Letter to the Editor

Effects of cannabis on in-patient diabetic patients with prior revascularized (PCI and/or CABG) myocardial infarction and health care service utilization

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The legalization of cannabis for recreational and medical purposes has contributed to its increased popularity and caused concern in the United States (US) (1). Cannabis users have been reported to have an increase in hospitalizations and emergency room visits for acute myocardial infarctions (MI) and other adverse effects of cannabis (2,3). The available literature supports the poor hospital outcomes following percutaneous coronary intervention (PCI), and increased risk for Major Adverse Cardiac and Cerebrovascular Events (MACCE), resulting in increased healthcare utilization and costs in patients having chronic cannabis use, and prior diabetes, revascularization procedures, chronic lung disease, concurrent tobacco use, hypertension, and dyslipidemia exhibited (4). We conducted propensity score-matched analysis to assess and better understand the implications of cannabis use disorder (CUD) on hospitalized patients with diabetes mellitus (DM) and prior revascularized MI, i.e., either PCI or coronary artery bypass graft (CABG), using a publicly available US population representative hospitalization sample database.

We identified hospitalizations with type 1 or type 2 DM, prior revascularized MI (PCI or CABG), and CUD from the National Inpatient Sample (NIS) database between October 2015 and December 2017 using previously validated ICD-10 codes. Propensity score analysis with 1:1 matching was conducted using a caliper width of 0.2 and near neighbor match adjusting age, sex, race, type of admission (elective/non-elective), payer status, median household income quartile of patient's zip code, hospital bed size, location/teaching status and region to identify two cohorts, CUD positive (CUD+, n=190) and CUD negative (CUD–, n=190). The CUD+ and CUD– groups were compared for comorbidities and in-hospital outcomes. The age groups in this study were 18–44, 45–64, and ≥65 years. MACCE, consisting of all-cause mortality, acute MI, cardiac arrest and stroke, and subsequent revascularization, were the primary outcomes in the analysis. Multivariable logistic regression model to assess MACCE with *vs.* without CUD was adjusted for age at admission, sex, race, hypertension, hyperlipidemia, obesity, renal failure, coagulopathy, congestive heart failure, chronic pulmonary disease, depression, drug abuse, alcohol abuse, and tobacco use disorder. C-statistics was performed for the fitness of model. The median duration of hospital stays, and charges were the secondary outcomes. We used Mann-Whitney U test and Pearson's Chi square test for P value statistics for continuous and categorical variables respectively. P value of less than 0.05 was taken as significant statistical association.

In this nationwide propensity-matched analysis (1:1), 380 DM patients with previous MI and revascularizations were stratified into CUD+ and CUD– cohorts with

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comparable baseline demographics and characteristics (*Table 1*). Cardiovascular disease (CVD) risk factors and comorbidities prevalent in both groups included hypertension, hyperlipidemia, tobacco use, obesity, renal failure, alcohol abuse, congestive heart failure, chronic pulmonary disease, fluid and electrolyte disorders, liver disease, and other neurological disorders. Both groups exhibited a balanced distribution of CVD risk factors except hypertension and renal failure. Both hypertension (92.1% *vs.* 97.4%; P=0.022) and renal failure (18.4% *vs.* 28.9%; P=0.016) were found to be less prevalent in the CUD+ arm than CUD– arm.

In both CUD– and CUD+ groups, the top 3 comorbidities reported were hypertension (97.4% *vs.* 92.1%; P=0.022), hyperlipidemia (71.1% *vs.* 68.4%; P=0.577), and tobacco use (68.4% *vs.* 73.7%; P=0.258). Composite MACCE (28.9% *vs.* 10.5%) and the subsequent revascularization (23.7% *vs.* 7.9%) were remarkably greater in the CUD+ than CUD– cohort (P<0.001). Multivariable regression analysis revealed adjusted odds ratio of 11.83 (95% CI: 1.36–102.92, P=0.027) for MACCE in CUD+ than CUD– cohort (*Table 2*). C-statistics for fitness of model was 0.778 thereby indicating adequacy of the model in between good to strong. CUD+ cohort had less frequent routine discharges (63.2% *vs.* 76.3%; P=0.005), higher duration of hospital stays (4 *vs.* 3 days; P<0.001), and higher median total hospital charges (USD $52,555 *vs.* $41,475; P=0.001) than the CUD– cohort.

The findings in this study highlight the association between CUD and increased MACCE and subsequent revascularization needs in patients with concomitant DM, prior MI, and revascularizations. The mechanistic effects of cannabis use on the human body, particularly the cardiovascular system, alongside the concurrent effects of DM and preexisting cardiovascular comorbidities, negatively impact cardiovascular health, resulting in adverse cardiac and cerebrovascular events. Contemporary literature supports the association between cannabis use and MACCE.

Table 1 Impact of cannabis use disorder on outcomes of patients with diabetes mellitus hospitalized with prior myocardial infarction and revascularization (PCI/CABG): a nationwide propensity-score matched analysis[#]

Variables	CUD– (N=190)	CUD+ (N=190)	Overall DM (N=380)	P value[#]
Demographics				
Age (years) at admission, median [IQR]	55 [50–61]	56 [51–62]	56 [51–62]	0.287
18–44, n (%)	20 (10.5)	15 (7.9)	35 (9.2)	0.327
45–64, n (%)	140 (73.7)	135 (71.1)	275 (72.4)	
≥65, n (%)	30 (15.8)	40 (21.1)	70 (18.4)	
Sex, n (%)				
Male	150 (78.9)	140 (73.7)	290 (76.3)	0.228
Female	40 (21.1)	50 (26.3)	90 (23.7)	
Race, n (%)				
White	75 (39.5)	80 (42.1)	155 (40.8)	0.321
Black	75 (39.5)	75 (39.5)	150 (39.5)	
Hispanic	35 (18.4)	25 (13.2)	60 (15.8)	
Non-elective admission, n (%)	165 (86.8)	170 (89.5)	335 (88.2)	0.427
Primary expected payer, n (%)				
Medicare	90 (47.4)	90 (47.4)	180 (47.4)	0.157
Medicaid	85 (44.7)	75 (39.5)	160 (42.1)	
Median household income quartile for patient zip code*, n (%)				
0–25th	80 (42.1)	100 (52.6)	180 (47.4)	0.118

Table 1 *(continued)*

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Variables	CUD– (N=190)	CUD+ (N=190)	Overall DM (N=380)	P value[#]
Comorbidities^				
Hypertension, n (%)	185 (97.4)	175 (92.1)	360 (94.7)	0.022
Hyperlipidemia, n (%)	135 (71.1)	130 (68.4)	265 (69.7)	0.577
Tobacco use, n (%)	130 (68.4)	140 (73.7)	270 (71.1)	0.258
Obesity, n (%)	50 (26.3)	40 (21.1)	90 (23.7)	0.228
Renal failure, n (%)	55 (28.9)	35 (18.4)	90 (23.7)	0.016
Alcohol abuse, n (%)	157.9)	20 (10.5)	35 (9.2)	0.375
Congestive heart failure, n (%)	35 (18.4)	35 (18.4)	70 (18.4)	1
Other neurological disorders, n (%)	25 (13.2)	25 (13.2)	50 (13.2)	1
Chronic pulmonary disease, n (%)	60 (31.6)	50 (26.3)	110 (28.9)	0.258
Fluid and electrolyte disorders, n (%)	55 (28.9)	45 (23.7)	100 (26.3)	0.244
Liver disease, n (%)	15 (7.9)	15 (7.9)	30 (7.9)	1
In-hospital outcomes				
MACCE, n (%)	20 (10.5)	55 (28.9)	75 (19.7)	<0.001
Subsequent revascularization (PCI/CABG), n (%)	15 (7.9)	45 (23.7)	60 (15.8)	<0.001
Routine discharge, n (%)	145 (76.3)	120 (63.2)	265 (69.7)	0.005
Length of stay (days), median [IQR]	3 [2–5]	4 [2–8]	3 [2–6]	<0.001
Total charges (USD), median [IQR]	41,475 [11,547–59,586]	52,555 [17,085–94,125]	44,331 [15,718–76,552]	0.001

Mann-Whitney U and Pearson Chi square test of association were used for P value. P<0.05 indicates statistical significance. [#], propensity score-matched analysis (1:1) was performed using caliper width of 0.2 and near neighbor match adjusting for demographic and hospital characteristics including age, sex, race, type of admission (elective/non-elective), payer status, median household income quartile of patient's zip code, hospital bed size, location/teaching status, and region. *, a quartile classification of the estimated median household income of residents within the patients' zip code, https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nrdnote.jsp. ^, Elixhauser Comorbidity Software Refined For ICD-10-CM, https://www.hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10_archive.jsp, https://www.hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comformat_icd10cm_2017_2.txt. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CUD, cannabis use disorder; DM, diabetes mellitus; IQR, interquartile range; MACCE, Major Adverse Cardiovascular and Cerebrovascular Events (including all-cause mortality, acute myocardial infarction, cardiac arrest, and stroke).

Table 2 Multivariable logistic regression for MACCE outcome[$]

Referent	C-statistics	Adjusted odds ratio	95% confidence interval	P
CUD– cohort	0.778	11.83	1.36 to 102.92	0.027

[$], multivariable logistic regression model adjusted for age, sex, race, hypertension, hyperlipidemia, obesity, renal failure, coagulopathy, congestive heart failure, chronic pulmonary disease, depression, drug abuse, alcohol abuse, and tobacco use disorder. MACCE, Major Adverse Cardiovascular and Cerebrovascular Events (including all-cause mortality, acute myocardial infarction, cardiac arrest, and stroke).

Patel *et al.* reported the association of acute MI with cannabis use in their systematic review. The study reported a mean age of 27.7±10.26, predominantly male (94.4%), with the use of 3.7 g of cannabis for 9.7 years and concluded to consider episodic cannabis use as a significant risk factor for MI (5). Similarly, the nationwide propensity-matched analysis also reported the CUD+ group to be predominantly male (73.7%) and increased rates of MACCE, including AMI (28.9%) (6). The study also reported associated CVD risk factors of tobacco use (48.39%) and alcohol use

disorder (20%) among patients, which was also prevalent in the CUD+ group of our reported analysis, tobacco use (73.7%) and alcohol abuse (10.5%).

A retrospective study conducted by Desai *et al.* on stroke-related hospitalizations among cannabis users aged 18–49 years reported a greater overall risk of young-onset stroke (16%), and acute ischemic stroke (41%) associated-hospitalizations and poor outcomes than non-cannabis users, along with the increased length of hospital stays and costs among the cannabis-related young-onset stroke admissions (6), similarly to our reported CUD+ and CUD– study groups (4 *vs.* 3 days). The rising trend of young-onset stroke admissions was noted to be more prevalent in male cannabis users (578 to 701 over a 7-year period; p_{trend} <0.001). From 2007 to 2014, in-hospital mortality rates increased from 3.7% to 4.3% among cannabis users with young-onset stroke admission (7). Another nationwide study reported two times higher odds of all-cause in-hospital mortality among cannabis users with the background history of pulmonary hypertension (8). On the other hand, studies by Desai *et al.* and Johnson-Sasso *et al.*, though reported higher acute MI, they reported that cannabis use was not associated with an increased risk of adverse short-term in-hospital outcomes following acute MI (9,10). These differences in shorter outcomes may be related to the proven and established efficacies of the MI treatment than stroke management.

Both type 1 and type 2 DM patients have similar degree of elevated CVD risk factors. In patients with type 2 DM, CVD is the leading cause of mortality and 50% of DM patients have CVD cause-specific deaths (7). Insulin resistance and hyperglycemic states can exacerbate the production of reactive oxygen species and glycation resulting in inflammation, in turn, raising the likelihood of CVD. Additionally, a greater atherosclerotic cardiovascular disease (ASCVD) risk score was noted regarding the dose-response association and cannabis use. Individuals that disclosed ≥1 day of cannabis use resulted in 87% increased odds of high-risk ASCVD score (OR 1.87; 95% CI: 1.16–3.01; P<0.001). Disclosure of ≥2 cannabis use/month had 79% greater odds of a high ASCVD risk score (OR 1.79; 95% CI: 1.10–2.92; P=0.02). Hyperglycemia causes fibrinolysis and thrombosis resulting in the development of atherosclerotic plaques. A multinomial logistic regression analysis was conducted by Skipina *et al.* examining the relationship between cannabis use and ASCVD risk category (low-risk ASCVD = reference range) (11). In this study, 63.9% of participants were in the 'ever used' cannabis group with 60% increased odds of high-risk ASCVD score (OR 1.60; 95% CI: 1.04–2.45, P=0.03).

When integrated with the demonstrated outcomes in the nationwide propensity-matched analysis, DM patients with a history of MI and/or revascularization alongside CUD are at increased risk for adverse impacts on cardiovascular disease and procedural outcomes (PCI/CABG revascularization). A retrospective study assessing the association between cannabis use and the rates of post-PCI complications reported greater risks for bleeding and cerebrovascular accidents in patients with cannabis use compared to non-cannabis users (12). Of 113,477 patients, 3,970 were cannabis users with a mean age of 53.9 years, and CVD risk factors and comorbidities included cerebrovascular disease (10.8%), chronic lung disease (23.2%), tobacco use (73.1%), DM (28.2%), dyslipidemia (69.2%), hypertension (77.8%), peripheral arterial disease (13.2%), prior CABG (10%), prior heart failure (13.1%), prior MI (36.3%), prior PCI (38.7%), and prior valve surgery (1%). The adjusted odds ratio was found to be significant for bleeding (OR 1.54; 95% CI: 1.20–1.97; P<0.001) and cerebrovascular accidents (OR 11.01; 95% CI: 1.32–91.67; P=0.026).

Despite being an administrative database depending on the accuracy of coding and unmeasured patient-related factors like type and duration of cannabis use and non-availability of therapeutic drugs utilized for MACCE as sources of limitation to our study, our analysis created a composite outcome, MACCE, and interpreted univariate associations between CUD and without CUD patient population. Our study can be viewed as the hypothesis-generating and supporting the clinical effects of cannabis on patients with DM and prior MI. Based on the study findings, and prior literature and society recommendations or consensus statements (2,13), we recommend few measures in DM patients with known cardiovascular disease risk or prior revascularization. These patients should be educated about recreational cannabis use with a neutral attitude by their physicians. The safety of chronic habitual cannabis use for diabetics has been questioned (possibly causing diabetic ketoacidosis), and this study indicates a higher risk of major adverse cardiac events in diabetic patients with established cardiac risk, which underscores the need to raise awareness of the potential for worse outcomes among patients. Patients with advanced cardiovascular disease risk can benefit from tailored healthcare resources, which provide individual assessment and counseling. It is important to make more online resources available for wide

circulation in light of the rapidly growing literature on this subject for time-to-time updates on the cardiovascular safety of chronic habitual or recreational cannabis use in diabetics, those with metabolic risk factors, or those with a previous coronary artery condition. It is essential to conduct randomized controlled studies to determine the relationship between cannabis use mode, dose, and duration and cardiovascular risk in DM and the modification effect of antidiabetic and preventive lifestyle measures/behavioral changes on cardiovascular risk.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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