

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Observational Studies Investigating the Temporal Relationship Between Cannabis Use and Onset of Psychosis or Outcome in Psychosis								
Study / Cohort	Study time points (T)	Cannabis measure	Psychosis measure	Analytical design	Findings	Controlled confounders	N	Quality assessment^b
Population studies investigating cannabis use as a risk factor for onset of psychosis								
Fergusson, et al. (2005) ¹ / New Zealand / General population	t ₁ : Age 18 t ₂ : Age 21 t ₃ : Age 25	C ₁ : Changes in frequency of cannabis use (t ₁ -t ₃) C ₂ : Frequency of cannabis use in 12 months prior assessment (t ₁ -t ₃)	P ₁ : Changes in psychotic symptom severity (SCL) (t ₁ -t ₃) P ₂ : Psychotic symptom severity (t ₁ -t ₃)	(1) Multivariate poisson regression (2) FEM (3) SEM	(1) C ₂ → P ₂ * (2) C ₁ → P ₁ * (3) C ₂ → P ₂ * (3) P ₂ → C ₂ (NS)	prior psychotic symptoms, prior cannabis use, other mental disorders, other substance use/alcohol use/cigarette use, stressful life events, deviant peer affiliations	1055	A: (+) B: (+) C: (+) D: (+) E: (+)
Kuepper, et al. (2011) ² / Germany / General population	t ₁ : Age 14-24 (R) t ₂ : Age 17-27 (R) t ₃ : Age 26-36 (R)	C ₁ : Initiation of use between t ₁ and t ₂ (use ≥ 5 times) C ₂ : Initiation of use between t ₂ and t ₃ (use ≥ 5 times) C ₃ : Persistence of use (use at t ₂ and t ₃)	P ₁ : P ₂ t: Incidence of psychosis between t ₂ and t ₃ (CIDI) P ₂ : Persistence of psychosis (presence at t ₂ and t ₃) P ₃ : Incidence of psychosis between t ₁ and t ₂	Multivariate logistic regression	C ₁ → P ₁ * C ₃ → P ₂ * P ₃ → C ₁ (NS)	Age, sex, SES, other drug use, childhood trauma, urbanicity	1923	A: (+) B: (-) C: (+) D: (+) E: (+)

Ferdinand, et al. (2005) ³ / Denmark / General population	t ₁ : Age 4-16 (R) t ₂ : Age 18-30 (R)	C ₁ : Initiation of cannabis use prior symptom assessment C ₂ : Initiation of cannabis use following symptom assessment	P ₁ : Psychotic symptoms (CIDI) following cannabis use P ₂ : Psychotic symptoms prior to cannabis use	Cox regression	C ₁ → P ₁ * P ₂ → C ₂ *	Age, gender	1580	A: (+) B: (-) C: (+) D: (+) E: (-)
Verdoux, et al. (2003) ⁴ / France / General population	t: ESM: 1 week, with 5 assessments/day	C ₁ : Cannabis use prior symptom assessment C ₂ : Cannabis use following symptom assessment	P ₁ : Risk of psychotic experience following cannabis use (MINI) P ₂ : Risk of psychotic experience prior cannabis use	Multilevel regression analysis	C ₁ → P ₁ * P ₂ → C ₂ (NS)	Age, gender, other illicit drug use	79	A: (+) B: (-) C: (+) D: (+) E: (-)
Henquet, et al. (2004) ⁵ / Germany / General population	t ₁ : Age 14-24 (R) t ₂ : Age 17-27 (R)	C ₁ : Cannabis use (yes/no) between t ₁ and t ₂ (≥ 4 times used) C ₂ : Cannabis frequency between t ₁ and t ₂	P ₁ : Risk of psychosis (CIDI) at t ₂ P ₂ : Psychotic symptoms (CIDI) at t ₁	Multivariate logistic regression	C ₁ → P ₁ * C ₂ → P ₁ * P ₂ → C ₁ (NS)	Age, gender, SES, urbanicity, childhood trauma, predisposition for psychosis, tobacco, alcohol and other drug use, baseline cannabis use	2437	A: (+) B: (-) C: (+) D: (+) E: (+)

Henquet, et al. (2010) ⁶ / Netherlands / General population	t: ESM: 6 consecutive days with 12 assessments each day	C ₁ : Cannabis use prior symptom assessment C ₂ : Cannabis use following symptom assessment	P ₁ : Level of psychotic experience following cannabis use P ₂ : Level of psychotic experience prior cannabis use	Multilevel regression analysis	C ₁ → P ₁ (NS) P ₂ → C ₁ (NS)	Age, gender, alcohol use and other drug use, level of	38	A: (+) B: (-) C: (+) D: (+) E: (-)
McGrath, et al. (2010) ⁷ / Australia / General population	t ₁ : Age 5 t ₂ : Age 14 t ₃ : Age 21	C ₁ : Duration since first cannabis use C ₂ : Duration since first cannabis use (following age 15)	P ₁ : Risk of psychosis (CIDI) P ₂ : Psychotic symptoms at age 15	Sibling pair analysis, logistic regression	C ₁ → P ₁ * P ₂ → C ₂ *	sex, age, parental mental illness, psychotic symptoms at t2	3801	A: (+) B: (+) C: (+) D: (+) E: (-)
McKetin, et al. (2013) ⁸ / Australia/ Methamphetamine abusers	t ₁ : Age 32 t ₂ : Age 33 t ₃ : Age 35	C ₁ : Changes in frequency of cannabis use (t ₁ -t ₃)	P ₁ : Presence of psychotic symptoms (BPRS) in 1 months prior assessment	FEM	C ₁ → P ₁ *	Other drug use	268	A: (+) B: (+) C: (-) D: (-) E: (+)
Prospective studies in patients with psychosis investigating the effects of cannabis use on outcome								
Barrowclough, et al. (2015) ⁹ / UK / Established psychosis with comorbid CUD	t ₁ : Baseline t ₂ : 9 months FU t ₃ : 18 months FU	C ₁ : Cannabis dose* prior to outcome assessment C ₂ : Change in cannabis dose* (t ₁ -t ₃)	P ₁ : Severity psychotic symptoms (PANSS) following cannabis use P ₂ : Relapse ^a	Multilevel regression analysis	C ₁ → P ₁ (NS) C ₁ → P ₂ (NS) C ₁ → P ₃ (NS) C ₂ → P ₄	Age, gender, living status, employment, education, SES, DAI, other substance use	110	A: (+) B: (-) C: (+) D: (-) E: (+)

		* measured based on frequency, type and grams used	(yes/no) following cannabis use P ₃ : Hospital admission (yes/no) following cannabis use P ₄ : Changes in positive symptoms (PANSS) (t1-t3)		(NS)			
Degenhardt, et al. (2007) ¹⁰ / Australia / Established psychosis	t ₁ : Baseline t ₂ : 1 month FU t ₃ : 2 months FU t ₄ : 3 months FU t ₅ : 4 months FU t ₆ : 5 months FU t ₇ : 6 months FU t ₈ : 7 months FU t ₉ : 8 months FU t ₁₀ : 9 months FU t ₁₁ : 10 months FU	C ₁ : Frequency of use (number of days per month) prior symptom assessment (t ₁ -t ₁₀) C ₂ : Frequency of use (number of days per month) following symptom assessment (t ₂ -t ₁₁)	P ₁ : Level of positive symptoms following cannabis use (BPRS) (t ₂ -t ₁₁) P ₂ : Level of positive symptoms prior to cannabis use (t ₁ -t ₁₀)	Generalized Estimating Equation	(1) C ₁ → P ₁ * (1) P ₂ → C ₂ (NS)	Medication adherence, other substance use	101	A: (+) B: (-) C: (+) D: (+) E: (+)

Henquet, et al. (2010) ⁶ / Netherlands / Established psychosis with comorbid cannabis use	t: ESM: 6 consecutive days with 12 assessments each day	C ₁ : Cannabis use prior symptom assessment C ₂ : Cannabis use following symptom assessment	P ₁ : Level of psychotic experience following cannabis use (ESM psychosis score) P ₂ : Level of psychotic experience prior cannabis use	Multilevel regression analysis	C ₁ → P ₁ * P ₂ → C ₂ (NS)	Age, gender, alcohol use and other drug use, level of cannabis use during the week	42	A: (+) B: (-) C: (+) D: (+) E: (-)
Foti, et al. (2010) ¹¹ / US / First episode psychosis	t ₁ : Baseline t ₂ : 0.5 years FU t ₃ : 2 years FU t ₄ : 4 years FU t ₅ : 10 years FU	C ₁ : Change in cannabis use status (non-user – user; use > 1) (t ₁ -t ₅) C ₂ : Cannabis use status prior symptom assessment C ₃ : Cannabis use status following symptom assessment	P ₁ : Changes in psychotic symptoms (SAPS) (t ₁ -t ₅) P ₂ : Level of psychotic symptoms following cannabis use P ₃ : Level of psychotic symptoms prior cannabis use	(1) FEM (2) SEM	(1) C ₁ → P ₁ * (2) C ₂ → P ₂ * (2) P ₃ → C ₃ *	SAPS, SANS, depression; other drug use, antipsychotic medications, demographic characteristics (age, sex, and SES)	229	A: (+) B: (+) C: (+) D: (+) E: (-)

Note. BPRS = Brief Psychiatric Rating Scale; CUD = Cannabis Use Disorder; DAI = Drug attitude Inventory; DUP = Duration of untreated psychosis; ESM = Experience Sampling Method; FEM = fixed effects models; FU= Follow up; Mini = Mini-International Neuropsychiatric

Interview 12 ; NOS = Not otherwise specified; PAS = Premorbid Adjustment Scale, R= Range; SANS = Scale for the Assessment of Negative; SAPS = Scale for the Assessment of Positive Symptoms ; SCL = Symptom Checklist 90 13; SEM = Structural Equation Modeling; SES = socioeconomic status

^a Relapse was defined as an exacerbation of psychotic symptoms that lasted for longer than 2 weeks and resulted in a change in patient management (increased observation by the clinical team; increase in antipsychotic medication or both).

^b Quality assessment based on whether a study did (+) or did not (–): A: Control for observed confounders B: Applied Fixed Effects Analysis (Fixed effects or sibling pair analysis) C: Used temporal ordering of risk factor (lagged outcome); D: Tested for directionality; E: Explored dose-response relationships

* $p < 0.05$

NS $p > 0.05$

eTable 2. Group Comparisons (Completers vs Refusers vs Subjects With Missing Data) in Relapse Outcome

Sample	Relapse (yes)^a
Completers (220)	78 (35.5%)
Refusers (133)	51 (38.3%)
Subjects with missing data (n=43)	19 (44.2%)

^a Chi-square test for independence to compare all groups for risk of relapse ($p=0.53$, $\chi^2=1.25$)

eTable 3. Exploratory Analysis (χ^2 Tests) to Select Covariates for Multiple Analyses^a

Covariates ^b	Relapse ^b		Cannabis (C _t) ^b		Cannabis (CD _t) ^b	
	χ^2	<i>p</i>	χ^2	<i>p</i>	χ^2	<i>p</i>
Gender	0.36	0.55	13.06	0.0003	13.07	0.001
Ethnicity	4.24	0.04	1.45	0.23	1.8	0.41
Age of onset	1.11	0.29	0.92	0.34	0.92	0.63
Medication adherence	15.88	0.0004	10.48	0.005	11.99	0.02
Premorbid cannabis use	2.13	0.14	71.36	<0.0001	71.57	<0.0001
Other illicit drug use (following onset)	8.91	0.01	21.92	<0.0001	26.33	<0.0001
Alcohol use (following onset)	4.26	0.12	11.1	0.004	13.3	0.01

^a Covariates were included in multiple analysis if significantly ($p \leq 0.05$) linked to relapse and cannabis use

^b Defined as: Relapse within the two years following the onset (coded as 1: admission to a psychiatric inpatient unit owing to exacerbation of psychotic symptoms following the first presentation of psychosis, 0: no admission to a psychiatric inpatient unit following the first presentation of psychosis); Cannabis use status (C_t) within the two years following the onset of illness (coded as 0: no use or use only once or twice; 1: used cannabis more than twice); Cannabis use (CD_t) within the two years following the onset of illness (coded as 0: no use or use only once or twice, 1: used cannabis more than twice but not every month, 2: used cannabis throughout all of the follow-up months); Gender (coded as 0: Female, 1: Male); Ethnicity (coded as 0: white ethnicity, 1: non-white ethnicity), age of onset (coded as 0: referral for psychosis before age 18, 1: referral for psychosis after age 18), medication adherence within the two years following the onset of illness [coded as 1: medication prescribed and non-compliance (67%-100% of the time non-compliant), 2: medication prescribed and irregular compliance (34%-66% of the time non-compliant), 3: medication not prescribed or good adherence with the prescribed medication (0% - 33% of the time non-adherent)], premorbid cannabis use (coded as 1: Subject who had a history of regular cannabis use (defined as use at least once/month for 6 consecutive months) prior to their onset), 0: Subjects without a history of regular cannabis use prior to their onset, other illicit drug use within the two years following the onset of illness [coded as 0=no use; 1=experimental use (less than 6 times); 2=regular use (6 times or more)], Alcohol use within the two years following the onset of illness (coded as 0:<1 month daily use, 1: >1 month daily use; 2: >6 months daily use)

eMethods. Measures and Analysis

Measures

To assess the reliability of the retrospective assessment of cannabis use, we compared data on premorbid cannabis use (ever used before onset) collected at onset of psychosis with data on premorbid cannabis use reported at follow-up. In 93% of those compared, reporting of premorbid cannabis use was consistent across both assessments (i.e., at onset and at follow-up); 4% denied premorbid use when assessed at the onset of psychosis but admitted it when re-examined at the follow up assessment, while 3% denied pre-morbid cannabis use at follow-up assessment although they had admitted use when assessed at onset.

We included two covariates in our analysis: (i) adherence to antipsychotic treatment plan and (ii) other drug illicit use within the first two years following onset of psychosis. Adherence to treatment plan was indexed in accordance with previous reports¹⁴, whereby patients were allocated a score ranging from 1 to 3 based on information on prescription and ratings of adherence: 3=medication not prescribed or good adherence with the prescribed medication (0% - 33% of the time non-adherent) within the two years following the onset of illness; 2=medication prescribed and irregular compliance (34%-66% of the time non-compliant); 1=medication prescribed and non-compliance (67%-100% of the time non-compliant). Other drug use was defined as use of illicit drugs other than cannabis within the two years following onset. This variable was coded as an ordinal variable, ranging from 0 to 2: 0=no use; 1=experimental use (less than 6 times); 2=regular use (6 times or more)]. None of the patients in this cohort received formal pharmacological or non-pharmacological treatment for illicit drug use and hence this was not controlled for in our analyses.

Two cannabis use variables were defined. The dichotomized variable ‘cannabis use status’ (C_{t1}/C_{t2}) classified patients during the respective time periods (t_1 & t_2) into ‘not cannabis user’ (NCU; no use or use only once or twice within the period under consideration) and ‘cannabis user’ (CU; used cannabis more than twice) categories. The ordinal variable ‘pattern of cannabis continuation’ (CP_{t1}/CP_{t2} , scored from 0 to 2) classified patients based on their pattern of cannabis use following onset of psychosis into (0) not cannabis user (NCU; as above), (1) intermittent cannabis user (ICU; used cannabis more than twice but not every month within the period under consideration) or (2) continued cannabis user (CCU; used cannabis every month throughout all of the follow-up months within the period under consideration).

Analysis

Fixed-effects analysis (FE) requires two conditions to be satisfied: (1) the outcome variable (relapse) must be measured for each subject using the same metric at least at two different points in time and (2) the exposure variable of interest (cannabis use) must change across these two time-points. In FE, each subject becomes their own control, wherein only subjects with a change in exposure ($C_{t1}.C_{t2}/CP_{t1}.CP_{t2}$) over the specified time-period are selected. As a result, if one subject is more likely to relapse during a period in which the subject was exposed to cannabis than during a period in which the subject was unexposed, this would indicate an effect of cannabis that is independent of the unmeasured potential confounding factors that did not change over this time period, such as the genetic make-up of the person, personality, age, gender and life events prior to the onset. Factors that vary over time following onset (e.g. other drug use, medication adherence) are adjusted for, as done in conventional multiple regression analysis. The regression coefficient from the fixed-effects

model (OR) gives the within-person (or fixed-effect) estimate, which is different to the estimate from conventional logistic regression (OR, which is a between-person estimate). FE uses only differences or changes in exposure occurring within individuals, which results in standard errors that are considerably higher than those estimated by methods that rely on between-person variation^{15, 16}. Conversely, between-group differences are likely to be over-estimated due to the lack of consideration of unmeasured personal characteristics that confound the relationship of interest.

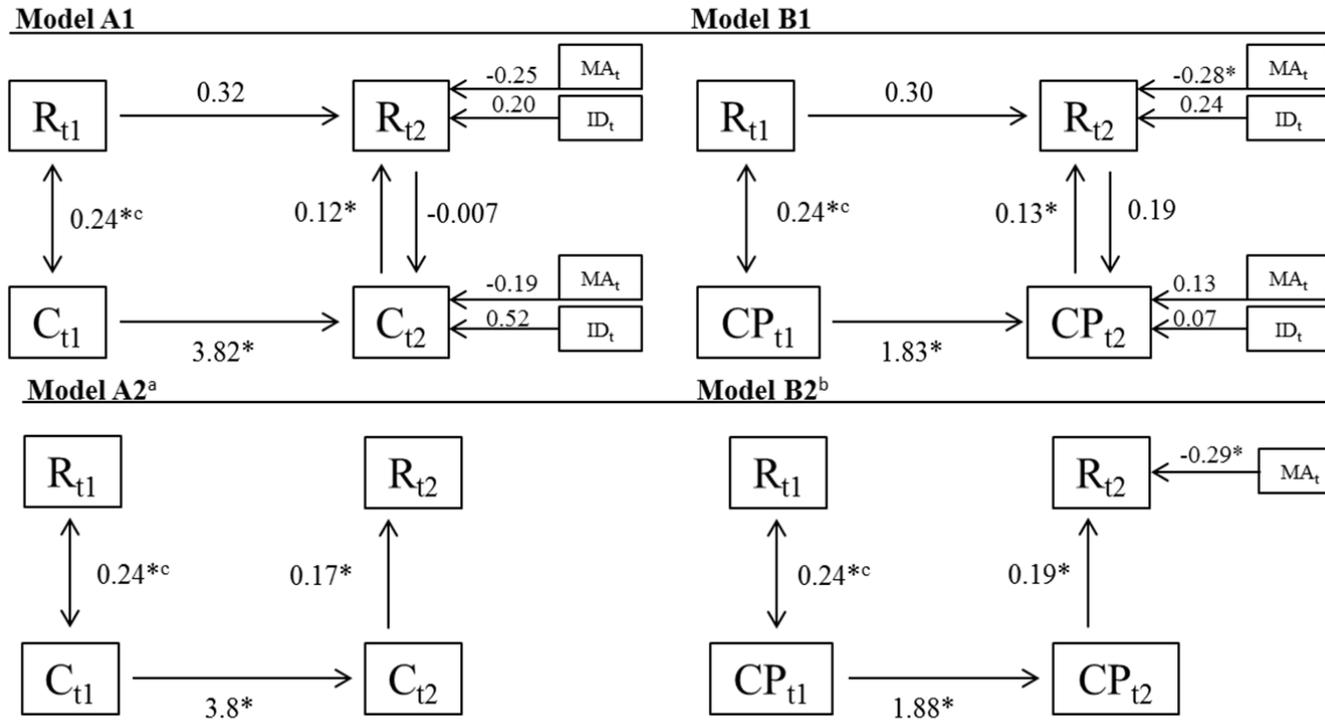
A reciprocal causal path model was tested to investigate the directionality of association. Different sets of reciprocal relationships can be modelled, including (1) models that incorporate cross-lagged paths that investigate the effects of a risk factor on outcome as observed at a later point in time and (2) models that incorporate reciprocal paths in which the risk factor is observed at the same time as the outcome. Similar to other studies investigating directionality of effects in the context of effects of cannabis use¹⁷, we chose the cross-lagged model in order to model subsequent cannabis use/relapse following exposure to the risk factor. The cross-lagged autoregressive path models were estimated using the lavaan package¹⁸. In the first step, we fitted a saturated path model in which all possible paths to the endogenous variables (C_{t2} and R_{t2}) were specified. In the second step, a more parsimonious model was tested that included only the statistically significant ($p \leq 0.05$) pathways tested. Model goodness of fit was assessed on the basis of a number of fit indices, including the model chi-squared goodness of fit statistic (a non-significant or small chi-square value indicating that the model fitted the data well), the root mean-squared error of approximation (RMSEA, with values of 0.05 indicating good fit and values up to 0.08 representing reasonable errors of approximation)¹⁹ and the comparative fit index (with values of 0.95 being acceptable and higher than 0.95 indicating good fit)²⁰. In order to validate the results, we also fitted a series of models incorporating reciprocal paths in which (i) R_{t1} and C_{t1}/CP_{t1} were correlated exogenous variables, (ii) R_{t1} predicted R_{t2} and C_{t1}/CP_{t1} predicted C_{t2}/CP_{t2} and (iii) R_{t2} and C_{t2}/CP_{t2} were reciprocally related (cf. *sFigure 1*. below).

eFigure. Reciprocal Paths Model

sFigure 1. Reciprocal paths model

A. ‘Cannabis use status’ (C_t) and risk of relapse

B. ‘Pattern of cannabis continuation’ (CP_t) and relapse



Note. C_t = ‘Cannabis use status’ (non-user – user) in the first year (C_{t1}) and in the second year (C_{t2}) following the onset; CP_t = ‘Pattern of cannabis continuation’ (non-user – intermittent user – continued user) in the first year (CP_{t1}) and in the second year (CP_{t2}) following the onset; ID_t : Illicit drug use (score 0-2) within the two years following the onset; MA_t : Medication adherence (score 0-2) within two years following the onset; R_t = Relapse (yes – no) in the first year (R_{t1}) and in the second year (R_{t2}) following the onset.

^a Goodness of fit indices: $\chi^2(1) = 0.03, p = 0.862$; RMSEA = 0.00, $p = 0.435$; CFI = 1.00

^b Goodness of fit indices: $\chi^2(2) = 1.56, p = 0.458$; RMSEA = 0.00, $p = 0.860$; CFI = 1.00

^c Correlations estimated using a polychoric correlation estimator

* $p \leq 0.05$

eResults. Sample Characteristics and Supplementary Results

Sample Characteristics

Two hundred and twenty patients with a first episode of psychosis were included in the analysis, comprising 213 (96.8%) subjects that were interviewed face-to-face and 7 (3.2%) that were interviewed in a phone conversation. Within the first two years following onset of illness, 35.5% of patients experienced a relapse in the form of admission to psychiatric hospital. Out of 121 subjects with pre and/or post onset regular cannabis use, only 3 (3.7%) subjects started using cannabis (use ≥ 2 times) following onset of psychosis (with no previous history of regular use). Sixty-nine (57 %) had used cannabis regularly prior to the onset and used it subsequently either intermittently or continuously, and 52 (43%) had a history of regular use prior to the onset of psychosis but did not use it regularly following onset. Fifty-nine (26.8%) patients had never tried cannabis in their lifetime.

eDiscussion. Study Limitations

While clinical data was assessed prospectively using patients' clinical records, cannabis use pattern following the onset of illness relied on retrospective self-reported assessments without objective drug screens. However, cannabis use information obtained at research interview was further validated by screening patient records as well as reports of premorbid cannabis use (ever used) that was collected at the baseline research assessment at onset, revealing a very high concordance (93%) between self-report data of cannabis use at the two research assessment points (onset and follow-up). Underreporting of cannabis use has also been found to be less of an issue in research studies, when self-report data on cannabis use has been compared to objective measures such as urine drug screen²¹. It is also important to note that the main predictor variable (pattern of cannabis continuation following onset) did not capture cumulative exposure to cannabis per year of follow up, since this was not feasible to assess with the retrospective cannabis assessment we employed in this study. We did not formally assess duration of untreated psychosis and severity of illness at onset, nor did we examine the effect of premorbid cannabis use and age of onset of cannabis use with regard to risk of relapse, which are essentially unmeasured, time-invariant sources of confounding. However, results from the fixed-effects analysis, which allowed us to control for such shared unmeasured time-invariant premorbid confounding factors did not suggest that these unmeasured factors confounded the association between continued cannabis use and risk of relapse. Nevertheless, future studies should investigate whether those factors may moderate the effect of continued cannabis use on risk of relapse. The measure of relapse employed in this study, i.e. hospitalisation, constitutes an essential outcome measure for psychosis²²⁻²⁴. Yet, because it is rather conservative, future longitudinal investigations should also include measures that may capture less severe psychotic episodes, e.g. relapse resulting in crisis team/emergency interventions without hospitalisation, or change in medication. Furthermore, although the statistical methods applied in this study were designed to minimize the possibility of a non-causal explanation for the association between continued cannabis use and relapse, it is possible that other unmeasured factors changing over time may have influenced the relationship. Nevertheless, we controlled for the most significant previously identified time-variant risk factors that have been linked to psychosis relapse²⁵. Hence, it seems unlikely that this was the case.

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