ANESTHESIOLOGY

Cannabis Use Disorder and Perioperative Outcomes in Major Elective Surgeries

A Retrospective Cohort Analysis

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ABSTRACT

Background: Although cannabis is known to have cardiovascular and psychoactive effects, the implications of its use before surgery are currently unknown. The objective of the present study was to determine whether patients with an active cannabis use disorder have an elevated risk of postoperative complications.

Methods: The authors conducted a retrospective population-based cohort study of patients undergoing elective surgery in the United States using the Nationwide Inpatient Sample from 2006 to 2015. A sample of 4,186,622 inpatients 18 to 65 yr of age presenting for 1 of 11 elective surgeries including total knee replacement, total hip replacement, coronary artery bypass graft, caesarian section, cholecystectomy, colectomy, hysterectomy, breast surgery, hernia repair, laminectomy, and other spine surgeries was selected. The principal exposure was an active cannabis use disorder, as defined by International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnostic codes for cannabis dependence and cannabis abuse. The primary outcome was a composite endpoint of in-hospital postoperative myocardial infarction, stroke, sepsis, deep vein thrombosis, pulmonary embolus, acute kidney injury requiring dialysis, respiratory failure, and in-hospital mortality. Secondary outcomes included hospital length of stay, total hospital costs, and the individual components of the composite endpoint.

Results: The propensity-score matched-pairs cohort consisted of 27,206 patients. There was no statistically significant difference between patients with (400 of 13,603; 2.9%) and without (415 of 13,603; 3.1%) a reported active cannabis use disorder with regard to the composite perioperative outcome (unadjusted odds ratio = 1.29; 95% CI, 1.17 to 1.42; $P < 0.001$; Adjusted odds ratio = 0.97; 95% CI, 0.84 to 1.11; $P = 0.63$). However, the adjusted odds of postoperative myocardial infarction was 1.88 (95% CI, 1.31 to 2.69; $P < 0.001$) times higher for patients with a reported active cannabis use disorder (89 of 13,603; 0.7%) compared with those without (46 of 13,603; 0.3%) an active cannabis use disorder (unadjusted odds ratio = 2.88; 95% CI, 2.34 to 3.55; $P < 0.001$).

Conclusions: An active cannabis use disorder is associated with an increased perioperative risk of myocardial infarction.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Cannabis is known to have cardiovascular and psychoactive effects
- The association between active cannabis use disorder and postoperative outcomes remains unclear

What This Article Tells Us That Is New

- In the United States, administrative data demonstrate that cannabis use disorder has increased in prevalence from 2010 to 2015
- Active cannabis use disorder is not associated with a change in overall perioperative morbidity, mortality, length of stay, or costs
- However, active cannabis use disorder is associated with a meaningful increase in the risk of postoperative myocardial infarction

Although cannabis has been used in the United States since the 1800s, recent changes regarding the legality of its recreational and medical use have led to an increase in its consumption. The 2016 American National Survey on Drug Use and Health showed that among the 7.4 million individuals with an illicit drug use disorder, the most common substance used was cannabis (4.0 million people).[1] An estimated 24.0 million Americans aged 12 or older in 2016 reported using cannabis in the last month.[1] Medical

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 612. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. A.G. and B.M. contributed equally to this article.

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cannabis is currently legal in the District of Columbia and 33 states.[1] Given that the prevalence of cannabis use is expected to continue to grow, healthcare providers are likely to encounter the sequelae associated with its use.

Recent literature has highlighted potential detrimental effects associated with cannabis use such as increased bronchial reactivity, cerebrovascular accidents, and myocardial infarctions (MI).[2–8] Surgical patients with an active cannabis use disorder may be at an increased risk of adverse outcomes given the potential for psychoactive and hemodynamic effects within the perioperative setting. No large cohort study has yet evaluated the perioperative outcomes of patients with cannabis use disorder. To anticipate and prevent postoperative complications, perioperative healthcare providers need to be aware of the associated risks of cannabis to ensure that appropriate counseling, safeguards, and monitoring can be applied.

We therefore conducted a retrospective cohort study to (1) identify whether patients with an active cannabis use disorder experienced worse postoperative outcomes and (2) describe national trends in the prevalence of cannabis use disorders in patients presenting for major elective operations. We hypothesized that patients with an active cannabis use disorder have a higher risk of postoperative complications and higher resource utilization.

Materials and Methods

Setting and Data Source

Using a retrospective cohort study design, we analyzed data obtained from the Nationwide Inpatient Sample from 2006 to 2015. We did not include Nationwide Inpatient Sample data after 2015 because of significant changes in procedure and diagnosis codes. The Nationwide Inpatient Sample is the largest all-payer inpatient healthcare database in the United States and is operated by the Agency for Healthcare Research and Quality. Each annual dataset represents a 20% stratified sample of discharges from more than 1,000 nonfederal hospitals. Discharges are included in the dataset based on a weighted sampling scheme that permits inferences for a nationally representative population. This study did not require review by an institutional review board (IRB) because these deidentified data are publicly available.

Cohort Definition

Patients undergoing any of the following common elective procedures were included in the analysis: coronary artery bypass graft (CABG), caesarian section, cholecystectomy, colectomy, total hip revision, total knee revision, hysterectomy, breast surgery (lumpectomy or mastectomy), hernia surgery, laminectomy, and other elective spine surgeries. Only procedures classified as elective in the Nationwide Inpatient Sample were included. These procedures were selected *a priori* because they are common elective procedures that encompass a variety of surgical subspecialties and incision types (Supplemental Digital Content, table E1, http://links.lww.com/ALN/C135). Procedures were identified using the Clinical Classification Software, a publicly available classification system developed by the Agency for Healthcare Research and Quality.[9]

To be included in the cohort, each admission had to have a length of stay of at least 1 day to ensure only nonambulatory surgery was assessed. Patients younger than 18 yr of age were excluded because pediatric patients have additional considerations, which should be analyzed separately. Additionally, individuals older than 65 yr of age were also excluded given that reported cannabis use was so low in this age group during the case-accrual period, their inclusion could have led to a violation of the assumption of positivity.[10] Patients with missing data were also excluded from the analysis (2.4%). Because of differences in state-level reporting of race data, 15.2% of patients were missing a race designation. Therefore, we used an indicator variable for missing race values in the analysis. Finally, the distribution of all variables was assessed for plausibility. Given that there were limited outliers and we could not assess their validity, they were included in the analysis without further modification. The cohort assembly process is outlined in figure 1.

Exposure

An active cannabis use disorder was defined by the presence of any of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnoses: cannabis dependence (304.30, 304.31, and 304.32) or cannabis abuse (305.20, 305.21, and 305.22). These codes have been previously used to define cannabis-related disorders in the literature.[11–14] Further, administrative diagnostic codes for illicit substance use disorders have very high specificity (greater than 95%).[15–17] There is no ICD-9 code for uncomplicated cannabis use, therefore this was not included.

Outcomes

The primary composite outcome was composed of clinically relevant postoperative complications, including myocardial infarction, stroke, sepsis, deep vein thrombosis/pulmonary embolus, acute kidney injury requiring dialysis, respiratory failure, and in-hospital mortality. These complications were identified using ICD-9-CM diagnostic codes designated as quality and patient safety indicators by the Agency for Healthcare Research and Quality.[18,19] These definitions have been validated in previous studies[11–14] and are outlined in Supplemental Digital Content, table E2 (http://links.lww.com/ALN/C135). Secondary outcomes included the individual components of the primary composite outcome, hospital length of stay, and total cost associated with hospitalization.

Covariates

Covariates were chosen based on clinical sensibility, biologic plausibility, and previous evidence of being predictors

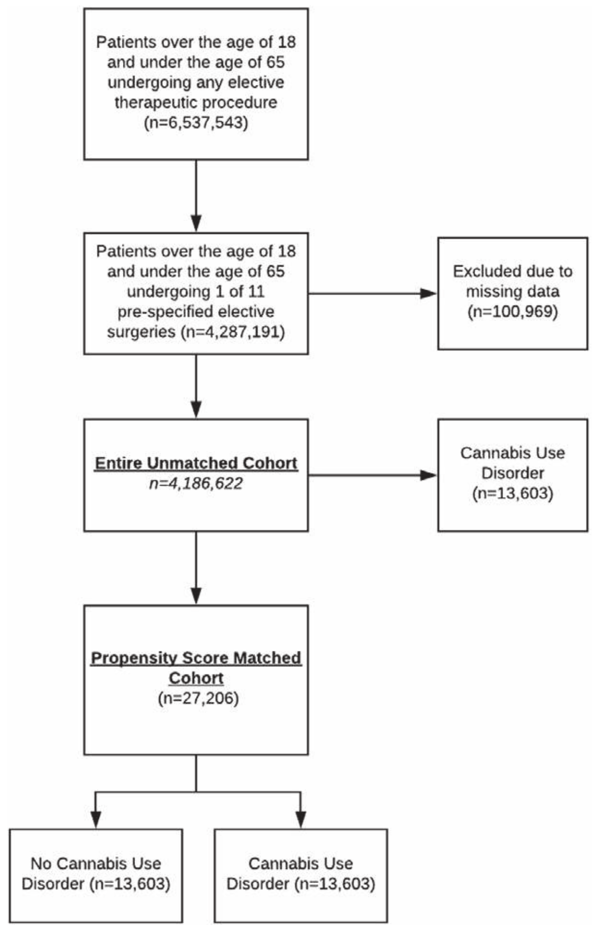

Fig. 1. Flowchart demonstrating cohort formation.

of reported active cannabis use disorder and postoperative outcomes.[4,5,11–13] Demographic characteristics such as sex, race, and age were included. Major comorbidities including substance use disorder, chronic pain, smoking, previous history of coronary artery disease, and heart failure were also incorporated. We ensured that codes distinguished between preexisting conditions and acute events for outcome classification. Hospital-level characteristics such as urbanicity, region, and size (number of beds) were collected. We included data on surgical procedure. Finally, to account for temporal trends in cannabis use and postoperative outcomes we included year as a covariate. A complete summary of covariates can be found in table 1, and the ICD-9-CM codes used to define covariates can be found in Supplemental Digital Content, table E3 (http://links.lww.com/ALN/C135).

Statistical Analysis

We plotted the annual weighted proportions of active cannabis use disorder among patients presenting for these surgical procedures to examine temporal trends. We assessed for a significant change in cannabis use between years using SAS survey functions to account for clustering and a chi-square test. We used a propensity-score matched-pairs analysis of the cohort to evaluate the adjusted association between active cannabis use disorders and the outcomes of interest. We estimated propensity scores for a patient having an active cannabis use disorder using a multivariable logistic regression model. All covariates were included in the model without further selection. To account for nonlinear associations a quadratic term was included for age and the Elixhauser Comorbidity Index was included as a categorical variable (0, 1, 2, and 3 or more). Patients were matched using a 1:1 nearest neighbor match with a caliper size of 0.05 on the propensity score scale. To control for any residual confounding by covariates with a standardized difference greater than 10% after matching, we included these variables as covariates in a multivariable logistic regression model analyzing the association between exposure and outcome.[20] Cost was analyzed using a generalized linear model assuming a gamma distribution and a log link function. Length of stay was analyzed using a negative binomial regression.

To assess the robustness of these results, we conducted three additional sensitivity analyses. First, we repeated the primary analysis across all outcomes in the entire unmatched cohort, using survey weighted multivariable regression. Sample weights provided by the Healthcare Cost and Utilization Project were utilized, with updated weights used for years before 2012 to account for changes in the sampling methodology of the Nationwide Inpatient Sample. These allow for appropriate weighting of Nationwide Inpatient Sample data to nationally representative figures and improved accuracy in estimates of variance. Appropriate survey procedures in SAS were used when determining frequencies and means as well as linear and logistic regressions. Covariates used in the regression model were the same as those used to generate the propensity score. Second, to determine the potential impact of unmeasured confounding, we calculated the E value for any statistically significant associations.[21] This method allows for the estimate of the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away a specific exposure–outcome association.[21] Finally, we conducted a *post hoc* propensity score match in the same cohort among patients with an isolated active cannabis use disorder (*i.e.*, excluding other substance use disorders) to assess for residual confounding. This was the only sensitivity analyses that was not determined *a priori* during statistical planning. A clinically meaningful minimum effect size was not defined before data access.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). Reported *P* values are two-sided, with $P < 0.05$ considered statistically significant when evaluating the composite outcome. Using the Bonferroni method, we considered a *P* value of 0.005 (0.05 divided by 10 outcomes studied) significant when

Table 1. Patient Characteristics of Unmatched Cohort without the Use of Sample Weights

	Active Cannabis Use Disorder		
	Yes (%)	No (%)	Standardized Difference
Total	13,877	4,256,631	
Sex			0.211
Female	9,456 (68.1)	3,254,420 (76.5)	
Race			0.450
Caucasian	7,340 (53.0)	2,524,601 (59.4)	
African American	3,443 (24.8)	416,167 (9.8)	
Hispanic	908 (6.6)	425,282 (10.0)	
Other	507 (3.7)	241,917 (5.7)	
Missing	1,679 (12.0)	648,664 (15.1)	
Age, mean ± SD	37 ± 15	44 ± 18	0.918
Yr			0.392
2006	922 (6.4)	448,093 (10.2)	
2007	980 (6.9)	471,810 (10.8)	
2008	998 (6.9)	477,316 (10.9)	
2009	1,023 (7.3)	447,051 (10.6)	
2010	1,218 (8.7)	445,485 (10.5)	
2011	1,484 (10.3)	455,485 (10.4)	
2012	1,558 (11.5)	413,977 (10.1)	
2013	1,674 (12.3)	403,215 (9.8)	
2014	2,099 (15.5)	400,565 (9.7)	
2015*	1,921 (14.2)	293,437 (7.1)	
Mean household income quartile by zip code			0.373
1	5,373 (39.5)	982,492 (23.5)	
2	3,746 (27.5)	1,056,585 (25.2)	
3	2,877 (21.1)	1,082,997 (25.9)	
4	1,618 (11.9)	1,058,257 (25.3)	
Surgery type			
Coronary artery bypass graft	442 (3.2)	94,461 (2.2)	0.007
Caesarian section	6,421 (46.2)	1,396,702 (32.8)	0.310
Cholecystectomy	313 (2.3)	108,611 (2.5)	0.032
Colectomy	737 (5.3)	200,525 (4.7)	0.025
Total hip revision	1,131 (8.2)	319,749 (7.5)	0.061
Total knee revision	949 (6.9)	592,306 (14.0)	0.303
Hysterectomy	966 (6.9)	611,532 (14.3)	0.129
Breast surgery	134 (1.0)	81,967 (1.9)	0.070
Hernia repair	503 (3.6)	192,222 (4.5)	0.044
Laminectomy	1,824 (13.2)	547,433 (12.9)	0.001
Spine surgery	1,832 (13.2)	520,913 (12.3)	0.020
Hospital urbanicity, teaching status			0.292
Rural	1,555 (11.3)	400,851 (9.5)	
Urban nonteaching	3,857 (27.8)	1,678,098 (39.4)	
Urban teaching	8,401 (60.9)	2,159,202 (51.1)	
Hospital size			0.060
Small	1,938 (13.7)	637,579 (14.6)	
Medium	3,716 (27.1)	1,096,446 (26.1)	
Large	8,159 (59.2)	2,504,126 (59.3)	
Chronic obstructive pulmonary disease	771 (5.6)	123,353 (2.9)	0.042
Liver disease	777 (5.6)	90,899 (2.1)	0.189
History of substance use disorder (cocaine, amphetamine, opioid)	2,475 (17.8)	36,330 (0.9)	0.598
History of alcohol abuse	1,231 (8.9)	32,716 (0.8)	0.455
Mood disorder	2,799 (20.3)	414,652 (9.8)	0.297
Personality disorder	77 (0.6)	2,002 (0.1)	0.103
History of schizophrenic disorder	188 (1.4)	10,946 (0.3)	0.107
History of chronic pain	792 (5.8)	96,946 (2.3)	0.190
History of smoking	5,807 (41.8)	729,065 (17.2)	0.598
Obese (body mass index > 25)	2,041 (14.8)	623,628 (14.7)	0.020
Solid tumor	897 (6.5)	360,286 (8.5)	0.128
Hematologic malignancy	56 (0.4)	20,156 (0.5)	0.004
Metastatic cancer	166 (1.2)	71,314 (1.7)	0.014
Diabetes	1,161 (8.4)	484,691 (11.4)	0.212

(*Continued*)

Table 1. (Continued)

	Active Cannabis Use Disorder		Standardized Difference
	Yes (%)	No (%)	
Coronary artery disease	832 (6.0)	238,723 (5.6)	0.214
History of congestive heart failure	192 (1.4)	45,782 (1.1)	0.087
Renal disease	176 (0.1)	53,278 (1.3)	0.078
Asthma	1,624 (11.7)	319,043 (7.5)	0.138
Rheumatoid arthritis	175 (1.3)	59,738 (1.4)	0.044
History of cerebrovascular accident	38 (0.3)	9,223 (0.2)	0.004
Elixhauser comorbidity score			0.030
0	4,471 (32.1)	1,809,683 (42.4)	
1	3,675 (26.5)	1,049,855 (24.7)	
2	2,807 (20.3)	737,516 (17.4)	
3 or more	2,924 (21.2)	659,577 (15.6)	

A standardized difference greater than 0.100 indicates a statistically significant difference between groups.
*Note that 2015 data were not available in ICD-9 after October 2015 and are therefore truncated.

testing the secondary outcomes. The sample size was based on the available data and no *a priori* power calculations were performed.

Results

Data were available for a total of 4,186,622 patients. The prevalence of cannabis use disorder among surgical patients increased from 21.1 per 1,000,000 surgical admissions in 2006 to 71.0 per 1,000,000 surgical admissions in 2015 (fig. 2; $P < 0.001$). We observed a similar time trend of increasing cannabis use among the overall cohort of all elective diagnostic or therapeutic procedures available in the Nationwide Inpatient Sample. The characteristics of the full cohort (*i.e.*, before matching) are summarized in table 1. Patients with a cannabis use disorder were more likely to be males, black, and younger.

The matched-pairs cohort consisted of 13,603 patients in each group. Differences between the group of patients with a reported active cannabis use disorder and the group of patients without were minimal. Aside from histories of other substance use disorders including amphetamine, opioid, and cocaine use (standardized difference = 11.1%), the maximum standardized difference in the matched-pairs cohort was 7.0% (table 2). To account for this residual imbalance, we adjusted for substance use disorder in the final regression model.[20]

There was no statistically significant difference between patients with (400 of 13,603; 2.9%) and without (415 of 13,603; 3.1%) a reported active cannabis use disorder with regard to the composite perioperative outcome (unadjusted odds ratio = 1.29; 95% CI, 1.17 to 1.42; $P < 0.001$; adjusted odds ratio = 0.97; 95% CI, 0.84 to 1.11; $P = 0.63$). There was also no difference with regard to in-hospital mortality (unadjusted odds ratio = 1.01; 95% CI, 0.57 to 1.78; $P = 0.884$; adjusted odds ratio = 0.87; 95% CI, 0.40 to 1.88; $P = 0.72$). However, the adjusted odds of postoperative myocardial infarction was 1.88 (95% CI, 1.31 to 2.69; $P < 0.001$) times higher for patients with a reported active cannabis use disorder (89 of 13,603; 0.7%) compared with those without (46 of 13,603; 0.3%) an active cannabis use disorder (unadjusted odds ratio = 2.88; 95% CI, 2.34 to 3.55; $P < 0.001$). The adjusted odds of acute cerebrovascular accident were 3.30 (95% CI, 1.22 to 8.96; $P = 0.019$) times higher for patients with a reported active cannabis use disorder; however, this was not deemed statistically significant after adjustment for multiple testing (unadjusted odds ratio = 2.01; 95% CI, 1.25 to 3.24; $P = 0.008$). Analysis of the length of stay ratio (unadjusted length of stay ratio = 1.10; 95% CI, 1.01 to 1.11; $P < 0.001$; adjusted length of stay ratio = 0.99; 95% CI, 0.97 to 1.00; $P = 0.148$) and cost ratio (unadjusted cost ratio = 1.05; 95% CI, 1.04 to 1.07; $P < 0.001$; adjusted cost ratio = 1.01, 95% CI, 0.99 to 1.03; $P = 0.159$) between patients with active cannabis use disorder and no active cannabis use disorder showed no statistically significant difference.

In sensitivity analyses, the primary analysis was repeated using survey-weighted multivariable logistic regression. The results for outcome measures were similar to the primary analysis (table 3); however, length of stay was statistically but not clinically significantly different (estimated difference in weighted cohort: −0.13 days; 95% CI, −0.19 to −0.07; $P < 0.001$ *vs.* estimated difference in matched cohort: −0.05 days, 95% CI, −0.13 to 0.03; $P = 0.272$). The magnitude of this difference was not clinically meaningful (Supplemental Digital Content, table E4, http://links.lww.com/ALN/C135). A *Post Hoc* sensitivity analysis was also performed with a separate match conducted while excluding those with a history of all substance use disorders, except cannabis use disorder. This again yielded similar results with an odds ratio for postoperative MI of 1.68 (95% CI, 1.12 to 2.53;

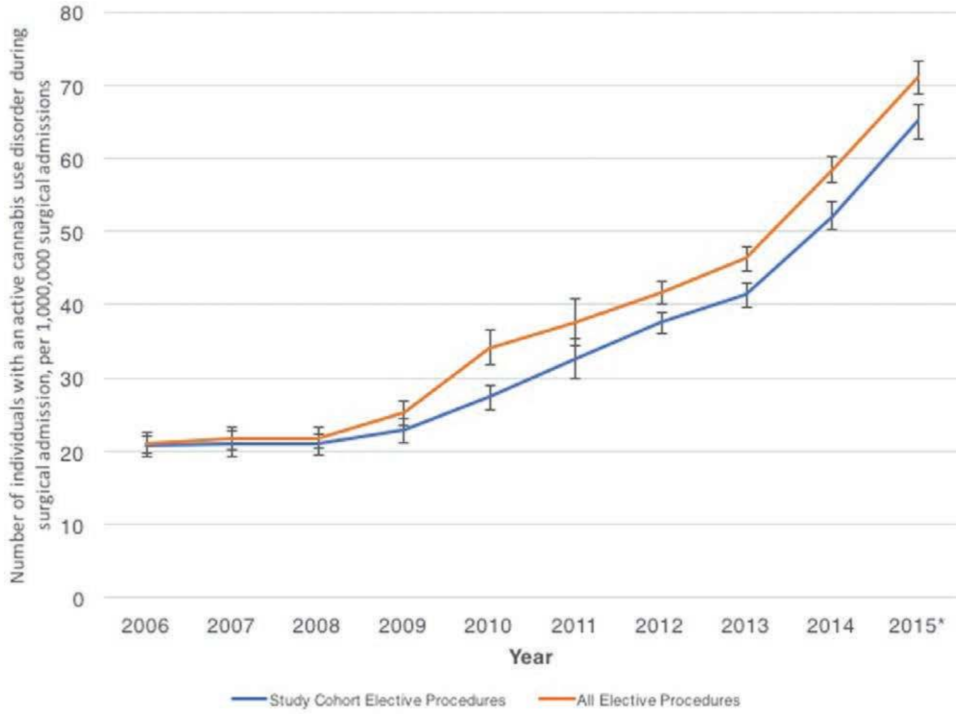

Fig. 2. Annual trends of surgical admissions with reported active cannabis use disorder, with standard errors indicated by error bars. *2015 data are truncated until October 2015 ($P < 0.001$).

$P < 0.001$). The primary and other secondary outcomes were in keeping with the primary analysis.

Lastly, an E value was calculated to quantify unmeasured residual confounding that could account for the relationship between an active cannabis use disorder and the estimated increased odds of postoperative myocardial infarction. Any such unmeasured confounder would have to be associated with both postoperative myocardial infarction and preoperative active cannabis use disorder by an odds ratio of at least 3.16 to completely explain the observed association.

Discussion

In this large cohort study of postoperative outcomes among surgical patients with an active cannabis use disorder, there was no difference in a composite of adverse postoperative outcomes related to an active cannabis use disorder. However, patients with a cannabis use disorder were more likely to experience a postoperative acute MI than their counterparts without a cannabis use disorder. A reported active cannabis use disorder may also be associated with higher adjusted odds of suffering a postoperative acute cerebrovascular accident, although this result was not statistically significant after Bonferroni adjustment.

The prevalence of cannabis use disorder recorded among surgical patients has increased over the past decade. This temporal trend may be related to increase in use or increase in diagnosis over time. If the stigma (and potential for legal risk) declined over time, patients may be more likely to admit use and physicians may be more willing to include the history in the medical record. On the other hand, growing cultural acceptance regarding cannabis use may mean patients do not receive a diagnosis from a physician despite admitting to its use.[22]

We did not find any difference in the composite outcome; however, there was a higher risk of postoperative myocardial infarction. The deleterious effects of smoked cannabis on the cardiovascular system have been well described in the existing literature.[23–34] Mittleman *et al.*[23] described the biologic effects of smoked cannabis to be complex and concluded that smoking cannabis may be a rare trigger of acute myocardial infarction, especially in patients with established coronary artery disease. One of the possible mechanisms behind this finding is the previously described dose-dependent increase in heart rate with cannabis use.[24–31] Although the effect of cannabis on heart rate exhibits high interpatient variability, heart rate appears to peak around 10 to 30 min after smoking.[29–32] Several studies also detail a hypertensive response to smoked cannabis in the supine position,[25,28,29] and orthostatic hypotension has also been described.[27,28] Moreover, smoked cannabis may be associated with an increase in blood carboxyhemoglobin, in particular in the recreational setting where it is commonly mixed with tobacco, thereby reducing oxygen-carrying

Table 2. Patient Characteristics of Propensity-matched Cohort without the Use of Sample Weights

	Active Cannabis Use Disorder		Standardized Difference
	Yes (%)	No (%)	
Total	13,603	13,603	
Sex			0.033
Female	9,289 (68.3)	9,079 (66.7)	
Race			0.066
Caucasian	7,208 (53.0)	7,295 (53.6)	
African American	3,406 (25.0)	3,476 (25.6)	
Hispanic	877 (6.5)	779 (5.7)	
Other	491 (3.6)	397 (2.9)	
Missing	1,621 (11.9)	1,656 (12.2)	
Age, mean ± SD	37 ± 14	37 ± 13	0.024
Yr			0.047
2006	897 (6.6)	878 (6.5)	
2007	955 (7.0)	890 (6.5)	
2008	981 (7.2)	976 (7.2)	
2009	993 (7.3)	966 (7.1)	
2010	1,205 (8.9)	1,253 (9.2)	
2011	1,448 (10.6)	1,451 (10.7)	
2012	1,524 (11.2)	1,524 (11.2)	
2013	1,641 (12.1)	1,634 (12.0)	
2014	2,071 (15.2)	2,123 (15.6)	
2015*	1,888 (13.9)	1,908 (14.0)	
Mean household income quartile by zip code			0.068
1	5,370 (39.5)	5,542 (40.7)	
2	3,743 (27.5)	3,768 (27.7)	
3	2,874 (21.1)	2,821 (20.7)	
4	1,616 (11.9)	1,472 (10.8)	
Surgery type			
Coronary artery bypass graft	438 (3.2)	427 (3.1)	0.005
Caesarian section	6,309 (46.4)	6,138 (45.1)	0.025
Cholecystectomy	304 (2.2)	281 (2.1)	0.012
Colectomy	720 (5.3)	795 (5.8)	0.024
Total hip revision	1,105 (8.1)	1,116 (8.2)	0.003
Total knee revision	929 (6.8)	918 (6.8)	0.003
Hysterectomy	944 (6.9)	890 (6.5)	0.016
Breast surgery	132 (1.0)	129 (1.0)	0.002
Hernia repair	491 (3.6)	505 (3.7)	0.006
Laminectomy	1,782 (13.1)	1,885 (13.9)	0.022
Spine surgery	1,796 (13.2)	1,921 (14.1)	0.027
Hospital urbanicity, teaching status			< 0.001
Rural	1,534 (11.3)	1,510 (11.1)	
Urban nonteaching	3,812 (28.0)	3,754 (27.6)	
Urban teaching	8,257 (60.7)	8,339 (61.3)	
Hospital size			< 0.001
Small	1,914 (14.1)	1,813 (13.3)	
Medium	3,650 (26.8)	3,654 (28.9)	
Large	8,039 (59.1)	8,136 (59.8)	
Chronic obstructive pulmonary disease	764 (5.6)	659 (4.8)	0.035
Liver disease	755 (5.6)	672 (4.9)	0.027
History of substance use disorder (cocaine, amphetamine, opioid)	2,401 (17.7)	1,854 (13.6)	0.111
History of alcohol abuse	1,195 (8.8)	994 (7.3)	0.054
Mood disorder	2,740 (20.1)	2,701 (19.9)	0.007
Personality disorder	74 (0.5)	47 (0.4)	0.030
History of schizophrenic disorder	188 (1.4)	135 (1.0)	0.036
History of chronic pain	772 (5.7)	680 (5.0)	0.030
History of smoking	5,705 (41.9)	6,176 (45.4)	0.070
Obese (body mass index > 25)	2,013 (14.8)	1,923 (14.1)	0.019
Solid tumor	874 (6.4)	783 (5.8)	0.028
Hematologic malignancy	53 (0.4)	65 (0.5)	0.013
Metastatic cancer	161 (1.2)	167 (1.2)	0.004
Diabetes	1,138 (8.4)	1,050 (7.7)	0.024
Coronary artery disease	823 (6.1)	745 (5.5)	0.025

(*Continued*)

Table 2. (Continued)

	Active Cannabis Use Disorder		Standardized Difference
	Yes (%)	No (%)	
History of congestive heart failure	191 (1.4)	171 (1.3)	0.013
Renal disease	172 (1.3)	173 (1.3)	< 0.001
Asthma	1,600 (11.8)	1,660 (12.2)	0.014
Rheumatoid arthritis	174 (1.3)	135 (1.0)	0.027
History of cerebrovascular accident	38 (0.3)	34 (0.3)	0.006
Elixhauser comorbidity score			0.029
0	4,373 (32.2)	4,339 (31.9)	
1	3,605 (26.5)	3,767 (27.7)	
2	2,746 (20.2)	2,761 (20.3)	
3 or more	2,879 (21.2)	2,736 (20.1)	

A standardized difference greater than 0.100 indicates a statistically significant difference between groups.
*Note that 2015 data were not available in ICD-9 after October 2015 and are therefore truncated.

capacity.[26] It is also very likely that patients were not continued on their cannabis products during in-patient hospitalization, and perioperative cessation of cannabis may lead to signs and symptoms of acute cannabis withdrawal, including hypertension and tachycardia.[34]

This supply–demand mismatch in oxygen, coupled with the increased cardiovascular oxygen demands during surgery, may underlie the higher perioperative risk of acute myocardial infarction among patients with cannabis use disorder. Furthermore, more recent and frequent use of cannabis may have exaggerated effects on these outcomes. Unfortunately, this study was limited by the absence of information on recent use or intensity of past cannabis exposure in the Nationwide Inpatient Sample. However, these results demonstrate the need for further research into this area to determine the mechanism behind this association.

If these findings are confirmed, future studies could evaluate whether additional postoperative cardiac monitoring is warranted for patients with a reported active cannabis use disorder.

This study has multiple strengths, including a large nationally representative sample with the power to precisely estimate the risks in this population across a variety of common elective surgical procedures. We were also able to control for relevant demographic and clinical comorbid conditions, including substance use disorders and mental-health disorders that may be associated with concomitant cannabis use and poor perioperative outcomes.

However, this study also has several limitations that must be considered. Given the observational nature of the study, the possibility of residual unmeasured confounding is a concern. For example, administrative databases have been shown to identify smokers with limited sensitivity owing to differences in status, intensity, duration, and even recency.[35] Furthermore, given the limitations of ICD-9, the Nationwide Inpatient Sample does not allow for adjustment of other potential confounders such as chronic, outpatient use of opioids. However, the sensitivity analysis using the E value demonstrated that any unmeasured confounder would have to be significantly large to explain away the observed association between a reported active cannabis use disorder and perioperative myocardial infarction.[21]

The observed rates of myocardial infarction in this study (0.7% in patients with cannabis use disorder, and 0.3% in patients without cannabis use disorder) were lower than what would be expected if there indeed was uniform troponin or electrocardiogram surveillance. However, we have no reason to believe that an active cannabis use disorder would have led to differential surveillance of cardiac events. The dataset used was originally intended for billing purposes, leading to the possibility of coding misclassification. Specifically, the exposure definition may not be able to precisely differentiate between cannabis dependence and abuse because of coding variability among providers. To mitigate this, we grouped users who were coded as "cannabis dependence" and "cannabis abuse" into one group. Although this strategy does not allow us to obtain granular detail about cannabis dose, formulation, or duration of use, it did allow us to reach overarching conclusions about cannabis use and perioperative morbidity.

A diagnosis of cannabis use disorder reflects a history that the patient was willing to share, and the physician was willing to include in the medical record. Thus, it is likely that a large proportion of individuals with cannabis use disorder were not captured in our data. Indeed, a systematic review identified the US prevalence of cannabis dependence to be 0.6%, which is a rate significantly higher than what we observed.[36] However, this estimate is from the general population, rather than patients undergoing surgery. Thus, it is unclear what proportion of diagnoses were missed in our analyses. Additionally, it is probable that heavy or recent users were more likely to be included in the group with reported active cannabis use disorder, resulting in high specificity but poor sensitivity in the classification of cannabis

Table 3. Analysis Examining the Association between Patients with Active Cannabis Use Disorder and the Primary and Secondary Outcomes in the Propensity-matched Cohort of Patients

	Unadjusted Analyses				Adjusted Analyses			
	Cannabis Use Disorder (n = 13,603)	No Cannabis Use Disorder (n = 4,172,619)	Odds Ratio, Length of Stay Ratio, or Total Cost Ratio (95% CI) (Cannabis Use Disorder *vs.* No Cannabis Use Disorder)	*P* Value	Cannabis Use Disorder (n = 13,603)	No Cannabis Use Disorder (n = 13,603)	Odds Ratio, Length of Stay Ratio, or Total Cost Ratio (95% CI) (Cannabis Use Disorder *vs.* No Cannabis Use Disorder)	*P* Value
Primary composite outcome (%)	405 (2.98)	97,020 (2.33)	1.29 (1.17 to 1.42)	< 0.001	400 (2.9)	415 (3.1)	0.97 (0.84 to 1.11)	0.631
Myocardial infarction (%)	89 (0.64)	9,523 (0.23)	2.88 (2.34 to 3.55)	< 0.001	89 (0.7)	46 (0.3)	1.88 (1.31 to 2.69)	< 0.001
Respiratory failure (%)	165 (1.21)	34,451 (0.83)	1.47 (1.26 to 1.72)	< 0.001	163 (1.2)	179 (1.3)	0.91 (0.74 to 1.13)	0.396
Acute kidney injury (%)	162 (1.19)	49,225 (1.18)	1.01 (0.86 to 1.18)	0.905	161 (1.2)	179 (1.3)	0.90 (0.72 to 1.11)	0.310
VTE (%)	26 (0.19)	9,997 (0.24)	0.80 (0.54 to 1.17)	0.291	25 (0.2)	38 (0.3)	0.68 (0.41 to 1.13)	0.134
Sepsis (%)	46 (0.34)	12,370 (.30)	1.14 (0.85 to 1.53)	0.344	45 (0.3)	55 (0.4)	0.83 (0.56 to 1.23)	0.360
CVA (%)	17 (0.12)	2,595 (0.06)	2.01 (1.25 to 3.24)	0.008	17 (0.1)	NR	3.30 (1.22 to 8.96)	0.019
Mortality (%)	12 (0.09)	3,646 (0.09)	1.01 (0.57 to 1.78)	0.884	12 (0.1)	14 (0.1)	0.87 (0.40 to 1.88)	0.719
Length of stay, days (95% CI)	3.61 (3.57 to 3.65)	3.29 (3.29 to 3.29)	1.10 (1.01 to 1.11)	< 0.001	N/A	N/A	0.99 (0.97 to 1.00)	0.148
Total cost, USD (95% CI)	13,100 (12,932 to 13,269)	12,450 (12,441 to 12,459)	1.05 (1.04 to 1.07)	< 0.001	N/A	N/A	1.01 (0.99 to 1.03)	0.159

Cell sites less than or equal to 10 cannot be published as per the data use agreement of the Nationwide Inpatient Sample. Survey weights were not used in this analysis. Significance defined as $P < 0.05$ for the composite outcome and $P < 0.005$ for the secondary outcomes. Results were obtained using regression models after adjusting for confounders. CVA, cerebrovascular accident; N/A, not applicable; NR, not reportable; USD, United States dollars; VTE, venous thromboembolism.

use disorders. This may have biased the results toward the null. In this case, these results are still valid, but only in cases of extreme or more recent exposure.

The lack of sensitivity of coding in administrative databases could also partially explain our negative findings with respect to the composite endpoint and cerebrovascular accident. Specifically with regard to cerebrovascular accident, we observed a nearly threefold increased odds in the perioperative period among individuals with a cannabis use disorder. However, this result was not deemed to be statistically significant given that we had prespecified a conservative approach (Bonferroni method) to adjust for multiple comparisons. The association between cannabis use and cerebrovascular events has been previously described in the literature, and biologic plausibility exists for this relationship.[37–39] Therefore, despite the result being nonsignificant in our analysis, we believe that this finding deserves further investigation given (1) our use of a conservative approach to control for multiple testing, (2) the under-reporting of cannabis use disorder in the Nationwide Inpatient Sample, and (3) the magnitude of the effect size.

Lastly, the authors recognize that Δ^9-Tetrahydrocannibinol (Δ^9 -THC) is the major psychoactive component of cannabis, and chemical composition of cannabis or its extracts determines the potential for cannabis use disorder. It is assumed that all patients with cannabis use disorder have been exposed to high Δ^9-THC cannabis varieties. Further exploration is necessary on the chemical compositions of cannabis that lead to cannabis use disorder, which is outside the scope of this report.

Conclusions

The data showed that although there was no increased risk for the composite outcome of perioperative complications in individuals with an active reported cannabis use disorder, there was a strong association with a higher incidence of perioperative acute myocardial infarction. This study serves to highlight a potentially at-risk group of patients that is growing. Further prospective studies with better measurement of cannabis use and postoperative complications are required to confirm the finding that perioperative cannabis use may result in an increased risk of myocardial infarction.

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Competing Interests

The authors declare no competing interests.

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