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Does a history of cannabis use influence onset and course of schizophrenia?

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Abstract

Introduction: While evidence strongly supports a causal effect of cannabis on psychosis, it is less clear whether the symptom pattern, clinical course, and outcomes differ in cases of schizophrenia with and without a background of cannabis use.

Methods: Analysis of medical records from a longitudinal follow-up of Swedish conscripts with data on cannabis use in adolescence and subsequent incidence of schizophrenia. One hundred sixty patients with schizophrenia were assessed using the OPCRIT protocol. Cases were validated for diagnosis schizophrenia according to OPCRIT.

Results: Patients with a cannabis history ($n = 32$), compared to those without ($n = 128$), had an earlier age at onset, a higher number of hospital admissions and a higher total number of hospital days. There was no significant difference in type of onset and clinical symptom profiles between the groups.

Conclusion: Our findings indicate that the disease burden of schizophrenia is greater in individuals who use cannabis during adolescence. Strengthening evidence on causality and teasing out long-term effects of pre-illness cannabis use from continued post-illness has clinical implications for improving schizophrenia outcomes.

KEYWORDS

cannabis, clinical course, psychosis, schizophrenia, symptoms

1 | INTRODUCTION

Cannabis use is thought to increase risk of developing schizophrenia and other non-affective psychoses.[1–4] Although the relationship between cannabis and psychosis is likely to be highly complex, evidence from experimental[5] and observational studies, including longitudinal studies that minimize reverse causation and robustly address confounding,[2] support a causal effect of cannabis on psychosis. Plausible biological mechanisms for the association have been identified, and the effects of THC exposure on brain function seem particularly prominent in the developing brain, including during adolescence.[6–8] Cannabis use has also been shown to be associated with increased risk of relapse and other markers of poorer outcome in psychosis,[9] but evidence of a bidirectional causal

relationship between cannabis and schizophrenia[10] increases the complexity of inferring causality in these associations.

While it has been shown that cannabis use is associated with a more chronic course and worse outcome in schizophrenia,[11–13] many studies have been cross-sectional in design, with cannabis use measured retrospectively, hence it is not clear whether cannabis use began (or became more frequently used) before or after onset of schizophrenia. A systematic review of longitudinal studies concluded that cannabis use among patients with schizophrenia was associated with an increased risk of relapse and rehospitalization, although the overall quality of studies when examining other outcomes was low and follow-up times were mostly around one or 2 years.[9] Foti et al[14] used repeat measures over a 10-year period to assess the longitudinal relationship between cannabis use and psychiatric symptoms, with cross-lagged models providing evidence of a bidirectional relationship between them, suggesting that cannabis might be used to alleviate some symptoms of schizophrenia. We are not aware of any study that has assessed whether cannabis use in adolescence, prior to first episode of psychosis, is associated with symptom severity and long-term outcome in schizophrenia.

It is also unclear whether cannabis use prior to onset can influence the type of symptoms experienced and clinical characteristics of the disorder. Some studies have shown a higher occurrence of positive symptoms among persons with previous substance use,[15,16] but in general no increased occurrence of negative symptoms.[9,17] Other studies have found no difference in clinical characteristics when comparing patients with and without a cannabis history.[18,19] Again, most studies are based on cross-sectional data or case report and few studies have been able to assess long-term outcomes.

In a long-term follow-up of Swedish conscripts, based on register data, we found that subjects with a history of cannabis use had longer duration of first admission to hospital, more readmissions, and more total time of hospital stay than those without cannabis use.[12] Cannabis use was assessed by self-report at around 18 years of age, and incidence of schizophrenia according to the national inpatient register was assessed up to ages 60–62 years. Furthermore, in an earlier study of medical records on a small sample of Swedish conscripts treated for schizophrenia in Stockholm County, we found that persons with a history of cannabis use had a more sudden onset and more positive symptoms than those without a history of cannabis use.[16] However, no formal assessment protocol was used and a longer follow up of a national sample is needed to reassess the findings. Another limitation in our previous studies is the lack of information on cannabis use at follow-up. Myles et al[20] reviewed continuation of cannabis use after first episode psychosis. While they found evidence of continued as well as cessation of cannabis use, there was no documentation of how this affected outcome of psychosis. By combining conscript cohort data with medical admission records and review of case records we aimed to examine the relationship between self-reported cannabis use at conscription, later record of cannabis abuse/dependence and outcomes in schizophrenia.

Significant outcomes

- Schizophrenia patients with a history of cannabis use in adolescence had earlier age at onset and more severe disease in terms of hospital admissions and length of stay compared to patients without cannabis history.
- Symptom profiles of schizophrenia did not seem to differ by previous cannabis history.

Limitations

- We did not have data on self-reported cannabis use during follow-up.
- In spite of a large national cohort, number of cases with schizophrenia was limited.

In contrast to other longitudinal studies that have examined psychoses more broadly or schizophrenia spectrum disorders as outcomes,[2] the outcome in our cohort has been recorded diagnosis of schizophrenia.[12,21,22] The validity of schizophrenia diagnoses in this cohort have been assessed qualitatively in a subsample[23] but a validation study of all cases has not previously been undertaken.

In this study we use data from an updated linkage of the Swedish Conscript Cohort to the national patient register in order to identify medical records of patients with schizophrenia that we then assessed for information on clinical characteristics, including record of cannabis abuse/dependence. Data were recorded using the OPCRIT system[24] which enabled us also to ascertain and validate diagnoses of schizophrenia.

The overall aim of the study was to assess differences in age and type of onset, clinical course and prognosis of schizophrenia between subjects with a history of cannabis use with those without such history. The following research questions were addressed:

i. Do patients in the patient register fulfill the diagnosis of schizophrenia according to defined criteria?
ii. Do subjects with cannabis use in adolescence differ from non-users with regard to age at onset, type of onset, clinical characteristics and outcomes of schizophrenia compared to non-users?

iii. Are differences in the course and outcome of schizophrenia related to cannabis abuse or dependence after conscription?

2 | METHODS

The study is based on a cohort of Swedish men born 1950–1952 conscripted for compulsory military training in 1969–1970, as used in previous studies.[21,22] The conscription procedure comprised medical examination, tests on physical and mental capacity, and for the particular period of conscription 1969–1970, also a series of questions on use of alcohol, tobacco and other drugs. In questionnaires, conscripts were asked whether they had ever used drugs, the first drug they used, which type of drug(s) they had used, and how many times they had used the drug.

By using the personal identity number, data were linked to the national inpatient register. The register was set up in the beginning of the 1970:s and achieved full national coverage for psychiatric care in 1973. While the original cohort previously use for register studies comprised 50,653 men, for this analysis of medical records we were able to access personal data for about half of the population, 24,875 persons, for legal and administrative reasons. Comparisons of this smaller cohort with the total cohort showed that the distribution of a number of variables were very similar, and the study population remains representative of the national population of Swedish young men at the time.

Linkage with the national patient register was performed through 2011, by which time conscripts had reached an age of around 60 years. Permission from the Ethical Review Board had been obtained at repeated occasions to perform record linkages, and a new permission was obtained to retrieve medical records for scrutiny.

From the register we identified all individuals with a psychotic disorder diagnosis (Table S1). In total 569 persons were identified, of whom 223 had a primary or secondary diagnosis of schizophrenia, and 346 had another psychotic diagnosis. We approached all treatment facilities identified and asked for copies of the medical records or, if required, access for reading these in their archives. Efforts were made to find the record for each given treatment episode. The procedure was difficult due to the numerous administrative changes in the organization of care and treatment during the >40 years of follow-up. Many of the treatment units recorded in the electronic system no longer existed or had merged with other units, and the system for archiving records varied between county councils and individual hospitals and over time. Some facilities (three clinics, 14 patients) required individual consent from patients for us to access their medical records, but we did not have permission from the Ethical review board to contact patients individually, so these records could not be accessed.

We accessed medical records for 402 patients, 204 with a recorded diagnosis of schizophrenia, and 198 with other psychotic diagnoses, from a total of 144 different treatment facilities. Treatment units of these patients were from all parts of the country, encompassing urban and rural areas, and represented all types of care; university hospitals, special centers for treatment of mental illness and standard hospital clinics.

Medical records were scrutinized by one of the authors, board certified specialist in psychiatry (TJ), using the OPCRIT system.[24] This was performed blind to data on cannabis use reported at conscription. The OPCRIT protocol was used to identify patients with schizophrenia according to ICD-10 and to assess clinical characteristics according to the protocol. To assess symptom profiles we selected OPCRIT items describing the following types of symptoms: Positive symptoms, divided into delusions, hallucinations, thought interference and severe delusions; negative symptoms; disorganized symptoms. Diagnosis of alcohol as well as cannabis abuse/dependence was defined in the OPCRIT guidelines as continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by the substance.

Of the 204 patients with a record diagnosis of schizophrenia, 17 had too little information to assess in the OPCRIT protocol. For the 198 patients with other psychotic diagnoses, records were screened informally and those suspected of possibly having schizophrenia ($n = 21$) were formally assessed using OPCRIT.

In the analyses we have compared schizophrenia clinical characteristics and outcomes in subjects who at conscription reported having used cannabis on zero or one occasions, with those who reported having used cannabis at least twice. In the text, we refer to these two groups as subjects without and with a history of cannabis use, respectively. Table S2 shows the distribution of the number of times subjects reported cannabis use. Statistical evidence of differences between the two groups was assessed using chi2-test, or Fisher's exact test in cases where cells had low numbers. Median number of hospital admissions and number of hospital days were compared using the Mann–Whitney U test. 95% confidence intervals (CI) were computed where relevant.

3 | RESULTS

3.1 | Diagnoses assessed

Of the 187 records from patients with a clinical diagnosis of schizophrenia on the NPR, 158 (84%) were found to

	Subjects without cannabis history		Subjects with cannabis history	
	N	%	*N*	%
Abrupt	2	1.6	0	0
Gradual	20	15.6	3	9.4
Insiduous	106	82.8	29	90.6
Total	128	100	32	100

TABLE 1 Mode of onset of schizophrenia among subjects with and without a history of cannabis use.

TABLE 2 No of hospital admissions and number of hospital days during follow-up.

	Subjects without cannabis history		Subjects with cannabis history		
	N	Median (range)	*N*	Median (range)	*p* value
All					
Median total number of hospital admissions	126	8 (1–151)	32	20 (1–131)	0.05
Median total number of hospital days	126	272.5 (1–9712)	32	876.5 (8–9023)	0.01
Median number of hospital days first admission	126	27 (1–1797)	32	38 (1–1058)	0.20
Subjects <24 years					
Median total number of hospital admissions	63	11 (1–151)	22	18 (1–51)	0.39
Median total number of hospital days	63	377 (1–9712)	22	1038 (8–9023)	0.12
Median number of hospital days first admission	63	39 (1–1797)	22	55 (2–1058)	0.31
Subjects >24 years					
Median total number of hospital admissions	63	5 (1–45)	10	20 (1–131)	0.14
Median total number of hospital days	63	216 (1–6793)	10	520 (26–3806)	0.18
Median number of hospital days first admission	63	14 (1–1216)	10	21 (1–71)	0.91

have confirmed schizophrenia according to ICD-10 criteria after OPCRIT assessment. Of the 21 patients with other psychoses, 10 patients met ICD-10 criteria for schizophrenia in OPCRIT that is, 5% of the total number of 198 subjects with a non-schizophrenia psychotic disorder diagnosis on the NPR.

From the 168 patients with an OPCRIT ICD-10 schizophrenia diagnosis, 160 were included in the analyses below. Eight subjects were excluded: four who at conscription reported use of other (non-cannabis) drugs (to avoid confounding), and four who had a psychosis diagnosis at conscription. Of these 160 patients, 32 had a history of cannabis use according to the data from conscription.

3.2 | Age and mode of onset

Mean age at onset of schizophrenia for patients was 23.4 years (SD ±6.6) among patients with a cannabis history, and 27.7 years (SD ± 9.3) among those without. Mean age difference was 4.3 years (95% CI 0.9–7.7).

Table 1 shows the distribution of mode of onset. There was no significant difference between patients with a cannabis history compared to those without ($p = 0.6$).

3.3 | Outcome and prognosis

Table 2 shows the number of hospital episodes and length of stay. Two patients had only outpatient records, bringing the number of subjects to 158. Patients with a cannabis history had a higher median number of hospital admissions than those without (20 vs. 8; $p = 0.05$). They also had a higher total number of hospital days (877 vs. 273; $p = 0.01$), but there was little evidence of any difference in length of first admission (38 vs. 27; $p = 0.20$). Individuals with an older age of onset had a greater number of admissions, total hospital days and length of first admission. Evidence of differences between those with and without a cannabis use history was weaker in these stratified analyses, though the direction of associations was consistent with the whole-sample analysis. OPCRIT assessment of medical records indicated little evidence of difference in long-term clinical outcome (Table 3). Both groups responded well to neuroleptics. Persons with a cannabis history had significantly higher rates of lifetime cannabis abuse/dependence as well as lifetime alcohol abuse/dependence. 28% of the patients who reported cannabis use at conscription did not have

TABLE 3 Course of disorder, response to neuroleptics, and life time alcohol/drug use according to OPCRIT assessment.

		Subjects without cannabis history		Subjects with cannabis history		
		N	%	*N*	%	*p* value
Course of disorder	Continued disease without recovery	76	59.4	14	43.8	0.111
	Not continued disease	52	40.6	18	56.3	
Psychotic symptoms respond to neuroleptics	False	5	3.9	3	9.4	0.204
	True	123	96.1	29	90.6	
Lifetime use of drugs	Yes	14	10.9	23	71.9	<0.001
	No	114	89.1	9	28.1	
Lifetime use of alcohol	Yes	50	39.1	22	68.8	0.003
	No	78	60.9	10	31.3	

TABLE 4 Association between level of cannabis use at conscription and later documentation of cannabis abuse/dependence in the medical records.

	Reported no of times used cannabis at conscription					
	0–1 time (non-users)	2–4 times	5–10 times	10–50 times	>50 times	*p* value
No record of cannabis abuse/dependence	114 (89%)	4 (50%)	3 (60%)	1 (17%)	1 (8%)	<0.001
Record of cannabis abuse/dependence	14 (11%)	4 (50%)	2 (40%)	5 (83%)	12 (92%)	

any record of lifetime cannabis abuse/dependence in their medical records (Table 3).

Table S3 shows that there was little evidence of difference between the groups regarding marital status or cohabitation (life time) as well as employment status at time of admission.

3.4 | Cannabis abuse/dependence according to medical records

Among the 32 subjects who reported cannabis use at conscription, 23 (72%) had documentation of cannabis abuse/dependence in the medical records. Of these, 6 patients also had a register diagnosis of cannabis use disorder (ICD-8 304,5 ICD-9 304D, ICD F12) in the patient register. Among the 126 subjects without a history of cannabis use, 14 (11%) had documentation of cannabis abuse/dependence, although none had a diagnosis in the patient register. Table 4 shows that there was a strong association between level of cannabis use at conscription and a later record of cannabis abuse/dependence in the medical records. Almost all (12 out of 13) of those who reported the heaviest cannabis use at conscription had a later record of cannabis abuse/dependence in their medical records.

Table 5 shows the association between having a record of cannabis abuse/dependence in the medical records and the indicators of hospital care use. There was a significantly higher level of number of hospital days and number of readmissions among those who had a record of cannabis abuse/dependence, and at a higher level among those who reported cannabis use at conscription.

3.5 | Clinical characteristics

As shown in Table 6, there were no significant differences between the groups in the presence of positive (delusions, severe delusions, hallucinations or thought interference), negative or disorganized symptoms.

4 | DISCUSSION

We confirmed our previous findings[12] of an earlier age at onset, more readmissions, and a higher total number of hospital days among patients with a history of cannabis use in adolescence compared to those without. The added value of this study is the use of information from medical records, and thorough validation of schizophrenia diagnoses.

Earlier age at onset of psychosis among subjects with a history of cannabis use has been described by several authors.[25,26] Studies have asked about cannabis use in

TABLE 5 Number of hospital admissions, total number of hospital days and number of hospital days at first admission among those who had record of cannabis use, compared to those who had not.

	Subjects without a record of cannabis abuse/dependence		Subjects with a record of cannabis abuse/dependence		
	N	Median (range)	*N*	Median (range)	*p* value
Subjects not reporting cannabis use at conscription					
Median total number of hospital admissions	112	7 (1–151)	14	17 (1–73)	0.02
Median total number of hospital days	112	258 (1–9712)	14	513 (1–3804)	0.12
Median number of hospital days first admission	112	28 (1–1797)	14	22 (1–113)	0.41
Subjects reporting cannabis use at conscription					
Median total number of hospital admissions	9	5 (1–27)	23	20 (1–131)	0.17
Median total number of hospital days	9	82 (8–1902)	23	1276 (59–9023)	0.03
Median number of hospital days first admission	9	15 (3–269)	23	50 (1–1058)	0.16

TABLE 6 Presence of positive, negative and disorganized symptoms.

		Subjects without cannabis history		Subjects with cannabis history		
Positive symptoms		*N*	%	*N*	%	*p* value
Delusions	No	0	0	2	2	1.0
	Yes	32	100	126	98	
Hallucinations	No	2	6	13	10	0.74
	Yes	30	94	115	90	
Thought interference	No	22	69	93	73	0.66
	Yes	10	31	35	27	
Severe delusions	No	2	6	9	7	1.0
	Yes	30	94	119	93	
Negative symptoms	No	1	3	3	2	1.0
	Yes	31	97	125	98	
Disorganized symptom	No	10	31	53	41	0.32
	Yes	22	69	75	59	

retrospect, so with possible recall bias, and few studies have specifically examined schizophrenia as an outcome. To our knowledge this is the first study in which cannabis use was assessed prior to incidence of psychosis, in a non-healthcare setting, and linked to later incidence of schizophrenia. The higher number of readmissions and greater total number of hospital days we observed in those with a history of cannabis use could be a consequence of an earlier age of onset. However, findings were similar when we stratified subjects by age of onset, although evidence was weaker and confidence intervals included the null. Thus individuals with pre-illness cannabis use seem to have a greater illness burden as well as, and independent of, a younger age of schizophrenia onset.

There was little evidence that the first hospital episode was longer or the mode of illness onset different in patients with a history of cannabis use. Our previous register-based data of first inpatient care episode in the full cohort[12] indicated a significantly longer first hospital episode among cannabis users. The weaker evidence here may be due to the smaller sample size or to the more specific case definition of schizophrenia.

While the issue of causal association has been addressed and discussed in many of the papers cited below, the type of psychotic outcome has hardly been addressed at all. In an early review, Thornicroft[27] pointed out the importance of outcome specification, yet few studies since then have specified type and characteristics of psychosis identified as outcome in longitudinal studies. An obvious reason is the low incidence of schizophrenia compared to the broader group of chronic psychotic disorders. Although the Danish register studies[28,29] did specify schizophrenia diagnoses, exposure in these studies

were diagnoses of cannabis use disorders in health care, and not cannabis use measured independently of contact with health services.

Previous population based studies on cannabis and psychosis have not addressed schizophrenia as a specific outcome, and our previous studies only used register-based clinical diagnoses. In this study we showed that 85% of those with a register-based diagnosis of schizophrenia were assessed as meeting criteria for ICD-10 defined schizophrenia according to OPCRIT assessment. Furthermore, screening and OPCRIT assessment of other psychotic disorder showed that only 5% of those with other psychotic disorder met criteria for ICD-10 schizophrenia. We can therefore have greater confidence that the increased risk of schizophrenia found in our previous studies was indeed schizophrenia according to research diagnostic criteria.

We did not find any difference in symptom pattern between the two groups. Our previous finding in a smaller sample of more rapid onset and more positive symptoms[16] may have been a chance finding, or the fact that the study was based on patients in an early stage of the disease. While the study by Caspari[15] found a higher rate of positive symptoms in cannabis users, this was based on a relatively small group of patients and shorter follow-up. It should be noted that the occurrence of negative symptoms may be underestimated, since patients with negative symptoms may be less prone to be admitted to hospital and thus less apparent in medical records. Negative symptoms may also be less consistently recorded in medical journals.

While the medical records in general had information enough to grade the OPCRIT items, including what we defined as positive symptoms, the clinical assessments of these were not recorded in a standardized way, for example, through the PANSS. In addition, information on cognitive function, particularly when assessed using standardized instruments, is rarely available in clinical records, though would also be of interest considering the possible effects of cannabis on cognitive function.[30]

Although cannabis use in adolescence is often considered experimental and self-limiting, there was a clear association between reported cannabis use at conscription and later cannabis abuse/dependence in medical records. In particular, more than 90% of the subgroup who reported the highest use of cannabis at conscription had a record of later cannabis abuse/dependence. There was also an association between cannabis abuse/dependence at follow-up and more readmissions and longer hospital stay, consistent with findings by for example, Kuepper et al[31] and Linszen et al.[11]

The proportion of patients who were married or cohabitating, as well as being employed, was lower among those with a cannabis history, although not significant. A larger study population might have shown a difference, but the findings confirm the general observation that a substantial proportion of patients with schizophrenia do manage social life, and that this is not substantially affected by previous cannabis use.

We acknowledge several limitations of this study, the main one being lack of regular and detailed assessment of cannabis use, as well as confounders, over time. It is, for example, possible that comorbid conditions occurring during follow-up may influence both cannabis use and schizophrenia outcome, or that early life characteristics such as childhood trauma or pleiotropic genetic effects explain part of our findings. Furthermore, although we stratified analyses by age of onset, it remains possible that markers of poorer outcome in the cannabis history group are due to an earlier age of onset. Another limitation is the sample size. Although a large cohort at baseline, the incidence of schizophrenia means that the number available for comparisons is low. It is notoriously difficult to get access to medical records on patients treated decades ago, and we could unfortunately only get access to patient records for half the original cohort. There was no systematic bias in the access to medical records, since these were retrieved from clinics distributed all over the country, and smaller hospitals as well as university hospitals.

It would have been an advantage to have two independent assessments of the medical records. However, the scrutiny of hundreds of psychiatric records, many of which were very extensive, and completing the OPCRIT, was time consuming and resources were not available for more than one experienced psychiatrist to perform the assessment.

The use of high potency cannabis has been increasing in recent years and seems to be associated with higher risk of psychosis.[2,32] Adolescents in the end of the 1960's were exposed to cannabis of lower potency, so the associations found in this study might be lower than what would be found today.

In conclusion, through scrutiny of medical records, we showed that cannabis use in adolescence is associated with higher levels of hospital use, likely partly due to continued use of cannabis during follow-up. The ongoing debate on legalization, and the apparently low risk perception of cannabis use in adolescence[33,34] indicate the need for interventions to mitigate against problematic cannabis use in young people.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13562.

DATA AVAILABILITY STATEMENT

Register data and copies of medical records have been obtained under strict rules for secrecy and confidentiality, and cannot be shared. Selected tabular data on aggregate level can be obtained on request.

ETHICS STATEMENT

Approval has been obtained from the Swedish Ethical Review Authority.

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REFERENCES

1. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370:319-328.
2. Gage SH, Hickman M, Zammit S. Association between cannabis and psychosis: epidemiological evidence. *Biol Psychiatry*. 2016;79:549-556.
3. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull*. 2016;42:1262-1269.
4. Hasan A, von Keller R, Friemel CM, et al. Cannabis use and psychosis: a review of reviews. *Eur Arch Psychiatry Clin Neurosci*. 2020;270:403-412.
5. Hindley G, Beck K, Borgan F, et al. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. *Lancet Psychiatry*. 2020;7:344-353.
6. Murray RM, Morrison PD, Henquet C, Di Forti M. Cannabis, the mind and society: he hash realities. *Nat Rev Neurosci*. 2007;8:885-895.
7. Trezza V, Cuomo V, Vanderschuren LJ. Cannabis and the developing brain: insights from behavior. *Eur J Pharmacol*. 2008;585(2–3):441-452.
8. James A, James C, Thwaites T. The brain effects of cannabis in healthy adolescents and in adolescents with schizophrenia: a systematic review. *Psychiatry Res*. 2013;214:181-189.
9. Zammit S, Moore TH, Lingford-Hughes A, et al. Effects of cannabis use on outcomes of psychotic disorders: systematic review. *Br J Psychiatry*. 2008;193:357-363.
10. Gage SH, Jones HJ, Burgess S, et al. Assessing causality I association between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. *Psychol Med*. 2017;47:971-980.
11. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry*. 1994;51:273-279.
12. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Prognosis of schizophrenia in persons with and without a history of cannabis use. *Psychol Med*. 2014;44:2513-2521.
13. Ringen PA, Nesvåg R, Helle S, et al. Premorbid cannabis use is associated with more sympoms and poorer functioning in schizophrenia spectrum disorder. *Psychol Med*. 2016;46:3127-3136.
14. Foti DJ, Kotov R, Guey LT, Bromet EJ. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *Am J Psychiatry*. 2010;167:987-993.
15. Caspari D. Cannabis and schizophrenia: results of a follow-up study. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(1):45-49.
16. Andréasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. *Acta Psychiatr Scand*. 1989;79:505-510.
17. Sabe M, Zhao N, Kaiser S. Cannabis, nicotine and the negative symptoms of schizophrenia. Systematic review and meta-analysis of observational studies. *Neurosci Biobehav Res*. 2020;116:415-425.
18. Stirling J, Lewis S, Hopkins R, White C. Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow-up. *Schizophr Res*. 2005;75:135-137.
19. Boydell J, Dean K, Dutta R, Giouroukou E, Fearon P, Murray R. A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cannabis psychosis. *Schizophr Res*. 2007;93:203-210.
20. Myles H, Myles N, Large M. Cannabis use in first episode psychosis: meta analysis of prevalence, and the time course of initiation and continued use. *Austr New Zealand J Psychiatry*. 2016;50:208-219.
21. Andréasson S, Allebeck P, Engström A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*. 1987;8574:1483-1486.
22. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*. 2002;325:1199.
23. Lewis G, David AS, Malmberg A, Allebeck P. non-psychotic disorder and subsequent risk of schizophrenia. Cohort study. *Br J Psychiatry*. 2000;177:416-420.
24. McGuffin P, Farmer A, Harvey I. A polydiagnostic application of operational critera in studies of psychotic illness. *Arch Gen Psychiatry*. 1991;48:764-770.
25. Veen ND, Selten JP, van der Tweel I, Feller WG, Hoek HW, Kahn RS. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry*. 2004;161:501-506.
26. Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis. A systematic meta-analysis. *Arch Gen Psychiatry*. 2011;68:555-561.
27. Thornicroft G. Cannabis and psychosis: is there epidemiological evidence for an association? *Br J Psychiatry*. 1990;157:25-33.

28. Nielsen M, Toftdahl NG, Nordentoft M, Hjorthøj C. Association between alcohol, cannabis and other illicit substance abuse and risk of developing schizophrenia: a nationwide population based register study. *Psychol Med*. 2017;67:1668-1677.
29. Hjorthøj C, Posselt CM, Nordentoft M. Development over time of the population attributable risk fraction for cannabis use disorder in schizophrenia in Denmark. *JAMA Psychiat*. 2021;78:1013-1019.
30. Solowij N, Jones KA, Rozman ME, Davis SM, Patrick CJ, et al. Verbal learning and memory in adolescent cannabis users, alcohol users and non users. *Psychopharmacology*. 2011;216:131-144.
31. Kuepper R, van Os J, Lieb R, Wittchen H-U, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ*. 2011;342:d738.
32. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H. 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;6:427-436.
33. Kvillemo P, Strandberg AK, Gripenberg J. Attitudes to cannabis use and public prevention information among young adults: a qualitative interview study with implications for prevention practice. *Front Public Health*. 2022;10:830201.
34. Waddell JT. Age-varying time trends in cannabis- and alcohol-related risk perceptions 2002-2019. *Addictive Behavior* 2022;124:107091.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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