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Cannabis Use and Inhalational Anesthesia Administration in Older Adults: A Propensity-matched Retrospective Cohort Study

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ABSTRACT

Background: Cannabis use is associated with higher intravenous anesthetic administration. Similar data regarding inhalational anesthetics are limited. With rising cannabis use prevalence, understanding any potential relationship with inhalational anesthetic dosing is crucial. Average intraoperative isoflurane or sevoflurane minimum alveolar concentration equivalents between older adults with and without cannabis use were compared.

Methods: The electronic health records of 22,476 surgical patients 65 yr or older at the University of Florida Health System between 2018 and 2020 were reviewed. The primary exposure was cannabis use within 60 days of surgery, determined *via* (1) a previously published natural language processing algorithm applied to unstructured notes and (2) structured data, including International Classification of Diseases codes for cannabis use disorders and poisoning by cannabis, laboratory cannabinoids screening results, and RxNorm codes. The primary outcome was the intraoperative time-weighted average of isoflurane or sevoflurane minimum alveolar concentration equivalents at 1-min resolution. No *a priori* minimally clinically important difference was established. Patients demonstrating cannabis use were matched 4:1 to non–cannabis use controls using a propensity score.

Results: Among 5,118 meeting inclusion criteria, 1,340 patients (268 cannabis users and 1,072 nonusers) remained after propensity score matching. The median and interquartile range age was 69 (67 to 73) yr; 872 (65.0%) were male, and 1,143 (85.3%) were non-Hispanic White. The median (interquartile range) anesthesia duration was 175 (118 to 268) min. After matching, all baseline characteristics were well-balanced by exposure. Cannabis users had statistically significantly higher average minimum alveolar concentrations than nonusers (mean ± SD, 0.58 ± 0.23 *vs.* 0.54 ± 0.22, respectively; mean difference, 0.04; 95% confidence limits, 0.01 to 0.06; $P = 0.020$).

Conclusion: Cannabis use was associated with administering statistically significantly higher inhalational anesthetic minimum alveolar concentration equivalents in older adults, but the clinical significance of this difference is unclear. These data do not support the hypothesis that cannabis users require clinically meaningfully higher inhalational anesthetics doses.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Cannabis use is associated with higher intravenous anesthetic administration for general anesthesia
- Similar data regarding cannabis users and inhaled volatile anesthetic administration are limited by challenges in accurately identifying cannabis users using structured electronic health record data and small sample size

What This Article Tells Us That Is New

- Using a combination of natural language processing of free text notes and structured electronic health record documentation, 268 older adults (age 65 yr or older) with documentation of cannabis use within 60 days before surgery were compared to 1,072 similar older adults without documentation of cannabis use
- Cannabis users received a time-weighted average volatile minimum alveolar concentration of 0.58 (SD, 0.23) compared to 0.54 (SD, 0.22)
- Although this mean difference of 0.04 minimum alveolar concentration was statistically significant, the clinical significance of this difference is unclear and does not support the hypothesis that older adult cannabis users require clinically meaningful higher inhalational anesthetic dosing

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 829. 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 a visual abstract available in the online version. Preliminary results of this study were presented during the Anesthesiology 2023 Annual Meeting (American Society of Anesthesiologists) in San Francisco, California, October 15, 2023.

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The increasing prevalence of cannabis use has stirred significant concerns among anesthesiologists challenged with providing care to an ever-growing patient population who uses the substance.[1–3] Cannabis is the most widely used federally illicit substance in the United States, with an estimated 53 million Americans aged 12 yr or older using cannabis in 2021, a 70% increase from 2002.[4,5] With the increasing state-level trend of cannabis legalization, these numbers are expected to continue rising.[4] Anesthesia-related concerns mainly stem from potential interactions between cannabinoids and anesthetic agents, potentially altering their efficacy and hindering effective and safe care.[1–3] Other concerns regarding potential adverse effects on cardiovascular, respiratory, and neurocognitive functioning and postoperative pain also exist.[1–3,6,7] These adverse effects may pose increased perioperative morbidity and mortality risks, particularly in vulnerable populations, including elderly patients and those with underlying comorbidities.[8,9]

Considering federal regulations and ethical considerations, clinical trials involving cannabis are limited.[5] Previous observational studies found positive associations between cannabis use and increased doses of anesthetic medications, mainly propofol, fentanyl, and ketamine at varying magnitudes (14 to 220%).[10–13] However, clinical evidence derived on the potential impacts on inhalational anesthesia is limited. Two case reports linked cannabis use to inhalational anesthetic tolerance.[14,15] A recent correspondence reported higher crude average total volume of consumed liquid sevoflurane in cannabis users undergoing tibia fracture open reduction and internal fixation compared to nonusers.[16] Preclinical studies highlighted mechanisms by which cannabinoids could alter inhalational anesthetics' efficacy. The two main cannabinoids, tetrahydrocannabinol and cannabidiol, interact with brain cannabinoid type 2 receptors, leading to hippocampal γ-aminobutyric acid inhibition,[17] interfering with a key inhibitory mechanism in general anesthesia.[18] Tetrahydrocannabinol-mediated activation of cannabinoid type 1 receptors inhibits key brain neurotransmitters for sleep and arousal.[19] These antagonistic effects could decrease inhalational anesthetics' efficacy, leading to inadequate hypnosis, increased risk of intraoperative awareness, and the need for delivering higher alveolar concentrations to compensate. As inhalational anesthesia is linked to postoperative neurocognitive dysfunction, specifically in older populations,[20] ascertaining potential associations between cannabis use and increased inhalational anesthesia administration is paramount.

Previous observational studies leveraging electronic health record data in this area relied on structured data types, such as International Classification of Diseases (ICD) codes for cannabis use disorders, to ascertain cannabis exposure status. However, this approach is highly likely to cause exposure misclassification and introduce bias.[21,22] Previous research estimated that greater than 80% of cannabis-related documentation exists in unstructured narrative clinical notes.[21] Cannabis use disorders ICD codes fail to capture the majority of patients who use cannabis without meeting cannabis use disorders diagnostic criteria.[22] Advanced data extraction techniques, namely natural language processing, can extract more reliable cannabis exposure data from large-sized unstructured notes. This study employed a novel high-performance natural language processing algorithm to extract cannabis-related data from unstructured clinical notes.[23]

We hypothesized that cannabis use would be associated with higher inhalational anesthesia administered during general anesthesia. To test this hypothesis, we compared intraoperative time-weighted average isoflurane and sevoflurane minimum alveolar concentration (MAC) equivalents between older adults who used cannabis *versus* those who did not.

Materials and Methods

Study Design

We conducted a propensity score–matched retrospective cohort study using electronic health record data from the PREsurgical Cognitive Evaluation *via* Digital clockfacE-drawing (PRECEDE) Bank, which collects medical data of patients 65 yr or older undergoing surgery at the University of Florida Health System.[24] Data include medical record

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information (demographics, past medical or surgical history, anesthesia and surgery, pain intensity, and family medical history), blood samples and biologic markers of neurocognitive functioning, and questionnaires.[24] The University of Florida Health System is a medical network composed of two academic hospitals (University of Florida Health, Shands Hospital, Gainesville, Florida, and University of Florida Health Jacksonville, Jacksonville, Florida) and other hospitals and facilities associated with the University of Florida in North Florida. An honest data broker retrieved data from patients who underwent surgery between 2018 and 2020 *via* the University of Florida Integrated Data Repository.[25] The study was designed to compare average isoflurane and sevoflurane MAC equivalents between older adults who used cannabis *versus* those who did not. Ethical approval was received from the University of Florida Institutional Review Board (IRB201700747). The written informed consent requirement was waived for secondary electronic health record data use. We followed the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology.[26]

Study Population

We used deidentified electronic health record data of all 22,476 patients aged 65 yr or older who underwent surgery at the University of Florida Health System between 2018 and 2020 in the PRECEDE Bank. We included patients with inpatient and ambulatory surgeries who received inhalational anesthetics during general anesthesia (MAC greater than 0 at any moment during general anesthesia). We excluded patients with American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status classifications greater than IV; patients who underwent emergent surgery (identified by the addition of "E" to their American Society of Anesthesiologists Physical Status); patients who underwent non–operating room procedures, nonoperative urinary system measurements, or psychologic and psychiatric evaluation and therapy; patients who received intraoperative total intravenous anesthesia; patients who received ketamine; and patients on prescription cannabinoids (cannabidiol, dronabinol). Furthermore, we excluded patients who were past cannabis users (patients with clinical documentation indicating past cannabis use, or those who had ICD codes for a cannabis use disorder with a clinical documentation clearly negating cannabis use within 60 days of surgery) and patients with unknown cannabis use status (patients who had no clinical documentation confirming absence of cannabis use within 60 days of surgery with absence of any ICD codes for cannabis user disorder). We did not exclude patients who received intraoperative intravenous anesthetic, sedative, or hypnotic agents. After applying eligibility criteria, we used propensity score matching techniques to match four nonusers for each identified cannabis user.

Exposure

The study exposure was cannabis use within 60 days of surgery. We employed a comprehensive data approach combining unstructured and structured electronic health record data to ascertain exposure (eFigure1 in Supplement 1, https://links.lww.com/ALN/D617). We utilized a keyword search–guided natural language processing algorithm we previously developed to extract preoperative cannabis use status and substance use negation documentation from unstructured clinical notes.[23] The algorithm achieved up to 95% precision and 93% recall for cannabis use classification and 99% precision and recall for substance use negation identification.[23] The detailed methods and results of developing and validating the natural language processing algorithm to identify and classify cannabis use documentation are published.[23] The methods of training the model to identify substance use negation are detailed in eMethods 1 in Supplement 1 (https://links.lww.com/ALN/D617). Structured data included ICD, Tenth Revision (ICD-10) codes for cannabis use disorders[27] and poisoning by cannabis,[28] medication names and RxNorm codes of medical cannabis products and prescription cannabinoids,[29] and screening laboratory results for cannabinoids (eTable 1 in Supplement 1, https://links.lww.com/ALN/D617). We found no structured data on medications or laboratory results related to cannabis use. Cannabis users were defined as having current cannabis use documentation within 60 days of surgery identified *via* natural language processing. Nonusers were defined as having negated cannabis use documentation (at least one documentation negating cannabis use without any documentation of current or past cannabis use in clinical notes identified *via* natural language processing) within 60 days of surgery and no cannabis use disorders ICD codes, or lacking documentation of cannabis use status or cannabis use disorders ICD codes but having negated substance use documentation within 60 days of surgery identified *via* natural language processing. eFigure 2 in Supplement 1 (https://links.lww.com/ALN/D617) summarizes the criteria applied to classify preoperative cannabis use status.

Primary Outcome

The primary outcome was the average isoflurane or sevoflurane MAC, defined as the intraoperative time-weighted average of end-tidal expiratory isoflurane and sevoflurane MAC equivalents sum at 1-min resolution. MAC is the minimum alveolar concentration of inhaled anesthetic needed to suppress responses to surgical stimuli in 50% of patients at 1 atm pressure.[30] For outcome calculation, end-tidal concentrations of isoflurane and sevoflurane were collected at 1-min intervals. End-tidal concentrations were converted to their corresponding MAC equivalent values for isoflurane and sevoflurane (dividing by 1.17 and 1.8, respectively),[31,32] and summed for each minute. Finally, we

calculated the time-weighted average MAC by adding the products of MAC values by the number of administration minutes and dividing by the total anesthesia duration (minutes).

Matching

To balance baseline characteristics, *a priori* selected potential confounders (eFigure 3 in Supplement 1, https://links.lww.com/ALN/D617), and imbalanced covariates identified in bivariate analyses, we performed a 4:1 fixed optimal matching on the exposure propensity score logit within a caliper width of 0.2 of the propensity score logit SD.[33] The propensity score was calculated *via* logistic regression, modeling cannabis use status as the outcome variable against 21 *a priori* identified independent variables, including age, sex, weight, anesthesia duration defined as the time between the first administered anesthetic dose and the time of anesthesia discontinuation, intraoperative coadministered propofol dose and oral morphine equivalents in micrograms per kilogram per minute, time-weighted average end-tidal nitrous oxide concentration, chronic pain, cancer, mood disorders, anxiety disorders, central nervous system conditions, chronic respiratory disease, hypertension, nonhypertensive congestive heart failure, other heart disease, lipid metabolism disorders, anemia, alcohol-related disorders, opioid use disorders, and tobacco smoking. The propensity score derivation model diagnostics are reported in eMethods 2 in Supplement 1 (https://links.lww.com/ALN/D617). To calculate oral morphine equivalents, opioid medication dose data were collected and recorded intraoperatively and then converted to oral morphine equivalents with conversion formulae according to published guidelines as detailed in eTable 2 in Supplement 1 (https://links.lww.com/ALN/D617).[34,35] We used available ICD-10 and Current Procedural Terminology codes to construct comorbidity and procedure categories, respectively, using the Healthcare Cost and Utilization Project Clinical Classification Software–Refined definitions.[36] We further collapsed some of the categories of interest (*e.g.*, for propensity score calculation) (eTable 1 in Supplement 1, https://links.lww.com/ALN/D617). We used literature definitions for chronic pain conditions,[37,38] opioid use disorders,[39] and tobacco smoking[27] (eTable 1 in Supplement 1, https://links.lww.com/ALN/D617).

Sample Size

We calculated an *a priori* sample size based on a two-sample *t* test with an overall type 1 error rate α of 0.05 and power of 0.8 to estimate the number of patients needed. No data were available on the potential effect size of cannabis use on MAC in the literature or what a clinically meaningful difference would be defined as. However, few studies reported dose increases for intravenous agents ranging from 14 to 220% in cannabis users.[10,12] Following a conservative approach considering the lower limit reported for intravenous agents, while expecting to detect a lower difference in our study given the employment of propensity score methods to control for potential confounding (not employed in previous studies), and based on input from clinical and statistical experts in our team, we estimated a 10% expected difference in mean average isoflurane or sevoflurane MAC between cannabis users and nonusers to be clinically meaningful. Considering matching at a 4:1 ratio, 745 patients (149 cannabis users and 596 nonusers) were needed.

Statistical Analysis

A data analysis and statistical plan was written, date-stamped beforehand, and recorded in the investigators' files before data were accessed. We used Wilcoxon rank sum, chi-square, and Fisher exact tests in the bivariate analysis. We applied propensity score matching to control for potential confounding and assessed the balance of baseline variables by calculating standardized differences before and after matching. A standardized difference less than 0.10 was indicative of balance. All quantitative data remained as continuous or discrete variables without categorization. All patients in the primary analysis had complete data for the exposure, outcome, and variables included in the propensity score calculation without exclusion or imputation (complete case analysis). To assess the primary outcome, we applied a two-sample *t* test comparing mean average isoflurane or sevoflurane MACs between matched cannabis users and nonusers, reported as absolute mean differences and 95% confidence limits. The test of the residuals of the Student's *t* test showed normal distribution. We used means and SDs to report normally distributed data and medians and interquartile ranges for abnormally distributed data. Statistical analyses were two-sided, with the α level set at 0.05 for statistical significance in the primary and sensitivity analyses and adjusted to 0.01 for the secondary and *post hoc* analysis to address multiple comparisons (99% confidence limits were reported accordingly). All analyses were performed *via* SAS, version 9.4 (SAS Institute Inc, USA).

Secondary Analysis. We utilized a quantile regression analysis at the 10th, 25th, 50th, 75th, and 90th quantiles of average isoflurane or sevoflurane MAC. Quantile regression compares the entire distribution or a specific quantile of a continuous outcome between exposure groups without excluding outliers, allowing for understanding relationships between variables outside of the conditional mean.[40] The quantile regression analysis was employed to help visualize the relationship between cannabis use status and MAC at different MAC quantiles, exploring if the association is more pronounced at higher quantiles.

Sensitivity Analysis. Given the small cell sizes for many surgical procedures, we did not include the procedure type in the matching. Thus we performed a sensitivity analysis by grouping the surgical procedures based on their corresponding surgical services in the eligible cohort. We excluded services with fewer than 10 cannabis users, further improving the balance of procedure types in the matched sample. The included and excluded surgical services are listed in eMethods 3 in Supplement 1 (https://links.lww.com/ALN/D617). We repeated the matching at a 3:1 ratio as we could not find four matches for each exposed patient in the new eligible cohort. We repeated the *t* test analysis to test the robustness of our results.

Additionally, we performed a sensitivity analysis to assess unmeasured or uncontrolled confounding using the E-value, defined as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates."[41] A small E-value indicates little unmeasured confounding would be needed to explain away an estimate. In contrast, a large E-value indicates a considerable unmeasured confounding would be needed to explain away an estimate.[41]

Post Hoc Analysis. We explored differences in hypnotic effects between cannabis users and nonusers in the primary matched by comparing their average intraoperative Bispectral Index (BIS). Patients with missing BIS scores were excluded from this analysis. The BIS monitor processes electroencephalographic signals to obtain a value (range, 0 to 100; 0, absent brain activity; 100, awake state) reflecting hypnotic drug effects.[42] BIS values within 40 to 60 represent adequate general anesthesia for surgery.[42]

Results

Primary Results

In the full cohort, we identified 800 (4%) cannabis users *via* natural language processing—of whom only 30 of 800 (4%) had ICD codes for cannabis use disorders—and 10,798 (48%) nonusers (eFigure 2 in Supplement 1, https://links.lww.com/ALN/D617). After applying the eligibility criteria, 5,118 patients were eligible (268 were cannabis users, and 4,850 were nonusers). We found four matches for each eligible cannabis user, making a total of 1,340 patients in the final matched sample (268 cannabis users and 1,072 nonusers). Figure 1 illustrates the study sample selection process.

In the matched sample, the median (interquartile range) for age was 69 (67 to 73) yr; 872 (65%) were male, and 1,143 (85%) were non-Hispanic White. The median (interquartile range) anesthesia duration was 175 (118.0 to 268.5) min. After matching, all baseline characteristics were well-balanced between the exposure groups. Select baseline variables are shown in table 1. Other comorbidities and surgical procedures are provided in eTables 3 and 4 in Supplement 1 (https://links.lww.com/ALN/D617), respectively.

The test of the residuals of the two-sample *t* test showed normal distribution. Cannabis users had significantly greater average isoflurane or sevoflurane MAC than nonusers (mean ± SD, 0.58 ± 0.23 *vs.* 0.54 ± 0.22, respectively; mean difference, 0.04; 95% confidence limits, 0.01 to 0.06; $P = 0.021$).

Secondary Analysis Results

The quantile regression analysis showed a positive relationship between cannabis use status and isoflurane or sevoflurane MAC values. However, this relationship was significant only at the 90th quantile of average MAC (table 2; eFigure 4 in Supplement 1, https://links.lww.com/ALN/D617).

Sensitivity Analysis Results

The sample selection process for the sensitivity analysis is illustrated in eFigure 5 in Supplement 1 (https://links.lww.com/ALN/D617). The baseline characteristics and procedure types were well-balanced and are summarized in eTables 5 and 6 in Supplement 1 (https://links.lww.com/ALN/D617). Consistent with the primary analysis, cannabis users had significantly greater average isoflurane or sevoflurane MAC than nonusers (mean ± SD, 0.57 ± 0.24 *vs.* 0.53 ± 0.22, respectively; mean difference, 0.04; 95% confidence limits, 0.001 to 0.07; $P = 0.029$).

Sensitivity analysis of unmeasured confounding indicated that based on the standardized mean difference of 0.18 and standard error of 0.02 in our study, E = 1.64, with E of the 95% CI lower bound estimate = 1.56. Thus, an unmeasured confounding associated with both cannabis use and MAC by a factor between 1.56 and 1.64 could explain away the difference in MAC between cannabis users and nonusers, but weaker confounding could not.

Post Hoc Analysis Results

From the matched sample, 114 cannabis users and 470 nonusers had intraoperative BIS recorded. There was no difference in average BIS between cannabis users and nonusers (mean ± SD, 44 ± 8 *vs.* 45 ± 8, respectively; mean difference, –1; 99% confidence limits, –3 to 1; $P = 0.251$).

Discussion

In this propensity score–matched retrospective cohort study, older adults with documentation of cannabis use undergoing general anesthesia for surgery received a statistically significantly higher volatile anesthetic concentration compared to older adults without documentation of cannabis use (time-weighted average mean MAC, 0.58 *vs.* 0.54), although the clinical significance of this difference

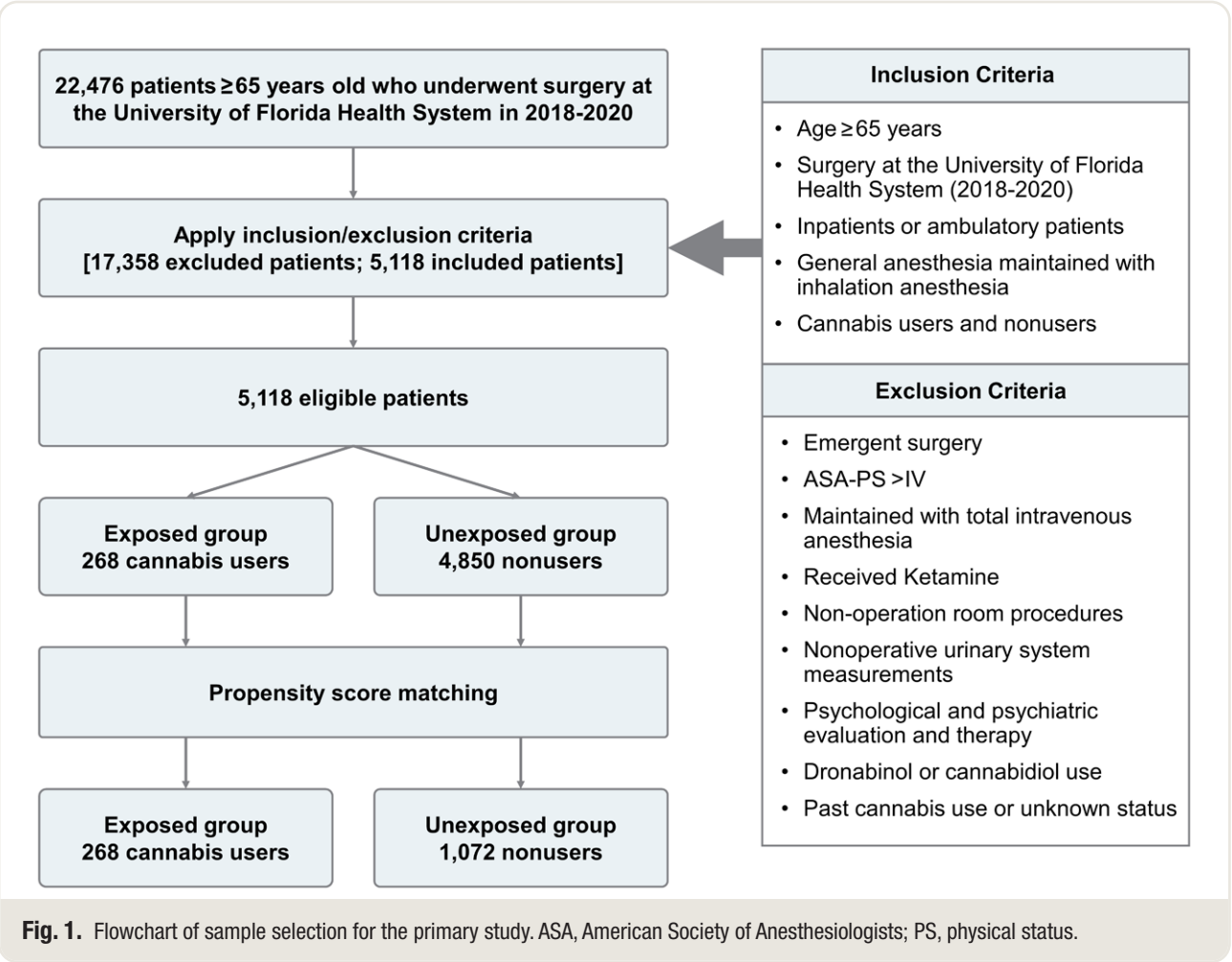

Fig. 1. Flowchart of sample selection for the primary study. ASA, American Society of Anesthesiologists; PS, physical status.

is questionable. This association persisted in the sensitivity analysis after excluding surgical services with less cannabis user representation and rematching. While statistically significant, ascertaining the clinical relevance of this absolute difference presents challenges. Notably, our study did not consider potential mediators, such as the impact of the anesthesiology team's clinical decision-making or other patient clinical factors (*e.g.*, hemodynamic status, signs of inadequate anesthesia) that might contribute to administering higher concentrations of inhalational anesthesia during surgery. Absent an evaluation of these potential mediators, the data cannot differentiate whether the observed statistically significant difference reflects higher inhalational anesthesia requirements related to cannabis use or if it merely reflects the anesthesia team's decision to administer higher inhalational anesthesia concentrations, particularly when knowledge of the patient's cannabis use status existed, regardless of the patient's actual requirements.

While the directionality of our findings is consistent with previous literature showing increases in intravenous anesthetic administration among cannabis users,[10,12,16] the magnitude of this difference was much lower in our study. The 7.4% relative effect size detected in our primary analysis was lower than that estimated in our *a priori* power analysis assumptions and did not have any clear clinical significance. This effect size was also lower than what was considered a clinically meaningful difference in previous studies focusing on other related outcomes of interest, such as postoperative pain scores.[1] However, another plausible explanation for the varied effect sizes observed across studies is the differential control for confounding and bias. Our study's comparatively smaller effect size might be explained by the current analysis use of propensity score matching, which enabled estimating the average treatment effect among the treated, a departure from approaches estimating the average treated effect among the entire population. Moreover, many previous studies did not adjust for potential confounders, variations in coadministered medications, or multiple comparisons. In this study, we investigated the association between cannabis use and the amount of inhalational anesthesia administered while adjusting for important potential confounders, coadministered anesthetic agents, and baseline patient and anesthesia characteristics. It is noteworthy that the difference between cannabis users and nonusers was

Table 1. Select Baseline Patient Characteristics, Anesthesia Characteristics, and Comorbidities before and after Matching

	Before Matching			After Matching		
Variable*	**Current User n = 268**	**Nonuser n = 4,850**	**Standardized Difference**	**Current User n = 268**	**Nonuser n = 1,072**	**Standardized Difference**
Age, yr, median (interquartile range)	69 (67–73)	72 (69–77)	–0.56	69 (67–73)	69 (67–73)	0.03
Sex, n (%)			–0.24			0.01
Female	95 (35.45)	2,298 (47.38)		95 (35.45)	373 (34.79)	
Male	173 (64.55)	2,552 (52.62)		173 (64.55)	699 (65.21)	
Race/ethnicity, n (%)			0.01			0.00
Non-Hispanic Black	15 (5.60)	332 (6.85)		15 (5.60)	76 (7.09)	
Non-Hispanic White	230 (85.82)	4,151 (85.59)		230 (85.82)	913 (85.17)	
Other	23 (8.58)	367 (7.57)		23 (8.58)	83 (7.74)	
Payer associated with primary health insurance, n (%)			0.09			–0.04
Medicaid/uninsured/other	2 (0.75)	60 (1.24)		2 (0.75)	10 (0.93)	
Medicare	234 (87.31)	4,412 (90.97)		234 (87.31)	929 (86.66)	
Private	32 (11.94)	378 (7.79)		32 (11.94)	133 (12.41)	
Weight, kg, median (interquartile range)	82.48 (71.69–95.46)	82.1 (70.43–95.3)	0.02	82.48 (71.69–95.46)	82.81 (72.60–96.20)	–0.03
ASA Physical Status classification, median (interquartile range)	3 (3–3)	3 (3–3)	–0.05	3 (3–3)	3 (3–3)	0.04
Patient type, n (%)			0.08			0.00
Ambulatory surgery	119 (44.40)	1,967 (40.56)		119 (44.40)	476 (44.40)	
Inpatient	149 (55.60)	2,883 (59.44)		149 (55.60)	596 (55.60)	
Preoperative nerve block, n (%)	71 (26.49)	1,412 (29.11)	0.06	71 (26.49)	299 (27.89)	0.03
Anesthesia duration, min, median (interquartile range)	179.5 (116.5–282)	185.00 (125.00–278.00)	–0.08	179.5 (116.5–282)	174.00 (119.00–266.50)	–0.01
Intraoperative propofol, $\mu g.kg^{-1}/min$, median (interquartile range)	13.81 (6.39–27.45)	12.47 (6.34–23.68)	–0.02	13.81 (6.39–27.20)	12.99 (6.36–22.63)	0.03
Intraoperative oral morphine equivalents, $\mu g.kg^{-1}/min$, median (interquartile range)	2.80 (1.54–4.61)	2.57 (1.37–4.14)	0.09	2.80 (1.54–4.61)	2.79 (1.60–4.46)	0.00
Intraoperative lidocaine, $\mu g.kg^{-1}/min$, median (interquartile range)	3.92 (1.45–7.40)	3.74 (1.37–6.96)	0.06	3.87 (1.44–7.36)	3.90 (1.46–7.10)	0.04
Average expiratory Nitrous oxide %, median (interquartile range)	0.01 (0.00–0.13)	0.01 (0.00–0.13)	0.01	0.01 (0.00–0.13)	0.01 (0.00–0.14)	–0.05
Cancer, n (%)	108 (40.30)	2,197 (45.30)	0.10	108 (40.30)	448 (41.79)	0.03
Hypertension, n (%)	205 (76.49)	3,801 (78.37)	0.045	205 (76.49)	826 (77.05)	0.01
Nonhypertensive congestive heart failure, n (%)	23 (8.58)	532 (10.97)	0.08	23 (8.58)	95 (8.86)	0.01
Other heart disease, n (%)	30 (11.19)	767 (15.81)	0.14	30 (11.19)	124 (11.57)	0.01
Deficiency and other anemia, n (%)	17 (6.34)	449 (9.26)	0.12	17 (6.34)	76 (7.09)	0.02
Disorders of lipid metabolism, n (%)	143 (53.36)	2,989 (61.63)	0.17	143 (53.36)	570 (53.17)	–0.01
Central nervous system conditions, n (%)	108 (40.30)	1,578 (32.54)	–0.16	108 (40.30)	436 (40.67)	0.01
Chronic respiratory disease, n (%)	106 (39.55)	1,751 (36.10)	–0.071	106 (39.55)	428 (39.93)	–0.01
Chronic pain conditions, n (%)	81 (30.22)	997 (20.56)	–0.22	81 (30.22)	309 (28.82)	–0.03
Anxiety disorders, n (%)	74 (27.61)	1,051 (21.67)	–0.14	74 (27.61)	271 (25.28)	–0.05
Mood disorders, n (%)	78 (29.10)	905 (18.66)	–0.25	78 (29.10)	298 (27.80)	–0.03
Alcohol use disorders, n (%)	8 (2.99)	62 (1.28)	–0.12	8 (2.99)	28 (2.61)	–0.03
Opioid use disorders, n (%)	0 (0.00)	5 (0.10)	—	0 (0.00)	0 (0.00)	—
Tobacco smoking, n (%)	134 (50.00)	2,260 (46.60)	–0.07	134 (50.00)	530 (49.44)	–0.01

*Percent values are column percent.
ASA, American Society of Anesthesiologists.

more pronounced at the 90th quantile of MAC after correcting for multiple testing in the secondary analysis (11% higher in cannabis users), showing that administering MAC values at the higher end was associated with cannabis use.

While recent guidelines underscore the importance of universal screening for cannabinoids before surgery,[1] caution is paramount to prevent clinical bias leading to the administration of unnecessary higher doses of inhalational anesthesia, especially as robust evidence supporting such practices remains lacking. Despite showing no difference in average BIS between the exposure groups, our exploratory *post hoc* analysis should be interpreted cautiously.

Table 2. Quantile Regression Analysis Comparing Cannabis Use Status at Average Isoflurane/Sevoflurane Minimum Alveolar Concentration Quantiles

Average Isoflurane/Sevoflurane MAC Quantile Level	Intercept β* (99% Confidence Limit)	Current Cannabis Users *vs.* Nonusers β* (99% Confidence Limit)	*P* Value
10th quantile	0.27 (0.23 to 0.30)	0.01 (–0.07 to 0.10)	0.646
25th quantile	0.39 (0.37 to 0.41)	0.05 (–0.01 to 0.10)	0.026
50th quantile	0.55 (0.53 to 0.57)	0.04 (–0.00 to 0.09)	0.018
75th quantile	0.68 (0.66 to 0.70)	0.04 (–0.00 to 0.10)	0.023
90th quantile	0.81 (0.78 to 0.83)	0.06 (0.00 to 0.11)	0.007

*β: the parameter estimate. The intercept estimate represents MAC values for nonusers at each quantile with 99% confidence limit. The current cannabis users *vs.* nonusers estimate represents the difference between cannabis users and nonusers at each quantile with 99% confidence limit. The difference between cannabis users and nonusers was statistically significant only at the 90th quantile.

MAC, minimum alveolar concentration.

The analysis used a subsample of the patients with nonmissing BIS in the primary matched sample without additional matching or adjustment. In this sample, cannabis users received significantly higher average MACs than nonusers, potentially concealing any actual differences that might have existed (type II error). Our study cannot establish whether the higher average MAC reflects genuinely increased anesthetic needs in cannabis users based on these findings. Our study also did not assess whether a potential increase in inhalational anesthesia alveolar concentration correlated with clinical outcomes, such as postoperative neurocognitive dysfunction or other potential side effects associated with inhalational anesthesia use.[20] Without additional evidence explaining the causal pathway or ascertaining the related clinical outcomes of the association under study, making clinical recommendations remains challenging. Future clinical trials may attempt to replicate the study by Flisberg *et al.*[10] to compare BIS and incorporate other processed electroencephalographic metrics (such as suppression ratio or spectral edge frequency) while delivering comparable MAC values at identical time intervals. This approach should also account for other clinical factors that could potentially mediate the observed association.

Finally, previous studies utilizing electronic health record data to investigate the perioperative implications of cannabis use have mainly relied on cannabis use disorders ICD codes or manual chart reviews. However, ICD codes fail to capture the majority of cannabis users who do not meet cannabis use disorders diagnostic criteria,[22] as confirmed in our study. Manual chart review, on the other hand, is inefficient, unscalable, and prone to information bias and extraction errors.[43] This study utilized state-of-the-art natural language processing techniques to extract cannabis use information from electronic health records in an older surgical population, providing a more scalable, reliable, reproducible, and efficient strategy than traditional methods. Using the natural language processing algorithm, we identified 800 cannabis users in the full cohort, capturing a use prevalence of 4%, consistent with that for the United States older population in the study period (3 to 5%),[4,44,45] *versus* only 30 patients identified with cannabis use disorders ICD codes.

Limitations

Our study has limitations, including those inherent in observational study designs. Nevertheless, we performed multiple steps to address potential sources of bias. For example, we employed natural language processing techniques to minimize selection and misclassification bias, improving the sensitivity and accuracy of measuring our exposure and reducing patient exclusion. Yet even with natural language processing, potential underdocumentation of cannabis use in medical records related to other patient-, clinician-, and system-level factors remains.[22] Future studies are needed to validate the natural language processing model and consequent computable phenotype classification where an independent sample with an accepted standard measure is available. Furthermore, the natural language processing algorithm did not capture quantitative aspects of cannabis use, including frequency, chronicity, or recency of use. However, it differentiated between current, past, and no use with high precision. Our study was also susceptible to residual confounding. Mainly, we did not have access to prescription or dispensed medications, including opioids. Nonetheless, we controlled for chronic pain conditions highly associated with chronic opioid use. While we used natural language processing to extract cannabis-related information, developing natural language processing algorithms for other substances within the study timeline was not feasible. We used propensity score matching techniques to minimize confounding and achieved well-balanced identified potential confounders and other baseline characteristics. The E-value of 1.64 in the sensitivity analysis suggested that unmeasured confounding would need to have a substantial impact to nullify the observed effect. However, potential residual confounding remains possible. Given the small cell sizes for many surgical

procedures, we could not include procedure types in the propensity score calculation or matching. Yet there were no significant differences in procedure types between the matched exposure groups, and the results remained consistent in the sensitivity analysis where additional procedure type balance was performed. Moreover, we included the anesthesia duration in the propensity score calculation, which is a close proxy for the procedure duration and arguably more relevant for intraoperative inhalational anesthetic concentration titration and agent selection than the procedure type.[46,47] Another limitation is that we did not perform additional age adjustments for MAC in our study. However, MAC values for 40-yr-old adults have been the most consistently reported in the literature.[48] While applying eligibility criteria and matching can limit the generalizability of the study findings, these approaches can also minimize confounding and balance baseline characteristics across the exposure groups, leading to more accurate effect estimation. Finally, we did not assess potential mediators in the association between cannabis use and increases in MAC, such as changes in vital signs, brain activity measures, muscle tone, among others, or clinical decision-making. Future prospective studies assessing these potential mediators in the association between cannabis use and increased anesthetic doses are needed.

Conclusions

In this study, older adults with documentation of cannabis use undergoing general anesthesia for surgery received a statistically significantly higher volatile anesthetic concentration compared to those without documentation of cannabis use, although the clinical significance of this difference remains unclear. Additional research is warranted to elucidate the intricate relationship between cannabis use, anesthesia requirements, and perioperative clinical outcomes.

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Competing Interests

Dr. Cook receives support from Merck (Rahway, New Jersey) and is funded by the Florida Department of Health (Tallahassee, Florida) for research on cannabis. Dr. Winterstein receives support from Bayer KG (Weimar, Germany), MSD (Rahway, New Jersey), and Genetech Inc. (San Francisco, California), and has received consulting fees from Arbor Pharmaceutical (Atlanta, Georgia) and Ipsen (Paris, France) in the past. Dr. Seubert is an editor of a Springer book on intraoperative neurophysiological monitoring, provides legal review and expert testimony typically on neurosurgical cases with intraoperative neurophysiological monitoring, and occasionally receives honoraria as an invited speaker at meetings related to intraoperative neurophysiology. Dr. Tighe serves with the American Academy of Pain Medicine, *Pain Medicine* (journal).

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Supplemental Digital Content

Supplement 1, https://links.lww.com/ALN/D617

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