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Original Article

Cannabinoid Use and Obstructive Sleep Apnea: A Retrospective Cohort Study

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ABSTRACT: ***Background:*** Obstructive sleep apnea (OSA) is a sleep disorder with no widely accepted pharmacological therapy. Cannabinoids have been suggested to reduce OSA severity in small human studies. The purpose of this retrospective cohort study was to explore the association of self-reported cannabis use on OSA severity and sleep parameters in a large cohort of adults undergoing in-laboratory polysomnography. ***Methods:*** Sleep and medication data were collected for all consecutive adults who completed diagnostic polysomnography at Sunnybrook Health Sciences Centre from 2010 to 2022. Multivariable linear regression models were employed that adjusted for age, sex, and BMI (minimally adjusted model), as well as medication and comorbidity data (maximally adjusted model). An exploratory subgroup analysis was additionally run in patients with moderate to severe OSA. ***Results:*** Of 6,958 individuals (mean age 54.7 ± 16.3, BMI 29.1 ± 6.8, 51.0% female), 71 reported cannabis use. In our minimally adjusted models, cannabis use predicted a reduced respiratory disturbance index (RDI) (β: −4.8 [95% CI: −9.4, −0.2]; $p = 0.042$); this association became nonsignificant in the fully adjusted models. In an exploratory analysis of patients with moderate to severe OSA ($n = 613$), cannabis use ($n = 7$) predicted increased stage N3 sleep (β: 33.5 [95% CI: 15.6, 51.4]; $p < 0.001$) and decreased REM sleep (β: 16.0 [95% CI: 0.3, 31.7]; $p = 0.046$). ***Conclusion:*** Self-reported cannabis use was not associated with OSA severity after adjusting for confounders. In an exploratory subgroup analysis of patients with moderate to severe OSA, cannabis use impacted sleep architecture. Future studies should further explore these findings.

RÉSUMÉ : Consommation de cannabinoïdes et apnée obstructive du sommeil : une étude de cohorte rétrospective. ***Contexte :*** L'apnée obstructive du sommeil (AOS) est un trouble du sommeil pour lequel il n'existe pas de traitement pharmacologique largement accepté. Pour réduire la sévérité de ce trouble, des cannabinoïdes ont été suggérés dans le cadre d'études incluant un petit nombre de sujets humains. Le but de cette étude de cohorte rétrospective a donc consisté à explorer l'association entre l'usage autodéclaré du cannabis et la gravité de l'AOS et les paramètres du sommeil. Pour ce faire, nous avons fait appel à une vaste cohorte de patients adultes soumis à une polysomnographie en laboratoire. ***Méthodes :*** Nos données sur le sommeil et les médicaments ont été recueillies pour tous les patients adultes vus consécutivement ayant subi entre 2010 et 2022 une polysomnographie diagnostique au *Sunnybrook Health Sciences Centre*. Des modèles de régression linéaire multivariable ont été utilisés ; ils ont été ajustés en fonction de l'âge, du sexe et de l'IMC (modèle ajusté au minimum) des patients. De plus, nous avons aussi recouru à des données portant sur les médicaments prescrits et les comorbidités présentes (modèle ajusté au maximum). Enfin, une analyse exploratoire de sous-groupes a également été conduite dans le cas de patients souffrant d'une AOS modérée à sévère. ***Résultats :*** Sur 6 958 patients adultes (âge moyen = 54,7 ± 16,3 ; IMC 29,1 ± 6,8 ; 51,0 % de femmes), 71 ont déclaré avoir consommé du cannabis. Dans nos modèles ajustés au minimum, la consommation de cannabis prédisait un indice de perturbation respiratoire (IPR) réduit (β : -4,8 [IC 95 % : -9,4, -0,2] ; $p = 0{,}042$). Cette association est néanmoins devenue non significative dans les modèles ajustés au maximum. Dans une analyse exploratoire des patients atteints d'AOS modérée à sévère ($n = 613$), la consommation de cannabis ($n = 7$) a prédit une augmentation du sommeil de stade N3 (β : 33,5 [IC 95 % : 15,6, 51,4] ; $p < 0{,}001$) et une diminution du sommeil paradoxal (β : 16,0 [IC 95 % : 0,3, 31,7] ; $p = 0{,}046$). ***Conclusion :*** La consommation déclarée de cannabis n'a donc pas été associée à la gravité de l'AOS après ajustement de variables de confusion (*confounders*). Dans une analyse exploratoire de sous-groupes de patients souffrant d'une AOS modérée à sévère, la consommation de cannabis a néanmoins eu un impact sur la structure du sommeil. À cet égard, de futures études devraient permettre d'approfondir ces résultats.

Keywords: Cannabinoid; cannabis; obstructive sleep apnea; sleep architecture

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Introduction

Obstructive sleep apnea (OSA) is a chronic disease characterized by periods of airway closure during sleep due to reduced pharyngeal dilator muscle tone.[1] Positive airway pressure (PAP) is currently the gold standard for OSA therapy, but its positive outcomes are limited by low patient adherence to therapy.[2–5] Due to the various drawbacks of current OSA therapeutics, new treatment options are required.

Cannabinoids (i.e., cannabis, cannabidiol [CBD], tetrahydrocannabinol [THC]) are a class of drugs which act on the CB1 and CB2 endocannabinoid receptors and have been shown to improve ventilatory stability and reduce apneic events in rodent models.[6–8] Cannabinoids may achieve these effects via vagal nerve suppression which prevents serotonin-induced apneas.[6,7,9,10] A synthetic form of THC known as dronabinol was shown to improve sleep apnea by acting on the CB1 and CB2 receptors.[8]

The data on how cannabinoids affect OSA and other sleep disorders in humans is currently limited. An initial investigation was conducted on the function of endocannabinoids in 20 humans with OSA.[11] The study revealed that patients with OSA had higher levels of an endocannabinoid known as oleoylethanolamide (OEA) compared to healthy controls, which suggested cannabinoids may serve a neuroprotective role in sleep apnea.[11] In a proof-of-concept study in 17 patients with moderate to severe OSA, dronabinol caused a significant reduction in OSA severity after 21 days and no significant adverse events were observed.[12] In another study, 73 patients were randomly assigned to receive either 2.5 mg or 10 mg of dronabinol, or placebo.[13] Treatment with dronabinol reduced OSA severity and daytime sleepiness but had no effect on the maintenance of wakefulness test (MWT), gross sleep architecture, or overnight oxygenation.[13] Because these two studies had small sample sizes and only examined one form of synthetic THC, the effect of cannabis on OSA severity and sleep architecture remains inconclusive.

While cannabinoids may hold therapeutic potential for sleep disorders, it is important to note the broader implications of recreational cannabis use and multi-substance use on sleep architecture and quality. To begin with, cannabinoid use has been linked to polysubstance use and illicit substance use disorders when initiated during adolescence,[14,15] and the use of cannabis, alcohol, and smoking have been associated with insomnia and sleep disturbances in adolescents.[16,17] Furthermore, cannabinoid use has been shown to induce psychotic-like symptoms, such as thought disorder, delusions, and visual disturbances,[18] and is thought to be a risk factor for the development of schizophrenia.[19] This is notable because psychosis has been associated with sleep disorders.[20] Withdrawal from heavy cannabinoid use has been shown to cause sleep disturbances, including reduced total sleep time, REM sleep, and worsened sleep efficiency, wake after sleep onset, and periodic limb movements,[21] with sleep disturbances peaking within the first week of abstinence.[22]

Cannabinoids have also been shown to affect sleep architecture. Animal studies and small studies in humans have shown that cannabinoid use may be associated with increased SWS and decreased REM sleep.[23–26] Some evidence suggests cannabinoid use reduces sleep onset latency, and there is mixed evidence on how it affects time spent in SWS and REM sleep.[27]

We performed a retrospective analysis of clinical, physiological, and polysomnographic data from adults who underwent overnight sleep studies at the Sunnybrook Health Sciences Centre Sleep Laboratory between January 1, 2010 and June 9, 2022. Our aim was to explore whether self-reported cannabis use was associated with changes in OSA severity and sleep architecture.

Methods

Objectives

The primary objective of this analysis was to explore whether cannabis use was associated with a reduction in OSA severity, as measured by the respiratory disturbance index (RDI). The RDI was defined as obstructive apneas, hypopneas with desaturation ≥ 4%, and respiratory event-related arousals per hour of sleep. Secondary objectives included assessing whether cannabis use was associated with changes in the following sleep metrics: OSA severity as measured by the apnea–hypopnea index (AHI, defined as obstructive apneas and hypopneas with oxygen desaturation ≥ 4% per hour of sleep), as well as the respiratory arousal index (RAI), total sleep time, sleep efficiency, wake after sleep onset, number of awakenings, sleep onset latency, the proportion of total sleep spent in each sleep stage, RDI and AHI during REM and non-REM sleep, lowest oxygen saturation, and the periodic limb movement index.[28] Additionally, the Epworth Sleepiness Scale (ESS) total scores were investigated to gauge how cannabis use affected daytime sleepiness.

We conducted two analyses: (i) a retrospective analysis of data from all patients in our dataset and (ii) a retrospective analysis involving the subset of patients who had complete comorbidity and medication information. In an exploratory subgroup analysis, we also assessed whether there would be an association between cannabinoid use and our sleep metrics of interest in the subset of patients who had moderate to severe OSA (AHI ≥ 15).

Study design

Sleep and medication data were retrospectively collected for all consecutive adults at Sunnybrook Health Sciences Centre who completed diagnostic overnight polysomnography from January 1, 2010 to June 9, 2022. Medication lists were recorded by a sleep technologist during the night of the sleep study. Cannabinoid use of any type or formulation (e.g., CBD and/or THC in liquid, solid, or inhaled form) was recorded based on self-reporting during discussions of medication use with the patient. We excluded patients who underwent a therapeutic study (e.g., used any form of PAP therapy, oral appliances, adaptive servo-ventilation, or split night studies) as well as those who were younger than 18 years of age and those with missing medication logs.

As previously described, participants underwent level 1 in-laboratory polysomnography (Compumedics Neuroscan, Australia) monitored by a technologist using conventional scoring and recording methods.[29,30] Sleep was manually staged using criteria delineated by the American Academy of Sleep Medicine.[30]

Statistical analysis

Analysis 1: analysis of all patients (2010–2022)

Descriptive statistics were used to characterize the cannabis users vs. the non-cannabis users. Normally distributed continuous variables were reported as means and standard deviations (SD), non-normally distributed continuous variables were reported as median and interquartile range (IQR), and categorical variables were reported as frequency counts. Cannabis users were compared to non-cannabis users using t tests and Mann–Whitney U tests for normally and non-normally distributed continuous variables, respectively. Chi-square tests were used to compare frequency count variables.

Multivariable linear regression models were constructed to investigate the relationship between cannabis use and sleep-related parameters. Sex, age, and BMI were included as covariates in the regression analysis for the minimally adjusted model.

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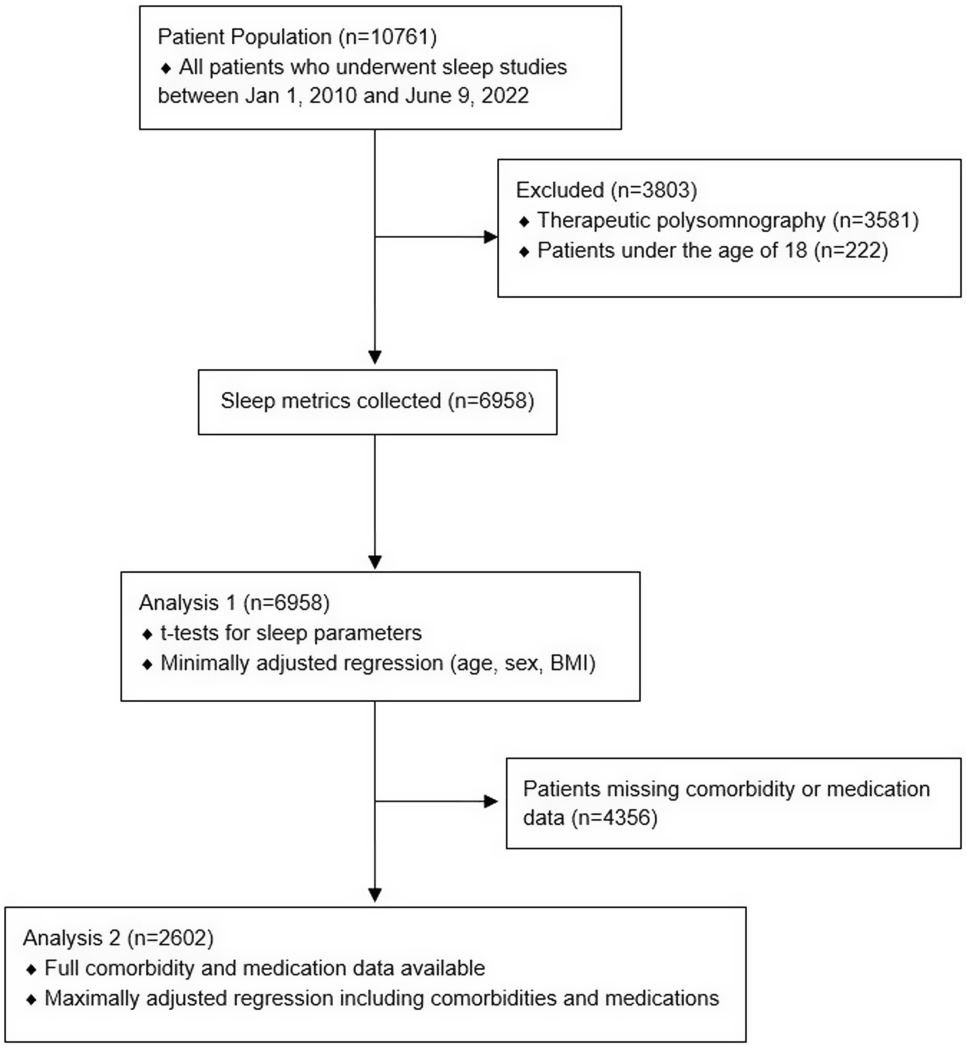


Figure 1: Flow diagram for patients included in analyses.

Analysis 2: fully adjusted regression (2010–2015)

In the fully adjusted model, comorbidities, medications, and other substances known to impact OSA severity were included as covariates in addition to sex, age, and BMI. This included a history of hypertension,[31] chronic lung disease,[32] diabetes,[33] stroke,[34] depression,[35] anxiety,[35] as well as the use of sedatives (i.e., benzodiazepines,[36] non-benzodiazepine hypnotics,[37] and barbiturates[36]), opioids,[38] and smoking.[39] These data were only available for patients that conducted sleep studies between 2010 and 2015.

Prior to modeling, multicollinearity was tested for all variables (tolerance statistic value < 0.4). If multicollinearity was confirmed, only one of the correlated variables was retained in the model. Residual plots were used to assess the final model for any violations to the assumptions of linear regression modeling.

For all analyses, a p-value < 0.05 was considered statistically significant. All data analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY).

Ethical considerations

This retrospective analysis was approved by the Sunnybrook research ethics board (study# 3095).

Data availability statement

To protect the privacy of patients included in this study, the data are not available publicly. The data are available through a data transfer agreement with the corresponding author (MIB).

Results

A total of 10,761 patients aged 18 years and older underwent a sleep study between January 1, 2010, and June 9, 2022. After excluding patients who had missing data or underwent therapeutic polysomnography, 6,958 patients remained; 71 of these were self-reported cannabis users (1.0% of our study sample; Fig. 1). Demographic and polysomnographic data are summarized in Tables 1 and 2, respectively. Cannabis users had a younger overall age than non-cannabis users (Table 1).

For analysis 1 (our minimally adjusted linear regression model), which included 6,958 patients who conducted sleep studies between January 1, 2010 and June 9, 2022, we adjusted for sex, age, and BMI (Table 3). Cannabis use ($n = 71$) was associated with a reduced RDI (β: −4.8 [95% CI: −9.4, −0.2]; $p = 0.042$) and RAI (β: −3.7 [95% CI: −7.3, −0.1]; $p = 0.046$) but did not reach statistical significance for AHI (β: −3.8 [95% CI: −8.0, 0.4];

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Table 1: Demographic information of patients who underwent polysomnography comparing cannabis users to non-cannabis users

Characteristic or sleep parameter	Cannabis users	Non-cannabis users	P-value
All patients (2010–2022)	$N = 71$	$N = 6887$	
Age (years)	47.2 ± 17.0	54.8 ± 16.3	**<0.001**
Male sex (percent)	27 (38%)	3384 (49%)	0.063
Body mass index	28.0 ± 6.7	29.1 ± 6.8	0.17
Patients with comorbidity data (2010–2015)	$N = 8$	$N = 2651$	
Age (years)	43.4 ± 13.8	54.3 ± 16.4	0.06
Male sex (percent)	4 (50.0%)	1229 (46.4%)	0.98
Body Mass Index	32.0 ± 11.1	28.9 ± 6.8	0.20
Hypertension	0 (0.0%)	828 (31.2%)	0.058
Lung disease	2 (25.0%)	200 (7.5%)	0.055
Diabetes	1 (12.5%)	317 (12.0%)	0.96
Stroke	0 (0.0%)	255 (9.6%)	0.36
Depression	5 (62.5%)	592 (22.3%)	**0.007**
Anxiety	3 (37.5%)	703 (26.5%)	0.488
Benzodiazepine use	5 (62.5%)	294 (11.1%)	**<0.001**
Non-benzo hypnotic use	3 (37.5%)	153 (5.8%)	**<0.001**
Barbiturate use	1 (12.5%)	5 (0.2%)	**<0.001**
Opioid use	2 (25.0%)	167 (6.3%)	**0.032**
Smoker	2 (25.0%)	274 (10.3%)	0.185
ESS total score	9.3 ± 6.7	7.8 ± 5.0	0.41

Continuous variables are reported as mean ± standard deviation. ESS = Epworth Sleepiness Scale. Statistically significant P-values (<0.05) have been bolded. All variables with significant P-values in this table were controlled for in the maximally adjusted linear regression models.

Table 2: Sleep parameters of patients who underwent polysomnography comparing cannabis users to non-cannabis users

Characteristic or sleep parameter	Cannabis users ($n = 71$)	Non-cannabis users ($n = 6887$)	P-value
RDI	10.9 ± 11.6	20.4 ± 22.2	**<0.001**
AHI	5.0 ± 8.1	12.6 ± 20.0	**0.001**
RAI	7.7 ± 8.6	14.5 ± 16.8	**<0.001**
Total sleep time (mins)	307.5 ± 88.5	299.1 ± 91.1	0.44
Sleep efficiency (%)	74.0 ± 17.1	71.6 ± 18.9	0.28
Number of awakenings	19.2 ± 10.7	22.3 ± 11.1	**0.022**
Wake after sleep onset (mins)	79.1 ± 65.2	92.1 ± 65.8	0.10
Sleep onset latency (mins)	28.0 ± 30.8	24.0 ± 32.5	0.30
N1 sleep (% of total)	17.4 ± 12.1	22.7 ± 16.7	**0.007**
N2 sleep (% of total)	48.2 ± 14.9	49.83 ± 13.7	0.34
N3 sleep (% of total)	19.4 ± 17.4	13.3 ± 11.3	**<0.001**
REM sleep (% of total)	15.0 ± 7.5	14.1 ± 8.0	0.34
REM RDI	14.7 ± 19.5	21.7 ± 23.0	**0.011**
REM AHI	10.0 ± 18.5	16.3 ± 22.2	**0.017**
Non-REM RDI	10.1 ± 11.4	19.7 ± 23.0	**<0.001**
Non-REM AHI	4.0 ± 6.9	11.7 ± 20.5	**0.002**
Lowest O_2 saturation (%)	88.3 ± 6.4	85.4 ± 8.7	**0.007**
Limb movements per hour	13.1 ± 28.0	13.0 ± 26.2	0.96

Continuous variables are reported as mean ± standard deviation. RDI = respiratory disturbance index, AHI = apnea–hypopnea index, RAI = respiratory arousal index, REM = rapid eye movement. Statistically significant P-values (<0.05) have been bolded.

$p = 0.077$). In this model, cannabis use was also associated with an increased percentage of N3 stage sleep (β: 4.0 [95% CI: 1.5, 6.5]; $p = 0.001$). When analyzing only the subset of patients who had moderate to severe OSA (n = 1,728, Table 4), cannabis use was significantly associated with the percentage of stage N3 sleep (β: 11.3 [95% CI: 4.0, 18.6]; $p = 0.002$) and the ESS total score (β: 12.0 [95% CI: 2.5, 21.6]; $p = 0.013$).

Analysis 2 (our maximally adjusted linear regression model) included 2,602 patients who completed sleep studies between January 1, 2010 and December 31, 2015 and had additional comorbidity and medication data available (Table 3) After adjusting for covariates, cannabis use (n = 8) was not associated with RDI (β: 6.6 [95% CI: −19.5, 6.3]; $p = 0.32$), AHI (β: −4.4 [95% CI: −16.2, 7.4]; $p = 0.47$), or percentage of stage N3 sleep (β: 4.7 [95% CI: −2.4, 11.8]; $p = 0.19$). When analyzing only patients with moderate to severe OSA (n = 613, Table 4), cannabis use was significantly associated with increased stage N3 sleep (β: 33.5 [95% CI: 15.6, 51.4]; $p < 0.001$) and decreased REM sleep (β: 16.0 [95% CI: 0.3, 31.7]; $p = 0.046$), but there was no association with RDI (β: −7.4 [95% CI: −51.2, 36.3]; $p = 0.74$) or AHI (β: −0.3 [95% CI: −43.7, 43.2]; $p = 0.99$). In this same subgroup, during REM sleep cannabis use was also associated with reduced RDI (β: 67.1 [95% CI: 11.3, 122.9]; $p = 0.018$) and AHI (β: 68.5 [95% CI: 12.6, 124.4]; $p = 0.016$) but there were no associations with changes in RDI (β: −20.4 [95% CI: −67.1, 26.4]; $p = 0.39$) or AHI (β: −13.3 [95% CI: −59.8, 33.2]; $p = 0.57$) in non-REM sleep (Table 4). Lastly, in this subgroup of patients with moderate to severe OSA, cannabis use was significantly associated with the ESS total score (β: 9.6 [95% CI: 0.0, 19.2]; $p = 0.049$).

Discussion

Our study explored the relationship between any self-reported cannabis use and changes in OSA severity and sleep architecture. We found that cannabis users had a younger overall age than the non-cannabis users, but age was controlled for in all of our linear regression models. Our minimally adjusted model showed an association between cannabis use and a reduced RDI and RAI, as well as an increased percentage of stage N3 sleep. In patients with moderate to severe OSA, only the association with N3 stage sleep was statistically significant. Our maximally adjusted model showed that when controlling for comorbidities and medication use (in addition to age, sex, and BMI), there were no significant associations between markers of OSA severity and cannabis use. However, in patients with moderate to severe OSA, this model demonstrated an association between cannabis use and increased

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Table 3: Multivariable linear regression models examining the association between cannabis use and sleep parameters

	Minimally adjusted models (n = 6,958)				Maximally adjusted models (n = 2,602)			
Sleep Parameter	β	CI (95%)	R^2	P-value	β	CI (95%)	R^2	P-value
RDI	− 4.8	− 9.4 – −0.2	0.2	**0.042**	− 6.6	− 19.5 – 6.3	0.2	0.32
AHI	− 3.8	− 8.0 – 0.4	0.2	0.077	− 4.4	− 16.2 – 7.4	0.2	0.47
RAI	− 3.7	− 7.3 – −0.1	0.2	**0.046**	− 6.0	− 15.8 – 3.9	0.2	0.24
Total sleep time (mins)	− 9.2	− 28.9 – 10.6	0.1	0.36	− 5.8	− 65.0 – 53.4	0.2	0.85
Sleep efficiency (%)	− 1.2	− 5.3 – 2.9	0.2	0.56	0.6	− 11.8 – 13.0	0.2	0.92
Number of awakenings	− 2.2	− 4.8 – 0.4	0.03	0.091	− 2.5	− 12.1 – 5.2	0.03	0.51
Wake after sleep onset (mins)	0.6	− 13.5 – 14.6	0.2	0.94	14.7	− 27.9 – 57.4	0.2	0.50
Sleep onset latency (mins)	4.8	− 2.7 – 12.4	0.01	0.21	− 14.9	− 37.8 – 7.9	0.03	0.20
N1 Sleep (% of total)	− 1.8	− 5.4 – 1.7	0.2	0.31	− 6.5	− 16.7 – 3.6	0.2	0.21
N2 Sleep (% of total)	− 2.0	− 5.2 – 1.2	0.01	0.21	1.2	− 8.1 – 10.5	0.03	0.81
N3 Sleep (% of total)	4.0	1.5 – 6.5	0.2	**0.001**	4.7	− 2.4 – 11.8	0.2	0.19
REM Sleep (% of total)	0.002	− 1.8 – 1.8	0.05	1.00	1.3	− 4.2 – 6.7	0.1	0.65
REM RDI	− 3.5	− 8.5 – 1.5	0.1	0.17	4.1	− 10.7 – 18.9	0.2	0.59
REM AHI	− 2.8	− 7.6 – 1.9	0.2	0.24	3.0	− 11.3 – 17.3	0.2	0.68
Non−REM RDI	− 4.8	− 9.6 – 0.0	0.2	0.051	− 8.3	− 21.7 – 5.1	0.2	0.23
Non−REM AHI	− 3.8	− 8.1 – 0.5	0.2	0.086	− 5.5	− 17.7 – 6.7	0.2	0.38
Lowest O_2 saturation (%)	1.0	− 0.8 – 2.8	0.2	0.26	0.08	− 4.7 – 4.8	0.3	0.97
Limb movements per hour	4.1	− 1.7 – 9.9	0.1	0.17	− 4.6	− 22.9 – 13.7	0.1	0.62
ESS total score	1.21	− 2.29 – 4.70	0.006	0.50	1.39	− 2.13 – 4.90	0.04	0.44

RDI = respiratory disturbance index, AHI = apnea–hypopnea index, RAI = respiratory arousal index, REM = rapid eye movement, ESS = Epworth Sleepiness Scale. Statistically significant P-values (<0.05) have been bolded.

Table 4: Multivariable linear regression models examining the association between cannabis use and sleep parameters in patients with moderate–severe OSA

	Minimally adjusted models (n = 1728)				Maximally adjusted models (n = 613)			
Sleep Parameter	β	CI (95%)	R^2	P-value	β	CI (95%)	R^2	P-value
RDI	− 12.9	− 30.1 – 4.3	0.09	0.14	− 7.4	− 51.2 – 36.3	0.1	0.74
AHI	− 12.2	− 29.4 – 5.0	0.1	0.17	− 0.3	− 43.7 – 43.2	0.1	0.99
RAI	− 11.8	− 27.0 – 3.5	0.06	0.13	− 17.1	− 55.0 – 20.9	0.07	0.38
Total sleep time (mins)	12.9	− 52.2 – 78.0	0.1	0.70	5.1	− 175.5 – 185.7	0.1	0.96
Sleep efficiency (%)	5.0	− 8.8 – 18.8	0.1	0.48	3.5	− 35.1 – 42.2	0.2	0.86
Number of awakenings	− 25.8	− 73.7 – 22.1	0.03	0.26	− 25.0	− 52.2 – 2.2	0.03	0.072
Wake after sleep onset (mins)	2.4	− 23.5 – 28.2	0.2	0.29	− 23.1	− 155.6 – 109.3	0.2	0.73
Sleep onset latency (mins)	− 6.0	− 16.6 – 4.5	0.03	0.86	− 14.6	− 87.0 – 57.7	0.1	0.69
N1 Sleep (% of total)	− 3.1	− 17.8 – 11.5	0.1	0.67	− 26.1	− 64.4 – 12.2	0.1	0.18
N2 Sleep (% of total)	− 9.9	− 21.4 – 1.6	0.03	0.091	− 23.4	− 53.6 – 6.8	0.06	0.13
N3 Sleep (% of total)	11.3	4.0 – 18.6	0.1	**0.002**	33.5	15.6 – 51.4	0.2	**<0.001**
REM Sleep (% of total)	1.7	− 4.0 – 7.5	0.06	0.56	16.0	0.3 – 31.7	0.06	**0.046**
REM RDI	9.6	− 11.0 – 30.1	0.06	0.36	67.1	11.3 – 122.9	0.06	**0.018**
REM AHI	10.7	− 9.8 – 31.1	0.07	0.31	68.5	12.6 – 124.4	0.06	**0.016**
Non−REM RDI	− 16.3	− 34.7 – 2.1	0.07	0.082	− 20.4	− 67.1 – 26.4	0.1	0.39
Non−REM AHI	− 15.9	− 34.3 – 2.5	0.09	0.090	− 13.3	− 59.8 – 33.2	0.1	0.57
Lowest O_2 saturation (%)	− 1.6	− 9.0 – 5.8	0.06	0.67	− 7.2	− 25.0 – 10.6	0.05	0.43
Limb movements per hour	16.0	− 1.7 – 33.6	0.06	0.076	− 0.5	− 50.4 – 49.4	0.07	0.98
ESS total score	12.04	2.52 – 21.56	0.01	**0.013**	9.59	0.04 – 19.15	0.07	**0.049**

RDI = respiratory disturbance index, AHI = apnea–hypopnea index, RAI = respiratory arousal index, REM = rapid eye movement, ESS = Epworth Sleepiness Scale. Statistically significant P-values (<0.05) have been bolded.

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stage N3 sleep and decreased REM sleep. It also showed an association between cannabis use and reduced RDI and AHI during REM sleep.

There are very few studies investigating the link between cannabis use and OSA severity in humans. The previous two studies that examined this association were experimental studies with overall sample sizes of 17 patients in Prasad's study and 73 patients in Carley's study.[12–13] In contrast, this study was a retrospective cross-sectional study with an overall sample size of 6,958 patients with 71 cannabis users.

Our finding that cannabis use was associated with increased stage N3 sleep and decreased REM sleep is consistent with prior literature.[23–25] Cannabinoids have been shown to alter the sleep–wake cycle, specifically by increasing the amount of time spent in slow-wave sleep (SWS). This increase may be dependent on the CB1 receptor, as its direct activation results in longer periods of SWS in mice.[26] Furthermore, the administration of a CB1 receptor antagonist has been shown to fragment SWS in rats.[40] Similar effects on sleep architecture have also been observed in humans. In an early clinical trial, patients receiving 70 mg/day of THC orally had a significantly higher proportion of total sleep time spent in SWS.[25] Another study demonstrated that dronabinol administration in 15 patients with OSA increased theta and delta frequencies in sleep.[41] A different study in 8 healthy volunteers showed that the combination of THC and CBD reduced the duration of stage 3 sleep but did not affect the duration of stages 3 and 4 combined, which are now known together as stage N3 sleep.[42] Therefore, cannabis appears to play a role in modulating SWS time. Cannabinoids have also been shown to reduce the time spent in REM sleep. Activation of the CB1 receptor in mice reduces the proportion of time spent in REM sleep and decreases the length of REM periods.[26] Another clinical trial, which used an oral dose of 61 ug/kg of THC per day, also supported these results.[23]

Since it is known that apnea is worse in REM sleep,[43–45] we also investigated the effects of cannabis use on AHI and RDI specifically within REM sleep and non-REM sleep. We found that in patients with moderate to severe OSA, cannabis use was associated with reduced AHI and RDI in REM sleep. This finding suggests that the overall improved RDI in cannabis users in our minimally adjusted model may be due to improvements in respiratory physiology rather than changes to the sleep architecture.

The impact of cannabis use on sleep stages may still be an important aspect of its potential therapeutic effect in OSA patients. Stage N3 sleep is widely known to play a pivotal role in healing, recovery, growth, memory, and immune function.[46] However, patients with obstructive sleep apnea–hypopnea syndrome (OSAHS) typically have increased stage N1 sleep and decreased stage N3 and REM sleep.[47] One study found that most of the symptoms in adults with OSAHS, such as excessive sleepiness, unrefreshing sleep, attention difficulties, snoring, and insomnia, are linked with a reduction in stage N3 sleep.[47] Therefore, increasing the proportion of stage N3 sleep may be a potential novel target for symptom alleviation in future therapies for OSA. To explore this hypothesis, we analyzed ESS total scores to determine if they were significantly associated with cannabis use. There was no association in our minimally or maximally adjusted models. However, in the exploratory subgroup analysis in patients with moderate to severe OSA, cannabis use predicted higher ESS scores despite also predicting greater stage N3 sleep. This finding would challenge the hypothesis that greater stage N3 sleep correlates with reduced daytime sleepiness as well as the hypothesis that cannabis alleviates OSA severity. However, it should be noted that these subgroup analyses are exploratory in nature due to the small sample size of cannabis users but warrant further investigation.

Cannabis use may cause a reduction in OSA severity, but the limitations of our experimental design have precluded a robust validation of this relationship. First, although there were 6,958 patients included in this study, only 71 of these patients were self-confirmed cannabis. Furthermore, data on comorbidities and medication use were only available for 2,602 patients, and only 8 of these were cannabis users. Therefore, the power was substantially reduced in the maximally adjusted linear regression models, which may explain the lack of association between cannabis use and OSA severity in these models.

Second, it is likely that some of the non-cannabis users were, in fact, consuming cannabis but had not reported their use. If this is true, it would have introduced a misclassification bias and diluted the actual effect of cannabis use on OSA severity. This limitation is supported by the low prevalence of cannabis use in our data (1.0%) compared to reported rates of use in the general population of Canada, even before legalization (14.8%).[48] This low prevalence is largely attributable to our data extraction methods. Patients undergoing polysomnography at Sunnybrook were asked about medication use. Therefore, our dataset only identifies cannabis users based on self-reporting during medication-related discussions. It is likely that many patients using cannabis recreationally before its legalization in 2018 were less inclined to self-report cannabis use.

Third, it is possible that only specific formulations and routes of administration for cannabis are effective for reducing OSA severity. The previous two human studies exclusively investigated the effects of dronabinol, an oral synthetic THC medication, but our study included several different formulations of cannabis with different combinations of THC and CBD. These formulations included dronabinol, nabilone (Cesamet), nabiximols (Sativex), and recreational marijuana, consumed in several different routes of administration including orally, sublingually, topically, and inhaled. There may also be a dose-dependent effect of cannabis on OSA severity as previous studies have demonstrated, which we were unable to account for due to a lack of dosing information.[21,22,42]

In conclusion, our data suggest that cannabis use is not associated with a reduction in OSA severity after controlling for confounding factors such as medical comorbidities and the impact of medication use. It is recommended that future larger studies investigating cannabis use in OSA control for potential confounding variables, as well as examine the impact of cannabinoid formulation, route, and dose on OSA severity. Our data also demonstrated that cannabis use was associated with an increased percentage of N3 stage sleep and decreased REM sleep in patients with moderate to severe OSA; moreover, cannabis use predicted reduced OSA severity during REM in these patients, suggesting improved respiratory physiology.

Pharmacological options are needed for OSA therapy due to the lack of compliance and comfort with PAP therapy, and cannabis could represent a pharmacological therapy option for some patients. This should continue to be investigated in future human studies.

Author contribution. MV: conceptualization, study design, data acquisition, data analysis and interpretation, and writing of the manuscript.

SJ: conceptualization, study design, data acquisition, data analysis, and writing of the manuscript.

PG: data acquisition and writing of the manuscript.

EC: data acquisition.

TK: study design and data analysis.

BJM: data acquisition, interpretation.

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MIB: conceptualization, study design, supervision of data acquisition, analysis, and interpretation, and writing of the manuscript.

All authors: critically revised the manuscript for important intellectual content, final approval of the manuscript for publication, and agreed to be accountable for all aspects of the work.

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