Psychiatry Research 308 (2022) 114387

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Full-length article

Geographical variation in hospitalization for psychosis associated with cannabis use and cannabis legalization in the United States
Submit to: Psychiatry Research

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ARTICLE INFO

Keywords:
Cannabis
Marijuana
Legalization
Psychosis
Schizophrenia

ABSTRACT

The 2017 National Inpatient Sample database was utilized to investigate the association between cannabis legalization in the United States and hospitalizations for psychosis associated with cannabis use. We compared the odds of hospital discharges for psychosis associated with cannabis use in adults between the Pacific census division (where most states legalized recreational cannabis use) and other divisions using multivariable logistic regression, adjusting for confounders. We calculated a score for each census division representing cannabis legality as the population-weighted sum of state scores: 1=illegal or cannabidiol/low potency cannabis; 2=medical marijuana; and 3=recreational and medical marijuana legalized. Pearson's correlation coefficients (r) quantified the relationship between scores and the proportion of hospitalizations with psychosis associated with cannabis. In 2017, there were an estimated 129,070 hospital discharges for psychosis associated with cannabis use. The Pacific census division had significantly higher odds of discharges than other divisions (adjusted odds ratio 1.55; 95% confidence interval 1.25 – 1.93). There was a significant correlation between the cannabis legality score and proportion of hospital discharges for psychosis associated with cannabis use ($r = 0.67$, $p<0.05$). In conclusion, we observed a higher proportion of hospital discharges for psychosis associated with cannabis use in areas with more liberal cannabis legalization laws.

1. Introduction

Cannabis is the most prevalent illicit substance in the United States (Substance Abuse Center for Behavioral Health Statistics and Quality 2019). As more states are legalizing cannabis for recreational and/or medical purposes in the US, the prevalence of cannabis use has increased. Among persons aged 18 years or older, the prevalence of current users in the past month increased from 6.0% in 2002 to 9.9% in 2017 (Center for Behavioral Health Statistics and Quality, 2018). Approximately 20–30% of individuals who use cannabis meet criteria for a cannabis use disorder (Hasin, 2018). As of November 2020, thirty-six states and the District of Columbia (D.C.) legalized medical marijuana use, with fifteen states and D.C. also legalizing recreational use in adults 21 years and older (Marijuana Policy Project website, 2021). Prior studies found increased marijuana use and cannabis use disorders among adults residing in states that have implemented medical and recreational marijuana laws compared to states without legalization (Cerdá et al., 2020; Hasin et al., 2017). Benefits of cannabis include improvement of chronic non-cancer pain and pain associated with cancer, multiple sclerosis, arthritis and human immunodeficiency virus (HIV)-associated neuropathy (Claflin et al., 2018; Johal et al., 2020; Phillips et al., 2010; Zajicek et al., 2012). Although the evidence for the use of medical cannabis is growing (Haffajee, 2021; Hesketh et al., 2017; Zajicek et al., 2012), so is the concern for the association

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https://doi.org/10.1016/j.psychres.2022.114387
Received 17 September 2021; Accepted 2 January 2022
Available online 4 January 2022

between cannabis use and psychotic disorders (Andréasson et al., 1987; Henquet et al., 2005; van Os, 2002). There is currently a paucity of research on the impact of cannabis legalization on the risk of psychosis.

Psychotic disorders typically start in adolescence or young adulthood, with a substantial proportion of patients having difficulty completing education, maintaining employment and living independently as well as an increased risk of suicide and homelessness (Chong et al., 2009; Folsom et al., 2005; Marwaha and Johnson, 2004; Palmer et al., 2005; Ramsay et al., 2012). Increased cannabis use could lead to a higher rate of hospitalizations for psychosis by increasing the risk of developing an initial episode of psychosis, precipitating acute toxic reactions with psychotic symptoms, or increasing the likelihood of hospitalization for those with pre-existing psychotic disorders. There is nearly a four-fold risk increase in risk of developing schizophrenia or other psychotic disorders among heavy users of cannabis compared to non-users (Marconi et al., 2016). Daily use and higher potency cannabis with greater levels of tetrahydrocannabinol (THC) confers the highest risk of developing a psychotic disorder (Di Forti et al., 2009). Randomized controlled studies reveal that acute administration of THC in healthy individuals is associated with induction of psychotic symptoms (D'Souza et al., 2004). Finally, existing research shows that patients with schizophrenia who use cannabis are more likely to experience relapses requiring hospitalization (van Dijk et al., 2012).

We conducted a cross-sectional nationwide study to examine the association between geographical variation in hospitalizations for psychosis associated with cannabis use and cannabis legalization policies in 2017. We hypothesized that census divisions with more liberal cannabis legalization policies would have a greater rate of hospitalizations for psychosis with cannabis use. If our hypothesis is confirmed, this initial study will justify the need for follow-up studies using longitudinal state-level data to examine impact of state policies on trends in psychosis associated with cannabis use.

2. Methods

2.1. Data source and study population

This cross-sectional study used hospital discharge data from the 2017 National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (Agency for Healthcare Research and Quality, 2017). The NIS utilizes a complex sampling design that samples 20% of hospital discharges from state hospital discharge databases in 47 states and D.C. Hospital discharges are stratified by census division, hospital location (urban or rural), teaching status, ownership and bed size. The complex sampling design allows for national estimates, as the sampling frame covers 96% of hospital discharges and more than 97% of the U.S. population. Billing data submitted by hospitals provide International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes for each hospitalization. The study population includes hospital discharges for adults between the ages of 18 and 64 years. This research is exempt from Institutional Review Board approval as it is minimal risk and limited to use of previously collected de-identified information.

2.2. Exposure

The NIS provides geographical data on census divisions but lacks information on individual states. The United States is composed of nine census divisions defined by the U.S. Census Bureau: New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific (Fig. 1A). Exposure was categorized as hospital discharges in the Pacific census division compared to the reference group of all other census divisions. The Pacific census division was the only division where most states legalized recreational and marijuana use by 2017 (Fig. 1B). The Pacific division is comprised of five states including four states that have legalized recreational use in adults 21 years and older as well as medical marijuana use (California, Oregon, Washington and Alaska) and one state (Hawaii) that has legalized medical marijuana only.

2.3. Cannabis legalization

The status of implementation of cannabis legalization in each state by 2017 was determined by review of the National Conferences of State Legislature website on medical marijuana laws, individual state statutes and the Marijuana Policy Project's state information websites (Marijuana Policy Project, 2021; National Conference of State Legislatures, 2021). We categorized each state based on implementation of legalization into three groups: 1) cannabis was illegal or medical cannabis programs restricted to cannabidiol (CBD)/low potency cannabis, 2) standard medical marijuana legalized (no potency restrictions), and 3) recreational and marijuana use was legalized. States where laws allowed personal cultivation were considered to have implemented cannabis legalization. For states restricting access to dispensaries, if dispensaries were open by 2017, they were considered to have implemented cannabis legalization. We grouped states that only legalized CBD/low potency cannabis with illegal states as these states generally restricted access to a small group of patients with refractory seizure disorders that failed conventional therapies. Cannabis legalization status established by this methodology is consistent with prior publications on medical and recreational cannabis legalization covering 2017 time period (Borodovsky et al., 2017; Shi and Liang, 2020). A detailed table of 2017 legalization status for each state can be found in Supplementary Table 1.

2.4. Outcome

The outcome of interest was the proportion of hospitalizations for psychosis associated with cannabis use out of all hospital discharges in individuals aged 18 to 64 years. We defined psychosis associated with cannabis use with ICD-10-CM diagnosis codes for cannabis-induced

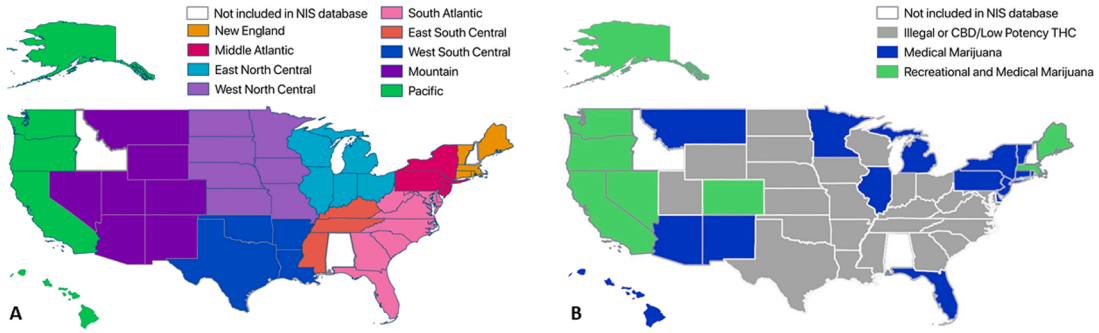

Fig. 1. A. Nine hospital census divisions represented in the National Inpatient Sample (NIS). B. Status of implementation of cannabis legalization laws in the United States in 2017 by state: illegal or cannabidiol (CBD)/low potency cannabis; standard medical marijuana, recreational and medical marijuana.

psychotic disorder (F12.15x, F12.25x, F12.95x) OR a combination of cannabis use disorder/poisoning (F12.x, T40.7x) and psychosis. Psychosis was defined as unspecified psychosis (F28, F29), brief psychotic disorder (F23), delusional disorder (F22), schizophrenia spectrum disorders (F20), schizoaffective disorder (F25), hallucinations (R44.0–3) and major depressive disorder or bipolar disorder with psychotic features (F32.3, F33.3, F30.2, F31.2, F31.5, F31.64).

2.5. Potential confounders

Covariates included age, sex, race, and hospital location (rural, urban non-teaching or urban teaching), socioeconomic status (income quartile based on median household income for patient's ZIP code) derived from NIS variables. We included binary variables denoting presence or absence of disorders based on ICD-10-CM codes for substance use and psychiatric disorders: alcohol use disorder, other substance use disorder, nicotine use disorder, depression or anxiety, post-traumatic stress disorder (PTSD) and other psychiatric illness. We also included covariates for illnesses consistently identified in medical marijuana laws as debilitating conditions that are prerequisites for treatment: arthritis, cancer, HIV or acquired immunodeficiency syndrome (AIDS), multiple sclerosis, Parkinson's disease, epilepsy, cachexia, nausea/vomiting, inflammatory bowel disorders (Crohn's disease or ulcerative colitis) and chronic pain. ICD-10-CM codes used to define these covariates can be found in Supplementary Table 2.

2.6. Statistical analysis

Survey techniques were used for all analyses to account for the complex survey design. Sampling weights for discharges were provided by the NIS to obtain national estimates with unbiased standard errors. Analyses were performed with STATA version 15.1. Missing indicators were used to handle missing data from three variables: sex (0.01%), race (3.75%), and income quartile (1.89%).

2.6.1. Primary analysis

Demographic factors and characteristics of the hospital discharges from the Pacific and other census divisions were compared. For the primary analysis, odds ratios (OR) and 95% confidence intervals (CI) were computed using logistic regression to compare the odds of hospital discharges for psychosis associated with cannabis use in the Pacific versus other census divisions. Univariable and multivariable models that include covariates specified above were used to provide unadjusted and adjusted estimates, respectively.

2.6.2. Secondary analysis

For each census division, we calculated a Census Division Cannabis Legality Score as the population-weighted sum of state legality scores for each state within a division. State population and census division population for individuals age 18 – 64 years were obtained from U.S. Census data for 2017 (U.S. Census Bureau, 2017). Each state was assigned a cannabis legality score of 1 = illegal or CBD/low potency cannabis only, 2 = standard medical marijuana (no potency restrictions) and 3 = recreational and medical use. The Census Division Cannabis Legality Score was calculated as

$$\sum_{n=1}^{k}\left(\frac{\text{state population}}{\text{total population of census division}}\right)*\text{State legality score}$$

where k = number of states within a census division. The possible range of values for the Census Division Cannabis Legality Score is 1 to 3, where 1 represents all states within a division have not implemented legalization of cannabis or are restricted to CBD/low potency cannabis, and 3 represents all states within a division have implemented legalization of recreational and medical cannabis use. Scores for each state and census division are provided in Supplementary Table 1. Pearson's correlation coefficients were calculated to estimate the relationship between the proportion of hospitalizations within each census division with diagnosis of psychosis associated with cannabis use (model adjusted) and the Census Division Cannabis Legality Score. This analysis is considered exploratory; due to the complex sampling design, the proportion of hospitalizations in a census division from a given state may not precisely reflect state's proportion of hospitalizations.

To validate the Census Division Cannabis Legality Score, we used state-wide estimates of cannabis measures obtained from the National Survey on Drug Use and Health (NSDUH) estimates for 2017–2018 (Substance Abuse and Mental Health Services Administration, 2019). For each census division, we used these estimates to calculate the proportion of adults in each census division reporting past month use of cannabis, initial cannabis use, and perception of great harm from past month use of cannabis (see Supplementary Material for details). Pearson correlation coefficients were performed to estimate relationship between the Census Division Cannabis Legality Score and each of these measures.

2.6.3. Subgroup analyses

Additional analyses included interaction terms for age and exposure (Pacific vs. other census divisions) and sex and exposure. Subgroup analyses were performed by age and sex. We divided age into categories by decade with additional division of younger patients into 18 – 20 and 21 – 29 years of age as recreational marijuana legalization is limited to adults 21 years and older.

2.6.4. Sensitivity analyses

Modified Exposure/Outcome Definitions: As a sensitivity analysis, we defined the exposure as a categorical variable with each census division compared to the reference East South Central division, where all states only legalized CBD or low potency cannabis with limited THC content limited to patients with refractory seizures. Univariable and multivariable logistic regression models using the pre-specified covariates were used to estimate odds ratios comparing the odds of risk of psychosis associated with cannabis use for each census divisions compared to the reference East South Central division.

As prior literature demonstrates a relationship between cannabis use and development of non-affective psychotic disorders (Løberg et al., 2014), we repeated the primary analysis excluding diagnoses for affective psychosis or hallucinations from the outcome definition (i.e., excluded F32.3, F33.3, F30.2, F31.2, F31.5, F31.64, R44.0–3). In addition, cannabis use may be inconsistently coded when individuals are hospitalized for psychosis. We compared the odds of psychosis and non-affective psychosis between the Pacific versus other census divisions overall, regardless of whether a cannabis use disorder/poisoning diagnosis was present.

3. Results

3.1. Study population

The sample included 25,814 discharges for psychosis associated with cannabis use, yielding a national estimate of 129,070 hospital discharges for psychosis associated with cannabis use in the year 2017 alone. Demographic and clinical characteristics associated with hospital discharges in the Pacific and other census divisions are presented in Table 1. There were 479,071 hospital discharges (13.9%) within the Pacific census division, compared to 2979,171 in other census divisions. Age distribution and gender were comparable between the two groups. Rates of alcohol use disorder were similar at 7.9% and 8.3% in the Pacific and other census divisions, respectively. Hospital discharges from the Pacific census division were more likely to occur in an urban location, involve patients of Hispanic or Asian/Pacific Islander race and of higher income quartile, were less likely to involve patients of Black race and more commonly had diagnosis codes for smoking or depression/

Table 1
Baseline characteristics of hospital discharges by census division.

	Pacific Census Division*N* = 479,071	Other Census Divisions*N* = 2979,171
Age, n (%)		
18 – 20 years	16,031 (3.4)	102,232 (3.4)
21 – 29 years	90,194 (18.8)	540,128 (18.1)
30 – 39 years	111,962 (23.3)	604,979 (20.3)
40 – 49 years	73,964 (15.4)	477,670 (16.0)
50 – 59 years	115,634 (24.1)	778,788 (26.1)
60 – 64 years	71,286 (14.9)	475,374 (16.0)
Female sex, n (%)	293,599 (61.3)	1795,345 (60.3)
Race, n (%)		
White	221,464 (46.2)	1764,239 (59.2)
Black	44,045 (9.2)	586,004 (19.7)
Hispanic	139,579 (29.1)	327,467 (11.0)
Asian/Pacific Islander	45,339 (9.5)	55,605 (1.9)
Other	20,870 (4.4)	124,087 (4.2)
Income level, n (%)		
0–25th percentile	95,934 (20.0)	1017,201 (34.1)
26–50th percentile	110,583 (23.1)	782,419 (26.3)
51–75th percentile	128,247 (26.8)	642,765 (21.6)
76–100th percentile	124,952 (26.1)	490,647 (16.5)
Location of hospital, n (%)		
Rural	14,398 (3.0)	268,578 (9.0)
Urban (non-teaching)	144,580 (30.2)	607,256 (20.4)
Urban (teaching)	320,093 (66.8)	2103,337 (70.6)
Alcohol use disorder, n (%)	37,735 (7.9)	247,929 (8.3)
Other substance use disorder, n (%)	44,928 (9.4)	234,912 (7.9)
Smoking, n (%)	76,397 (16.0)	686,336 (23.0)
Depression/Anxiety, n (%)	84,954 (17.7)	704,686 (23.7)
PTSD, n (%)	10,835 (2.3)	90,279 (3.0)
Other psychiatric disorder, n (%)	2570 (0.5)	18,737 (0.6)
Debilitating conditions required for medical cannabis use		
Arthritis, n (%)	28,935 (6.0)	231,609 (7.8)
Cancer, n (%)	23,707 (5.0)	146,841 (4.9)
HIV/AIDS, n (%)	2709 (0.6)	19,808 (0.7)
Multiple sclerosis, n (%)	2164 (0.5)	18,973 (0.6)
Parkinson's Disease, n (%)	1076 (0.2)	6658 (0.2)
Epilepsy, n (%)	17,820 (3.7)	125,476 (4.2)
Nausea and vomiting, n (%)	9194 (1.9)	66,581 (2.2)
Cachexia, n (%)	2840 (0.6)	17,001 (0.6)
Glaucoma, n (%)	2134 (0.5)	14,788 (0.5)
Inflammatory bowel disease, n (%)	4865 (1.0)	38,381 (1.3)
Chronic pain, n (%)	37,417 (7.8)	237,036 (8.0)

PTSD = post-traumatic stress disorder. n is the study sample size with weighted %.

anxiety. Rates for conditions for which medical cannabis is indicated including arthritis, cancer, HIV/AIDS, multiple sclerosis, and nausea/vomiting were largely comparable between the Pacific and other census divisions.

3.2. Primary analysis

Hospitalizations for psychosis associated with cannabis use were more likely to occur in the Pacific division than other census divisions with an unadjusted OR of 1.32 (95% CI 1.01 – 1.72) and adjusted OR of 1.55 (95% CI 1.25 – 1.93), after adjusting for demographics, hospital characteristics and presence of other disorders (Table 2).

3.3. Census division cannabis legality score

The division with the highest Census Division Cannabis Legality Score was the Pacific division (2.97) while the divisions with the lowest scores were East South Central and West South Central (1.00) (Supplementary Table 1). We found a significant correlation between the proportion of hospitalizations for psychosis associated with cannabis use and the Census Division Cannabis Legality Score (Fig. 2; $r = 0.67$, $p<0.05$).

There were significant positive correlations between the Census Division Cannabis Legality Score and NSDUH estimates of the proportion of individuals with past month cannabis use ($r = 0.90$, $p = 0.0008$) and initial use of cannabis ($r = 0.80$, $p = 0.01$) (Supplementary Figure 1). We also observed a trend between the Census Division Cannabis Legality Score and perception of great harm from past month use of cannabis ($r=-0.61$, $p = 0.08$), where divisions with more liberal cannabis legalization had a lower perception of harm. These findings from NSDUH estimates support the validity of the Census Division Cannabis Legality Score.

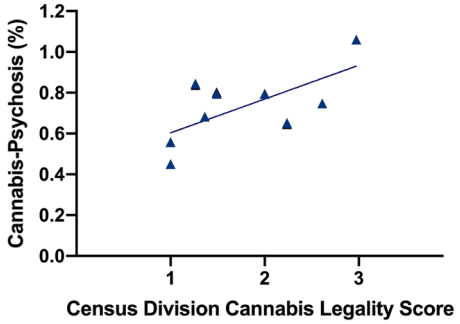

Fig. 2. Correlation between percentage of hospitalizations with diagnosis of psychosis associated with cannabis use (adjusted for covariates) in each census division and Census Division Cannabis Legality Score ($r = 0.67$, $p<0.05$). The Census Division Cannabis Legality Score was calculated as sum of state legality scores weighted by proportion of state population in census division. State legality scores were defined as: 1 = illegal or cannabidiol/low potency cannabis, 2 = standard medical marijuana and 3 = recreational and medical marijuana. Census Division Cannabis Legality Scores ranged from 1 – 3.

Table 2
Psychosis Associated with Cannabis Use and Pacific vs. Other Census Divisions in the 2017 National (Nationwide) Inpatient Sample.

	Study Sample		National Estimates			
	Pacific Census Division*N* = 479,071	Other Census Divisions*N* = 2979,171	Pacific Census Division*N* = 2395,348	Other Census Divisions*N* = 14,895,853	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Psychosis associated with Cannabis Use Hospitalizations, n (%)	4502 (0.94)	21,312 (0.72)	22,510 (0.94)	106,560 (0.72)	1.32 (1.01, 1.72)	1.55 (1.25, 1.93)
Other Hospitalizations (Not psychosis associated with cannabis use), n (%)	474,569 (99.1)	2957,859 (99.3)	2372,838 (99.1)	14,789,293 (99.3)	–	–

OR = odds ratio, CI = confidence interval. *Adjusted for age, sex, race, income quartile, hospital location, alcohol use disorders, other substance use disorders, smoking, depression/anxiety, post-traumatic stress disorder, other psychiatric disorders, arthritis, cancer, HIV/AIDS, multiple sclerosis, Parkinson's disease, epilepsy, nausea/vomiting, cachexia, glaucoma, inflammatory bowel disease and chronic pain. Survey methods were used to derive weighted percentages and standard errors.

3.4. Subgroup analyses

We identified a significant interaction between age and exposure (Pacific vs. other census divisions; $p = 0.02$). Subgroup analyses by age category are presented in Supplementary Table 3 and indicated a greater association between census division and psychosis associated with cannabis use as age increased. Interestingly, hospital discharges from the Pacific census division had a significantly greater odds of having diagnosis of psychosis in all age groups except for age 18 – 20 years (OR 1.22, 95% CI 0.98 – 1.53). There was no significant interaction between exposure and sex ($p = 0.47$) with similar adjusted OR for females and males (OR 1.60, 95% CI 1.27 – 2.02 for females; OR 1.52, 95% CI 1.22 – 1.89 for males).

3.5. Sensitivity analyses

Hospitalizations for psychosis associated with cannabis use were significantly more likely to occur in all census divisions compared to East South Central, with the notable exception of West South Central (Table 3). Of note, East and West South Central are the only two census divisions where all states had not implemented legalization of medical or recreational cannabis or restricted medical use to CBD/low potency cannabis.

Hospitalizations for non-affective psychosis associated with cannabis use were also more likely to occur in the Pacific division than other census divisions with an unadjusted OR of 1.47 (95% CI 1.10 – 1.97) and adjusted OR of 1.75 (95% CI 1.38 – 2.22). Hospitalizations for psychosis and non-affective psychosis, regardless of whether cannabis use diagnosis was present, were also more likely to occur in the Pacific division compared to other census divisions [psychosis overall: adjusted OR 1.32 (95% CI 1.12 – 1.57); non-affective psychosis: adjusted OR 1.45 (95% CI 1.21 – 1.73)].

4. Discussion

This nationwide study identified a greater proportion of hospital discharges for psychosis associated with cannabis use in the Pacific census division, the area with the most liberal cannabis legalization policies in the United States. We found a significant correlation between the proportion of hospitalizations for psychosis associated with cannabis use within each division and the Census Division Cannabis Legality Score, a novel score that we developed and validated to represent the status of cannabis legalization within each census division, suggesting that areas that implemented more liberal cannabis legalization policies were more likely to have a greater proportion of discharges for psychosis associated with cannabis use. Consistent with our hypothesis, each census division had a greater proportion of hospitalizations for psychosis associated with cannabis use compared to the East South Central division, the region with the most restrictive laws, except for the West South Central division. The West South Central division was the only other census division where all states only legalized CBD/low potency cannabis use or cannabis use was fully illegal.

Table 3
Psychosis Associated with Cannabis Use and Census Division vs. East South Central in the 2017 National Inpatient Sample.

Census Division	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Pacific	2.03 (1.33, 3.10)	2.46 (1.75, 2.09)
New England	1.55 (1.06, 2.27)	1.70 (1.24, 2.32)
Mid-Atlantic	1.86 (1.30, 2.66)	1.81 (1.35, 2.44)
East North Central	1.78 (1.24, 2.58)	1.83 (1.36, 2.47)
West North Central	1.92 (1.32, 2.80)	1.92 (1.42, 2.58)
South Atlantic	1.62 (1.13, 2.33)	1.54 (1.15, 2.07)
Mountain	1.28 (0.83, 1.98)	1.45 (1.01, 2.09)
West South Central	0.98 (0.67, 1.45)	1.25 (0.91, 1.71)
East South Central	–	–

OR = odds ratio, CI = confidence interval. *Adjusted for age, sex, race, income quartile, hospital location, alcohol use disorders, other substance use disorders, smoking, depression/anxiety, post-traumatic stress disorder, other psychiatric disorders, arthritis, cancer, HIV/AIDS, multiple sclerosis, Parkinson's disease, epilepsy, nausea/vomiting, cachexia, glaucoma, inflammatory bowel disease and chronic pain.

Our findings are consistent with studies identifying an increase in cannabis use and cannabis use disorders in states that have legalized medical and/or recreational marijuana (Cerdá et al., 2020; Haffajee, 2021; Hasin et al., 2017), as well as studies finding an increased risk of poisoning following commercialization of recreational cannabis use and increased hospitalizations associated with cannabis legalization (Davis et al., 2016; Shi and Liang, 2020). However, this is the first study to specifically examine the association between cannabis legalization and hospital discharges for psychosis associated with cannabis use. Increased hospitalizations for psychosis in areas experiencing an increase in cannabis use or cannabis use disorders associated with legalization could be due to multiple reasons. First, multiple cohort studies have found that individuals who are daily users of cannabis have an increased risk of psychosis and schizophrenia (Andréasson et al., 1987; Henquet et al., 2005; van Os, 2002). A case control study identified an increased risk of heavy cannabis use in those with first episode psychosis, with a greater association in those who used cannabis with high levels of THC (Di Forti et al., 2009). In a study of European cities, the incidence of psychosis in various cities was correlated with local prevalence of daily cannabis use and high potency cannabis use (Di Forti et al., 2019). Secondly, patients without pre-existing history of psychosis may experience an acute self-limited toxic reaction to cannabis with psychotic symptoms, consistent with studies showing that acute administration of THC in healthy individuals leads to an increase in psychotic-like symptoms (D'Souza et al., 2004). Finally, patients with pre-existing psychotic disorders such as schizophrenia have been shown to be more likely to experience a relapse requiring hospitalization if they are using cannabis (van Dijk et al., 2012). By studying hospitalizations, this study focuses on serious cases of psychosis with diagnosis codes that link psychosis to cannabis use.

Multiple studies have consistently shown that legalization of medical marijuana and recreational marijuana are associated with an increase in cannabis use and cannabis use disorders in adults (Cerdá et al., 2020; Haffajee, 2021; Hasin et al., 2017), but not adolescents (Sarvet et al., 2018). In our study, the proportion of hospitalization discharges for psychosis associated with cannabis use was significantly higher in the Pacific Division than other census divisions in all age groups except for those 18 – 20 years of age. Since legalization of recreational use is limited to adults 21 years and older, this finding is suggestive of a possible association between hospitalizations for psychosis and recreational legalization more so than medical marijuana legalization. A previous study of the impact of recreational legalization on cannabis use did not find any changes in cannabis use or use disorders in adults 18 – 25 years but did not divide this group of adults into those legally impacted (21 years and older) (Cerdá et al., 2020). This same study found no increase in use or frequent use in the past month in adolescents age 12–17 years after recreational legalization with a slight increase in cannabis use disorders, which the authors acknowledged may have been due to time-varying confounding. In contrast, in adults 26 years and older, legalization of recreational marijuana was associated with an increase in past month use, past-month frequent use, and cannabis use disorders. This constellation of findings suggest that recreational legalization increases cannabis use and adverse consequences of cannabis use in adults who are legally impacted by laws.

A strength of this study is the large sample size that facilitates detection of rare events. The complex sampling design allows for national estimates, with an estimated 129,070 hospitalizations for psychosis associated with cannabis use in the year 2017 alone. Our findings are strengthened by consistency of results from primary, secondary and sensitivity analyses even after adjusting for covariates reflecting demographic factors, hospital characteristics and presence of other

disorders associated with psychosis or cannabis use. We constructed a novel Census Division Cannabis Legality Score and found a significant correlation between these scores and the proportion of hospital discharges for psychosis associated with cannabis use within census divisions. This score was validated by correlations with NSDUH estimates of cannabis use measures. If confirmed, the finding of increased psychosis with cannabis legalization is an important consideration when weighing the risks and benefits of such policies, with appropriate education of the public of such risk and strengthening of support programs for psychosis associated with cannabis use when laws are enacted.

This study has several limitations including the cross-sectional design and restriction to one year of hospital data. The database of hospital discharges does not have subject-level data, such that a patient hospitalized more than once in 2017 will be represented as multiple hospital discharges. Diagnoses were limited to ICD-10-CM billing data, and hospital discharges for psychosis may have under-reporting of cannabis use or other medical comorbidities. NIS data has no information on the potency of cannabis used by patients, and strains of cannabis differ in terms of the quantity of THC and CBD (ElSohly et al., 2016). This study is also limited by the lack of state-specific data, as there is heterogeneity in state cannabis policies within census divisions. Any association between legalization policies and hospitalizations for psychosis associated with cannabis use may be due to other factors such as increased potency of cannabis over time (National Academies of Sciences, Engineering, and Medicine et al., 2017) or increases in perceived safety of cannabis (Compton et al., 2016; Pacek et al., 2015). It is possible that other unmeasured factors may be responsible for our findings; for example, California, the largest state in the Pacific census division, has a high rate of homelessness, with 1.9 times the national rate (The Council of Economic Advisers, 2019). Individuals who are homeless are disproportionately afflicted with substance use disorders and serious mental illnesses such as schizophrenia (Fischer and Breakey, 1991; Folsom and Jeste, 2002). Future studies employing a longitudinal design using state data to examine trends in psychosis over time associated with cannabis use and legalization are required.

In summary, this is the first cross-sectional population-based study of hospital discharges that revealed there is geographic variation in hospitalizations for psychosis associated with cannabis use that was associated with implementation of cannabis legalization policies. Given the rapid changes in legislative landscape, there is a need for further longitudinal research to better understand the nature of the relationship between cannabis legalization and the risk of psychosis.

5. CRediT author statement

All authors edited and approved the final manuscript.

6. Funding

This research was supported by grants from the National Institute of Mental Health (K23MH110564, R01MH122427 to Lauren Moran) and by the Laboratory for Early Psychosis (LEAP) center (P50 MH115846 to Dost Ongur and John Hsu; pilot grant to Lauren Moran).

CRediT authorship contribution statement

Lauren V. Moran: Conceptualization, Software, Data curation, Formal analysis, Writing – original draft. **Erica S. Tsang:** Conceptualization, Software, Data curation, Formal analysis, Writing – review & editing. **Dost Ongur:** Supervision, Writing – review & editing. **John Hsu:** Supervision, Writing – review & editing. **May Y. Choi:** Conceptualization, Software, Data curation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

All authors report no conflicts of interest.

Acknowledgments

The authors would like to thank Dr. Ellen McCarthy and Aaron Fleishman, MPH for input on study design and statistical analyses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114387.

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