Cannabis use disorder and perioperative outcomes in vascular surgery

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ABSTRACT

Background: Heavy cannabis use is known to have an adverse impact on cardiovascular and cerebrovascular outcomes in the general population and in patients presenting for surgery. However, there have been no studies that have focused on patients undergoing vascular surgical procedures. The objective of this study was to determine the perioperative risk of cannabis use disorder (CUD), primarily cardiovascular risk, in perioperative vascular surgery patients.

Methods: Using the National Inpatient Sample from 2006 to 2015, we conducted a retrospective cohort study involving those undergoing one of six elective and emergent vascular surgical procedures (carotid endarterectomy [CEA], infrainguinal bypasses, open abdominal aortic aneurysm repair, aortobifemoral bypass, endovascular aortic aneurysm repair, or peripheral arterial endovascular procedures). Patients with CUD identified by the *International Classification of Diseases, 9th edition*, were matched with patients without CUD in a 1:1 ratio using propensity scores. The primary outcome was perioperative myocardial infarction (MI). Secondary outcomes include stroke, sepsis, deep vein thrombosis, pulmonary embolus, acute kidney injury requiring dialysis, respiratory failure, in-hospital mortality, total cost, and length of stay.

Results: We identified a total cohort of 510,007 patients. Over the study period, the recorded prevalence of CUD increased from 1.3/1000 to 10.3/1000 admissions ($P < .001$). After propensity score matching the cohort consisted of 4684 patients. Those with CUD had a higher incidence of perioperative MI (3.3% vs 2.1%; odds ratio [OR], 1.56; 95% confidence interval [CI], 1.09-2.24; $P = .016$) and perioperative stroke (5.5% vs 3.5%; OR, 1.59; 95% CI, 1.20-2.12; $P = .0013$) than patients without CUD. In a sensitivity analysis, where the risk was evaluated separately by type of procedure, the higher incidence of perioperative stroke was primarily seen among those undergoing CEA. Patients with CUD had a lower incidence of sepsis (3.3% vs 5.1%; OR, 0.64; 95% CI, 0.47-0.85; $P = .0024$). We obtained similar results in a sensitivity analysis that included all patients in the complete unmatched cohort and adjusted for confounding using logistic regression models accounting for the survey design, although the findings of sepsis and stroke failed to reach statistical significance after correcting for multiple testing (MI $P = .001$; stroke $P = .031$; sepsis $P = .009$).

Conclusions: CUD was associated with a significantly higher incidence of perioperative MI in vascular surgery patients. Those with CUD had a greater incidence of diagnosis of acute perioperative stroke when undergoing CEA. Owing to limitations in administrative data, it is unclear if this represents a true effect or selection bias. These findings warrant further investigation in a prospective cohort. (J Vasc Surg 2021;73:1376-87.)

Keywords: Marijuana; Myocardial infarction; Stroke; Vascular surgical procedures; Carotid endarterectomy

Mounting concerns have been raised in recent years regarding the potential negative impact of regular, heavy, cannabis use on cardiovascular and perioperative outcomes.[1-3] It is estimated that 24 million Americans have used cannabis in the last month and 1.5% (4 million) of the population has a cannabis use disorder (CUD).[4] The accepted diagnostic criteria for CUD come from the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV or DSM-V). The definition is dependent on diagnostic criteria reflecting heavy or increasing use with the inability to cut down despite negative impacts on health and societal function.[5-7]

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Cannabis use has previously been identified as a trigger for both myocardial infarction (MI) and an important risk factor for stroke in young populations.[1,2,8-10] A recent study demonstrated these effects may extend to the perioperative setting.[3] In patients undergoing elective, primarily low-risk, procedures there was a significantly increased rate of MI and a nonstatistically significant signal for increased risk of stroke at the time of elective surgery.[3]

Vascular surgery patients represent a particularly high-risk group for cardiovascular and cerebrovascular events.[11-13] Owing to the unique profile of comorbidities in this population, prior findings may not generalize directly to them. Understanding of this risk profile is important, both to allow for risk stratification and adequate perioperative monitoring. To date, no study has investigated the association of cannabis use on perioperative outcomes specifically for vascular surgery patients.

We therefore conducted a retrospective cohort study with the objective to (1) describe trends in the prevalence of CUD in vascular surgery patients and (2) determine the incidence of adverse perioperative outcomes, specifically perioperative MI. We hypothesized that CUD would be associated with an increased risk of MI in those undergoing vascular surgery.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cohort study using the National Inpatient Sample
- **Key Findings:** Cannabis use disorder (CUD) in 510,007 vascular surgery patients increased from 1.3/1000 to 10.3/1000 admissions between 2006 and 2015. CUD was associated with a higher incidence of perioperative myocardial infarction (odds ratio, 1.56; 95% confidence interval, 1.09-2.24; $P = .016$). There was a trend that CUD may increase the risk of stroke during carotid endarterectomy.
- **Take Home Message:** Those with regular, heavy cannabis use are at increased risk for perioperative myocardial infarction.

METHODS

Dataset. A retrospective cohort was derived from the Nationwide Inpatient Sample (NIS) from 2006 to 2015. Owing to changes from the *International Classification of Diseases, 9th edition* (ICD-9) to the ICD 10th edition (ICD-10), data after October 1, 2015, were not included. The NIS is a stratified random sample of discharges from US hospitals, including 20% of all discharges that can be weighted to estimate nationally representative figures. Data are collected at the time of discharge from inpatient discharge abstracts. The dataset is administered by the Agency for Healthcare Research and Quality (AHRQ) and is the largest all-payer inpatient database in the US. This study did not require review by an institutional review board because the deidentified data are publicly available.

Cohort definition. We limited the cohort to those between the ages of 18 and 75 undergoing one of six vascular surgery procedures: carotid endarterectomy (CEA), infrainguinal bypasses, open abdominal aortic aneurysm repair, aortobifemoral bypass, endovascular aortic aneurysm repair or peripheral arterial endovascular procedures. These procedures were identified by ICD-9 codes and selected a priori because they represent a typical subset of operations performed within vascular surgery (Supplementary Table I, online only).

Patients were required to have an admission of at least 1 day to ensure only inpatients were selected. Those over 75 years of age were excluded, because CUD is rare in this age group and may lead to violations of the assumption of positivity.[14] Patients with missing data were excluded. An indicator variable was used for missing race data, as values are missing for 13.7% of the cohort.

Exposure. We identified patient with CUD by ICD-9 codes input during their admission corresponding with cannabis dependence (304.30, 304.31, 304.32) or cannabis abuse (305.20, 305.21, and 305.22). These codes have been used in prior studies evaluating cannabis abuse within the NIS.[8,10] Prior studies have demonstrated high specificity for ICD-9 codes for substance abuse disorders within administrative databases (>95%), but sensitivity is limited (55%-75%).[15,16]

Outcomes. Our primary outcome was perioperative MI, identified by ICD-9 codes, consistent with those used for the AHRQ quality indicator for acute MI (Supplementary Table I, online only). Secondary outcomes included perioperative stroke, sepsis, deep vein thrombosis, pulmonary embolus, acute kidney injury requiring dialysis, respiratory failure, mortality, length of stay (LOS), and costs. Cost to charge ratios provided by the Healthcare Cost and Utilization Project were used to convert total inpatient charges to costs.

Covariates. Potential confounders were identified based on prior literature as well as biological and clinical plausibility as being associated with CUD and the investigated perioperative outcomes. Demographic and institutional covariates included sex, race, age, year of admission, median household income by zip code (categorized into quartiles), hospital size, urbanicity, and teaching status. Patient comorbidities were identified by ICD-9 code or clinical classification code, which are derived by AHRQ and available in the NIS. These include chronic obstructive pulmonary disease, diabetes, prior history of coronary artery disease, dyslipidemia, hypertension, congestive heart failure, renal disease, smoking, obesity (defined as a body mass index of >25 in the NIS),

asthma, prior history of stroke, liver disease, cancer (solid tumor, hematologic, or metastatic), substance use disorders, mood disorder, personality disorder, schizophrenia, and chronic pain (Supplementary Table I, online only). We additionally included the Elixhauser comorbidity score categorized into four levels (0, 1, 2, >3) to allow for nonlinear associations. Procedure type, urgency of admission (elective or nonelective), and year of admission were included in the model as categorical variables.

Statistical analysis. For our first objective, we plotted proportions of those with a diagnosis of CUD undergoing vascular surgical procedures over time to assess temporal trends. These were scaled to nationally representative figures using weights provided by HCUP and appropriate survey functions to account for clustering within hospitals. A χ^2 test was applied to test for significance of this trend while accounting for survey weights.

For our primary analysis, we performed a propensity score match with all identified covariates of interest, identified a priori, to predict CUD. Patients with CUD were matched in a 1:1 nearest neighbor match, to patients without a diagnosis of CUD, using a maximum caliper width of 0.2 of the standard deviation of the logit of the propensity score.[17] Standardized differences were calculated and assessed for both the unmatched and matched cohort to examine adequacy of adjustment. We prespecified a standard difference of greater than 10% after the match to represent inadequate balance requiring additional statistical adjustment; however, this factor was not required.[18] Binary outcome variables were analyzed using logistic regression. LOS was analyzed using a generalized linear model assuming a negative binomial distribution and a log link function. Cost was analyzed with a generalized linear model assuming a gamma distribution and a log link function.

Owing to the inability to use survey weights in the propensity-matched cohort, we conducted a sensitivity analysis, planned a priori, for the entire unmatched cohort. We adjusted for the potential confounders used to create the propensity scores using survey weights and survey-specific logistic regression procedures. This strategy allows for improved estimation of variance by accounting for the sampling methodology and clustering in the NIS. We also conducted post hoc stratified sensitivity analyses on perioperative stroke, sepsis, and MI by procedure performed, elective status and patient age. We analyzed incidence of lower extremity infection, urinary tract infection (UTI), surgical site infection (SSI), and pneumonia (Supplementary Table I, online only), which are known to be important sources of postoperative infection.[19]

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). *P* values reported are 2 sided, with a *P* value of less than .05 being considered statistically significant for the primary outcome. For secondary outcomes, level of statistical significance was adjusted using the Bonferroni method, with a *P* value of less than .00625 being considered significant (eight outcomes). Sample size was based on available data and no a priori power calculation was performed.

RESULTS

From a total of 46,149,634 unweighted discharges 510,007 patients were identified as having undergone one of six vascular surgical operations. The final propensity score matched cohort included 4684 patients (Fig 1).

National estimates of the prevalence of CUD among those undergoing vascular surgical procedures increased from 1.3/1000 admissions in 2006 to 10.3/1000 admissions in 2015 ($P < .001$; Fig 2).

Table I shows the baseline covariate distribution for those with and without CUD in the full unmatched cohort. Those with CUD were more likely to be younger, male, smokers, of low income status, and have other mental health or substance use disorders. Those without CUD were more likely to have previous coronary artery disease, hypertension, and dyslipidemia. Of 2344 patients with CUD, 2342 were successfully matched. Following matching on the propensity score, all covariates yielded a standardized difference of less than 10% (Table II).

Those with a diagnosis of CUD had a higher incidence of perioperative MI (3.3%, 2.1%; odds ratio [OR], 1.56; 95% confidence interval [CI], 1.09-2.24; $P = .016$) and stroke (5.5%, 3.5%; OR, 1.59; 95% CI, 1.20-2.12; $P = .001$) than propensity-matched patients without CUD. We observed a lower incidence of perioperative sepsis among those with CUD relative to those without CUD (3.3%, 5.1%; OR, 0.64 95% CI, 0.47-0.85; $P = .0024$). There were no statistically significant associations between CUD and incidence of respiratory failure, acute kidney injury, or venous thromboembolism. Despite increased incidence of MI in those with CUD, there was no significant association between CUD and mortality, cost or LOS (Tables III and IV). Those who had an MI in the matched cohort (n = 127) overall demonstrated higher rates of mortality (8.7% vs 1.3%), LOS (10.7 ± 8.6 days vs 8.2 ± 9.7 days), and total costs ($49,207 ± $40,032 vs $30,429 ± $34,443).

In sensitivity analyses, we found similar associations between CUD and perioperative MI and stroke in the entire cohort, after adjusting for the potential confounders that were used to create the propensity score, in logistic regression models accounting for the survey weights. However, the association between CUD and perioperative sepsis was no longer statistically significant (Supplementary Table II, online only).

We then evaluated the association between CUD and of MI and stroke within the propensity-matched cohort stratified by operation (admission for CEA vs no-CEA) (Supplementary Table III, online only). With the cohort

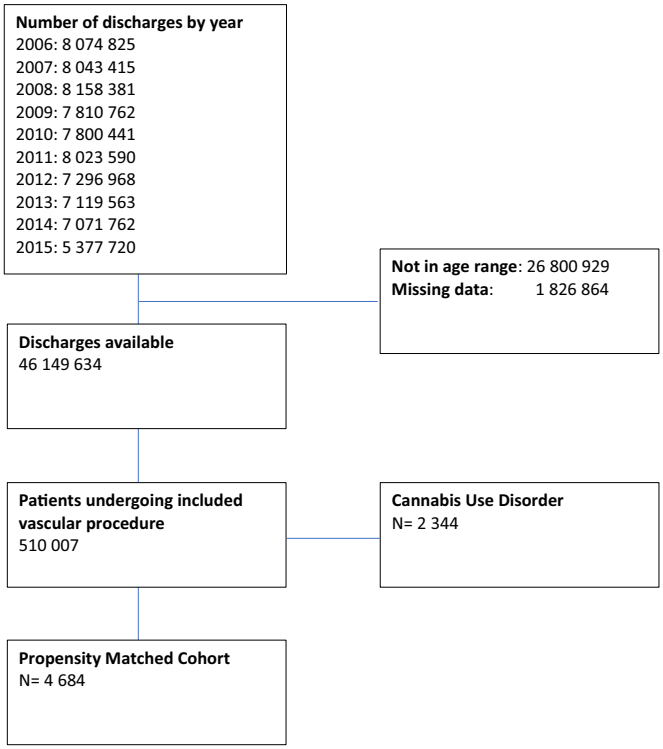

Fig 1. Flowchart demonstrating cohort formation.

limited to the CEA patients (n = 584), we again saw a higher incidence of stroke in those with CUD vs those without (29.7%,18.2%; OR, 1.90 95% CI, 1.29-2.79; P = .0011). In a cohort limited to all operations but excluding CEA (n = 4112), there was no statistically significant association between CUD and incidence of stroke (1.7%, 1.4%; OR, 1.22 95% CI, 0.75-2.01; P = .42). We otherwise observed consistent results with regard to the primary end point in sensitivity analyses stratified by age, procedure type, and elective vs nonelective admission.

We evaluated the incidence of common infectious foci in vascular surgical patients among those with and without CUD in the matched cohort.[20] We hypothesized that this result would clarify whether cannabis use was associated with a lower incidence of infection, or instead a diminished ability to develop systemic inflammatory response syndrome (SIRS) owing to cannabis-induced immunosuppression. The majority of cases of sepsis occurred in those undergoing open or endovascular revascularization of the lower extremity (91.3%). Among those undergoing lower extremity revascularization, those with CUD had a lower incidence of perioperative sepsis, similar to the primary analysis in the entire cohort (5.9% no CUD; 4.0% CUD). Similar proportions of those with and without CUD had a diagnosis of lower extremity infection (16.6% no CUD; 16.8% CUD), critical limb ischemia (22.7 % no CUD; 23.6% CUD), pneumonia (4.2% no CUD; 3.6% CUD), UTI (3.0 % no CUD; 3.5% CUD), and SSI (1.7% no CUD; 1.4% CUD).

DISCUSSION

In this retrospective cohort of patients undergoing both elective and urgent vascular surgical procedures, a diagnosis of CUD was associated with a statistically significantly higher incidence of MI. We also observed a statistically significant higher incidence of perioperative stroke, which was limited to those undergoing CEA. We also observed a statistically significantly lower incidence of perioperative sepsis in those with CUD relative to those without.

Over the course of our study period from 2006 to 2015, there was a statistically significant change in prevalence of diagnosed CUD among those undergoing vascular surgical procedures. This result has been demonstrated in both the general population, inpatients, and in the elective perioperative setting.[3,21-23] Although this finding may reflect a true increase in the use of cannabis, it may also reflect changes in reporting patterns.[24,25] In a study by Compton et al,[25] there was no change in the prevalence of CUD (2002-2014); however, they report increased daily use and decreased perception of harm. This cohort was significantly younger than ours and differences may exist between self-reported data and a physician assessment of CUD. Our findings could be impacted by patients being more willing to disclose cannabis use to their physicians, and therefore have it appear in the medical record. In contrast, increased cultural acceptance of cannabis use may lead physicians to be less willing to diagnose CUD and underestimation of prevalence of CUD in more recent years. The DSM V was released in 2013; however, the diagnostic criteria remained relatively unchanged from the DSM IV and it was not believed to substantially alter reporting of CUD.[6] Fig 2 shows the overall trend was present before the release of the DSM V and did not acutely change after its release.

Numerous mechanisms by which cannabis use may increase perioperative MI have been postulated. Inhalation of cannabis smoke has been demonstrated in animal models to cause endothelial dysfunction.[26] This is due to the inhalation of products of plant matter combustion, independent of Δ^9-tetrahydrocannabinol (THC).[26]

THC is the most commonly referenced, most potent psychoactive agent in cannabis and generally believed to predominantly exert the cardiovascular effects.[27,28] Cannabinoids have a complex interaction with the cardiovascular system mediated by direct arterial effects and effects mediated by the autonomic nervous system.[28,29] These effects include elevation of the systolic blood pressure, tachycardia, orthostatic hypotension, and depressed myocardial function, occurring in the presence of increase in carboxyhemoglobin levels.[28-31] These conditions can lead to a supply demand mismatch within the myocardium. Aronow and Cassidy[30,31] observed in those with chronic stable angina,

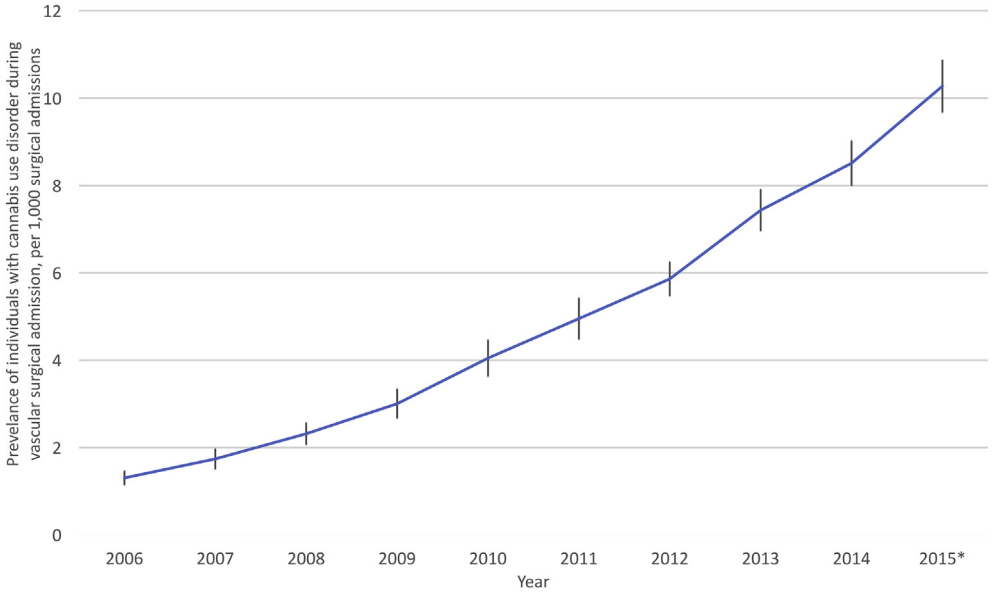

Fig 2. Annual trend of vascular surgery patients with a diagnosis of CUD, standard error indicated by bars. ($P < .001$). [a]Data for 2015 are truncated at October 2015.

cannabis use decreased the average time to angina more than placebo or nicotine cigarettes (48%, 8.6%, 23% respectively). Other authors have suggested that cannabinoid use may negatively impact the coronary microcirculation.[32] Although interaction with the coagulatory system is complex and still subject to debate, cannabinoid-mediated platelet aggregation has been suggested as a cause for coronary artery thrombosis.[33,34] Finally, cannabis has been associated with arteritis in the peripheral vasculature.[35] This phenomenon is still poorly understood, but if it were to have a systemic effect, this could also play a role in the development in MI in those with CUD.

The risk of MI in the first hour after cannabis exposure is increased by 4.8 times over baseline.[1] Although patients likely would not use cannabis directly before their operation, cannabis accumulates in the fatty tissue, with an elimination half-life of 7 days.[27] The increased hemodynamic stress associated with an operation in combination with the increased cardiovascular risk mediated through these mechanisms could lead to MI. Additionally, cessation of cannabis can lead to a hypertensive response in heavy users, which may add additional intraoperative myocardial demand.[36]

Despite an increased incidence of MI in those with CUD, we failed to detect a difference in mortality, cost, or LOS between those with and without CUD. This result was likely due to inadequate power, because MI was an infrequent outcome, as was mortality, and the standard deviation of costs and LOS was high. Those who developed MI in the overall cohort demonstrated higher mortality, costs, and LOS, indicating that these events were likely clinically important. Given the association we have observed between CUD and perioperative MI we believe that practitioners should be including assessment of cannabis use in preoperative screening. These patients owing to their elevated risk should be monitored for cardiovascular complications. Further research is warranted regarding the management of cannabinoids in chronic users in the perioperative period.

We observed a statistically significant higher incidence of having an acute stroke diagnosis in those with CUD relative to those without, in our propensity-matched analysis. This finding seems to be predominantly among those undergoing CEA. Cannabis use has been previously identified as a risk factor for stroke. These are often vasoconstrictive in nature and more commonly involve the posterior circulation.[9,35,37]

Our ability to interpret the findings is complicated owing to the administrative nature of our dataset. We are unable to identify the timeline of when the stroke occurred during admission. A patient admitted with stroke owing to symptomatic carotid artery stenosis who then underwent CEA, and a patient who had a CEA for asymptomatic carotid artery stenosis but had an intraoperative stroke would both have a diagnosis of acute stroke in the NIS. Surgeons may be less likely to offer CEA for asymptomatic lesions in those with CUD. It is known that patients with substance use disorders face barriers to care.[38-40] If patients with CUD are, therefore, not offered surgery for asymptomatic lesions, the ratio of symptomatic lesions would be higher, and this

Table I. Patient characteristics of unmatched cohort without the use of sample weights

	CUD		
	Yes	No	Standardized difference
Total	n = 2344	n = 507,665	
Female sex	570 (24.3)	198,210 (39.0)	0.32
Race			0.45
Caucasian	1204 (51.4)	324,639 (63.9)	
African American	706 (30.1)	63,246 (12.5)	
Hispanic	127 (5.4)	31,211 (6.2)	
Other	73 (3.1)	18,977 (3.7)	
Missing	234 (10.0)	69,652 (13.7)	
Age, years	50.5 ± 13.0	62.5 ± 10.0	1.04
Year			0.66
2006	78 (3.3)	59,813 (11.8)	
2007	99 (4.2)	56,055 (11.0)	
2008	135 (5.8)	58,433 (11.5)	
2009	160 (6.8)	51,937 (10.2)	
2010	199 (8.5)	49,727 (9.8)	
2011	266 (11.4)	54,295 (10.7)	
2012	282 (12.0)	47,825 (9.4)	
2013	354 (15.1)	47,254 (9.3)	
2014	403 (17.2)	46,944 (9.3)	
2015[a]	368 (15.7)	35,442 (7.0)	
Mean household income quartile by zip code			0.29
1	1042 (44.5)	160,146 (31.5)	
2	609 (26.0)	140,992 (27.8)	
3	459 (19.6)	118,515 (23.3)	
4	234 (10.0)	88,072 (17.4)	
Elective admission	706 (30.1)	302,330 (59.6)	0.62
Surgery type			
CEA	313 (13.4)	127,824 (25.2)	0.30
Infrainguinal open	891 (38.0)	134,950 (26.6)	0.25
Open AAA repair	74 (3.2)	15,639 (3.1)	0.00
ABF	139 (5.9)	20,225 (4.0)	0.09
EVAR	98 (4.2)	37,165 (7.3)	0.14
Endovascular peripheral arterial procedure	1068 (45.6)	215,268 (42.4)	0.06
Hospital urbanicity, teaching status			0.36
Rural	90 (3.8)	34,088 (6.7)	
Urban nonteaching	548 (23.4)	188,828 (37.2)	
Urban teaching	1706 (72.8)	284,809 (56.1)	
Hospital size			0.00
Small	226 (9.6)	51,308 (10.1)	
Medium	536 (22.8)	115,205 (22.7)	
Large	1582 (67.5)	341,212 (67.2)	
COPD	479 (20.4)	103,898 (20.5)	0.00
Diabetes	696 (28.5)	202,154 (39.8)	0.24
CAD	697 (29.7)	218,624 (43.1)	0.28
Dyslipidemia	897 (38.3)	244,615 (48.2)	0.20
Hypertension	1599 (68.2)	385,457 (75.9)	0.17

(Continued on next page)

Table I. Continued.

	CUD		
	Yes	No	Standardized difference
History of CHF	244 (10.4)	62,283 (12.3)	0.06
Renal disease	443 (18.9)	109,154 (21.5)	0.06
History of smoking	1859 (79.3)	230,846 (45.5)	0.75
Obese (BMI > 25)	233 (9.9)	50,068 (9.9)	0.00
Asthma	144 (6.1)	21,986 (4.3)	0.08
History of stroke	81 (3.5)	17,069 (3.4)	0.01
Liver disease	272 (11.6)	20,204 (4.0)	0.29
Solid tumor	169 (7.2)	41,571 (8.2)	0.04
Hematologic malignancy	25 (1.1)	5467 (1.1)	0.00
Metastatic cancer	26 (1.1)	4322 (0.9)	0.03
Amphetamine or cocaine substance use disorder	367 (15.7)	1888 (0.4)	0.59
Other substance use disorder	193 (8.3)	5478 (1.1)	0.34
History of alcohol abuse	556 (23.7)	16,129 (3.2)	0.63
Mood disorder	462 (19.7)	43,021 (8.5)	0.33
Personality disorder	25 (1.1)	338 (0.1)	0.13
History of schizophrenic disorder	56 (2.4)	3548 (0.7)	0.14
History of chronic pain	196 (8.4)	14,051 (2.8)	0.25
Elixhauser comorbidity score			0.17
0	195 (8.3)	42,767 (8.4)	
1	417 (17.8)	115,310 (22.7)	
2	533 (22.7)	131,790 (26.0)	
≥3	1199 (51.1)	217,858 (42.9)	

AAA, Abdominal aortic aneurysm; *ABF*, aortobifemoral bypass; *BMI*, body mass index; *CEA*, carotid endarterectomy; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; CUD; cannabis use disorder; EVAR, endovascular aortic aneurysm repair. Data from 2015 were not available in ICD-9 after October 2015 and are therefore truncated. Values are mean ± standard deviation or number (%) unless otherwise noted.

would produce a higher observed incidence of acute stroke diagnosis owing to selection bias.

Alternatively, it is possible that cannabis use increases the risk of stroke in the perioperative setting. A signal, although not statistically significant, for an increased risk of stroke in patients undergoing elective nonvascular surgical operations has been reported.[3] THC may act to mediate platelet aggregation and this could therefore increase risk of stroke during CEA.[33,34] Cannabis also has vasoactive effects in the cerebral vasculature.[9,10,41-43] It has been associated with vasospasm and those using cannabis have demonstrated alterations in cerebral blood flow on transcranial Doppler examination.[9,10,41,43] This dysregulation of cerebral autoregulation could also mediate an increased risk of stroke, which would be more predominant during CEA relative to other procedures.[41,43]

In our sensitivity analysis, conducted in the entire cohort, using survey specific logistic regression procedures, the increased incidence of stroke among those with CUD did not reach statistical significance. Survey specific regression procedures take into account clustering in the data and give more conservative estimates of variance, which may explain the larger *P* value observed.[44,45] It should be noted the Bonferroni method we used for the secondary analysis is a conservative means of correcting for multiple testing, and confers a greater risk of a type II error.[46] We believe our findings in the sensitivity analysis, along with concerns identified for selection bias, prevent us from making a causal conclusion at this time regarding cannabis use and perioperative stroke. Despite this outcome, there is a concerning signal and further research with a more granular dataset to specifically investigate intraoperative or postoperative stroke in those undergoing CEA is warranted.

We observed a lower incidence of sepsis among those with CUD. This finding is in contrast with what would be expected, because chronic cannabis use is generally believed to act as an immunosuppressant.[47-49] Chronic heavy cannabis use has been shown to decrease inflammatory cytokine production, functionality of lymphocytes and natural killer cells and risk of developing SIRS.[48-50] It is possible that our finding was due to misclassification. Because our data were from before 2015, it is likely the diagnosis of sepsis was based on older diagnostic criteria reliant on the SIRS

Table II. Patient characteristics of matched cohort without the use of sample weights

	CUD		
	Yes (%)	No (%)	Standardized difference
Total	n = 2342	n = 2342	
Female sex	570 (24.3)	560 (23.9)	0.01
Race			0.03
Caucasian	1204 (51.4)	1217 (52.0)	
African American	705 (30.1)	692 (29.6)	
Hispanic	126 (5.4)	110 (4.7)	
Other	73 (3.1)	77 (3.3)	
Missing	234 (10.0)	246 (10.5)	
Age, years	50.5 ± 13.0	49.9 ± 12.6	0.05
Year			0.06
2006	78 (3.3)	66 (2.8)	
2007	99 (4.2)	97 (4.1)	
2008	135 (5.8)	141 (6.0)	
2009	160 (6.8)	142 (6.1)	
2010	199 (8.5)	190 (8.1)	
2011	266 (11.4)	282 (12.0)	
2012	282 (12.0)	287 (12.3)	
2013	354 (15.1)	383 (16.4)	
2014	404 (17.2)	381 (16.3)	
2015[a]	367 (15.7)	373 (15.9)	
Mean household income quartile by zip code			0.05
1	1041 (44.5)	1078 (46.0)	
2	608 (26.0)	575 (25.0)	
3	459 (19.6)	468 (20.0)	
4	234 (10.0)	221 (9.4)	
Elective admission	706 (30.2)	655 (28.0)	0.05
Surgery type			
CEA	313 (13.4)	291 (12.4)	0.03
Infrainguinal open	890 (38.0)	851 (36.3)	0.03
Open AAA repair	74 (3.2)	64 (2.7)	0.03
ABF	138 (5.9)	154 (6.6)	0.03
EVAR	98 (4.2)	111 (4.7)	0.03
Endovascular peripheral arterial procedure	1067 (45.6)	1095 (46.75)	0.02
Hospital urbanicity, teaching status			0.00
Rural	90 (3.8)	85 (3.6)	
Urban nonteaching	548 (23.4)	534 (22.8)	
Urban teaching	1704 (72.8)	1723 (73.6)	
Hospital size			0.04
Small	226 (9.7)	204 (8.7)	
Medium	534 (22.8)	551 (23.5)	
Large	1582 (67.6)	1587 (67.8)	
COPD	479 (20.5)	470 (20.1)	0.01
Diabetes	669 (28.6)	670 (28.6)	0.00
CAD	697 (29.8)	658 (28.1)	0.04
Dyslipidemia	897 (38.3)	908 (38.8)	0.01
Hypertension	1598 (68.2)	1599 (68.3)	0.00
History of CHF	244 (10.4)	215 (9.2)	0.04

(Continued on next page)

Table II. Continued.

	CUD		
	Yes (%)	No (%)	Standardized difference
Renal disease	443 (18.9)	432 (18.5)	0.01
History of smoking	1857 (79.3)	1894 (80.9)	0.04
Obese (BMI > 25)	233 (10.0)	232 (9.9)	0.00
Asthma	144 (6.2)	149 (6.4)	0.01
History of stroke	81 (3.5)	78 (3.3)	0.01
Liver disease	272 (11.6)	256 (10.9)	0.02
Solid tumor	169 (7.2)	156 (6.7)	0.02
Hematologic malignancy	25 (1.1)	30 (1.3)	0.02
Metastatic cancer	26 (1.1)	34 (1.5)	0.03
Amphetamine or cocaine substance use disorder	365 (15.6)	288 (12.3)	0.095
Other substance use disorder	192 (8.2)	182 (7.8)	0.02
History of alcohol abuse	554 (23.7)	505 (21.6)	0.05
Mood disorder	462 (19.7)	445 (19.0)	0.02
Personality disorder	25 (1.1)	20 (0.9)	0.02
History of schizophrenic disorder	56 (2.4)	60 (2.6)	0.01
History of chronic pain	196 (8.4)	210 (9.0)	0.02
Elixhauser comorbidity score			0.07
0	195 (8.3)	223 (9.5)	
1	417 (17.8)	405 (17.3)	
2	533 (22.8)	536 (22.9)	
≥3	1197 (51.1)	1178 (50.3)	

AAA, Abdominal aortic aneurysm; *ABF*, aortobifemoral bypass; *BMI*, body mass index; *CEA*, carotid endarterectomy; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; CUD; cannabis use disorder; EVAR, endovascular aortic aneurysm repair.
Values are mean ± standard deviation or number (%) unless otherwise indicated.
Data from 2015 were not available in the ICD-9 after October 2015 and are therefore truncated.

Table III. Association between cannabis use disorder (*CUD*) and the primary and perioperative clinical outcomes among patients undergoing major vascular surgical procedures in a propensity-matched cohort (Nationwide Inpatient Sample [NIS], 2006-2015)

	Unadjusted analyses				Adjusted analyses			
	CUD (n = 2344) (%)	No CUD (n = 507,725) (%)	Crude OR (95% CI) (CUD vs no CUD)	*P* value	CUD (n = 2342) (%)	No CUD (n = 2342) (%)	Adjusted OR (95% CI) (CUD vs no CUD	*P* value
MI	77 (3.3)	12,400 (2.4)	1.36 (1.08-1.71)	.0084	77 (3.3)	50 (2.1)	1.56 (1.09-2.24)	.016
Respiratory failure	198 (8.5)	30,769 (6.1)	1.43 (1.24-1.66)	<.001	197 (8.4)	202 (8.6)	0.97 (0.79-1.20)	.79
Acute kidney injury	242 (10.3)	39,717 (7.8)	1.36 (1.19-1.55)	<.001	241 (10.3)	222 (9.5)	1.10 (0.90-1.33)	.35
VTE	124 (5.3)	17,262 (3.4)	1.59 (1.32-1.90)	<.001	124 (5.3)	159 (6.8)	0.77 (0.60-0.98)	.032
Sepsis	77 (3.3)	18,827 (3.7)	0.88 (0.70-1.10)	.2797	77 (3.3)	119 (5.1)	0.64 (0.47-0.85)	.002
Stroke	128 (5.5)	14,015 (2.8)	2.04 (1.70-2.44)	<.001	128 (5.5)	82 (3.5)	1.59 (1.20-2.12)	.001
Mortality[a]	28 (1.2)	8813 (1.7)	0.69 (0.47-1.00)	.0481	28 (1.2)	40 (1.7)	0.70 (0.43-1.13)	.146

CI, Confidence interval; MI, myocardial infarction; *OR*, odds ratio; *VTE*, venous thromboembolism.
Survey weights were not used in this analysis. Significance defined as $P < .05$ for the primary outcome and $P < .006$ for the secondary outcomes.
Values are number (%).
[a]Mortality data were missing for 202 patients in the unmatched cohort and 6 patients in the matched cohort.

definition.[51,52] This definition is known to be less specific and of lower predictive validity than those based on the contemporary Sequential [Sepsis-related] Organ Failure Assessment score.[51,53] It has also been shown that automated alerts in electronic medical records may misclassify SIRS as sepsis.[54] The lower incidence of a sepsis diagnosis among those with CUD may reflect a reduced ability to mount a systemic inflammatory response owing to cannabis related immune suppression. The similar incidence of lower extremity infection, pneumonia, SSI, and

Table IV. Analysis examining the association between patients with active cannabis use disorder (*CUD*) and total costs or length of stay (*LOS*) in the propensity-matched cohort

	Unadjusted analyses				Adjusted analyses			
	CUD (n = 2349)	No CUD (n = 509,389)	Crude cost or LOS ratio (95% CI) (CUD vs no CUD)	*P* value	CUD (n = 2342)	No CUD (n = 2342)	Adjusted cost or LOS ratio (95% CI) (CUD vs no CUD)	*P* value
LOS, days (95% CI)	8.29 (7.95-8.63)	6.10 (6.08-6.11)	1.36 (1.30-1.42)	<.001	8.28 (7.99-8.59)	8.34 (8.04-8.64)	0.99 (0.94-1.05)	.8066
Total cost, USD[a] (95% CI)	31,477 (30,459-32,530)	22,811 (22,760-22,862)	1.38 (1.34-1.43)	<.001	31,476 (30,509-32,473)	30,390 (29,457-31,351)	1.04 (0.99-1.08)	.1186

CI, Confidence interval.
Significance defined as $P < .006$ for the secondary outcomes. Results were obtained using regression models after adjusting for confounders. Owing to the regression models used, ratio of cost and LOS in cannabis users to noncannabis users is given.
[a]Cost data are missing for 18,964 individuals in the unmatched and 156 individuals in the matched cohort.

UTI among those with and without CUD demonstrates that cannabis use does not lead to a lower risk of specific infectious foci.

There are several limitations of this study worth consideration. Although we believe the NIS is an excellent resource to address questions such as this one, owing to its large and nationally representative sample, it is limited by its administrative nature. Granular data regarding the use of cannabis such as frequency, dose, and method of ingestion are not available. We are therefore unable to determine if our findings are isolated to smoked methods of cannabis or apply to oral consumption as well. Our results only apply those with diagnosed CUD, reflecting heavy cannabis use. We are unable to generalize our findings to those with infrequent or low-dose consumption. Finally, administrative data for substance use disorders are highly specific (>90%) but less sensitive (55%-75%).[15,16] Not surprisingly the prevalence of diagnosed CUD in our cohort is low compared with national estimates of the prevalence of cannabis use, because our data reflect only a subset of heavy users.[4] The presence of those using cannabis, who were classified as nonusers in the dataset, may bias our results toward the null, and the true impact of cannabis use may be greater than what we observed. Finally, this is a retrospective cohort study and there may be residual unmeasured confounding that we are unable to account for. Nonetheless, our observed associations warrant further investigation in prospective designs with more detailed data capture.

CONCLUSIONS

This study demonstrated an increased incidence of perioperative MI among patients with CUD undergoing one of six vascular surgical procedures. Associations were also demonstrated between CUD and two secondary outcomes, namely, stroke and sepsis. However, these findings were not robust to sensitivity analyses, putting into question their validity. These findings should be confirmed in a dedicated prospective study.

AUTHOR CONTRIBUTIONS

Conception and design: BM, AG, FE, TR, MM, KL
Analysis and interpretation: BM, AG, FE, TR, MM, KL
Data collection: BM, AG, KL
Writing the article: BM, AG
Critical revision of the article: FE, TR, MM, KL
Final approval of the article: BM, AG, FE, TR, MM, KL
Statistical analysis: BM, AG, KL
Obtained funding: Not applicable
Overall responsibility: BM

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Supplementary Table I (online only). Values used to identify exposures, outcomes and covariates. Either the diagnostic codes were queried by *International Classification of Diseases, 9th edition* (*ICD-9*), codes or clinical classification codes (*CCS*) for variable creation

Diagnosis	Code type	Values
Exposure		
CUD	ICD-9	'30430' '30431' '30432' '30433' '30520' '30521' '30522' '30523'
Covariates		
Disorders of lipid metabolism	CCS	'53'
Hypertension	CCS	'98' '99'
Diabetes	CCS	'49' '50'
History of coronary artery disease	CCS	'101'
History of cerebrovascular disease	CCS	'113'
Chronic kidney disease	CCS	'158'
COPD	CCS	'127'
Congestive heart failure	CCS	'108'
Liver disease	CCS	'151' '16' '6'
Alcohol-related disorders	CCS	'660'
Malignancy, nonskin cancer	CCS	'11' '12' '13' '14' '15' '16' '17' '18' '19' '20' '21' '24' '25' '26' '27' '28' '29' '30' '31' '32' '33' '34' '35' '36' '41' '43' '44'
Hematologic malignancy	CCS	'37' '38' '39' '40' '41'
Metastatic cancer	CCS	'42'
Schizophrenia	CCS	'659'
Personality disorders	CCS	'658'
Mood disorders	CCS	'657'
Asthma	CCS	'128'
Substance use disorder (excluding cannabis, stimulant, amphetamines)	ICD-9	'2920 ' '29211' '29212' '2922 ' '29281' '29282' '29283' '29284' '29285' '29289' '2929 ' '30400' '30401' '30402' '30403' '30410' '30411' '30412' '30413' '30450' '30451' '30452' '30453' '30460' '30461' '30462' '30463' '30470' '30471' '30472' '30473' '30480' '30481' '30482' '30483' '30490' '30491' '30492' '30493' '30530' '30531' '30532' '30533' '30540' '30541' '30542' '30543' '30550' '30551' '30552' '30553' '30580' '30581' '30582' '30583' '30590' '30591' '30592' '30593' '64830' '64831' '64832' '64833' '64834' '96500' '96501' '96502' '96509' 'V6542'
Amphetamine or cocaine use disorder	ICD-9	'30420' '30421' '30422' '30423' '30440' '30441' '30442' '30443' '30560' '30561' '30562' '30563' '30570' '30571' '30572' '30573'
Smoking	ICD-9	'V1582' '3051 '
Chronic pain syndromes	ICD-9	'3380 ' '33821' '33822' '33828' '33829' '3384 '
Obesity	ICD-9	'27800' '27801' '27802' '27803'
Outcomes		
Acute MI	ICD-9	'41000' '41001' '41010' '41011' '41020' '41021' '41030' '41031' '41040' '41041' '41050' '41051' '41060' '41061' '41070' '41071' '41080' '41081' '41090' '41091'
Acute cerebrovascular accident	ICD-9	'430 ' '431 ' '4320 ' '4321 ' '4329 ' '43301' '43311' '43321' '43331' '43381' '43391' '43401' '43411' '43491'
Sepsis	ICD-9	'0380 ' '0381 ' '03810' '03811' '03812' '03819' '0382 ' '0383 ' '03840' '03841' '03842' '03843' '03844' '03849' '0388 ' '0389 ' '78552' '99591' '99592' '9980' '99802'
Acute kidney injury	ICD-9	'5845 ' '5846 ' '5847 ' '5848 ' '5849 ' '586 ' '9975 '
Respiratory failure	ICD-9	'51851' '51853' '51881' '51884' '9670 ' '9672 ' '9671' '9604 '
Venous thromboembolism	ICD-9	'45111' '45119' '4512 ' '45181' '4519 ' '45340' '45341' '4538 ' '4539 ' '4151 ' '41511' '41513' '41519'
Critical limb ischemia	ICD-9	'44022' '44023' '44024'

Supplementary Table I (online only). Continued.

Diagnosis	Code type	Values
OR		
Code for tissue loss	ICD-9	'7854 ' '70710' '70712' '70713' '70714' '70715' '70719' '73006' '73007' '73016' '73017' '6826 ' '6827 ' '68110'
AND lower extremity atherosclerosis	ICD-9[a]	'44020' '44021' '44029' '4400 ' '44030' '44031' '44032' '4404' '4408 ' '4409 ' '24970' '24971' '25070' '25071' '25072' '25073' '44381' '4431 '
Tissue loss	ICD-9	'7854 ' '70710' '70712' '70713' '70714' '70715' '70719' '73006' '73007' '73016' '73017' '6826 ' '6827 ' '68110' '44023' '44024'
Lower extremity infection	ICD-9	'7854 ' '73006' '73007' '73016' '73017' '6826 ' '6827 ' '68110' '44024'
Pneumonia	CCS	'122'
UTI	CCS	'159'
SSI	ICD-9	'99859'
Procedures		
CEA	ICD-9	'3812'
Infrainguinal bypass	ICD-9	'3829' '3808' '3818' '3838' '3848' '3868'
Open abdominal aortic aneurysm repair	ICD-9	'3834' '3844' '3864'
Aortobifemoral bypass	ICD-9	'3925'
Endovascular aortic aneurysm repair	ICD-9	'3971' '3978'
Peripheral arterial endovascular repair	ICD-9	'3950' '3990' '0055'

CEA, Carotid endarterectomy; *COPD*, chronic obstructive pulmonary disease; *MI*, myocardial infarction; *SSI*, surgical site infection; *UTI*, urinary tract infection.
[a]Code had to be the primary diagnosis.

Supplementary Table II (online only). Analysis of primary and secondary end points using sample weights and survey specific regression procedures

	Adjusted OR (95% CI)	*P* value
MI	1.49 (1.17-1.89)	.0011
Respiratory failure	0.97 (0.83-1.15)	.7424
Acute kidney injury	1.08 (0.93-1.25)	.3087
VTE	0.85 (0.70-1.03)	.1002
Sepsis	0.73 (0.58-0.92)	.0087
Stroke	1.23 (1.02-1.49)	.0306
Mortality[a]	0.72 (0.49-1.06)	.0960

CI, Confidence interval; *CUD*, cannabis use disorder; *MI*, myocardial infarction; *OR*, odds ratio; *VTE*, venous thromboembolism.
Level of significance for secondary end points is set at $P < .006$.
[a]Mortality data were missing for 202 patients.

Supplementary Table III (online only). Rates of myocardial infarction (*MI*) and stroke stratified by carotid endarterectomy (*CEA*) as the index procedure

	No CEA during admission				CEA during admission			
	CUD (n = 2035) (%)	No CUD (n = 2077) (%)	Adjusted OR (95% CI) (CUD vs no CUD)	*P* value	CUD (n = 313) (%)	No CUD (n = 271) (%)	Adjusted odds ratio (95% CI) (CUD vs no CUD)	*P* value
MI (%)	67 (3.3)	46 (2.2)	1.49 (1.02-2.18)	.025	NR	NR	2.37 (0.73-7.64)	.45
Stroke (%)	35 (1.7)	29 (1.4)	1.22 (0.75-2.01)	.4248	93 (29.7)	53 (18.2)	1.90 (1.29-2.79)	.0011

CI, Confidence interval; CUD, cannabis use disorder; *CVA*, cerebrovascular accident; *NR*, not reported (in accordance with the National Inpatient Sample data use agreement, specific values in cell sizes <10 cannot be published); *OR*, odds ratio.