

Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the National Inpatient Sample

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Background Cannabis for medicinal and/or recreational purposes has been decriminalized in 28 states as of the 2016 election. In the remaining states, cannabis remains the most commonly used illicit drug. Cardiovascular effects of cannabis use are not well established due to a limited number of studies. We therefore utilized a large national database to examine the prevalence of cardiovascular risk factors and events amongst patients with cannabis use.

Methods Patients aged 18–55 years with cannabis use were identified in the National Inpatient Sample 2009–2010 database using the Ninth Revision of International Classification of Disease code 304.3. Demographics, risk factors, and cardiovascular event rates were collected on these patients and compared with general population data.

Results Prevalence of heart failure, cerebrovascular accident (CVA), coronary artery disease, sudden cardiac death, and hypertension were significantly higher in patients with cannabis use. After multivariate regression adjusting for age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, tobacco use, and alcohol use, cannabis use remained an independent

predictor of both heart failure (odds ratio = 1.1, 1.03–1.18, $P < 0.01$) and CVA (odds ratio = 1.24, 1.14–1.34, $P < 0.001$).

Conclusion Cannabis use independently predicted the risks of heart failure and CVA in individuals 18–55 years old. With continued legalization of cannabis, potential cardiovascular effects and their underlying mechanisms need to be further investigated.

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Introduction

Cannabis is a psychoactive drug which was first used in China as early as 4000 BC.¹ Cannabis use has gained international popularity over the centuries and has acquired several cultural references including *marijuana*, *hashish*, and *bang*. According to the WHO, cannabis is currently consumed by approximately 147 million people worldwide (2.5% of the population) making cannabis the most widely cultivated, trafficked, and abused drug.² Previously prohibited in the United States, cannabis for medicinal and/or recreation purposes is now legal in over half of the states.

Adverse psychiatric and pulmonary outcomes associated with cannabis have been well described in the literature.³ Cardiovascular effects of cannabis use are less well understood. A 2011 multicenter study found cardiovascular disorders accounted for 9.5% of the total adverse events amongst patients with cannabis-related hospital admissions.⁴ Subsequent studies have described temporal associations between cannabis use and cardiomyopathies,

acute coronary syndromes, and ischemic cerebrovascular accidents (CVAs).⁵ These findings, however, are derived from case reports and a limited number of studies.

We utilized the National Inpatient Sample (NIS), a large national database comprising discharge diagnoses, to examine the relationship between cardiovascular risk factors and events amongst patients with cannabis use.

Methods

National Inpatient Sample database

We analyzed data from the NIS database for the year 2009–2010 which contains data on inpatient hospital stays from states participating in the Healthcare Cost and Utilization project. Each year, the NIS provides data on roughly 8 million hospitalizations from about 1000 hospitals. The NIS is designed to approximate a 20% sample of US community hospitals, defined as ‘all non-federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions,’ representing more than 95% of the US population. Criteria used for stratified sampling of hospitals into the NIS include

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Table 1 Demographics, risk factors, and cardiac events in patients 18–55 years old with and without cannabis use

	Cannabis use, <i>n</i> = 316 397 (1.5%)	No cannabis use, <i>n</i> = 20 499 215 (98.5%)	<i>P</i> value
Demographics			
Age (years)	33.1 (32.9–33.2)	26.3 (26.31–26.35)	<0.001
Sex (% male)	189 838 (60)	7789 702 (38)	<0.0001
Risk factors			
Hypertension (%)	62 963 (19.9)	3218 377 (15.7)	<0.0001
Diabetes mellitus (%)	22 148 (7.0)	1598 939 (7.8)	<0.0001
Hyperlipidemia (%)	22 781 (7.2)	1455 444 (7.1)	0.9
Tobacco use (%)	149 339 (47.2)	2336 911 (11.4)	<0.0001
Alcohol use (%)	88 908 (28.1)	778 970 (3.8)	<0.0001
Obesity (%)	22 148 (7.0)	1332 449 (6.5)	<0.001
Cardiac events			
Heart failure (%)	4430 (1.4)	245 991 (1.2)	<0.01
Cerebrovascular accident (%)	3259 (1.03)	127 095 (0.62)	<0.0001
Coronary artery disease (%)	15 820 (5.0)	942 964 (4.6)	<0.0001
Sudden cardiac death (%)	664 (0.21)	34 849 (0.17)	0.02
Atrial fibrillation (%)	348 (1.1)	204 992 (1.0)	0.08

ownership, bed size, teaching status, urban/rural location, and US region. All discharges from sampled hospitals are included in the NIS database. The NIS is an all-payer database that covers all patients, including those covered by Medicare, Medicaid, or private insurance, and those who are uninsured. Inpatient stay records in the NIS include clinical and resource use information available from discharge abstracts derived from state-mandated hospital discharge reports. Discharge weights provided by the NIS allow extrapolation to calculate expected national hospitalization rates.

Study population

In 2009–2010, a total of 7810 762 hospital records corresponding to a national estimate of 39 434 956 hospital discharges in the United States were analyzed. We extracted all patients aged 18–55 years of age with all listed diagnoses of cannabis use using the International Classification of Diseases (ICD)-Ninth Edition-Clinical Modification code 304.3 (*n* = 316 397). Patient characteristics including demographics, risk factors, and cardiovascular event rates were collected on these patients using corresponding ICD codes.

Statistical analysis

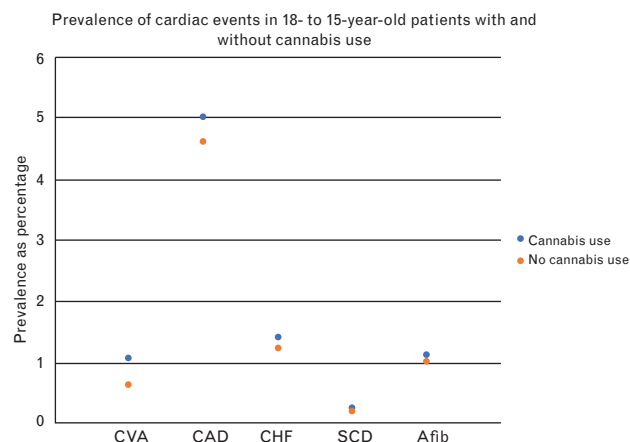
Categorical variables were presented as numbers (percentages), whereas continuous variables were presented as mean ± SD for normally distributed variables and median (interquartile range) for others. *P* value was calculated by chi-square test for categorical variables and *t* test for continuous variables. *P* value less than 0.05 was considered statistically significant. Univariate and multivariable adjusted logistic regressions were performed to determine predictors of heart failure and CVA. All statistical analyses were performed using STATA 10.0 (StataCorp LLC., College Station, Texas, USA).

Results

Cannabis use was diagnosed in 316 397 patients (1.5% of total population; Table 1). Compared with noncannabis

users, cannabis users were older (33.1 vs. 26.3 years of age, *P* < 0.001) and predominantly men (60 vs. 38%, *P* < 0.0001). Cannabis users had an increased prevalence of most risk factors including hypertension (HTN; 19.9 vs. 15.7%, *P* < 0.0001), obesity (7 vs. 6.5%, *P* < 0.001), tobacco use (47.2 vs. 11.4%, *P* < 0.0001), and alcohol use (28.1 vs. 3.8%, *P* < 0.0001), although diabetes mellitus was more frequently observed in noncannabis users (7 vs. 7.8%, *P* < 0.0001). Hyperlipidemia rates were similar between both groups (7.2 vs. 7.1%, *P* = 0.9).

Prevalences of heart failure (1.4 vs. 1.2%, *P* < 0.01), CVA (1.03 vs. 0.62%, *P* < 0.0001), coronary artery disease (CAD; 5 vs. 4.6%, *P* < 0.0001), and sudden cardiac death (0.21 vs. 0.17%, *P* = 0.02) were all significantly higher in cannabis users compared with noncannabis users (Fig. 1). After multivariate regression analysis adjusting for age, sex, HTN, diabetes mellitus, hyperlipidemia, CAD, tobacco use, and alcohol use (all of which were independent predictors of heart failure and CVA; Tables 2 and 3),

Fig. 1

Prevalence of cardiovascular events in patients 18–55 years old with and without cannabis use.

Table 2 Multimodel adjusted logistic regression of different variables in predicting cerebrovascular accident

Variables ^a	Odds ratio	P value
Age	1.03 (1.034–1.035)	<0.001
Female	0.79 (0.78–0.80)	<0.001
Diabetes mellitus	1.12 (1.11–1.14)	<0.001
Hypertension	1.96 (1.94–1.99)	<0.001
Hyperlipidemia	1.34 (1.33–1.36)	<0.001
Prior history of CAD	0.69 (0.68–0.70)	<0.001
Tobacco use	1.29 (1.26–1.33)	<0.001
Alcohol abuse	1.29 (1.26–1.33)	<0.001
Cannabis use	1.26 (1.16–1.36)	<0.001

CAD, coronary artery disease. ^a Model adjusted for all variables listed including age, sex, diabetes mellitus, hypertension, hyperlipidemia, prior history of CAD, tobacco use, alcohol abuse, and cannabis use.

cannabis use remained an independent risk factor for both heart failure [odds ratio (OR)=1.1, 1.02–1.18, $P=0.01$] and CVA (OR=1.26, 1.16–1.36, $P<0.001$). Conversely, the positive association between cannabis use and rates of CAD and sudden cardiac death no longer remained after multivariate regression analysis. There was no significant difference in the rate of atrial fibrillation between the two groups.

As multi drug abuse may be prevalent in patients using cannabis, we extracted cannabis patients who had also used cocaine, amphetamine, and other psychostimulant drugs. We found that the prevalence of cocaine abuse among the cannabis users in the age group of 18–55 was only 1.6%, and only 0.3% with amphetamine and other psychostimulant drug abuse. Hence, we did not run additional analyses as the prevalence of multidrug abuse in this hospitalized patient population of cannabis users between the age of 18 and 55 years was so low and cannot provide meaningful data.

Discussion

The major finding of this study is that after adjusting for cardiovascular risk factors, cannabis use predicted the risks of both heart failure and CVA in individuals 18–55 years old. CAD and sudden cardiac death were more frequent in cannabis users, although these associations did not remain positive after multivariate regression

Table 3 Multimodel adjusted logistic regression of different variables in predicting heart failure

Variables ^a	Odds ratio	P value
Age	1.05 (1.051–1.055)	<0.001
Female	0.98 (0.97–0.99)	<0.001
Diabetes mellitus	1.92 (1.90–1.93)	<0.001
Hypertension	1.08 (1.07–1.09)	<0.001
Hyperlipidemia	0.72 (0.71–0.73)	<0.001
Prior history of CAD	1.93 (1.92–1.94)	<0.001
Tobacco use	1.10 (1.08–1.11)	<0.001
Alcohol abuse	1.07 (1.08–1.11)	<0.001
Cannabis use	1.1 (1.02–1.18)	0.01

CAD, coronary artery disease. ^a Model adjusted for all variables listed including age, sex, diabetes mellitus, hypertension, hyperlipidemia, prior history of CAD, tobacco use, alcohol abuse, and cannabis use.

analysis. Cannabis users were more likely men, hypertensive, obese, and users of tobacco and alcohol, but had a lower rate of diabetes mellitus.

Cannabis is currently the most commonly used drug in the United States and approximately 9% of individuals who experiment with the drug become addicted.⁶ Under the evolving political landscape, legalization of cannabis for both medicinal and recreational purposes has expanded to over half of the states, which may lead to increased use of the drug in the future. Investigating the adverse and beneficial effects of cannabis is therefore prudent. Associations between regular cannabis use and both mental illness^{7–9} and lung cancer^{10,11} have been well established. Recently, Jouanjus *et al.*⁴ reported that in a multicenter study looking at cannabis-related hospitalizations ($n=200$), cardiovascular complications accounted for 9.5% of all adverse events. Further studies assessing the cardiovascular effects of cannabis are sparse and many of these studies were limited in sample size.

In our population aged 18–55 years old, cannabis use independently predicted the risk of heart failure. This finding is supported by previous in-vitro studies of human atrial muscle cells¹² and in-vivo animal studies^{13,14} that demonstrated that CB-1 receptors are expressed in the myocardium and mediate decreased contractility of these cells. Clinically, the association between cannabis use and development of heart failure is likely multifactorial. In a case report, Nogi *et al.*¹⁵ described a young, otherwise healthy patient developing takotsubo cardiomyopathy in the setting of cannabinoid hyperemesis syndrome. More recently, Singh *et al.*¹⁶ identified patients with transient ventricular regional ballooning (TVRB) from the Nationwide Inpatient Sample database 2003–2011 ($n=71\,753\,900$) and reported that cannabis use was an independent predictor of TVRB with an OR=1.994 [95% confidence interval (CI)=1.72–2.32; $P<0.001$]. In addition, cannabis users with TVRB ($n=210$) had increased morbidity compared with cannabis abstainers with TVRB.¹⁶

Hypertensive cardiomyopathy may be another cause of increased prevalence of heart failure in cannabis users. The prevalence of HTN amongst cannabis users was significantly higher in our population compared with the general population. Furthermore, the effect of cannabis on blood pressure was assessed in the US National Health and Nutrition Examination Surveys 2005–2012 ($n=12\,426$) and after adjusting for age and sex, a positive association between recent cannabis use and SBP was found.¹⁷

Cannabis users may also have an increased prevalence of heart failure secondary to ischemic cardiomyopathy. In the current study, cannabis users had a significantly higher prevalence of CAD in a single variate analysis. Mittleman *et al.*¹⁸ obtained data on cannabis use in patients with an acute myocardial infarction (MI)

($n = 3882$) and deduced that within 60 min of cannabis use, the relative risk of MI increased by 4.8-fold (CI 2.9–9.5; $P < 0.001$). Several other case reports have also described young patients with acute coronary syndromes soon after consumption of cannabis due to either poor coronary flow¹⁹ or a coronary artery thrombus.^{20–23} Mortality post MI may additionally be increased in cannabis users based on a large, prospective study ($n = 1913$) which found that compared with nonusers, use of cannabis less than weekly and weekly or more had a hazards ratio of 2.5 (95% CI, 0.9–7.3) and 4.2 (95% CI 1.2–14.3), respectively.²⁴

The risk of CVA was independently predicted by cannabis use in our study. Similarly, Barber *et al.* compared patients admitted with an ischemic CVA or transient ischemic attack (TIA) to a cohort of age, sex, and race matched patients admitted without cardiovascular or neurologic diagnoses and found cannabis predicted the risk of ischemic CVA/TIA. However, unlike our study, this association did not remain significant after adjusting for tobacco use.²⁵ A temporal relation between cannabis use and occurrence of CVA in young patients without risk factors has been described in many case reports.^{26–30} In a series of case reports, Singh *et al.*³¹ reviewed 17 cases of cannabis-related CVA of which five cases demonstrated a recurrence of CVA with re-exposure to cannabis. Several mechanisms of action have been postulated including vasospasm, vasculitis, cardioembolism, and hypotension.³²

The current study is a cross-sectional, retrospective review of a database of hospital discharge diagnoses. Hence, the limitations of our study include the inability to assess the amount of cannabis used, the temporal relation of drug use to cardiovascular events, and the lack of longitudinal follow-up data. In addition, due to the fact that cannabis was considered an illegal drug at the time the data were collected, under reporting of cannabis use may have occurred. The percentage of cannabis users was lower in the studied population when compared with national averages.³³ However, it is important to note that the study population consisted of only hospitalized patients, and not a healthy outpatient group that may include more recreational users of cannabis. Social status would be an important variable to assess. However, the NIS database does not include this variable. We only found zip code-related median household income, and not individualized patient data to include in our analysis. Conversely, the strength of this analysis is derived from the large sample size and the nationwide sampling.

Conclusion

Cannabis use was associated with a higher prevalence of heart failure, CVA, CAD, and sudden cardiac death in individuals aged 18–55 years old from the NIS. After multivariate regression analysis, cannabis use remained an independent predictor of both heart failure and CVA.

These results extend the findings of previous studies, although further investigations into the pathophysiology of these adverse events is warranted.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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