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Cannabis Use Disorder and Subsequent Risk of Psychotic and Nonpsychotic Unipolar Depression and Bipolar Disorder

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IMPORTANCE Cannabis use is increasing worldwide and is suspected to be associated with increased risk of psychiatric disorders; however, the association with affective disorders has been insufficiently studied.

OBJECTIVE To examine whether cannabis use disorder (CUD) is associated with an increased risk of psychotic and nonpsychotic unipolar depression and bipolar disorder and to compare associations of CUD with psychotic and nonpsychotic subtypes of these diagnoses.

DESIGN, SETTING, AND PARTICIPANTS This prospective, population-based cohort study using Danish nationwide registers included all individuals born in Denmark before December 31, 2005, who were alive, aged at least 16 years, and living in Denmark between January 1, 1995, and December 31, 2021.

EXPOSURE Register-based diagnosis of CUD.

MAIN OUTCOME AND MEASURES The main outcome was register-based diagnosis of psychotic or nonpsychotic unipolar depression or bipolar disorder. Associations between CUD and subsequent affective disorders were estimated as hazard ratios (HRs) using Cox proportional hazards regression with time-varying information on CUD, adjusting for sex; alcohol use disorder; substance use disorder; having been born in Denmark; calendar year; parental educational level (highest attained); parental cannabis, alcohol, or substance use disorders; and parental affective disorders.

RESULTS A total of 6 651 765 individuals (50.3% female) were followed up for 119 526 786 person-years. Cannabis use disorder was associated with an increased risk of unipolar depression (HR, 1.84; 95% CI, 1.78-1.90), psychotic unipolar depression (HR, 1.97; 95% CI, 1.73-2.25), and nonpsychotic unipolar depression (HR, 1.83; 95% CI, 1.77-1.89). Cannabis use was associated with an increased risk of bipolar disorder in men (HR, 2.96; 95% CI, 2.73-3.21) and women (HR, 2.54; 95% CI, 2.31-2.80), psychotic bipolar disorder (HR, 4.05; 95% CI, 3.52-4.65), and nonpsychotic bipolar disorder in men (HR, 2.96; 95% CI, 2.73-3.21) and women (HR, 2.60; 95% CI, 2.36-2.85). Cannabis use disorder was associated with higher risk for psychotic than nonpsychotic subtypes of bipolar disorder (relative HR, 1.48; 95% CI, 1.21-1.81) but not unipolar depression (relative HR, 1.08; 95% CI, 0.92-1.27).

CONCLUSIONS AND RELEVANCE This population-based cohort study found that CUD was associated with an increased risk of psychotic and nonpsychotic bipolar disorder and unipolar depression. These findings may inform policies regarding the legal status and control of cannabis use.

Multimedia

Supplemental content

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Cannabis is one of the most widely used psychoactive drugs in the world,[1] and an increasing number of countries are legalizing its production and sale for medicinal and recreational use.[2] Over the past decades, both the use and the average potency of cannabis have increased.[3,4] Use of cannabis may, however, lead to addiction (ie, cannabis use disorder [CUD]).[5] Cannabis use disorder is frequent among individuals with affective disorders[6] and, in this group, is associated with increased symptom severity,[7,8] suicidality,[9] and mortality.[10] Although disputed, evidence suggests that use of cannabis may be associated with increased risk of developing psychiatric disorders[11]; however, the association could also be reversed (ie, premorbid illness leading to cannabis use) or attributable to confounding (ie, common genetic liability for cannabis use and psychiatric disorders[12]). Mendelian randomization studies, which use genetic variants as instrumental variables to infer causal relationships, suggest a causal effect of cannabis use on schizophrenia[13] but not on bipolar disorder[14] or major depressive disorder, although this may be due to lack of statistical power.[15,16] The accumulating epidemiologic evidence, which supports an association between cannabis use and psychosis,[17,18] includes dose-response relationships[19] and a positive association between cannabis potency (Δ9-tetrahydrocannabinol concentration) and risk of psychosis.[20] When taking the increased use and potency of cannabis into consideration, an increased incidence of schizophrenia may be expected. The incidence of schizophrenia[21] and the population-attributable risk fraction (PARF) of CUD for schizophrenia[22] have increased over recent years. Based on the existing evidence, it is possible that cannabis use may be associated with risks of other mental disorders, such as affective disorders.

Evidence regarding the association between use of cannabis and affective disorders is limited. Self-reported cannabis use was not found to be associated with unipolar depression or bipolar disorder after adjustment for confounders in a sample of Swedish military conscripts aged 18 to 20 years,[23] although a dose-dependent association with the risk of schizophrenia was identified.[24] Similarly, no association was found between cannabis use and subsequent risk of affective disorders in a nationally representative sample of US adults.[5] However, a positive association between cannabis use and subsequent depression,[25] bipolar disorder,[26] and manic symptoms[27] has been demonstrated in other longitudinal studies. Risk estimates may be smaller for the association between cannabis use and affective disorders than estimates for the association between cannabis use and schizophrenia.[23,24,28-30] It is possible that the effects of cannabis might primarily be psychotogenic, in which case, higher risk of psychotic (vs nonpsychotic) subtypes of affective disorders would be expected. Still, this hypothesis remains to be tested.

The aim of the current study was to analyze whether CUD was associated with a subsequent diagnosis of unipolar depression or bipolar disorder. To assess whether an association was primarily psychotogenic, we conducted separate analyses with respect to psychotic and nonpsychotic subtypes of these affective disorders. These questions were studied using longitudinal data from nationwide Danish health registers.

Key Points

Question Is cannabis use disorder associated with an increased risk of psychotic and nonpsychotic unipolar depression and bipolar disorder?

Findings In this cohort study of 6 651 765 individuals in Demark, cannabis use disorder was associated with an increased risk of both psychotic and nonpsychotic unipolar depression and bipolar disorder.

Meaning The findings suggest that cannabis use disorder is independently associated with bipolar disorder and unipolar depression.

Methods

Study Design, Data Sources, and Study Population

We conducted a register-based prospective cohort study by linking nationwide Danish register data. Since 1968, the Danish Civil Registration System[31] has provided all permanent residents in Denmark with a unique identification number, which allows for individual-level linkage of data from different registers. The Civil Registration System[31] also contains information on date of birth, birthplace, and vital status. Data on contacts with psychiatric and somatic hospitals, including information on diagnoses, were obtained from the Psychiatric Central Research Register since 1969[32] and the National Patient Register since 1977,[33] respectively. Finally, we obtained data on treatments provided for substance use from the municipal Register of Substance Abusers in Treatment.[34] Information on redeemed prescriptions was derived from the National Prescription Registry[35] since 1995. We included all individuals born no later than December 31, 2005, who were alive, aged at least 16 years, and living in Denmark at some point between January 1, 1995, and December 31, 2021. The study was approved by the Danish Data Protection Agency. Register-based studies do not require informed consent according to Danish law. The present analyses were conducted using encrypted personal identification numbers on servers at Statistics Denmark. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Exposures

Cannabis use disorder was defined as a recorded diagnosis during a hospital contact in either the Psychiatric Central Research Register or the National Patient Register or a record of treatment for CUD provided by a municipality. Diagnoses of CUD were recorded using *International Classification of Diseases, Eighth Revision (ICD-8)* code 304.5 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* code F12.X. The *ICD-8* was used in Denmark until 1994, when it was replaced by the *ICD-10*. The *International Classification of Diseases, Ninth Revision* was never implemented in Denmark. Information on CUD was also obtained from the municipal register of substance users seek-

ing treatment, with information as to whether cannabis was the person's primary misused substance.

Covariates

We obtained information on alcohol use disorder (AUD) and substance use disorders (SUDs) using psychiatric diagnostic codes (eTable 1 in Supplement 1) and registered treatment in the municipal register of substance users seeking treatment. Finally, redeeming a prescription of naltrexone counted toward AUD, while buprenorphine or methadone counted toward SUD.

In addition to the aforementioned data, we obtained information on sex; date of birth; country of birth; parental CUD, AUD, and SUD; parental affective disorders; and highest level of parental education. In addition, history of other psychiatric disorders (*ICD-8*: 290-309; *ICD-10*: any code in the F chapter except for those already part of other variables) was included.

Outcomes

Information on affective disorders was obtained from the Psychiatric Central Research Register[32] and the psychiatric segment of the National Patient Registry.[36] To distinguish affective disorders with and without psychotic features, we restricted the study period to the years when *ICD-10* codes were used. The following *ICD-10* codes were used for the outcome categories: unipolar depression (F32.X or F33.X), unipolar depression with psychotic features (F32.3 or F33.3), unipolar depression without psychotic features (F32 and F33, excluding F32.3 and F33.3), bipolar disorder (F31.X), bipolar disorder with psychotic features (F31.2 or F31.5), and bipolar disorder without psychotic features (F31, excluding F31.2 and F31.5).

Statistical Analysis

We plotted cumulative probabilities for affective disorders using Kaplan-Meier curves and applied Cox proportional hazards regression to estimate hazard ratios (HRs) to compare the risk of affective disorders depending on the exposure (CUD vs no CUD). Individuals were entered into the analysis on their 16th birthday or January 1, 1995, whichever came last. Individuals were followed up until development of an affective disorder; censoring due to development of schizophrenia, death, or emigration; or the end of data collection on May 3, 2022. We included CUD, AUD, and SUD as time-varying covariates in all models. Men and women were examined separately if an interaction between sex and CUD was detected in crude preliminary analyses. In the adjusted analyses, we included sex (if not stratified by sex); AUD and SUD; born in Denmark (yes, no); calendar year; parental educational level (highest attained); parental CUD, AUD, and SUD; and parental affective disorders. Age was used as the underlying time scale in all analyses. When calculating risk of unipolar depression, individuals were censored at the date of diagnosis of bipolar disorder as this diagnosis would preclude a later unipolar depression diagnosis. Individuals who had been diagnosed with an affective disorder (*ICD-8*: 296.X) prior to 1995 were not considered to have incident cases of unipolar depression or bipolar disorder and were thus censored before inclusion in the analyses. We estimated relative HRs for associations between CUD and the psychotic and nonpsychotic subtypes by dividing the 2 HRs. The SE for this metric was estimated by summing the nonexponentially transformed SEs of the 2 estimated HRs, and this was then used to estimate a 95% CI around the relative HR. We conducted 2 sensitivity analyses to address potential confounding by other psychiatric disorders; we adjusted for the presence of other psychiatric disorders (1) prior to CUD diagnosis and (2) over the entire follow-up period. We estimated PARFs from the adjusted HRs as previously reported.[22]

All analyses were conducted using STATA/MP, version 17.0 (StataCorp LLC). Two-sided $P < .05$ was considered significant.

Table 1. Characteristics of the Population

Characteristic	Individuals, No. (%) (N = 6 651 765)
Sex	
Female	3 347 142 (50.3)
Male	3 304 623 (49.7)
Born in Denmark	521 840 (7.9)
Parental CUD, AUD, and/or SUD	666 427 (10.0)
Parental affective disorder	313 305 (4.7)
Parental educational level	
Primary or lower secondary	1 145 564 (17.2)
Upper secondary	1 095 498 (16.5)
Short-cycle tertiary	75 650 (1.1)
Bachelor's degree	297 728 (4.5)
Master's degree or higher	107 305 (1.6)
Not registered	3 930 020 (59.1)
CUD	55 968 (0.8)
AUD	399 086 (6.0)
SUD	214 110 (3.2)

Abbreviations: AUD, alcohol use disorder; CUD, cannabis use disorder; SUD, substance use disorder.

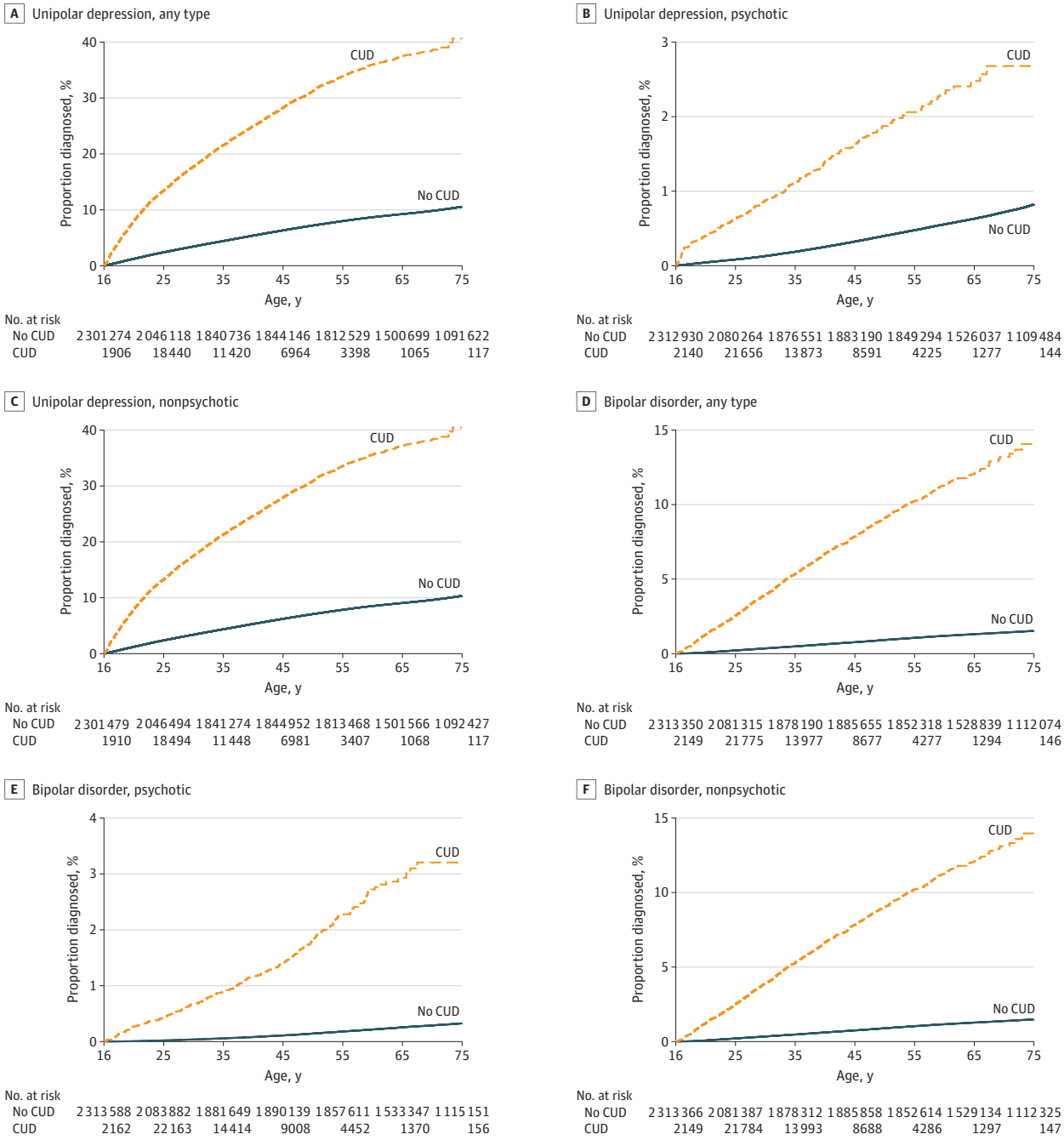
Results

A total of 6 651 765 individuals were included and followed up over 119 526 786 person-years (50.3% female; 49.7% male). **Table 1** presents study population characteristics, all of which were significantly associated with the outcomes. The study population had a broad age distribution, as shown in the eFigure in Supplement 1. In all, 60 696 individuals (0.9% of the study population) received a diagnosis of CUD during follow-up, and 260 746 (3.9%) developed an affective disorder.

CUD and Unipolar Depression

All analyses regarding unipolar depression were conducted jointly for men and women as no interaction between sex and CUD was observed (any type of unipolar depression: χ^2_1, 1.01; $P = .03$; psychotic unipolar depression: χ^2_1, 0.43; $P = .51$; nonpsychotic unipolar depression: χ^2_1, 1.37; $P = .24$). Altogether, 40.7% of individuals with CUD received a diagnosis of unipolar depression, as shown in the Kaplan-Meier plot (**Figure 1**).

Figure 1. Kaplan-Meier Plots for Exposure to Cannabis Use Disorder (CUD) and the Outcomes of Unipolar Depression and Bipolar Disorder



The majority of these individuals (96.1%) were diagnosed with nonpsychotic unipolar depression, while 3.9% were diagnosed with psychotic unipolar depression.

When adjusting for sex; AUD and SUD; having been born in Denmark; calendar year; parental CUD, AUD, and SUD; and parental affective disorders, individuals with CUD had a higher risk of any type of unipolar depression (HR, 1.84; 95% CI, 1.78-1.90) compared with individuals with no records of a CUD (**Table 2**). Elevated risks were also found with respect to psychotic depression (HR, 1.97; 95% CI, 1.73-2.25) and nonpsychotic depression (HR, 1.83; 95% CI, 1.77-1.89). We found no statistically significant difference in the associations between CUD and the psychotic vs nonpsychotic type of unipolar depression (relative HR, 1.08; 95% CI, 0.92-1.27). The PARFs for unipolar depression associated with CUD ranged from 0.71% (95% CI, 0.69%-0.73%) to 0.85% (95% CI, 0.84%-0.87%). The HRs for the associations between AUD or SUD and any type of unipolar depression were found to be nominally greater than those for the association between CUD and any type of unipolar depression (eTable 2 in Supplement 1).

Table 2. Associations of CUD With Unipolar Depression and Bipolar Disorder and PARFs

Outcome	Incident cases, No.	HR (95% CI)		PARF, % (95% CI)[b]
		Unadjusted	Adjusted[a]	
Unipolar depression				
Any type	240 347	4.89 (4.75-5.04)	1.84 (1.78-1.90)	0.85 (0.84-0.86)
Psychotic	17 906	4.72 (4.05-5.51)	1.97 (1.73-2.25)	0.71 (0.69-0.73)
Nonpsychotic	235 157	4.91 (4.77-5.06)	1.83 (1.77-1.89)	0.85 (0.84-0.87)
Bipolar disorder				
Any type[c]				
Males	12 545	11.36 (10.60-12.17)	2.96 (2.73-3.21)	4.72 (4.58-4.86)
Females	19 330	11.94 (10.96-13.02)	2.54 (2.31-2.80)	1.68 (1.63-1.73)
Psychotic	6567	12.26 (10.86-13.84)	4.05 (3.52-4.65)	3.22 (3.03-3.41)
Nonpsychotic[c]				
Males	12 198	11.51 (10.74-12.35)	2.96 (2.73-3.21)	4.79 (4.64-4.93)
Females	18 907	12.32 (11.30-13.43)	2.60 (2.36-2.85)	1.76 (1.71-1.82)

Abbreviations: CUD, cannabis use disorder; HR, hazard ratio; PARF, population-attributable risk fraction.

[a] Adjusted for sex (if not stratified by sex); alcohol use disorder; substance use disorder; born in Denmark (yes, no); calendar year; parental educational level (highest attained); parental CUD, alcohol use disorder, and substance use disorder; and parental affective disorders. The associations were conditioned on age since age was used as the underlying time scale in all analyses.

[b] Calculated from the estimates of the adjusted HRs.

[c] Estimates for the associations are reported for males and females separately as there was a significant interaction between CUD and sex for these outcomes. There was no interaction between sex and CUD for psychotic bipolar disorder or for any of the outcomes under unipolar depression.

When assessing risks with respect to the time between the first diagnosis of CUD and subsequent unipolar depression, the highest risk was found within the first 6 months of being diagnosed (HR, 6.84; 95% CI, 6.34-7.38) compared with no diagnosis of CUD (**Figure 2**). However, the excess risk of unipolar depression among those with CUD remained significant up to 10 years after the initial diagnosis.

In the sensitivity analyses adjusting for other psychiatric disorders prior to CUD, associations remained between CUD and unipolar depression (HR, 1.72; 95% CI, 1.67-1.77) and the psychotic (HR, 1.87; 95% CI, 1.65-2.13) and nonpsychotic (HR, 1.71; 95% CI, 1.65-1.76) subtypes, but the HRs were smaller than in the main analysis. After adjusting for other psychiatric disorders over the entire follow-up period (both before and after CUD), HRs were even smaller for associations with unipolar depression (HR, 1.08; 95% CI, 1.04-1.11) and the nonpsychotic subtype (HR, 1.07; 95% CI, 1.04-1.10), and there was no association with the psychotic subtype (HR, 1.05; 95% CI, 0.92-1.19).

Cannabis Use Disorder and Bipolar Disorder

We found an interaction between sex and CUD for any type of bipolar disorder (χ^2_1, 5.02; P = .03) and nonpsychotic bipolar disorder (χ^2_1, 6.62; P = .01) but not for psychotic bipolar disorder (χ^2_1, 0.43; P = .51). Analyses for the first 2 outcomes were thus stratified by sex.

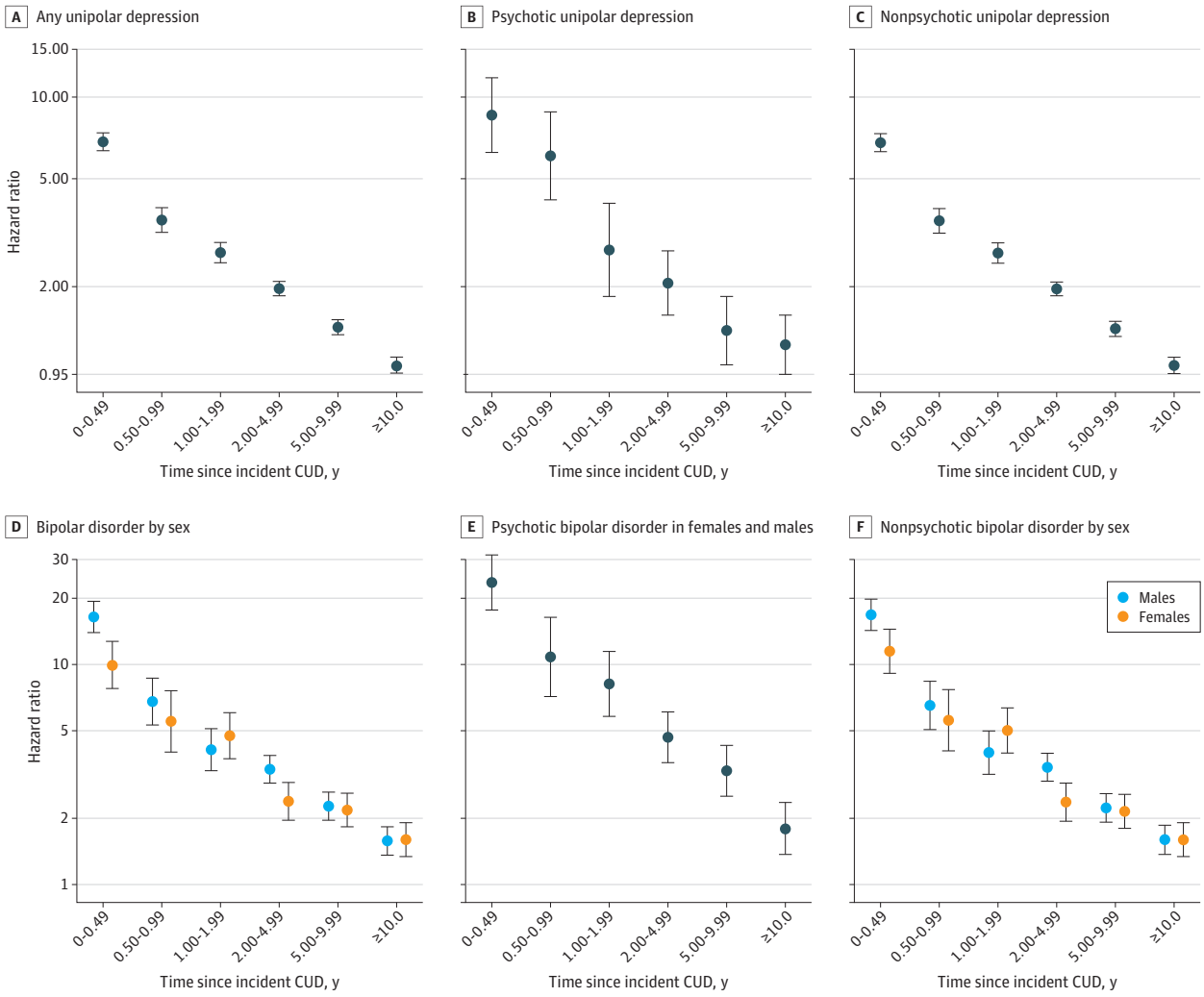
The Kaplan-Meier curves revealed that 14.1% of individuals with CUD eventually received a diagnosis of bipolar disorder (Figure 1). The majority of these individuals (90.2%) were diagnosed with nonpsychotic bipolar disorder, while 9.8% were diagnosed with psychotic bipolar disorder.

Cannabis use disorder was associated with a higher risk of any type of bipolar disorder among both men (HR, 2.96; 95% CI, 2.73-3.21) and women (HR, 2.54; 95% CI, 2.31-2.80) compared with nonexposed individuals in the adjusted analysis (Table 2). Likewise, CUD was associated with psychotic bipolar disorder (HR, 4.05; 95% CI, 3.52-4.65) and with nonpsychotic bipolar disorder in both men (HR, 2.96; 95% CI, 2.73-3.21) and women (HR, 2.60; 95% CI, 2.36-2.85). Cannabis use disorder was associated with a higher risk for the psychotic type than the nonpsychotic type of bipolar disorder (relative HR, 1.48; 95% CI, 1.21-1.81). The PARF for bipolar disorder varied from 1.68% (95% CI, 1.63%-1.73%) for any type of bipolar disorder in women to 4.79% (95% CI, 4.64-4.93) for nonpsychotic bipolar disorder in men (Table 2). Alcohol use disorder was associated with a nominally greater risk of bipolar disorder compared with CUD (eTable 3 in Supplement 1).

When assessing risks with respect to the time between first diagnosis of CUD and subsequent bipolar disorder, the highest risk was found within the first 6 months of diagnosis (HR, 16.45; 95% CI, 13.97-19.38) compared with no diagnosis of CUD (Figure 2). However, the risk of bipolar disorder among those with CUD remained elevated even after 10 or more years (Figure 2).

In the sensitivity analyses, after adjustment for other psychiatric disorders prior to CUD, associations remained between CUD and bipolar disorder in both men (HR, 2.79; 95% CI, 2.59-3.02) and women (HR, 2.46; 95% CI, 2.24-2.69), but HRs were smaller. The HR was similar for the association between CUD and psychotic bipolar disorder (HR, 4.04; 95% CI, 3.54-4.60). For nonpsychotic bipolar disorder, after adjustment for other psychiatric disorders prior to CUD, the associations remained for both men (HR, 2.79; 95% CI, 2.58-3.01) and women (HR, 2.50; 95% CI, 2.28-2.40), but the HRs were smaller. After adjusting for other psychiatric disorders over the entire follow-up period (both before and after CUD), HRs were even smaller for the associations between CUD and bipolar disorder in men (HR, 1.49; 95% CI, 1.38-1.61) and women (HR, 1.53; 95% CI, 1.39-1.67), between CUD and psychotic bipolar disor-

Figure 2. Risk of Unipolar Depression and Bipolar Disorder Among Individuals With vs Without Cannabis Use Disorder (CUD)



Whiskers indicate 95% CIs. D and F, Due to a significant interaction between sex and CUD for any type of bipolar disorder and psychotic bipolar disorder, these analyses were performed for males and females separately.

der (HR, 2.07, 95% CI, 1.82-2.36), and between CUD and nonpsychotic bipolar disorder in men (HR, 1.48; 95% CI, 1.37-1.60) and women (HR, 1.55; 95% CI, 1.41-1.69).

Discussion

In this nationwide cohort study of 6 651 765 individuals, CUD was found to be associated with an increased risk of unipolar depression and bipolar disorder when adjusting for relevant confounders. Although excess risks of unipolar depression and bipolar disorder were highest immediately after diagnosis of CUD, they remained significantly elevated up to 5 to 10 years after CUD.

Our findings add support to previous large-scale studies showing an association between CUD and affective disorders.[23,26,27] Two previous studies found significant associations between cannabis use and unipolar depression but not bipolar disorder.[23,26] We found significant associations between CUD and both bipolar disorder and unipolar depression, but the risk of bipolar disorder was nominally higher. Importantly, differences in the information on cannabis use (self-reported use vs nationwide health records) and analytical strategies may explain some of these discrepancies. Specifically, some studies adjusted for baseline depressive or manic symptoms[27] or baseline psychiatric disorders.[23,26] When we adjusted for other psychiatric disorders prior to CUD, the associations with mood disorders remained. After adjustment for other psychiatric disorders over the entire follow-up period to reduce potential residual confounding, associations remained with the exception of the association between CUD and psychotic unipolar depression. Adjustment for psychiatric disorders diagnosed after CUD may, however, induce collider stratification bias by conditioning on mediators between the exposure and the outcome; thus, the latter analysis may be overadjusted.[37]

Implications

Our findings lend support to the notion that cannabis use may represent an independent factor associated with unipolar depression and bipolar disorder. The risk of psychiatric disorders appears to be higher for schizophrenia[18,22] than for affective disorders[38] and higher for psychotic bipolar disorder than for nonpsychotic bipolar disorder, potentially pointing to a primarily psychotogenic effect of cannabis. Δ9-Tetrahydrocannabinol, the main psychoactive constituent of cannabis, acts on cannabinoid (CB1) receptors and is suggested to increase the risk of psychosis by altering striatal dopaminergic function[39,40] or by disrupting normal endocannabinoid modulation of cortical development and function.[41,42] In addition to its links with psychosis, the dopaminergic system is intricately linked with neurocognitive processes relevant for affective disorders, such as reward processing.[43-45] However, a coherent model for how cannabis may influence the development of affective disorders is lacking. Future studies may further elucidate these effects in a transdiagnostic framework.

Based on our findings and the evidence regarding cannabis and schizophrenia, interventions to reduce cannabis use through both public education and more targeted interventions may be advisable. Direct evidence that cannabis cessation can reduce the risk of affective disorders is, however, lacking, and although several interventions appear to be associated with reducing cannabis use in adolescents[46] and healthy adults,[47] they may be less effective in individuals with mental disorders.[48] Although some trials have demonstrated significant improvements in depressive symptoms after a psychosocial intervention to reduce cannabis use,[49] these improvements may be mediated by broader effects of the psychosocial interventions, providing little evidence for the beneficial effects of cannabis cessation itself.[50] Targeted interventions for at-risk individuals are currently hindered by sparse knowledge on factors associated with transition from cannabis use (disorder) to psychiatric disorders,[51,52] calling for further studies.

Strengths and Limitations

A strength of this study is the large sample size, which makes it, to our knowledge, the largest investigation of the association between CUD and affective disorders to date. Data were collected prospectively and uniformly for all studied groups, eliminating recall bias and reducing selection bias. The availability of sociodemographic and historic psychiatric information on individuals and their parents enabled us to adjust for relevant confounders.

Important limitations should be mentioned. First, while individuals registered with a CUD diagnosis are likely to have CUD (ie, high positive predictive value), individuals without a register-based diagnosis of CUD may still have CUD (ie, suboptimal negative predictive value). This misclassification could bias our findings toward the null if the misclassification was random or could confound our findings if individuals with a diagnosis of CUD were not representative of (heavy) cannabis users.[52,53] Second, the validity of the register-based diagnosis of affective disorders is evaluated as good in Denmark,[54] but individuals with mild to moderate depression might be seen only in primary care and thus were not detected in our study.[55] Third, detection bias is possible. Receiving a diagnosis and clinical care for CUD may imply that clinicians divert more attention to these individuals and, hence, are more likely to detect psychiatric disorders that might otherwise go undetected among nonexposed individuals. This could be an explanatory factor for the increased risk during the first year(s) after diagnosis of CUD. However, the sustained increased risk observed up to 10 years after the initial CUD diagnosis supports the notion of an association beyond the putative detection bias.

Conclusions

The results of this cohort study suggest that cannabis use is associated with an increased risk of psychotic and nonpsychotic bipolar disorder and unipolar depression. These findings have implications regarding the legalization and control of cannabis use. Importantly, there appears to be a need for improved knowledge on the dose-dependent effects of cannabis use on brain, cognition, and behavior; identification of risk factors for transition from cannabis use (disorder) to psychiatric disorders; and the effects of cannabis cessation on long-term psychiatric risk.

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REFERENCES

1. United Nations Office on Drugs Crime. World drug report 2019. Accessed January 10, 2023. https://www.un-ilibrary.org/content/publication/a4dd519a-en

2. Hall W, Stjepanović D, Caulkins J, et al. Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. *Lancet*. 2019;394(10208):1580-1590. doi:10.1016/S0140-6736(19)31789-1

3. Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008-2017). *Eur Arch Psychiatry Clin Neurosci*. 2019;269(1):5-15. doi:10.1007/s00406-019-00983-5

4. Rømer Thomsen K, Lindholst C, Thylstrup B, et al. Changes in the composition of cannabis from 2000-2017 in Denmark: analysis of confiscated samples of cannabis resin. *Exp Clin Psychopharmacol*. 2019;27(4):402-411. doi:10.1037/pha0000303

5. Blanco C, Hasin DS, Wall MM, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. *JAMA Psychiatry*. 2016;73(4):388-395. doi:10.1001/jamapsychiatry.2015.3229

6. Toftdahl NG, Nordentoft M, Hjorthøj C. Prevalence of substance use disorders in psychiatric patients: a nationwide Danish population-based study. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51(1):129-140. doi:10.1007/s00127-015-1104-4

7. Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. *J Affect Disord*. 2015;171:39-47. doi:10.1016/j.jad.2014.09.016

8. Schoeler T, Petros N, Di Forti M, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *Lancet Psychiatry*. 2016;3(10):947-953. doi:10.1016/S2215-0366(16)30188-2

9. Østergaard MLD, Nordentoft M, Hjorthøj C. Associations between substance use disorders and suicide or suicide attempts in people with mental illness: a Danish nation-wide, prospective, register-based study of patients diagnosed with schizophrenia, bipolar disorder, unipolar depression or personality disorder. *Addiction*. 2017;112(7):1250-1259. doi:10.1111/add.13788

10. Hjorthøj C, Østergaard MLD, Benros ME, et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. *Lancet Psychiatry*. 2015;2(9):801-808. doi:10.1016/S2215-0366(15)00207-2

11. Ganesh S, D'Souza DC. Cannabis and psychosis: recent epidemiological findings continuing the "causality debate." *Am J Psychiatry*. 2022;179(1):8-10. doi:10.1176/appi.ajp.2021.21111126

12. Johnson EC, Demontis D, Thorgeirsson TE, et al; Psychiatric Genomics Consortium Substance Use Disorders Workgroup. A large-scale genome-wide association study meta-analysis of cannabis use disorder. *Lancet Psychiatry*. 2020;7(12):1032-1045. doi:10.1016/S2215-0366(20)30339-4

13. Gage SH, Jones HJ, Burgess S, et al. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. *Psychol Med*. 2017;47(5):971-980. doi:10.1017/S0033291716003172

14. Jefsen OH, Speed M, Speed D, Østergaard SD. Bipolar disorder and cannabis use: a bidirectional two-sample Mendelian randomization study. *Addict Biol*. 2021;26(6):e13030. doi:10.1111/adb.13030

15. Hodgson K, Coleman JRI, Hagenaars SP, et al; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Cannabis use, depression and self-harm: phenotypic and genetic relationships. *Addiction*. 2020;115(3):482-492. doi:10.1111/add.14845

16. Treur JL, Demontis D, Smith GD, et al. Investigating causality between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization. *Addict Biol*. 2021;26(1):e12849. doi:10.1111/adb.12849

17. Gage SH, Hickman M, Zammit S. Association between cannabis and psychosis: epidemiologic evidence. *Biol Psychiatry*. 2016;79(7):549-556. doi:10.1016/j.biopsych.2015.08.001

18. Nielsen SM, 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;47(9):1668-1677. doi:10.1017/S0033291717000162

19. 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(5):1262-1269. doi:10.1093/schbul/sbw003

20. Di Forti M, Sallis H, Allegri F, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr Bull*. 2014;40(6):1509-1517. doi:10.1093/schbul/sbt181

21. Kühl JOG, Laursen TM, Thorup A, Nordentoft M. The incidence of schizophrenia and schizophrenia spectrum disorders in Denmark in the period 2000-2012: a register-based study. *Schizophr Res*. 2016;176(2-3):533-539. doi:10.1016/j.schres.2016.06.023

22. Hjorthøj C, Posselt CM, Nordentoft M. Development over time of the population-attributable risk fraction for cannabis use disorder in schizophrenia in Denmark. *JAMA Psychiatry*. 2021;78(9):1013-1019. doi:10.1001/jamapsychiatry.2021.1471

23. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Allebeck P. Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts. *BMC Psychiatry*. 2012;12(1):112. doi:10.1186/1471-244X-12-112

24. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. *Psychol Med*. 2012;42(6):1321-1328. doi:10.1017/S0033291711002078

25. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med*. 2014;44(4):797-810. doi:10.1017/S0033291713001438

26. Feingold D, Weiser M, Rehm J, Lev-Ran S. The association between cannabis use and mood disorders: a longitudinal study. *J Affect Disord*. 2015;172:211-218. doi:10.1016/j.jad.2014.10.006

27. Henquet C, Krabbendam L, de Graaf R, ten Have M, van Os J. Cannabis use and expression of mania in the general population. *J Affect Disord*. 2006;95(1-3):103-110. doi:10.1016/j.jad.2006.05.002

28. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ*. 2002;325(7374):1212-1213. doi:10.1136/bmj.325.7374.1212

29. McGee R, Williams S, Poulton R, Moffitt T. A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction*. 2000;95(4):491-503. doi:10.1046/j.1360-0443.2000.9544912.x

30. Fergusson DM, Horwood LJ, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction*. 2002;97(9):1123-1135. doi:10.1046/j.1360-0443.2002.00103.x

31. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7)(suppl):22-25. doi:10.1177/1403494810387965

32. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7)(suppl):54-57. doi:10.1177/1403494810395825

33. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7)(suppl):30-33. doi:10.1177/1403494811401482

34. Ministry of Children and Social Affairs. Bekendtgørelse om dataindberetninger på socialområdet. Executive order on data reporting on social services. 2018. Accessed April 12, 2023. https://www.retsinformation.dk/eli/lta/2021/2351

35. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7)(suppl):38-41. doi:10.1177/1403494810394717

36. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

37. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol*. 2019;34(3):211-219. doi:10.1007/s10654-019-00494-6

38. 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(9584):319-328. doi:10.1016/S0140-6736(07)61162-3

39. Murray RM, Mehta M, Di Forti M. Different dopaminergic abnormalities underlie cannabis dependence and cannabis-induced psychosis. *Biol Psychiatry*. 2014;75(6):430-431. doi:10.1016/j.biopsych.2014.01.011

40. Colizzi M, Weltens N, McGuire P, et al. Delta-9-tetrahydrocannabinol increases striatal glutamate levels in healthy individuals: implications for psychosis. *Mol Psychiatry*. 2020;25(12):3231-3240. doi:10.1038/s41380-019-0374-8

41. Bara A, Ferland JN, Rompala G, Szutorisz H, Hurd YL. Cannabis and synaptic reprogramming of the developing brain. *Nat Rev Neurosci*. 2021;22(7):423-438. doi:10.1038/s41583-021-00465-5

42. Volk DW, Lewis DA. The role of endocannabinoid signaling in cortical inhibitory neuron dysfunction in schizophrenia. *Biol Psychiatry*. 2016;79(7):595-603. doi:10.1016/j.biopsych.2015.06.015

43. Heller AS, Johnstone T, Shackman AJ, et al. Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance

of fronto-striatal brain activation. *Proc Natl Acad Sci U S A*. 2009;106(52):22445-22450. doi:10.1073/pnas.0910651106

44. Kasanova Z, Ceccarini J, Frank MJ, et al. Striatal dopaminergic modulation of reinforcement learning predicts reward-oriented behavior in daily life. *Biol Psychol*. 2017;127:1-9. doi:10.1016/j.biopsycho.2017.04.014

45. Parsons LH, Hurd YL. Endocannabinoid signalling in reward and addiction. *Nat Rev Neurosci*. 2015;16(10):579-594. doi:10.1038/nrn4004

46. Porath-Waller AJ, Beasley E, Beirness DJ. A meta-analytic review of school-based prevention for cannabis use. *Health Educ Behav*. 2010;37(5):709-723. doi:10.1177/1090198110361315

47. Chatters R, Cooper K, Day E, et al. Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review. *Addict Res Theory*. 2016;24(2):93-110. doi:10.3109/16066359.2015.1073719

48. Hjorthøj C, Fohlmann A, Nordentoft M. Treatment of cannabis use disorders in people with schizophrenia spectrum disorders—a systematic review. *Addict Behav*. 2009;34(6-7):520-525. doi:10.1016/j.addbeh.2009.02.001

49. González-Ortega I, Echeburúa E, Alberich S, et al. Cognitive behavioral therapy program for cannabis use cessation in first-episode psychosis patients: a 1-year randomized controlled trial. *Int J Environ Res Public Health*. 2022;19(12):7325. doi:10.3390/ijerph19127325

50. Arias AJ, Hammond CJ, Burleson JA, et al. Temporal dynamics of the relationship between change in depressive symptoms and cannabis use in adolescents receiving psychosocial treatment for cannabis use disorder. *J Subst Abuse Treat*. 2020;117:108087. doi:10.1016/j.jsat.2020.108087

51. Valmaggia LR, Day FL, Jones C, et al. Cannabis use and transition to psychosis in people at ultra-high risk. *Psychol Med*. 2014;44(12):2503-2512. doi:10.1017/S0033291714000117

52. Van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Predicting the transition from frequent cannabis use to cannabis dependence: a three-year prospective study. *Drug Alcohol Depend*. 2013;133(2):352-359. doi:10.1016/j.drugalcdep.2013.06.009

53. Feingold D, Livne O, Rehm J, Lev-Ran S. Probability and correlates of transition from cannabis use to *DSM-5* cannabis use disorder: results from a large-scale nationally representative study. *Drug Alcohol Rev*. 2020;39(2):142-151. doi:10.1111/dar.13031

54. Kessing L. Validity of diagnoses and other clinical register data in patients with affective disorder. *Eur Psychiatry*. 1998;13(8):392-398. doi:10.1016/S0924-9338(99)80685-3

55. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health*. 2009;5(1):4. doi:10.1186/1745-0179-5-4