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Association of Cannabis Use With Self-harm and Mortality Risk Among Youths With Mood Disorders

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IMPORTANCE Cannabis use and cannabis use disorder (CUD) are common among youths and young adults with mood disorders, but the association of CUD with self-harm, suicide, and overall mortality risk is poorly understood in this already vulnerable population.

OBJECTIVE To examine associations of CUD with self-harm, suicide, and overall mortality risk in youths with mood disorders.

DESIGN, SETTING, AND PARTICIPANTS A population-based retrospective cohort study was performed using Ohio Medicaid claims data linked with death certificate data. The analysis included 204 780 youths (aged 10-24 years) with a diagnosis of mood disorders between July 1, 2010, and December 31, 2017, who were followed up to 365 days from the index diagnostic claim until the end of enrollment, the self-harm event, or death. Statistical analysis was performed from April 4 to July 17, 2020.

EXPOSURE Physician-diagnosed CUD defined using outpatient and inpatient claims from 180 days prior to the index mood disorder diagnostic claim through the 365-day follow-up period.

MAIN OUTCOMES AND MEASURES Nonfatal self-harm, all-cause mortality, and deaths by suicide, unintentional overdose, motor vehicle crashes, and homicide. Marginal structural models using inverse probability weights examined associations between CUD and outcomes.

RESULTS This study included 204 780 youths (133 081 female participants [65.0%]; mean [SD] age at the time of mood disorder diagnosis, 17.2 [4.10] years). Cannabis use disorder was documented for 10.3% of youths with mood disorders (n = 21 040) and was significantly associated with older age (14-18 years vs 10-13 years: adjusted risk ratio [ARR], 9.35; 95% CI, 8.57-10.19; and 19-24 years vs 10-13 years: ARR, 11.22; 95% CI, 10.27-12.26), male sex (ARR, 1.79; 95% CI, 1.74-1.84), Black race (ARR, 1.39; 95% CI, 1.35-1.44), bipolar or other mood disorders (bipolar disorders: ARR, 1.24; 95% CI, 1.21-1.29; other mood disorders: ARR, 1.20; 95% CI, 1.15-1.25), prior history of self-harm (ARR, 1.66; 95% CI, 1.52-1.82), previous mental health outpatient visits (ARR, 1.26; 95% CI, 1.22-1.30), psychiatric hospitalizations (ARR, 1.66; 95% CI, 1.57-1.76), and mental health emergency department visits (ARR, 1.54; 95% CI, 1.47-1.61). Cannabis use disorder was significantly associated with nonfatal self-harm (adjusted hazard ratio [AHR], 3.28; 95% CI, 2.55-4.22) and all-cause mortality (AHR, 1.59; 95% CI, 1.13-2.24), including death by unintentional overdose (AHR, 2.40; 95% CI, 1.39-4.16) and homicide (AHR, 3.23; 95% CI, 1.22-8.59). Although CUD was associated with suicide in the unadjusted model, it was not significantly associated in adjusted models.

CONCLUSIONS AND RELEVANCE Cannabis use disorder is a common comorbidity and risk marker for self-harm, all-cause mortality, and death by unintentional overdose and homicide among youths with mood disorders. These findings should be considered as states contemplate legalizing medical and recreational marijuana, both of which are associated with increased CUD.

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Supplemental content

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Mood disorders in youths, including depression and bipolar disorders, are associated with increased risk of disability and mortality, including suicide, and account for nearly 4% of the burden of disease worldwide.[1] Previous studies have identified high rates of co-occurrence for cannabis use and cannabis use disorders (CUDs) in youths and young adults with mood disorders,[2-4] and there is evidence that cannabis use may interfere with recovery from depression.[5] Although recent reviews of the association between cannabis use and all-cause mortality in the general population have been inconclusive,[6,7] some evidence supports an elevated risk of motor vehicle traffic deaths and drug overdose–related injury in cannabis users.[6]

Cannabis use has also been associated with a heightened risk of suicidal behavior in adults, as well as a greater likelihood of dying by suicide.[8,9] In a sample of 277 adult same-sex twin pairs, cannabis users were 2.9 times more likely to attempt suicide than non-cannabis-dependent co-twins.[10] Another longitudinal study of young adults found a strong association between regular cannabis use and suicide attempts after adjusting for a wide array of confounders (odds ratio [OR], 2.9; 95% CI, 1.3-6.1).[11] A follow-up study of Swedish conscripts reported that those who used cannabis more than 50 times by age 18 years were at increased risk of dying by suicide.[12] A case-control study comparing individuals who died by suicide with those who died of unintentional injuries linked CUD with heightened suicide risk (OR, 2.85; 95% CI, 1.31-6.24).[13] A large case-control study of 1463 suicides and 7392 natural deaths found an association between any cannabis use and suicide risk after adjusting for depression, alcohol use, and mental health services.[14,15] Another longitudinal study with a 4-year follow-up of 6445 patients with CUD in Denmark found an increased risk of suicide for both male patients (OR, 2.28; 95% CI, 1.54-3.37) and female patients (OR, 4.82; 95% CI, 2.47-9.39) among those with CUD.[16]

To our knowledge, no studies to date have examined the association of CUD with overall mortality risk and nonfatal self-harm in the vulnerable population of youths with mood disorders. Given the high prevalence of CUD, as well as the elevated risk of suicide in youths with mood disorders,[17] a better understanding of the association between CUD and suicide risk in this population could prove critical to suicide prevention efforts, given that both mood disorders and CUD are potentially remediable risk factors. The aim of this study was to examine the association of CUD with the risk of mortality risk, self-harm, and suicide among youths and young adults with diagnosed mood disorders. We hypothesized that youths with comorbid mood disorders and CUD would be at increased risk for nonfatal self-harm, all-cause mortality, deaths by suicide, unintentional overdose, motor vehicle crashes, and homicide, relative to those with mood disorders but not CUD.

Key Points

Question Is cannabis use disorder associated with heightened risk of self-harm, suicide, and mortality among youths with mood disorders?

Findings This population-based cohort study of Medicaid-enrolled youths with mood disorders found that the presence of cannabis use disorder was significantly associated with an increased risk of nonfatal self-harm, all-cause mortality, and death by unintentional overdose and homicide.

Meaning Cannabis use disorder is common among adolescents and young adults with mood disorders and is associated with an elevated risk of self-harm, overall mortality, and death by unintentional overdose and homicide in this already vulnerable population.

Methods

Study Design and Cohort

A retrospective cohort design was used to examine the association of CUD with nonfatal self-harm and mortality among youths and young adults with a diagnosis of mood disorders. The study population included all those between 10 and 24 years of age who had 2 or more outpatient claims for mood disorders (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 296.0-296.9, 300.4, 301.13, and 311 or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] codes F30-F39) between July 1, 2010, and December 31, 2017, and were continuously enrolled in Ohio's Medicaid program during the 180-day period prior to the index diagnostic claim (first diagnosis for mood disorder). Those with a diagnosis of schizophrenia (n = 16 467; *ICD-9-CM* codes 295, 297, and 298 and *ICD-10* codes F20-F29) were excluded, resulting in a sample of 204 780. Youths were followed up to 365 days, until the end of enrollment, the event, or other death, whichever came first. All procedures were approved by The Ohio State University institutional review board, and a waiver of informed consent was granted because the study involved secondary data only, with deidentified patient information; the research involved only minimal risk to participants; and it would not affect the rights and welfare of participants.

Data Sources

Data were abstracted from Ohio Medicaid claims data and death certificate files. Medicaid claims data were obtained from the state's Department of Job and Family Services, while death records were obtained from the state's Department of Health. Medicaid claims data included information on eligibility status and paid claims for inpatient and outpatient services. Eligibility files included information on monthly enrollment status and demographic characteristics of enrollees. Institutional and professional files provided information on service claims for hospitalizations, physician visits (office or hospital based), and other outpatient services and included dates of service, *Current Procedural Terminology* and Healthcare Common Procedure Coding System procedure codes, and up to 15 *ICD-9-CM* and/or *ICD-10* diagnoses.

Information on suicide and all-cause mortality was abstracted from death certificates. Data on suicides and all causes of death were based on *ICD-10* cause of death codes reported on death certificates. Medicaid claims data were linked with

the death certificate file using an algorithm from prior studies[18,19] that incorporates social security numbers, date of birth, and sex.

Measures

Outcomes

Primary outcomes of interest were nonfatal self-harm (*ICD-9-CM* codes E950-E959 and *ICD-10* codes X71-X83), suicide deaths (*ICD-10* codes X60-X84, Y87.0, and *U03), all causes of death, drug overdose or poisoning (*ICD-10* codes X40-X44), motor vehicle deaths (*ICD-10* codes V02-V04, V09.0, V09.2, V12-V14, V19.0-V19.2, V19.4-V19.6, V20-V79, V80.3-V80.5, V81.0-V81.1, V82.0-V82.1, V83-V86, V87.0-V87.8, V88.0-V88.8, V89.0, and V89.2), and homicides (*ICD-10* codes X85-Y09, Y87.1, and *U01-*U02). Individuals with a self-harm event were subsequently followed up for mortality within the year. We included all-cause mortality as an outcome in addition to specific causes of death because prior research has shown an association between CUD and all-cause mortality.[7]

Exposure

The primary exposure variable was recent or current CUD (*ICD-9-CM* codes 304.30-304.33 and 305.20-305.23 and *ICD-10* code F12). If an individual had a CUD claim during the 6 months prior to the mood diagnosis claim, the participant was classified as having CUD during the entire follow-up period. If no prior CUD claims existed, individuals were classified as non-CUD until the first CUD claim during follow-up, when they were reclassified as CUD. If no CUD claims occurred in the 6 months prior to or during follow-up, the individual remained classified as non-CUD throughout the study. This variable was treated as a time-varying covariate, allowing the analysis to account for when cannabis use was first diagnosed.

Covariates

Covariates included demographic, clinical, and treatment characteristics. Demographic variables included age at time of index diagnosis (10-13, 14-18, or 19-24 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other [Asian American, Native American or Alaska Native, Native Hawaiian or other Pacific Islander, and more than 1 race] as reported by Medicaid), area of residence (metropolitan or nonmetropolitan), and Medicaid eligibility (disability, foster care, low income, or other [incarceration and unknown Medicaid eligibility categories]). Clinical variables were identified based on medical claims submitted during the 180 days prior to the index diagnosis date. They included psychiatric and medical comorbidities and prior history of nonfatal self-harm (*ICD-9-CM* codes E950-E959 and *ICD-10* codes X71-X83). Psychiatric comorbidities were present if 2 or more claims were associated with the diagnosis. They included attention-deficit/hyperactivity disorders (ADHD), conduct disorders, other substance use disorders (excluding CUD), anxiety disorders, and other mental health disorders. The following chronic medical conditions were examined[20]: type 1 and 2 diabetes and other diabetes, seizure disorders, cerebral palsy, asthma, cancer, congenital anomalies, major organ disease, autoimmune disease, trisomy, congenital heart disease, and sickle cell disease (eTable in the Supplement). Treatment variables included any inpatient, outpatient, or emergency department mental health care during the 180 days preceding the index diagnosis.

Statistical Analysis

Statistical analysis was performed from April 4 to July 17, 2020. Data for all variables were tabulated and summarized. Absolute counts in addition to percentages and risk estimates were reported for all exposures and outcomes, following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards.[21] Association of CUD with covariates (demographics, psychiatric and other medical comorbidities, prior history of self-harm, and prior psychiatric care) was modeled using Poisson regression, to account for variable length of follow-up per participant. Risk ratios and 95% CIs were reported for both unadjusted and adjusted models (which included all covariates). Association of CUD with outcomes was modeled using Cox proportional hazards regression models with time-varying covariates to account for timing of CUD. Hazard ratios (HRs) and 95% CIs were reported for both unadjusted and covariate-adjusted models. Owing to small outcome numbers, inverse probability weights from marginal structural models accounted for confounding.[22] Stabilized weights were used for improved efficiency and better coverage of 95% CIs.[23] Two marginal structural models were fit, one that controlled for demographic covariates (age, sex, race/ethnicity, eligibility status, and residence) and a second that controlled for demographics and all additional covariates. All analyses were performed using SAS, version 9.4 (SAS Institute Inc) and R, version 4.0.0 (R Foundation for Statistical Computing),[24] with R package *ipw* used to fit marginal structural models.[25]

Results

Sample Description

The sample included 204 780 youths and young adults aged 10 to 24 years with a mood disorder (**Table 1**). Mean (SD) age was 17.2 (4.1) years at the time of mood disorder diagnosis. Most participants were female (133 081 [65.0%]), non-Hispanic White (136 950 [66.9%]), enrolled in Medicaid owing to poverty (179 370 [87.6%]), and living in a metropolitan location (157 850 [77.1%]). The most common primary diagnosis was depressive disorder (148 970 [72.7%]); 25 352 participants (12.4%) had bipolar disorder and 30 458 (14.9%) had another mood disorder (ie, unspecified mood disorder or persistent mood disorder). Attention-deficit/hyperactivity disorder (25 416 [12.4%]), anxiety (21 102 [10.3%]), and other mental health disorders (26 787 [13.1%]) were the most common psychiatric comorbidities. Only 17 018 participants (8.3%) had a chronic medical condition, 1995 (1.0%) had prior self-harm, 5303 (2.6%) had prior psychiatric hospitalizations, 11 112 (5.4%) had prior mental health emergency department visits, and 102 995 (50.3%) had prior mental health outpatient visits. A total of 21 040 participants (10.3%) received a diagnosis of CUD.

Table 1. Sample Characteristics of Youths and Young Adults With Mood Disorders

Characteristic	No. (%) (N = 204 780)
Age group, y	
10-13	43 097 (21.0)
14-18	83 309 (40.7)
19-24	78 374 (38.3)
Sex	
Female	133 081 (65.0)
Male	71 699 (35.0)
Race/ethnicity	
Non-Hispanic White	136 950 (66.9)
Non-Hispanic Black	43 454 (21.2)
Hispanic	6274 (3.1)
Other[a]	2563 (1.3)
Missing[b]	15 539 (7.6)
Medicaid eligibility status	
Poverty	179 370 (87.6)
Disability	16 471 (8.0)
Foster care	7747 (3.8)
Other[c]	1192 (0.6)
Residence	
Metropolitan	157 850 (77.1)
Nonmetropolitan	46 930 (22.9)
Primary diagnosis	
Depressive disorders	148 970 (72.7)
Bipolar disorders	25 352 (12.4)
Other mood disorders[d]	30 458 (14.9)
Cannabis use disorder	21 040 (10.3)
Psychiatric comorbidities[e]	
Anxiety disorder	21 102 (10.3)
ADHD	25 416 (12.4)
Conduct disorder	13 641 (6.7)
Substance use disorder[f]	13 980 (6.8)
Other mental health disorder	26 787 (13.1)
Chronic medical condition[e]	17 018 (8.3)
Prior history[e]	
Self-harm	1995 (1.0)
Psychiatric hospitalizations	5303 (2.6)
Outpatient mental health care	102 995 (50.3)
Mental health ED visit	11 112 (5.4)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ED, emergency department.

[a] Other race/ethnicity includes Asian, Native American, and 2 or more races.

[b] Individuals with no data on race/ethnicity in the Medicaid data during the study period.

[c] Other includes incarceration and unknown Medicaid eligibility categories.

[d] Includes *International Classification of Diseases, Ninth Revision, Clinical Modification* code 296.9 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F34.8, F34.9, and F39.

[e] Includes all claims in the 6 months prior to the first mood diagnosis.

[f] Excludes cannabis use disorder.

Demographic, Clinical, and Treatment Characteristics Associated With CUD

Associations between demographic, clinical, and treatment characteristics and any CUD during the study are presented in **Table 2**. Older age groups (14-18 years and 19-24 years) were at higher risk than the youngest age group (10-13 years) in both unadjusted and adjusted models (14-18 years vs 10-13 years, adjusted risk ratio [ARR], 9.35; 95% CI, 8.57-10.19; and 19-24 years vs 10-13 years, ARR, 11.22; 95% CI, 10.27-12.26). Male participants had a higher risk of CUD than female participants (ARR, 1.79; 95% CI, 1.74-1.84). The non-Hispanic Black group had a higher relative risk than the non-Hispanic White group (ARR, 1.39; 95% CI, 1.35-1.44). Those eligible for Medicaid through disability were at lower risk (ARR, 0.61; 95% CI, 0.58-0.65), while those in foster care were at higher risk (ARR, 1.10; 95% CI, 1.02-1.18) for CUD compared with the group eligible for Medicaid owing to poverty. Those living in a metropolitan county were also at increased risk for CUD compared with those living in a nonmetropolitan county (ARR, 1.21; 95% CI, 1.17-1.26).

Youths with bipolar disorders and other mood disorders were at increased risk for CUD compared with those with depressive disorders (bipolar disorders: ARR, 1.24; 95% CI, 1.21-1.29; and other mood disorders: ARR, 1.20; 95% CI, 1.15-1.25). Youths with conduct disorders and other substance use disorders were at higher risk for CUD than those without these disorders (conduct disorders: ARR, 1.46; 95% CI, 1.38-1.53; and substance use disorders: ARR, 2.83; 95% CI, 2.73-2.93). However, those with comorbid ADHD, other mental health disorders, and chronic medical conditions had a lower risk for CUD than those without the conditions (ADHD: ARR, 0.82; 95% CI, 0.78-0.86; other mental health disorders: ARR, 0.72; 95% CI, 0.69-0.76; and chronic medical conditions: ARR, 0.89; 95% CI, 0.84-0.93). Prior self-harm (ARR, 1.66; 95% CI, 1.52-1.82), psychiatric hospitalizations (ARR, 1.66; 95% CI, 1.57-1.76), mental health outpatient visits (ARR, 1.26; 95% CI, 1.22-1.30), and mental health emergency department visits (ARR, 1.54; 95% CI, 1.47-1.61) were all associated with increased risk for CUD.

Associations Between CUD and Nonfatal Self-harm, Suicides, and All Other Mortality Categories

Associations of CUD with nonfatal self-harm, suicides, and all other mortality categories appear in **Table 3**. Cannabis use disorder was strongly associated with all outcomes in the unadjusted models. Unadjusted HRs for CUD ranged from 2.13 (95% CI, 1.89-2.40) for nonfatal self-harm to 6.38 (95% CI, 4.05-10.04) for unintentional overdose. The association between CUD and nonfatal self-harm was significant and remained significant after adjustment for all covariates (HR, 3.28; 95% CI 2.55-4.22). Those with CUD were at 3.46 (95% CI, 1.48-8.07) times the risk of suicide compared with those without CUD in the unadjusted model. After adjusting for age, sex, race/ethnicity, Medicaid eligibility status, and residence, the association between CUD and suicide was nonsignificant (HR, 2.23; 95% CI, 0.93-5.39). After further adjusting for all additional covariates (psychiatric comor-

Table 2. Association Between Youths and Young Adult Characteristics and CUD

Characteristic	CUD anytime during study, No. (%)		Risk ratio (95% CI)	
	Yes (n = 21 040)	No (n = 183 740)	Unadjusted	Adjusted
Age group, y				
10-13	552 (2.6)	42 545 (23.2)	1 [Reference]	1 [Reference]
14-18	9599 (45.6)	73 710 (40.1)	9.09 (8.34-9.90)	9.35 (8.57-10.19)
19-24	10 889 (51.8)	67 485 (36.7)	11.58 (10.63-12.61)	11.22 (10.27-12.26)
Sex				
Female	11 463 (54.5)	121 618 (66.2)	1 [Reference]	1 [Reference]
Male	9577 (45.5)	62 122 (33.8)	1.54 (1.50-1.59)	1.79 (1.74-1.84)
Race/ethnicity				
Non-Hispanic White	12 976 (61.7)	123 974 (67.5)	1 [Reference]	1 [Reference]
Non-Hispanic Black	5290 (25.1)	38 164 (20.8)	1.27 (1.23-1.31)	1.39 (1.35-1.44)
Hispanic	500 (2.4)	5774 (3.1)	0.84 (0.77-0.92)	0.96 (0.88-1.05)
Other[a]	286 (1.4)	2277 (1.2)	1.19 (1.06-1.34)	1.05 (0.93-1.18)
Missing[b]	1988 (9.4)	13 551 (7.4)	1.39 (1.33-1.46)	1.22 (1.16-1.27)
Medicaid eligibility status				
Poverty	18 571 (88.3)	160 799 (87.5)	1 [Reference]	1 [Reference]
Disability	1381 (6.6)	15 090 (8.2)	0.78 (0.74-0.83)	0.61 (0.58-0.65)
Foster care	920 (4.4)	6827 (3.7)	1.09 (1.02-1.17)	1.10 (1.02-1.18)
Other[c]	168 (0.8)	1024 (0.6)	1.42 (1.22-1.65)	1.01 (0.86-1.17)
Residence				
Nonmetropolitan	4104 (19.5)	42 826 (23.3)	1 [Reference]	1 [Reference]
Metropolitan	16 936 (80.5)	140 914 (76.7)	1.21 (1.17-1.26)	1.21 (1.17-1.26)
Primary diagnosis				
Depressive disorder	14 166 (67.3)	134 804 (73.4)	1 [Reference]	1 [Reference]
Bipolar disorder	3745 (17.8)	21 607 (11.8)	1.53 (1.48-1.59)	1.24 (1.2-1.29)
Other mood disorder[d]	3129 (14.9)	27 329 (14.9)	1.04 (1.00-1.09)	1.20 (1.15-1.25)
Psychiatric comorbidities[e]				
Anxiety disorder	2790 (13.3)	18 312 (10.0)	1.36 (1.31-1.41)	0.97 (0.93-1.02)
ADHD	2114 (10.0)	23 302 (12.7)	0.76 (0.73-0.80)	0.82 (0.78-0.86)
Conduct disorder	1997 (9.5)	11 644 (6.3)	1.42 (1.35-1.48)	1.46 (1.38-1.53)
Substance use disorder[f]	4975 (23.6)	9005 (4.9)	4.45 (4.31-4.59)	2.83 (2.73-2.93)
Other mental health disorder	2263 (10.8)	24 524 (13.3)	0.79 (0.75-0.82)	0.72 (0.69-0.76)
Chronic medical condition[e]	1818 (8.6)	15 200 (8.3)	1.03 (0.99-1.09)	0.89 (0.84-0.93)
Prior history[e]				
Self-harm	472 (2.2)	1523 (0.8)	2.31 (2.11-2.53)	1.66 (1.52-1.82)
Psychiatric hospitalizations	1656 (7.9)	3647 (2.0)	3.32 (3.16-3.49)	1.66 (1.57-1.76)
Outpatient mental health care	12 030 (57.2)	90 965 (49.5)	1.31 (1.27-1.34)	1.26 (1.22-1.30)
Mental health ED visit	2684 (12.8)	8428 (4.6)	2.61 (2.50-2.72)	1.54 (1.47-1.61)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ED, emergency department; CUD, cannabis use disorder.

[a] Other race/ethnicity includes Asian, Native American, and 2 or more races.

[b] Individuals with no data on race/ethnicity in the Medicaid data during the study period.

[c] Other includes incarceration and unknown Medicaid eligibility categories.

[d] Includes *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 296.9 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F34.8, F34.9, and F39.

[e] Includes all claims in the 6 months prior to the first mood diagnosis.

[f] Excludes cannabis use disorder.

bidities, including other substance use disorders; chronic medical conditions; prior self-harm; and prior inpatient, emergency department, and outpatient treatment) the association was nonsignificant (HR, 1.22; 95% CI, 0.44-3.43). Hazard ratios between CUD and all nonsuicide mortality outcomes were attenuated after adjusting for demographic covariates but remained statistically significant, except for mortality due to motor vehicle deaths; this latter category occurred infrequently (20 total occurrences). Hazard ratios were attenuated further after including all other covariates but remained statistically significant, with an HR of 1.59 (95% CI, 1.13-2.24) for all-cause mortality, and the strongest associations for homicides (HR, 3.23; 95% CI 1.22-8.59) and unintentional overdose (HR, 2.40; 95% CI, 1.39-4.16).

Table 3. Unadjusted and Marginal Structural Model–Adjusted HRs for Associations Between CUD and Nonfatal Self-harm, Suicides, and All Other Mortality Categories

Characteristic	No. of events	Follow-up, person-years	Rate per 100 000 person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
					Marginal structural model 1[a]	Marginal structural model 2[b]
Nonfatal self harm						
No CUD	1819	162 660	1118.3			
CUD	307	14 335	2141.6	2.13 (1.89-2.40)	3.67 (2.88-4.68)	3.28 (2.55-4.22)
Suicides						
No CUD	23	163 660	14.1			
CUD	7	14 640	47.8	3.46 (1.48-8.07)	2.23 (0.93-5.39)	1.22 (0.44-3.43)
All-cause deaths						
No CUD	215	163 660	131.4			
CUD	63	14 640	430.3	3.28 (2.47-4.34)	2.06 (1.53-2.78)	1.59 (1.13-2.24)
Unintentional overdose						
No CUD	53	163 660	32.4			
CUD	29	14 640	198.1	6.38 (4.05-10.04)	3.82 (2.38-6.13)	2.40 (1.39-4.16)
Motor vehicle deaths						
No CUD	16	163 660	9.8			
CUD	4	14 640	27.3	2.68 (0.90-8.03)	1.75 (0.56-5.46)	2.49 (0.79-7.86)
Homicides						
No CUD	14	163 660	8.6			
CUD	8	14 640	54.6	6.23 (2.61-14.87)	3.85 (1.52-9.74)	3.23 (1.22-8.59)

Abbreviations: CUD, cannabis use disorder; HR, hazard ratio.

[a] Marginal structural model 1 includes demographic variables only (age, sex, race/ethnicity, Medicaid eligibility status, and residence).

[b] Marginal structural model 2 includes all variables in Table 1 except primary diagnosis.

Discussion

Cannabis is the most commonly used illicit drug among US adolescents and the most common drug problem reported by US teens presenting for substance use treatment.[26] In our study population of youths aged 10 to 24 years with mood disorders, 10.3% received a diagnosis of CUD, a rate significantly higher than that reported in the general population (2.2% for adolescents and 5.2% for young adults).[26] Those with CUD in addition to their mood disorder were significantly more likely to engage in nonfatal self-harm and to die. Unintentional overdoses, suicide, and homicide were the 3 most frequent causes of death. Increased risk for nonfatal self-harm, unintentional overdose, and homicide remained significant even after controlling for a wide array of potentially confounding variables. Cannabis use disorder was significantly associated with increased suicides and motor vehicle deaths in the univariable analysis but not after adjusting for potential confounders. Study findings highlight the importance of cannabis use as a potentially remediable risk factor for self-harm and death in youths with mood disorders, particularly among African American youths and those in foster care. Overall, these findings are particularly troubling, especially in the context of increasing statewide medical and recreational legalization of marijuana, which has been associated with increased CUD in adolescents.[27,28]

Although no prior studies have, to our knowledge, examined the association between CUD and mortality among youths with mood disorders, our findings are generally consistent with findings of adult studies. Cannabis use has been associated with nonfatal self-harm, suicidal ideation, and suicide in adults.[10,29-32] In addition, cannabis use has been linked with increased risk of unintentional traffic-related injuries and other types of unintentional injuries in adults[7,33-37] and is often detected in homicide victims.[33,37] One prospective register-based cohort study of the association between CUD and all-cause mortality among adults with severe mental illness (ie, schizophrenia, bipolar disorder, and depression) reported that CUD was associated with all-cause mortality and unintentional death in individuals with schizophrenia but not for individuals with bipolar disorder or depression.[38]

It is unclear how cannabis use is associated with all-cause mortality. The observed heightened risk of unintentional overdoses could be associated with the misuse of substances other than cannabis (eg, opioids, cocaine, or amphetamines). Cannabis use may be associated with greater impulsivity, increased risk-taking behaviors, and impaired judgment, and may increase vulnerability to development of manic symptoms,[39] as well as decreased likelihood of help seeking. The increased risk of self-harm in those with CUD might be associated with negative associations of cannabis with mood and increased severity of depression and/or anxiety,[40-43] an impulsive response to a stressful event,[44] and/or emergence of psychotic symptoms.[45] For example, a meta-analysis of 14 studies and more than 76 000 adolescent or adult participants showed that cannabis users had a moderate increase in risk for developing depression (OR, 1.17; 95% CI, 1.05-1.30) and that heavy users were at even greater risk (OR, 1.62; 95% CI, 1.21-2.16) compared with light users or nonusers.[41] A subsequent meta-analysis of 11 studies examining more than 23 000 adolescents indicated that those who use cannabis are at significantly increased risk for depression (OR, 1.37; 95% CI, 1.16-1.62), suicidal ideation (OR, 1.50; 95% CI, 1.11-2.03), and suicide attempt (OR, 3.46; 95% CI, 1.53-7.84) in young adulthood.[9] Cannabis may also interfere with the course of treatment for those with mood disorders and may affect adherence to medication treatment and psychotherapy.[46,47]

Limitations and Strengths

Several limitations of this study should be considered. First, substance use disorders, including CUD, are underdiagnosed,[48] which would likely result in underestimation of associations. Cannabis use disorder is also inconsistently reported; that is, individuals who see more clinicians may be more likely to receive the diagnosis. Second, death records may misclassify suicide deaths as unintentional or undetermined deaths, leading to underreporting of suicide and underestimation of associations from this sample.[49] Third, because the data are from a single state Medicaid population, study findings may not be generalizable to other states or non-Medicaid populations, although there is no reason to believe that these results would not be typical, as Ohio is a microcosm of the US as a whole in terms of its geographical and demographic characteristics. Fourth, because the data are observational, it is not possible to infer causality. Fifth, although we controlled for a wide range of potential confounders, it is impossible to exclude confounding owing to unmeasured factors. For example, we were unable to control for other potentially relevant factors (eg, trauma history or chaotic home life) that are often associated with mortality. Sixth, some outcomes occurred infrequently, which reduced power to detect a difference between participants with and without CUD. Seventh, diagnostic classification of mood disorders is based on clinical diagnoses, not standardized diagnostic procedures.

However, there are several strengths of this study. First, we examined a large population-based sample of youths and young adults with mood disorders. Second, we reported on specific reasons for death, including some not examined previously in cohort studies. Third, we controlled for multiple potentially confounding variables, including demographics, psychiatric and medical comorbidities, prior history of self-harm, and prior treatment history. Fourth, we conducted a longitudinal analysis of mortality risk. Fifth, we measured the association of CUD with outcomes. The few existing cohort studies concern relatively infrequent users of cannabis, for whom potential damaging effects are less likely to be detected.[7]

Conclusions

Mood disorders in youths and young adults are associated with increased risk of self-harm and mortality, including suicide. Comorbid CUD and mood disorders are associated with an even higher risk of self-harm and death in already vulnerable youths with mood disorders. All-cause deaths, unintentional overdose deaths, and homicide are more common among youths and young adults with comorbid CUD and mood disorders, even after controlling for many other relevant risk factors. Although this observational study calls attention to these associations, it is unable to contribute to our understanding of causality or mechanism. Youths with mood disorders of greater severity and intractability might be more inclined to use cannabis than youths with less severe mood disorders, and cannabis use can also exacerbate symptoms of mood disorders and interfere with the successful treatment of youths already with depression or bipolar disorder. Risk reduction via decreasing rates of CUD nevertheless appears to be a reasonable strategy to pursue. Family-based models and individual approaches such as cognitive behavioral therapy both alone and with motivational enhancement therapy have been shown to be efficacious for treatment of children and adolescents with substance use disorder, including CUD.[50] In light of legislative action across the US to permit both recreational marijuana use and medical marijuana use, which have been shown to increase rates of CUD, information about the known risks, including mortality, and benefits associated with cannabis should be readily available to youths and young adults, their parents, health care professionals, and legislators. A national study examining the mortality risk for youths and young adults with comorbid mood disorders and CUD could further inform policy and treatment trials.

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REFERENCES

1. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1575-1586. doi:10.1016/S0140-6736(13)61611-6

2. Hayatbakhsh MR, Najman JM, Jamrozik K, Mamun AA, Alati R, Bor W. Cannabis and anxiety and depression in young adults: a large prospective study. *J Am Acad Child Adolesc Psychiatry*. 2007;46(3):408-417. doi:10.1097/chi.0b013e31802dc54d

3. Mojtabai R, Olfson M, Han B. National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics*. 2016;138(6):e20161878. doi:10.1542/peds.2016-1878

4. Gukasyan N, Strain EC. Relationship between cannabis use frequency and major depressive disorder in adolescents: findings from the National Survey on Drug Use and Health 2012-2017. *Drug Alcohol Depend*. 2020;208:107867. doi:10.1016/j.drugalcdep.2020.107867

5. Bahorik AL, Leibowitz A, Sterling SA, Travis A, Weisner C, Satre DD. Patterns of marijuana use among psychiatry patients with depression and its impact on recovery. *J Affect Disord*. 2017;213:168-171. doi:10.1016/j.jad.2017.02.016

6. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. National Academies Press; 2017. doi:10.17226/24625

7. Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug Alcohol Rev*. 2010;29(3):318-330. doi:10.1111/j.1465-3362.2009.00149.x

8. Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. *J Affect Disord*. 2016;195:63-74. doi:10.1016/j.jad.2016.02.007

9. Gobbi G, Atkin T, Zytynski T, et al. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. *JAMA Psychiatry*. 2019;76(4):426-434. doi:10.1001/jamapsychiatry.2018.4500

10. Lynskey MT, Glowinski AL, Todorov AA, et al. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Arch Gen Psychiatry*. 2004;61(10):1026-1032. doi:10.1001/archpsyc.61.10.1026

11. Pedersen W. Does cannabis use lead to depression and suicidal behaviours? a population-based longitudinal study. *Acta Psychiatr Scand*. 2008;118(5):395-403. doi:10.1111/j.1600-0447.2008.01259.x

12. Andréasson S, Allebeck P. Cannabis and mortality among young men: a longitudinal study of Swedish conscripts. *Scand J Soc Med*. 1990;18(1):9-15. doi:10.1177/140349489001800102

13. Palacio C, García J, Diago J, et al. Identification of suicide risk factors in Medellín, Colombia: a case-control study of psychological autopsy in a developing country. *Arch Suicide Res*. 2007;11(3):297-308. doi:10.1080/13811110600894223

14. Kung H-C, Pearson JL, Wei R. Substance use, firearm availability, depressive symptoms, and mental health service utilization among white and African American suicide decedents aged 15 to 64 years. *Ann Epidemiol*. 2005;15(8):614-621. doi:10.1016/j.annepidem.2004.09.011

15. Kung H-C, Pearson JL, Liu X. Risk factors for male and female suicide decedents ages 15-64 in the United States: results from the 1993 National Mortality Followback Survey. *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(8):419-426. doi:10.1007/s00127-003-0656-x

16. Arendt M, Munk-Jørgensen P, Sher L, Jensen SOW. Mortality following treatment for cannabis use disorders: predictors and causes. *J Subst Abuse Treat*. 2013;44(4):400-406. doi:10.1016/j.jsat.2012.09.007

17. Goldstein TR. Suicidality in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am*. 2009;18(2):339-352, viii. doi:10.1016/j.chc.2008.11.005

18. Koroukian SM. Linking the Ohio Cancer Incidence Surveillance System with Medicare, Medicaid, and clinical data from home health care and long term care assessment instruments: paving the way for new research endeavors in geriatric oncology. *J Registry Manag*. 2008;35(4):156-165.

19. Fontanella CA, Warner LA, Hiance-Steelesmith DL, et al. Service use in the month and year prior to suicide among adults enrolled in Ohio Medicaid. *Psychiatr Serv*. 2017;68(7):674-680. doi:10.1176/appi.ps.201600206

20. Silber JH, Gleeson SP, Zhao H. The influence of chronic disease on resource utilization in common acute pediatric conditions: financial concerns for children's hospitals. *Arch Pediatr Adolesc Med*. 1999;153(2):169-179. doi:10.1001/archpedi.153.2.169

21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology*. 2007;18(6):800-804. doi:10.1097/EDE.0b013e3181577654

22. Robins J. Marginal structural models. 1997 Proceedings of the American Statistical Association, Section on bayesian statistical science. Published 1998. Accessed May 7, 2020. https://cdn1.sph.harvard.edu/wp-content/uploads/sites/343/2013/03/msm-web.pdf

23. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164

24. R Core Team. R: the R project for statistical computing. R Foundation for Statistical Computing. 2020. Accessed May 7, 2020. https://www.r-project.org/

25. van der Wal WM, Geskus RB. ipw: an R package for inverse probability weighting. *J Stat Softw*. 2011;43(1):1-23.

26. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: results from the 2016 national survey on drug use and health. Published September 7, 2017. Accessed April 2, 2020. https://www.samhsa.gov/data/report/key-substance-use-and-mental-health-indicators-united-states-results-2016-national-survey

27. Cerdá M, Mauro C, Hamilton A, et al. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry*. 2020;77(2):165-171. doi:10.1001/jamapsychiatry.2019.3254

28. Wall MM, Poh E, Cerdá M, Keyes KM, Galea S, Hasin DS. Adolescent marijuana use from 2002 to 2008: higher in states with medical marijuana laws, cause still unclear. *Ann Epidemiol*. 2011;21(9):714-716. doi:10.1016/j.annepidem.2011.06.001

29. Beautrais AL, Joyce PR, Mulder RT. Cannabis abuse and serious suicide attempts. *Addiction*. 1999;94(8):1155-1164. doi:10.1046/j.1360-0443.1999.94811555.x

30. Chabrol H, Chauchard E, Girabet J. Cannabis use and suicidal behaviours in high-school students. *Addict Behav*. 2008;33(1):152-155. doi:10.1016/j.addbeh.2007.04.029

31. Huas C, Hassler C, Choquet M. Has occasional cannabis use among adolescents also to be considered as a risk marker? *Eur J Public Health*. 2008;18(6):626-629. doi:10.1093/eurpub/ckn065

32. Price C, Hemmingsson T, Lewis G, Zammit S, Allebeck P. Cannabis and suicide: longitudinal study. *Br J Psychiatry*. 2009;195(6):492-497. doi:10.1192/bjp.bp.109.065227

33. Darke S, Duflou J. Toxicology and circumstances of death of homicide victims in New South Wales, Australia 1996-2005. *J Forensic Sci*. 2008;53(2):447-451. doi:10.1111/j.1556-4029.2008.00679.x

34. Eksborg S, Rajs J. Causes and manners of death among users of heroin, methadone, amphetamine, and cannabis in relation to postmortem chemical tests for illegal drugs. *Subst Use Misuse*. 2008;43(10):1326-1339. doi:10.1080/10826080801922124

35. Gerberich SG, Sidney S, Braun BL, Tekawa IS, Tolan KK, Quesenberry CP. Marijuana use and injury events resulting in hospitalization. *Ann Epidemiol*. 2003;13(4):230-237. doi:10.1016/S1047-2797(02)00411-8

36. Laumon B, Gadegbeku B, Martin J-L, Biecheler M-B; SAM Group. Cannabis intoxication and fatal road crashes in France: population based case-control study. *BMJ*. 2005;331(7529):1371. doi:10.1136/bmj.38648.617986.1F

37. Macdonald S, Anglin-Bodrug K, Mann RE, et al. Injury risk associated with cannabis and cocaine use. *Drug Alcohol Depend*. 2003;72(2):99-115. doi:10.1016/S0376-8716(03)00202-3

38. 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

39. 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

40. Degenhardt L, Hall W, Lynskey M. Exploring the association between cannabis use and depression. *Addiction*. 2003;98(11):1493-1504. doi:10.1046/j.1360-0443.2003.00437.x

41. 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

42. Botsford SL, Yang S, George TP. Cannabis and cannabinoids in mood and anxiety disorders: impact on illness onset and course, and assessment of therapeutic potential. *Am J Addict*. 2020;29(1):9-26. doi:10.1111/ajad.12963

43. Lowe DJE, Sasiadek JD, Coles AS, George TP. Cannabis and mental illness: a review. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(1):107-120. doi:10.1007/s00406-018-0970-7

44. Wrege J, Schmidt A, Walter A, et al. Effects of cannabis on impulsivity: a systematic review of neuroimaging findings. *Curr Pharm Des*. 2014;20(13):2126-2137. doi:10.2174/13816128113199990428

45. Sideli L, Quigley H, La Cascia C, Murray RM. Cannabis use and the risk for psychosis and affective disorders. *J Dual Diagn*. 2020;16(1):22-42. doi:10.1080/15504263.2019.1674991

46. Grella CE, Hser YI, Joshi V, Rounds-Bryant J. Drug treatment outcomes for adolescents with comorbid mental and substance use disorders. *J Nerv Ment Dis*. 2001;189(6):384-392. doi:10.1097/00005053-200106000-00006

47. Wise BK, Cuffe SP, Fischer T. Dual diagnosis and successful participation of adolescents in substance abuse treatment. *J Subst Abuse Treat*. 2001;21(3):161-165. doi:10.1016/S0740-5472(01)00193-3

48. Hansen SS, Munk-Jørgensen P, Guldbaek B, et al. Psychoactive substance use diagnoses among psychiatric in-patients. *Acta Psychiatr Scand*. 2000;102(6):432-438. doi:10.1034/j.1600-0447.2000.102006432.x

49. Mohler B, Earls F. Trends in adolescent suicide: misclassification bias? *Am J Public Health*. 2001;91(1):150-153. doi:10.2105/AJPH.91.1.150

50. Bukstein OG, Bernet W, Arnold V, et al; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with substance use disorders. *J Am Acad Child Adolesc Psychiatry*. 2005;44(6):609-621. doi:10.1097/01.chi.0000159135.33706.37