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Adverse Cardiovascular Outcomes in Young Cannabis Users: A Nationwide Analysis

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Abstract: Background: With the growing trends in recreational marijuana use, our study aims at analyzing the association between acute coronary syndromes (ACS) and ventricular fibrillation (Vfib) and cannabis use disorder in young adults (18–45). **Methods**: Young adult hospitalizations (18–45 years) with documented ACS/ventricular fibrillation and documented cannabis use were identified from the National Inpatient Sample (2019). Primary outcomes included prevalence and odds of ACS/ventricular fibrillation with cannabis use disorder. Patient factors that held significant association with adverse cardiovascular events in young cannabis users were studied. Propensity scoring and neighbor matching were used to compare resource utilization and in-hospital outcomes in the study population. **Results**: Among young patients (18–45) admitted for ACS, documented cannabis use disorder (CUD) had a statistically significant association with an odds ratio of 2.29 (2.48–3.04) after adjusting for age, sex, race, household income, smoking, cocaine use, uncontrolled hypertension, diabetes and hyperlipidemia. Documented CUD had a significant association with ventricular fibrillation in the population with an odds ratio of 2.29 (1.51–3.49) after adjusting for the above-mentioned factors. Among admissions with documented CUD, patient factors that held significant association with admitting diagnosis of ACS/Vfib were: black race (OR: 1.73), uncontrolled hypertension (OR: 4.08) and diabetes (OR: 2.45). Propensity-matched cohorts with documented CUD and ACS had significantly higher mean length of hospital stay 3.28 (2.98–3.53) days when compared to the cohort without documented CUD, 2.69 (2.32–2.82) days. The mean of total hospital charges was higher in the cohort with documented CUD at $92,390.64 (92,240.31–92,445.76) compared to $90,886.44 (89,932.21–91,042.56) in the cohort without cannabis use disorder. **Conclusions**: Documented diagnosis of cannabis use disorder had statistically significant association with admission diagnosis of ACS/Vfib even after accounting for confounders. A documented race as black and co-existing diagnosis of uncontrolled hypertension and diabetes had a significant association with admission diagnosis of ACS in the population with documented cannabis use disorder. Propensity-matched cohorts with cannabis use disorder with the main admitting diagnosis of ACS/Vfib were associated with a higher mean length of hospital stay and a higher mean of total charges compared to the matched cohorts without documented cannabis use disorder.

Keywords: cannabis use disorder; ACS; ventricular fibrillation

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1. Introduction

Cannabis use has become widely prevalent throughout society, especially in younger adults, amidst recent decriminalization/legalization. Parekh et al. found a higher percentage of cannabis users to be less than <34 years of age [1], and a recent NIH Monitor the Future survey reported an all-time high of young adult marijuana users (age 18–30) in 2021 [2]. This alludes to higher tendencies toward recreational marijuana use in the young adult population.

Despite its growing prevalence, the physiological effects of cannabis use have not been well studied. Few preliminary studies have advocated for the therapeutic benefit

of cannabis for its analgesic and anti-inflammatory effects, reporting that in some experimental models of heart disease, cannabidiol downregulates oxidative stress, inflammatory processes and apoptosis [3]. While this may be reassuring, recent research describes the detrimental effects of cannabis use. Two separate studies, one using a national inpatient sample from 2007–2014 and the other from 2015–2017, demonstrated statistically significant trends in hypertensive emergency-related admissions in cannabis use disorder despite adjusting for comorbid conditions [4,5]. Cannabis use has also been associated with smoking, and the odds of cannabis users using cocaine have been significant [6]. Some studies even suggest a possible association between cannabis use and diabetes via endocannabinoid system modulation [7], and cannabis use and hyperlipidemia via cannabinoid inhibition of reverse cholesterol transport [8].

Despite these known trends, the available research includes few (cohort) studies that have focused on cannabis use and cardiovascular trends, specifically in the young adult population. A recent cross-sectional study showed an association between cannabis use and ACS admissions; however, this study utilized self-reported data looking at adults aged 18–74 [9]. One retrospective study demonstrated cannabis use associated with acute MI from a national inpatient sample from 2010–2014 looking at ages 11–70 [10].

Even fewer studies have looked at cannabis use and ventricular arrhythmias, with one isolated case study describing a patient who had an episode of ventricular fibrillation after smoking more cannabis than usual (and may be the first ever reported) [11].

The aim of our study was to analyze admissions of young patients (18–45) with an admitting diagnosis of ACS/Vfib and study the association between documented cannabis use disorder and adverse cardiovascular events. The patient risk factors that were associated with the occurrence of adverse cardiovascular events in young cannabis users were also studied. Propensity-matched cohorts (documented cannabis use vs. no documented cannabis use) were used to analyze secondary in-hospital outcomes, including mortality and resource utilization.

2. Materials and Methods

The National Inpatient Sample (NIS) is the largest publicly accessible all-payer inpatient database in the U.S. and is part of the Healthcare Cost and Utilization Project (HCUP). The NIS 2019 was used for the study. ICD 10 codes were used to select appropriate admissions. Young patients (Age 18–45) with a main diagnosis of ACS/ Vfib and documented cannabis use disorder were selected. The ICD 10 codes used were F12.1* and F12.2* (excluding F12.21).

The inclusion criteria included young patients (18–45) admitted with a main diagnosis of ACS/Vfib. The study design used a retrospective case-control format. Admissions with ACS/Vfib were selected based on their age group and divided into a case-control format based on documented cannabis use. The odds of association between admissions for ACS/Vfib and documented cannabis use disorder were carried out after adjusting for demographic characteristics (age, sex, race, income) and comorbidities (smoking, cocaine abuse, uncontrolled hypertension, diabetes, hyperlipidemia). Secondary analysis was carried out on young admissions (18–45) with documented cannabis use. Patient factors that held significant association for the occurrence of ACS/Vfib as the main diagnosis in the study population were analyzed.

A two-tailed $p < 0.05$ was considered as the threshold for clinical significance. Propensity-matched analysis was performed at a ratio of 1:1, without replacement, using a caliper width of 0.01. An absolute standardized difference of <10% was obtained for most variables before and after propensity matching.

Data were matched with all baseline characteristics, comorbidities and hospital characteristics. Only 1:1 propensity-matched data were utilized to analyze outcomes. A Chi-square test (categorical data reported as percentages) and a Mann–Whitney U test (reporting median and interquartile ranges) were performed to compare the baseline characteristics. Outcomes and predictors were adjusted for age, sex, race, median income, payer status,

hospital characteristics and relevant comorbidities. The outcomes studied were in-hospital all-cause mortality, mean length of hospital stay and mean of total hospital charges. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for mortality predictors. The overall balance test (Hansen and Bowers: Chi-square 2.52, dF 6.00) using relative multivariate imbalance (Lacus, King and Porro 2010) reached 0.161 after matching (no covariates exhibited a large imbalance > 0.25). SPSS 29 and R 4.3 were used to create the propensity-score-matched cohorts. STATA 18 and SPSS 28 were used to perform the statistics.

3. Results

A total of 543,445 admissions were identified with documented cannabis use disorder in the age group range of 18–45. The prevalence of hypertension, diabetes, hyperlipidemia, smoking, other substance abuse and mental health issues were calculated among the admissions with documented cannabis use using CMR comorbidity software (Table 1).

Table 1. Baseline characteristics of patient admissions with documented cannabis use disorder (age 18–45).

Total Number of Admissions	**543,445**
Mean Age	36.574 (36.023–36.897)
Sex	Male 56.17% Female 43.83%
Race	White 52.93% Black 28.77% Hispanic 12.33%
Quarterly Income (calculated from the zip codes of the household)	1st quartile 40.25% 2nd quartile 25.67% 3rd quartile 21% 4th quartile 13.08%
Hospital Region	1. Northeast 18.02% 2. Midwest 24.9% 3. South 36.64% 4. West 20.44%
Prevalence of Hypertension	13.86%
Prevalence of Diabetes	5.4%
Prevalence of Hyperlipidemia	4.40%
Prevalence of Smoking	32.43%
Prevalence of Other Drug Abuse	64.46%
Prevalence of Depression/Psychosis	15.135%

Using the above-mentioned ICD 10 codes, 32,990 admissions under the age of 45 for the diagnosis of ACS were identified, of which 2295 admissions had documented cannabis use disorder. In addition, 1939 admissions under the age of 45 with a diagnosis of ventricular fibrillation were identified, of which 125 admissions had a coexisting diagnosis of cannabis use disorder.

The association between admission diagnosis of ACS and co-existing diagnosis of cannabis use was found to be statistically significant after matching for potential confounders (Table 2). The unadjusted odds of association between documented CUD and ACS as the admitting diagnosis was 2.95 (2.68–3.24, $p = 0.00$). Association remained significant after adjusting for age, sex, race, household income and comorbidities such as smoking, cocaine use, uncontrolled hypertension, diabetes and hyperlipidemia: OR 2.74 (2.48–3.04, $p = 0.00$).

Table 2. Association between documented diagnosis of cannabis use disorder and admission diagnosis of ACS. (Age 18–45).

Association between ACS Admissions and Cannabis Use Disorder Diagnosis	OR	*p* Value	Confidence Interval
Unadjusted Odds	2.95068	0.000	2.683–3.244
Adjusted Odds for Age, Sex, Race and Household Income	2.67347	0.000	2.4255–2.9504
Additional Adjustment For Coexisting Diagnosis of Smoking, Cocaine Use, Uncontrolled Hypertension, Diabetes and Hyperlipidemia	2.749	0.000	2.485–3.040

The association between admission diagnosis of Vfib and co-existing diagnosis of cannabis use was found to be statistically significant after matching for potential confounders (Table 3). The unadjusted odds of association between documented CUD and Vfib as the admitting diagnosis was 2.71 (1.80–4.06, $p = 0.00$). Association remained significant after adjusting for age, sex, race, household income and comorbidities such as smoking, cocaine use, uncontrolled hypertension, diabetes and hyperlipidemia: OR 2.29 (1.51–3.49, $p = 0.00$).

Table 3. Association between admission diagnosis of ventricular fibrillation and documented diagnosis of cannabis use disorder (Age 18–45).

Association between Vfib Admissions and Cannabis Use Disorder Diagnosis	OR	*p* Value	Confidence Interval
Unadjusted Odds	2.713	0.000	1.809–4.069
Adjusted Odds for Age, Sex, Race and Household income	2.561	0.000	1.873–3.876
Additional Adjustment For Coexisting Diagnosis of Smoking, Cocaine Use, Uncontrolled Hypertension, Diabetes and Hyperlipidemia	2.2974	0.000	1.5103–3.493

The NIS was used to select all admissions with documented CUD aged 18–45. In this patient cohort, the association of patient characteristics and occurrence of ACS as the main admitting diagnosis was determined after adjusting for patient and hospital factors. The following patient factors were found to have a significant association with the occurrence of ACS as the admitting diagnosis in young patients (18–45) with documented CUD (Table 4): Black race: OR: 1.73 (1.43–2.09, $p = 0.00$), diagnosis of uncontrolled hypertension: OR: 4.08) 3.37–4.91, $p = 0.00$) and diagnosis of diabetes: OR: 2.37 (1.85–3.24, $p = 0.00$).

Propensity Score and Nearest-Neighbor-Matching and Analysis among ACS Admissions in Young Adults

Since the total number of ACS admissions in young adults was much higher than that compared to the subpopulation with cannabis use disorder, which was used to analyze the in-hospital outcomes of ACS, namely all-cause mortality, mean length of stay and mean of total charges; propensity score-matched samples from the main sample were selected.

The propensity score and nearest neighbor matching (caliper width 0.01) were determined among the ACS admissions in young adults: exact matching was carried out for age, sex, race, income, prevalence of smoking and cocaine use; each cohort had 380 subjects, differing only in cannabis use (CUD+ and CUD− cohorts) and the outcomes of all-cause mortality, mean length of stay and total charges during the admission were studied.

Table 4. Association between patient characteristics and main diagnosis of ACS in young patients (18–45) with documented diagnosis of Cannabis Use Disorder.

Characteristics of Admissions with Cannabis Use Disorder	Association with ACS as Admission Diagnosis: Unadjusted Odds Ratio	Association with ACS as Admission Diagnosis: Adjusted Odds Ratio
Admissions with Black as the documented race	1.73848 (1.4428–2.09711) *p* value 0.000	1.73522 (1.4391–2.0935) *p* value 0.000
Admissions with diagnosis of uncontrolled hypertension	4.082651 (3.3829–4.927039) *p* value 0.00	4.08102 (3.37617–4.9185) *p* value 0.000
Admissions with diagnosis of diabetes	2.45692 (1.8591–3.24958) *p* value 0.000	2.37651 (1.8532–3.2458) *p* value 0.000
Admissions with diagnosis of smoking	1.5346 (0.04912–4.7935) *p* value 0.000	
Admissions with diagnosis of cocaine use	1.3361 (0.097481–1.82455) *p* value 0.000	

The mean length of hospital stay and mean total charges were higher in the cohort with cannabis use disorder among ACS admissions compared to the cohort without cannabis use. No difference in all-cause mortality was seen between the two cohorts (Table 5).

Table 5. Analysis of in-hospital and health utilization outcomes between propensity-matched cohorts with and without CUD among admissions with ACS.

	CUD+ Cohort	CUD− Cohort
Total Cohort Size	380	380
Mean Age	38.8236	38.8236
Sex	Male 74.73% Female 25.26%	Male 74.73% Female 25.26%
Race	Whites 43.68% Blacks 40.23% Hispanics 13.94%	Whites 43.68% Blacks 40.23% Hispanics 13.94%
Quarterly Income	1st quartile 45.51% 2nd quartile 23.42% 3rd quartile 19.73% 4th quartile 11.31%	1st quartile 45.51% 2nd quartile 23.42% 3rd quartile 19.73% 4th quartile 11.31%
Proportion of Smokers	0.005263	0.005263
Proportion of Cocaine	0.03157	0.03157
Proportion of All-Cause Mortality	0.78%	0.78%
Mean Length of Stay (Days)	3.28 (2.98–3.53)	2.69 (2.32–2.82) (p = 0.002)
Mean of Total Hospital Charges (US $)	92,390.64 (92,240.31–92,445.76)	90,886.44 (89,932.21–91,042.56) (p = 0.001)

4. Discussion

As far as we know, this is the largest population-based analysis to date examining CUD+ and ACS/Vfib admissions in the young adult population.

In this retrospective analysis, we determined a highly significant odds ratio between cannabis users aged 18–44 and ACS-related admissions. This odds ratio remained highly significant even after running logistic regression models accounting for demographics (race, sex, age, socioeconomic status), comorbid conditions, cocaine use, marijuana use, etc. (OR 2.95, aOR 2.749). A previous retrospective NIS analysis including ages 11–70 demonstrated

a significant odds ratio at 1.041 for acute MI and cannabis use disorder after adjusting for confounders [10]. After similar adjustments were made in our analysis, the odds ratio for CUD+ and ACS was even more significant at 2.749 when looking only at ages 18–44. These odds imply a stronger association between cannabis use and ACS admissions and younger adults. This may be due to stronger associations of confounders such as diabetes, hypertension, etc., in older adults, again suggesting that cannabis use has a more significant role in younger populations with precipitating ACS.

In the ACS and CUD+ groups, there were higher percentages of males (73.64% vs. 66.93%), blacks (40.93% vs. 22.54%), 1st quartile income (45.6% vs. 35.57%) and Medicaid recipients (39.52% vs. 27.88%). Further analysis revealed significantly higher odds of blacks with CUD+ and ACS admissions, confirming our initial sample findings. Similar findings have been previously documented [12].

To further delineate in-hospital outcomes in ACS admissions with cannabis use, we used propensity score analysis with exact matching to compare all-cause mortality, requirement of IABP, mean length of stay and mean of total charges between CUD+ and CUD− patients. Patients in the ACS and CUD+ groups had longer lengths of stay (~3.3 vs. ~2.7 days) and subsequently higher average hospital costs ($92,340 vs. $90,864).

Some studies have provided insight into what may be the cause of these significant trends. In one case crossover study, the risk of myocardial infarction onset was elevated 4.8 times over baseline within the first 60 min of marijuana use, suggesting that it may be a rare trigger of MI [13]. One proposed mechanism is that CB1 receptors, a receptor in the human body that plays a protective role in myocardial ischemia and has been implicated to modulate chemotaxis, can be overactivated with exogenous delta-9-tetrahydrocannabinol (THC) consumption. In turn, inflammatory molecules are increased in the body, promoting endothelial dysfunction and the subsequent exacerbation of atherosclerosis [14].

Other studies have discussed how smoking marijuana facilitates carboxyhemoglobin via combustion as well as upregulating sympathetic response [15]. This sympathetic response primarily manifests as tachycardia, as cannabis increases sinus node automaticity via b-adrenergic stimulation [16,17]. Increased tachycardia coupled with possible decreased cellular oxygenation may provide the perfect storm for myocardial supply-demand mismatch, thereby inducing a type II myocardial infarction. There have also been animal models demonstrating larger atherosclerotic plaques compared to the control when injected with THC comparable to one joint [14].

Vfib association: Our analysis also looked at CUD+ and ventricular fibrillation hospital admissions. Unadjusted odds were statistically significant at 2.713; however, after adjusting for demographics and comorbidities, the odds remained significant at 2.29. This correlates with previously documented findings, in which a sample population that underwent ambulatory Zio patch monitoring had a higher burden of arrhythmias with current cannabis use [18]. As previously mentioned, this may be driven by the acute sympathetic changes that cannabis causes [17].

5. Limitations

One of the limitations with utilizing the National Inpatient Sample (NIS) is the inability to further evaluate CUD+ patients with the amounts used or the duration of use. Over/under-reporting is also possible if there are ICD-10 coding errors in a database, such as the NIS. Additionally, while there is a significant adjusted odds ratio, no clear causation can be drawn from the data given the nature of the study, which would require more prospective/randomized controlled trials.

6. Conclusions

Based on the results of our retrospective case control study, documented cannabis use in the study population (aged 18–45) was associated with a significant association with admitting diagnosis of acute coronary syndrome (ACS) and ventricular fibrillation (Vfib). This association remained significant after accounting for patient/hospital factors

and comorbidities such as smoking, cocaine abuse, uncontrolled hypertension and diabetes. Among young patients in the same age group with documented cannabis use, black race, uncontrolled hypertension and diabetes were factors that held significant association with the admitting diagnosis of ACS/Vfib. Among the propensity-matched cohorts with and without cannabis use among young patients admitted with a main diagnosis of ACS, mean length of hospital stay and mean of total charges were higher in the cohort with documented cannabis use disorder.

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Institutional Review Board Statement: study was done using National Inpatient Sample retrospective study model: no IRB consent was required.

Informed Consent Statement: Patient consent was waived due to retrospective study model.

Data Availability Statement: All analysis was done using National In-patient sample data for the year 2019.

Conflicts of Interest: The authors declare no conflict of interest.

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