cannabis use and risk of psychosis relapse causal or likely attributable to confounding or reverse causation?

Findings Using a quasi-experimental design in 220 patients with first-episode psychosis, this study found that continued cannabis use after the onset of psychosis was associated with increased risk of relapse of psychosis, resulting in psychiatric hospitalization.

Meaning Changes in cannabis use after the onset of psychosis are likely to affect outcome in the early stages of psychosis.

population.[22] However, these approaches have not been fully incorporated in studies of the effect of cannabis use on outcomes in patients with first-episode psychosis (FEP) (eTable 1 in the Supplement).

To date, no study has systematically addressed the issues of confounding from shared predisposition, reverse causation, and dose-response relationship and established whether cannabis use can affect the outcome of psychosis, leading to hospitalization. Hospitalization can be reliably measured and objectively compared across studies and has hence been proposed as an ideal outcome measure for randomized clinical trials[25] and studies on illness course in FEP.[26] Hospitalization is also linked to high personal, economic, and societal costs[27] and therefore remains a major public health concern.

To address the limitations in existing evidence[13,28] (eTable 1 in the Supplement), we investigated the nature of the association between continued cannabis use and relapse of psychosis in a large sample of patients with FEP. First, we controlled for unobserved time-invariant genetic and environmental confounders and observed time-variant sources of confounding (other illicit drug use, medication adherence) using a fixed-effects analysis approach. Second, we used cross-lagged path analysis to investigate the directionality of the association between continued cannabis use and risk of relapse after the onset of psychosis. Third, we used 2 measures of cannabis use: (1) change in cannabis use status over time (nonuser status vs user status) and (2) a more detailed measure of cannabis use during the follow-up period that takes into account the pattern of continued cannabis use after onset of illness.
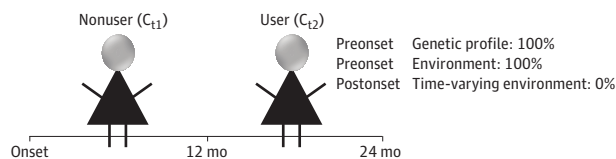
Methods

Study Sample

Patients with nonorganic (nonaffective [*International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) codes F20-F29] or affective [*ICD-10* codes F30-F33]) FEP[29] (mean [SD] age, 28.62 [8.58] years; age range, 18-65 years; 90 women [40.9%] and 130 men [59.1%]) were recruited by the study team from local early-intervention services (community setting) for psychosis and adult inpatient units of the South London and Maudsley National Health Service Foundation Trust covering the South London, England, boroughs of Lambeth, Southwark, Croydon, and Lewisham from April 12, 2002, to July 26,

2013. They were assessed twice as part of the research, with the first assessment being close to the onset of their illness. Follow-up assessment involved a face-to-face or telephone interview (if the individual was unable to appear in person) at least 2 years after the onset of their psychotic illness. Interview data were complemented by a screening of clinical records to extract health care use data (eg, dates of admission and discharge, medication use). Outcome data (admission to the hospital after psychosis onset) were also collected from clinical records for those who refused to take part in research interviews (n = 133) or those who had missing data (n = 43). Comparison of outcome (risk of relapse) for those patients who provided complete data, those with missing data, and those who refused revealed that they were not significantly different in their risk of relapse during the 2-year follow-up period after onset (χ^2 = 1.25, P = .53) (eTable 2 in the Supplement). This study was granted ethical approval by the South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry Local Research Ethics Committee. All participants provided written informed consent, and data were deidentified.

Outcome Measures

Diagnosis (affective vs nonaffective psychosis) was based on *ICD-10* diagnosis assessed with the Operational Criteria Checklist[30] using information recorded after psychiatric interview by the clinical team. Information regarding the age at onset of psychosis, defined as the age on the date of referral for FEP, was obtained from electronic patient records. Cannabis use during the first 2 years after onset of psychosis was assessed using a modified version of the Cannabis Experience Questionnaire.[31] Reliability of retrospective assessment of cannabis use was established by comparing data on premorbid cannabis use (ever used before onset) collected at onset of psychosis with data on premorbid cannabis use reported at follow-up, which revealed a high overlap (eMethods in the Supplement). Participants were classified based on their pattern of reported cannabis use after onset, assessing cannabis use within the first year after onset (C_{t1}) and cannabis use within the second year after onset (C_{t2}). Two cannabis use variables were defined, including the dichotomized variable cannabis use status (C_{t1}/C_{t2}) and the ordinal variable pattern of cannabis use continuation (CP_{t1}/CP_{t2}, scored from 0 to 2, with a higher score indicating longer duration of use) (eMethods in the Supplement). Relapse was defined as admission (yes or no) to a psychiatric inpatient unit because of exacerbation of symptoms of psychosis within the first year (R_{t1}) and the second year (R_{t2}) after the first presentation of psychosis. If the patient was hospitalized at the first presentation to psychiatric services with a diagnosis of psychosis, this was not considered a relapse event. Hospitalization as a result of a suicide attempt was not counted as a relapse event unless there was documentation in the clinical notes of exacerbation of symptoms of psychosis. This definition of relapse is most commonly used in epidemiologic research in psychosis.[32,33] Covariates included in the analyses were selected based on previous literature (including the strongest predictors for relapse in psychosis[34]) and exploratory analysis to identify those factors that were linked to

Figure 1. Adaptation of Sibling Design for Fixed-Effects Analysis to Assess Change in Cannabis Use Over Time

C_{t1} indicates cannabis use in the first year; C_{t2}, cannabis use in the second year.

cannabis use and relapse within the 2 years after onset (eTable 3 in the Supplement) and were (1) medication adherence and (2) other illicit drug use within the first 2 years after onset of psychosis (eMethods in the Supplement).

Statistical Analysis

In the first step, fixed-effects logistic regression models were fitted using the R package lme4[35] for binary outcome to adjust for factors that vary across individuals and may affect outcome but were not measured and do not vary over time, such as familial and genetic factors, duration of untreated psychosis, age at onset of psychosis, illness severity at onset, or premorbid adjustment. This approach allows estimation of the effect of within-person changes over time in their pattern of cannabis use in the first year ($C_{t1} - CP_{t1}$) and the second year ($C_{t2} - CP_{t2}$) after onset of psychosis. This analysis estimates the likelihood of an event (defined in this study as relapse) during periods when an individual is exposed to the risk factor of interest (cannabis use) compared with when the same individual is not exposed to the risk factor (**Figure 1** and eMethods in the Supplement). Other illicit drug use and medication adherence were included as covariates that change over time in the multivariate models.

In the second step, cross-lagged autoregressive path models were estimated using the lavaan package[36] to investigate the directionality of the association (eFigure and eMethods in the Supplement). Relapse variables ($R_{t1} - R_{t2}$) were treated as dependent variables, with cannabis use ($[C_{t1} - C_{t2}]/[CP_{t1} - CP_{t2}]$) variables as the independent variables, to examine whether cannabis use predicted subsequent risk of relapse and vice versa for the reverse lagged association to examine whether relapse ($R_{t1} - R_{t2}$) predicted cannabis use ($[C_{t1} - C_{t2}]/[CP_{t1} - CP_{t2}]$). Model paths were estimated while controlling for other illicit drug use and medication adherence. The models were fitted using the robust weighted least squares approach. Model goodness of fit was assessed using a number of fit indexes (eMethods in the Supplement).

Results

Sample Characteristics

A total of 220 patients with FEP were included in the analysis (eResults in the Supplement). When the different groups were compared based on their cannabis use patterns (nonusers vs intermittent users vs continued users) (**Table 1**), it appeared that

Table 1. Demographic Characteristics of the Study Participants[a]

Characteristic	All Participants (N = 220)	Nonusers (n = 151)	Intermittent Users (n = 25)	Continued Users (n = 44)	P Value[b]
Age at onset, mean (SD), y	28.62 (8.58)	29.52 (8.92)	28.79 (8.94)	25.44 (6.32)	.02
Male	130 (59.1)	77 (51.0)	19 (76.0)	34 (77.3)	.001
Ethnicity other than white	147 (66.8)	97 (64.2)	17 (68.0)	33 (75.0)	.41
Onset diagnosis (nonaffective)	184 (83.6)	126 (83.4)	18 (72.0)	40 (90.9)	.12
Preonset (regular) cannabis use	118 (53.6)	52 (34.4)	23 (92.0)	43 (97.7)	<.001
Age at onset of (regular) cannabis use, mean (SD), y[c]	17.18 (3.91)	17.25 (4.06)	17.62 (3.91)	16.84 (3.78)	.60
Other illicit drug use					
No use	186 (84.5)	139 (92.0)	19 (76.0)	28 (63.6)	
Experimental use	13 (5.9)	6 (4.0)	3 (12.0)	4 (9.1)	<.001
Regular use	21 (9.5)	6 (4.0)	3 (12.0)	12 (27.3)	
Medication adherence					
Nonadherence	39 (17.7)	24 (15.9)	6 (24.0)	9 (20.5)	
Irregular adherence	92 (41.8)	55 (36.4)	11 (44.0)	26 (59.1)	.02
Full adherence	89 (40.5)	72 (47.7)	8 (32.0)	9 (20.5)	
Relapse in 2 y after onset	78 (35.5)	43 (28.5)	9 (36.0)	26 (59.1)	<.001

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

[b] P value estimates from Kruskal-Wallis test for means and χ^2 tests for independence for percentages to compare all cannabis groups.

[c] Age at onset of cannabis use was estimated for a subset of patients (n = 120) with preonset initiation of (regular) cannabis use or postonset initiation (use ≥2 times) of cannabis use; data were missing for 1 participant.

they significantly differed in the age at onset of their psychosis (29.52 vs 28.79 vs 25.44 years, Kruskal-Wallis test, $P = .02$) and sex (77 [51.0%] vs 19 [76.0%] vs 34 [77.3%] men, $\chi^2 = 13.07$, $P = .001$).

No differences between the groups were found for diagnosis (affective vs nonaffective psychosis) (126 [83.4%] vs 18 [72.0%] vs 40 [90.9%] with nonaffective psychosis, $\chi^2 = 4.18$, $P = .12$). With regard to outcome, the different cannabis use groups (nonuser vs intermittent user vs continued user in the 2 years after onset) were significantly different with regard to risk of relapse (43 [28.5%] vs 9 [36.0%] vs 26 [59.1%] relapsed, $\chi^2 = 13.96$, $P < .001$). To illustrate, the highest risk of relapse was present in those who used it continuously after onset, whereas those who did not continue cannabis use were at lowest risk (59.1% vs 28.5%). Furthermore, the cannabis use groups significantly differed with regard to the level of medication adherence (72 [47.7%] vs 8 [32.0%] vs 9 [20.5%] classified as fully adherent, $\chi^2 = 11.99$, $P = .02$) (eg, those who continued to use cannabis were less likely to have remained adherent to their antipsychotic medication plan). Similarly, the degree of other illicit drug use (other than cannabis) was different between the cannabis use groups (6 [4.0%] vs 3 [12.0%] vs 12 [27.3%] reporting regular use, $\chi^2 = 26.33$, $P < .001$), which indicated that those who continued to use cannabis also used other illicit drugs more frequently throughout the 2 years after onset of psychosis.

Fixed-Effects Analysis: Changes in Cannabis Use and Relapse

As indicated in **Table 2**, the unadjusted fixed-effects analysis revealed that risk of relapse was higher during the year in which cannabis was used (odds ratio [OR], 1.18; 95% CI, 1.08-1.29) when compared with the year in which cannabis was not used, and this effect remained significant when we controlled for time-varying factors, such as medication adherence and other illicit drug use (OR, 1.13; 95% CI, 1.03-1.24). Furthermore, there was a dose-response relationship between pattern of cannabis con-

tinuation and risk of relapse such that a 1-unit change in cannabis use pattern, signifying greater regularity in cannabis use over time (eg, from intermittent cannabis use to continued cannabis use), was associated with an increase in the odds for risk of relapse (OR, 1.10; 95% CI, 1.05-1.15). This effect was reduced but remained significant when we controlled for medication adherence and other illicit drug use (OR, 1.07; 95% CI, 1.02-1.13). In this model, medication nonadherence (OR, 0.92; 95% CI, 0.87-0.97) but not other illicit drug use (OR, 1.04; 95% CI, 0.98-1.12) remained a significant predictor of risk of relapse.

Cross-Lagged Modeling: Continuation of Cannabis Use and Subsequent Relapse

Examination of the different pathways in the saturated cross-lagged path model (**Figure 2**) revealed that the effect of cannabis use (during the first year of follow-up) on subsequent (during the second year of follow-up) risk of relapse was significant for cannabis use status ($C_{t1} \rightarrow R_{t2}$: $\beta = 0.44$, $P = .04$) and pattern of cannabis continuation ($CP_{t1} \rightarrow R_{t2}$: $\beta = 0.23$, $P = .05$) while controlling for medication adherence and other illicit drug use. The alternative paths, that is, relapse within the first year after onset of psychosis predicting subsequent cannabis use status ($R_{t1} \rightarrow C_{t2}$: $\beta = -0.29$, $P = .59$) and pattern of cannabis continuation ($R_{t1} \rightarrow CP_{t2}$: $\beta = -0.10$, $P = .76$), were not significant, indicating a unidirectional effect of cannabis use on risk of relapse of psychosis. Separate models considering the simultaneous reciprocal association between cannabis use and relapse of psychosis (eFigure in the Supplement) further supported the conclusion that cannabis use predicted relapse but not vice versa.

Discussion

In this study, we estimated the longitudinal effects of cannabis use status and pattern of continued cannabis use after the

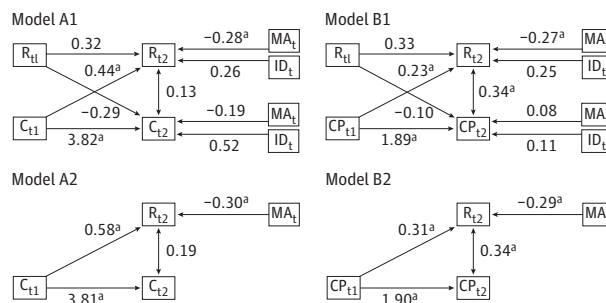**Table 2. Fixed-Effects Logistic Regression Analysis: Risk of Relapse**

Variable	OR (95% CI)
Change in Cannabis Use Status	
Simple analysis	
Cannabis use status ($C_{t1} - C_{t2}$)	1.18 (1.08-1.29)
Multiple analysis	
Cannabis use status ($C_{t1} - C_{t2}$)	1.13 (1.03-1.24)
Medication adherence[a]	0.92 (0.87-0.97)
Other illicit drug use[a]	1.05 (0.98-1.12)
Change in Pattern of Cannabis Continuation	
Simple analysis	
Pattern of cannabis continuity ($CP_{t1} - CP_{t2}$)	1.10 (1.05-1.15)
Multiple analysis	
Pattern of cannabis continuity ($CP_{t1} - CP_{t2}$)	1.07 (1.02-1.13)
Medication adherence[a]	0.92 (0.87-0.97)
Other illicit drug use[a]	1.04 (0.98-1.12)

Abbreviations: CP_{t1}, pattern of cannabis use continuation in the first year; CP_{t2}, pattern of cannabis use continuation in the second year; C_{t1}, cannabis use status in the first year; C_{t2}, cannabis use status in the second year; OR, odds ratio.

[a] Included as random effects.

Figure 2. Cross-Lagged Path Analysis

Model A, Cannabis use status (C_t) and risk of relapse in the saturated model (A1) and the reduced model (A2). Model B, Pattern of cannabis continuation (CP_t) and relapse in the saturated model (B1) and the reduced model (B2). CP_{t1} indicates pattern of cannabis use continuation in the first year; CP_{t2}, pattern of cannabis use continuation in the second year; C_{t1}, cannabis use status in the first year; C_{t2}, cannabis use status in the second year; ID_t, time-variant other illicit drug use; MA_t, time-variant medication adherence; R_{t1}, risk of relapse in the first year; and R_{t2}, risk of relapse in the second year.

[a] Statistically significant.

onset of psychosis on risk of relapse. The results implicate change in cannabis use status (eg, from user to nonuser) and change in pattern of continued cannabis use within the first 2 years after onset as risk factors for relapse. With this study design, we were able to compare periods of use with periods of nonuse within the same individual, signifying that this association cannot be explained by stable premorbid confounding factors, such as shared familial and genetic vulnerability, predisposing personality traits, duration of untreated psychosis, childhood trauma, expressed emotion, or cannabis use history before the onset of psychosis. Furthermore, changes in cannabis use status and pattern of cannabis continuation over time were linked to relapse independent of the effects of other potential confounders that vary over time, such as medication adherence and other illicit drug use. These results indicate that the association found here is unlikely to result from a common underlying genetic and environmental vulnerability shared by cannabis use and psychotic relapse as a genetic predisposition for psychosis that is also linked to cannabis use.[18] This finding is consistent with a study[37] that failed to replicate the association between polygenic risk for psychosis and cannabis use, indicating that even if a shared genetic vulnerability exists, this contribution would not fully account for the adverse effects of cannabis use on outcome in those patients with psychosis who continue using the substance. In line with these results, another genome-wide association study[38] that compared data concerning cannabis use with data on 5 different psychiatric disorders found a small overlap with depression but none with schizophrenia. Overall, our results are in accordance with previous research that used fixed-effects analysis and reported that change in cannabis use status (from nonuser to user) was linked to change in the severity of symptoms of psychosis.[15] Our findings also support a dose-response relationship (ie, the longer the period of continued [monthly] cannabis use after onset of psy-

chosis, the more likely a patient is to experience a relapse). This finding is consistent with previous evidence[23] that duration of exposure since first use of cannabis was significantly linked to psychotic outcome in previously healthy individuals. Our results from cross-lagged path analysis also indicate that cannabis use status and pattern of continued cannabis use after onset of psychosis are predictive of subsequent relapse but not vice versa, suggesting that continuation of cannabis use after onset of psychosis is a direct risk modifier for relapse in psychosis. These results are consistent with previous studies in patients with preexisting psychosis that reported cannabis use as a predictor for an increase in severity of psychotic symptoms in the short term (1 week)[17] and longer term (10 months)[16] and suggest that the association between cannabis use and relapse of psychosis is unlikely to be the consequence of self-medication.[39]

Some limitations, such as the retrospective assessment of cannabis use based only on self-report, lack of data on other potential predictors or moderators (eg, duration of untreated psychosis, illness onset severity, age at onset of psychosis, and premorbid cannabis use), and unmeasured potential time-varying confounders, need to be considered when interpreting our results. We also did not consider relapse-related outcomes other than hospitalization. However, as discussed in detail elsewhere (eDiscussion in the Supplement), those limitations are unlikely to affect the direction of these results.

Notwithstanding these limitations, the results presented here have important implications. Together, these results suggest that it is more likely than not that continued cannabis use after onset of psychosis is causally associated with increased risk of relapse of psychosis, resulting in psychiatric hospitalization. Because cannabis use is a potentially modifiable risk factor that has an adverse influence on the risk of relapse of psychosis and hospitalization in a given individual, with limited efficacy of existing interventions,[40] these results

underscore the importance of developing novel intervention strategies and demand urgent attention from clinicians and health care policymakers. Results from both of the analytical methods used (fixed-effects and cross-lagged path analysis) were consistent and point to a dose-response relationship between continued cannabis use and relapse of psychosis, resulting in hospitalization. The analyses implicate cannabis use as a risk-modifying factor, suggesting that discontinuation of cannabis use after the onset of psychosis may help in reducing the risk of relapse. However, we did not test whether discontinuation of cannabis use has a beneficial effect on outcome in the present study.

Conclusions

Using a quasi-experimental design wherein we assessed cannabis use patterns after the onset of psychosis, we were able to investigate the causal nature of the association between cannabis use and risk of relapse in psychosis. Although it has been proposed that a common genetic liability or reverse causation may underlie the association between continued cannabis use and relapse,[13] our results indicate that change in cannabis use represents a robust risk factor for relapse in patients with FEP.

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