Medical Cannabis Authorization and the Risk of Cardiovascular Events: A Longitudinal Cohort Study

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Abstract

Background

Despite the rising rates of legalization of cannabis worldwide, very few investigators have studied the effects of medical cannabis use on healthcare utilization and subsequent cardiovascular (CV) risk. This study assesses the risk of CV-related emergency department (ED) visit/hospitalization in adult patients authorized to use medical cannabis in Ontario, Canada from 2014–2017.

Methods

This is a longitudinal cohort study of patients who received medical cannabis authorization and followed-up in cannabis clinics, matched to population-based controls. The primary outcome was an ED visit/hospitalization for any CV event; and secondary outcome was for acute coronary syndrome (ACS)/stroke. Conditional Cox proportional hazards regression was used to assess the association between cannabis use and risk.

Results

18,653 cannabis patients were matched to 5,1243 controls. Incidence rates for any CV event were 28.34/1000 person-years and 19/1000 person-years in the cannabis and controls group, respectively-(aHR) of 1.52 (95%CI: 1.31–1.77). The aHR among patients with a history of CV event and those without were 1.50 (1.28–1.75) and 1.26 (1.03–1.55), respectively. The aHR among males and females were 1.52 (1.24–1.87) and 1.41 (1.11–1.80). For the ACS and stroke, the aHR was 1.44 (95%CI: 1.08–1.93). When stratified by sex, only men had an increased risk of ACS and stroke; aHR 1.77 (1.23–2.56).

Conclusions

Medical cannabis authorization was associated with an increased risk of ED visits or hospitalization for CV events including stroke and ACS - among males and for patients with a prior CV condition.

Highlights

- Among the safety concerns of medical cannabis use, there is limited data on the possible increased risk of cardiovascular events associated with the use of cannabis.
- This study is one of the few large epidemiological cohort studies that assesses the risk of CV events associated with the use of medical cannabis among patients in Ontario, Canada – 2014–2017.
- Overall, medical cannabis authorization showed a short-term increased risk of emergency department/hospitalization visits for CV events.

Background

The number of individuals using cannabis to manage a health condition is increasing despite the lack of conclusive evidence on the efficacy and safety of cannabis for many of the indications for which it is used (1, 2). In the first half of 2019, approximately 2.7 million Canadians were using cannabis for medical purposes (3). Cannabis is also the most commonly consumed licit/illicit substance in the world (recreational use) (4, 5). Because the safety profile of cannabis remains unclear (6), the increasing use of cannabis could have unintended negative consequences for the users, the healthcare systems and public health in general.

Among the safety concerns, the possible increased risk of cardiovascular (CV) events associated with the use of cannabis is of concern (7). Different mechanisms have been suggested as possible causes of cannabis-related CV risk including a reversible cerebral vasoconstriction triggered by cannabis use (a possible mechanism of stroke) (8), increase in procoagulant proteins (7–9), ischemia by modulating cannabinoid receptors on vascular smooth muscles and human cardiomyocytes (10, 11) arrhythmia, and others (12). In a systematic review of 116 case reports, 29 observational studies, the authors concluded that while the data are limited (20 of the 29 studies were cross-sectional or case series), there is some suggestion that cannabis use may have negative CV consequences (7). Of note, the 116 individuals cases were young (mean age was 31 years), and mainly males (81.9%) and they mainly suffered from ischemic strokes or myocardial infarctions(7). Moreover, most of the studies included non-medical cannabis users. In other studies, however, an association between cannabis use and the risk of CV event was not found (13, 14).

Overall, the current state of evidence is limited to conclude on the CV safety of cannabis. Therefore, this study aimed to assess the risk of CV events associated with the use of cannabis among patients who received medical cannabis authorization in Ontario, Canada. We hypothesized that the medical use of cannabis will be associated with an increased risk of CV events compared to non-use.

Methods

Study design

This is a retrospective longitudinal cohort study of adult patients who have been authorized for medical cannabis (the exposure) matched to patients selected from the general population of Ontario who did not receive cannabis authorization. Each authorized cannabis patient was matched to up to three controls.

To proceed to control matching, first, an index date is assigned to each patient who is eligible to be selected as control (from the general population) so that the distribution of the eligible controls' index dates is similar to that of the cannabis patients. Next, baseline characteristics were assessed before or at the index date. Finally, each cannabis patient was matched to up to three controls based on age (±1 years), sex, Local Health Integration Network location, income quartile, and history of health conditions including diabetes, heart disease, chronic obstructive pulmonary disease, asthma, cancer,

musculoskeletal issues, neurological issues, pain, behavioral issues, fatigue, malnutrition, and other metabolic diseases. Matching was completed with replacement and thus an unauthorized patient could have been utilized for one or more authorized patients.

Cannabis users and their matched controls were followed from the index date (first date of cannabis authorization for the cannabis cohort and pseudo date for the controls) until the occurrence of the event of interest, censoring (death or moved out of province), or the end of the study data (March 31st, 2017) which ever occurred first. Data collected during follow-up visits in the clinics served to assess cannabis exposure time. Cannabis could be consumed by smoking, vaporising or oral ingestion.

Study population

The study population was Ontario adult patients who received an authorization to access cannabis for medical purposes in a chain of cannabis clinics between April 2014 and March 2017. These clinics offer consultation for cannabis use and follow-up to all patients based on self-referral or physician referral (15). To be included in the initial matched cohort, patients had to be aged 18 years or over and have been registered as eligible for the Ontario Health Insurance Plan (i.e., residents of Ontario). Patients were excluded if they had invalid or duplicate identifiers. Controls who had any diagnostic codes related to cannabis use during the study period (ICD-10 codes T407 and F12) were excluded.

Data sources

This study mainly used Ontario administrative health data that served to select the controls and assess the study outcomes and co-variates. The cannabis cohort was selected using data collected in a group of Ontario cannabis clinics. These data were described in a previous paper [Eurich, 2019]. Briefly, in the study period (2014-2017), cannabis access for medical use in Canada was conditional on obtaining a medical prescription and administrative authorization (from Health Canada). Thus, all patients in our cannabis cohort (group) were formally authorized to use cannabis. Patients could be referred in the cannabis clinics by other physicians or self-referred. A comprehensive assessment was made during the initial visit and follow-up visits and data were captured electronically with patients' consent. As these rich clinical data are only available for the cannabis cohort, both the controls and cannabis cohort administrative health data were used to assess the study variables. The Ontario Institute for Clinical Evaluative Sciences (ICES) provided the administrative data. These data include individual data files for each beneficiary, inpatient files, physician billings (inpatient and outpatient physician services) and prescription drug claims (16). The Ontario Health Insurance Plan (OHIP) (17) contains information on physician services, including diagnostic codes. The Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS) contain all data on hospitalizations and emergency department visits, respectively. For each emergency visit or hospitalization, up to 25 possible diagnoses were registered according to the *International Classification of Diseases* system- *tenth Revision* (*ICD-10*). Of these entries, only one indicated the most responsible diagnosis for the visit. The administrative databases were linked using the unique and encrypted patient health insurance number and covered the

period of April 24, 2012 to March 31, 2017. We have previously assessed the healthcare utilizations of the cannabis cohort compared to controls using these data [Eurich, 2020].

Outcomes

For primary CV endpoint, we considered emergency department (ED) visits or hospitalizations with a main diagnostic code for acute coronary syndrome (ACS) or stroke. The following ICD-10 codes were used to assess this outcome in the databases: I20, I21, I24, I60-I64 (see appendix 1 for more details).

A secondary outcome was defined as ED visit or hospitalization with a main diagnostic code for any CV event. The ICD-10 codes I00 to I99 excluding codes I05 to I09, (i.e., chronic rheumatic heart disease) were used to assess this secondary outcome (see appendix 1).

Other variables

Demographic variables included age, sex, nearest census-based neighbourhood income quintile and area of residence. We also assessed the following existing morbidities in the period going from 2012 to the index date: asthma, diabetes, metabolic disease, CHF, COPD, cancer, musculoskeletal issues, fatigue, pain, behavioural issues and neurological disorders (see appendix 2 for ICD-9 and ICD-10 codes used to assess these variables). Finally, as only congestive heart failure was considered in the initial matching, we also assessed the presence of any cardiovascular event as well as the presence of ACS or stroke in the period before the index date (see appendix 2 for details on the definitions and ICD-9 and ICD-10 codes used to define these variables) to characterize CV event history.

Statistical Analysis

Descriptive statistics were used to assess the characteristics of the study sample (mean and standard deviation or median for continuous variables; numbers and proportions for categorical variables). Incidence rates of CV events per 1000 person-years and 95% confidence intervals were calculated for each group. For both the primary and secondary outcomes, conditional Cox proportional hazards regressions, that account for the matching, were used to assess the association between cannabis use and the study outcomes. The models were further sequentially adjusted for history of ACS/stroke and for history of any CV event, respectively. Schoenfeld residuals were used to assess the proportional hazards assumption while the Martingale residuals were used to assess nonlinearity (for continuous covariates). Hazard ratios (HR) and 95% confidence intervals (95%CI) were derived for each model.

In sensitivity analyses, we stratified each outcome-specific analysis by sex to assess possible sex-difference. We finally tested for interaction between sex and cannabis exposure. For all analyses, a two-side $P<0.05$ was considered as statistically significant. The analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

From 29,153 adult patients who received medical cannabis authorization and were followed-up in the cannabis clinics between 2014 and 2017, 18,653 matched to 51243 controls were included for analysis (Fig. 1). The majority of exposed and non-exposed patients were aged 31 to 60 years and 54% were male (Table 1).

The most prevalent morbidities were respectively musculoskeletal disorders (42.87%), asthma (18.83%), behavioral disorders (17.70%), neurological disorders (13.87%) and metabolic diseases (12.23%) (Table 1). Overall, 7.7% of the cannabis users and 6.0% of controls had a history of ACS or stroke (i.e., outpatient, inpatient or ED visit between 2012 and index date with a CV related code, either primary or secondary).

Table 1
Characteristics of the study sample

Characteristics	Non-cannabis consumers N = 51243 (%)		Cannabis users N = 18653 (%)	
Age, years				
< 21	331	(0.65)	119	(0.64)
21–30	5578	(10.89)	1972	(10.57)
31–40	10088	(19.69)	3822	(19.32)
41–50	10545	(20.58)	4842	(20.49)
51–60	13227	(25.81)	2858	(25.96)
61–70	7771	(15.16)	1050	(15.32)
71–80	2745	(5.36)	1050	(5.63)
> 81	958	(1.87)	386	(2.07)
Sex				
Female	23206	(45.29)	8528	(45.72)
Male	28037	(54.71)	10125	(54.28)
Nearest census based neighbourhood income quintile				
1	10943	(21.36)	4053	(21.73)
2	10524	(20.54)	3859	(20.69)
3	9943	(19.40)	3595	(19.27)
4	10327	(20.15)	3726	(19.98)
5	9506	(18.55)	3420	(18.33)
Rural	6046	(11.80)	1798	(9.64)
Comorbidities considered in the initial matching				

CV: cardiovascular; ED: emergency department; OHIP: Ontario Health Insurance Plan;

ACS: acute coronary syndrome.

**includes any ED visit or hospitalization or* outpatient visit *to physician with a diagnostic code (either primary or secondary) for ACS or stroke*

*** includes any ED visit or hospitalization or outpatient visit to physician with a diagnostic code for a CV event*

Characteristics	Non-cannabis consumers N = 51243 (%)		Cannabis users N = 18653 (%)	
Asthma	9478	(18.50)	3690	(19.78)
Behavioural disorders	8800	(17.17)	3573	(19.16)
Cancer	4472	(8.73)	1828	(9.80)
Congestive heart failure	295	(0.58)	166	(0.89)
Chronic obstructive pulmonary disease	5722	(11.17)	2351	(12.60)
Diabetes	5390	(10.52)	2214	(11.87)
Fatigue	460	(0.90)	277	(1.49)
Metabolic disease	5945	(11.60)	2605	(13.97)
Musculoskeletal disorders	21716	(42.38)	8250	(44.23)
Neurological disorders	6812	(13.29)	2886	(15.47)
ED or hospitalization with a main diagnosis code for ACS or stroke before the index date	483	(0.94)	210	(1.13)
History of ACS or stroke before*	3097	6.04	1429	7.66
History of any cardiovascular event**	14902	(29.08)	6302	(33.79)
CV: cardiovascular; ED: emergency department; OHIP: Ontario Health Insurance Plan;				
ACS: acute coronary syndrome.				
**includes any ED visit or hospitalization or* outpatient visit *to physician with a diagnostic code (either primary or secondary) for ACS or stroke*				
*** includes any ED visit or hospitalization or outpatient visit to physician with a diagnostic code for a CV event*				

During a median follow-up of 242 days (Q1:113-Q3:401), the incidence rate for the primary outcome (i.e., ED visits or hospitalization with a main diagnosis code for ACS or stroke) was 5.67 (95% CI 4.97–6.46) per 1000 person-years in the control group and 7.19 (95% CI 5.92–8.72) per 1000 person-years in the cannabis group during a median follow-up of 242 days (Q1:113-Q3:401) (Table 2).

Table 2
Incidence rates of hospitalization or emergency department (ED) visits for any cardiovascular (CV) event (primary outcome), or for acute coronary syndrome (ACS) or stroke (secondary outcome)

Outcome	Exposition	Number of events	Total person-years	Incidence rates per 1000 person-years (95% CI)
Primary outcome (ACS or stroke)	Cannabis users	102	14186.68	7.19 (5.92–8.72)
	Controls	223	39342.55	5.668 (4.97–6.46)
Secondary outcome (any CV event)	Cannabis users	398	14039.99	28.34 (25.73–31.23)
	Controls	742	39044.22	19.00 (17.69–20.41)

Patients with medical cannabis authorization had an increased risk of ED visit or hospitalization for ACS or stroke compared to controls (aHR: 1.44 (95%CI: 1.08–1.93) (Table 3).

Table 3
Association between the medical use of cannabis and the risk of hospitalization or emergency department (ED) visits for any cardiovascular (CV) event (primary outcome), or for acute coronary syndrome (ACS) or stroke (secondary outcome)

Outcome	Statistical model	Hazard ratio (95% confidence interval)
Primary outcome (ACS or stroke)	Conditional Cox model*	1.48 (1.11–1.97)
	Conditional model further adjusted for prior ACS or stroke and area of living	1.41 (1.05–1.90)
	Conditional model adjusted for history of any CV event and area of living	1.44 (1.08–1.93)
Secondary outcome (any CV event)	Conditional Cox model*	1.52 (1.31–1.77)
	Conditional model further adjusted for history of any CV event and for area of living (rural versus urban)	1.47 (1.26–1.72)

**Accounts for the matching that was based on age, sex, income quartile and previous diagnosis of: diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), asthma, cancer, musculoskeletal disorders, neurological disorders, pain, fatigue, behavioural disorders, malnutrition, and metabolic disease*

The incidence rates and the hazard ratios for ACS/stroke, stratified by sex, are presented in Table 4. For these analyses, the aHR was only statistically significant among males HR: 1.77 (95%CI: 1.23–2.56) (Table 4). However, the interactions between cannabis authorization and sex was not significant, suggesting that the risks were similar between groups (p-value of interaction was 0.0703).

Table 4
Incidences rates and hazard ratios for emergency department (ED) or hospitalization visit for acute coronary syndrome (ACS) or stroke according to sex.

Sex	Exposure group	Number of events	Total person-years	Incidence rate per 1000 persons-years (95% CI)	Adjusted Hazard ratio (95% CI)*	p-value for interaction
Males	Cannabis users	69	7896.50	8.73 (6.91–11.05)	1.77 (1.23–2.56)	0.0703
	Controls	132	21496.29	6.14 (5.18–7.28)	1 [Reference]	
Females	Cannabis users	33	6290.18	5.25 (3.73–7.37)	0.98 (0.59–1.62)	
	Controls	91	17846.26	5.10 (4.15–6.26)	1 [Reference]	

*Conditional Cox model further adjusted for history of any CV

In our secondary analysis, the incidence rates was 19.00 (95% CI 17.69–20.40) per 1000 person-years in the control group and 28.34 (95%CI 25.73–31.23) per 1000 person-years for the cannabis patients (Table 2). In the model adjusted for history of any CV event, medical cannabis authorization was associated with a significant increased risk of ED or hospitalization for any CV event 1.47 (95%CI: 1.26–1.70) (Table 3).

The incidence rates and the hazard ratios for the secondary outcome, stratified by sex, are presented in Table 5. Overall, the risk of CV events was not statistically different among males and females as the interaction term between sex and cannabis authorization was not significant (p-value for interaction was 0.6209).

Table 5
Incidence rates and hazard ratios for hospitalization or emergency department visit for any cardiovascular (CV) event stratified by sex

Sex	Exposure group	Number of events	Total person-years	Incidence rate per 1000 persons-years (95% CI)	Adjusted Hazard ratio (95% CI)*	P-value for interaction
Males	Cannabis users	233	7819.88	29.79 (26.25–33.81)	1.52(1.24–1.86)	0.6209
	Controls	416	21341.38	19.49 (17.72–1.44)	1 [Reference]	
Females	Cannabis users	165	6220.11	26.53 (22.82–30.84)	1.41(1.11–1.79)	
	Controls	326	17702.85	18.41 (16.54–20.51)	1 [Reference]	

*Conditional Cox model further adjusted for history of any CV event and area of living.

Discussion

This longitudinal cohort study showed that medical cannabis authorized patients showed an observed short-term increased risk of hospitalization or ED visit due to ACS or stroke and due to any CV event in general. When considering stratification by sex, the risk of ACS or stroke was only statistically significant among males. However, the interaction between cannabis authorization and sex was not significant, suggesting that the risk was similar in both groups.

Our findings are consistent with those of some previous studies suggesting that cannabis use may increase CV risk. A 2017 systematic review of case reports and few observational studies (mainly cross-sectional and including recreational cannabis users) found a possible CV risk with the use of cannabis (7). More recent studies also suggest an increased cannabis-related CV risk (18, 19). In fact, evidence suggests that the endocannabinoid system has a significant role in the regulation of cardiovascular system (20, 21). The activation of cannabinoid receptors (CB1 and CB1) has effect on blood pressure, heart rate and myocardial contractility (21) that could explain the cannabis-related CV risk. However, not all studies show an association between cannabis use and the CV risk. With some limitations including small sample size, inability to adjust for potential confounders, minimal exposure to cannabis, low-risk profile of the population (young and healthy), cannabis use was not associated with an increased risk of CV events in some studies (14, 22).

The observed similarity of CV risk among males and females is to be interpreted with caution as the lack of statistical power could not be excluded. There is evidence of sex difference in the endocannabinoid system that could differentially affect the cannabis effects among males and females (23). Research on rodent models of cardiomyopathy showed that the activation of the CB1 receptor triggers cardiomyocyte injury, increases collagen deposition and cardiomyocyte overgrowth whereas activation of CB2 receptors leads to cardioprotective, antifibrotic and antihypertrophic action(24, 25). A study of the sex differences in the distribution of cannabinoid receptors showed that CB1 receptors are significantly more expressed in the heart of males over 50 years than in the heart of females of the same age group (21). The opposite was observed for the CB2 receptors (21). Studies that are specifically power to detect sex differences in the cannabis-related CV risk are needed.

One of the strengths of our study is the use of one of the largest cohorts of patients with medical cannabis authorization (n = 18,653). This study is one of the few studies that assessed the CV risk among medical cannabis users (most of current studies included non-medical users, who are mainly young and healthy). Our ability to match cannabis patients with population-based controls on a number of important variables also represents a strength of the study.

Among the limitations, we were not able to match all the cannabis cohort patients to at least one control (about 19% were not matched and were excluded from the analysis). This issue has probably led to an underestimation of the CV events as the excluded patients were more likely to be older and had higher rates of morbidities. Moreover, we were not able to account for the concomitant use of drugs that could differentially affect the cardiovascular risk in both groups (drug information was only available for a subset of the study sample). Moreover, residual confounding cannot be refuted because information on

variables such as lifestyle parameters (e.g., alcohol, physical activity level, tobacco, body mass index) are not available in the administrative data. Although we excluded controls who had cannabis-related diagnostic codes during the entire follow-up, there is a possibility that some controls may have used recreational cannabis or self-medicated with cannabis. If present, this misclassification bias would have led to an underestimation of the CV effects of cannabis in our analyses. Finally, we were not able to fully assess cannabis exposure as we did not account for the chemical components, cannabis dosing, and the route of administration. Future studies should consider these variables to determine whether the CV risk differs accordingly.

Conclusion

Overall, this study suggests that there may be increased short-term risk for CV-related ED visit or hospitalization including major events such as ACS and stroke – for medical cannabis authorized patients. We did not observe a difference in the risk among males and females. Considering that the CV risk of cannabis is not well characterized, this study provides new data that can inform practicing physicians and clinicians about the benefit risk-assessment to patients seeking cannabis for medical use. This data is also relevant to better target patients that present in emergency departments with cannabis-related issues, particularly considering the increasing self-medication with cannabis.

Abbreviations

CV – cardiovascular event

ACS – acute coronary syndrome

ED – emergency department

Declarations

All methods were carried out in accordance with relevant guidelines and regulations.

Ethics approval and consent to participate

Research ethics approval was obtained from the University of Alberta Health Research Ethics Board (PRO 00083651) and Veritas Research Ethics Board (Ontario) (16111-13:21:103-01-2017). Informed consent was provided by the patients attending the cannabis clinics during the first visit, which allows data to be collected and used for clinical and research purposes. The administrative data were provided by the ICES who hold the Ontario administrative databases and all data was released as de-identified data.

Consent for publication

This study made use of de-identified data from the Ontario administrative data, which is managed by the Institute for Clinical Evaluative Sciences with support from its funders and partners: Canada's Strategy for

Patient-Oriented Research (SPOR), the Ontario SPOR Support Unit, the Canadian Institutes of Health Research and the Government of Ontario. The opinions, results and conclusions reported are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute of Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are only those of the authors.

Availability of data and materials

The dissemination of data results to study participants and or patient organizations in this research project is not possible/applicable as there are restrictions that apply to the availability of these data. The data is not available. The laws in Canada and the province of Alberta forbid the data to be shared with anybody outside of the province and not in academia. There is no avenue to access this data and no contact that allows permission, as dictated by the privacy and health laws for data in Canada.

Dissemination Declaration

The dissemination of data results to study participants and or patient organizations in this research project is not possible/applicable as the data are de-identified. Being administrative health data, the data cannot be shared publicly. However, requests for the data can be sent to ICES. No special access privileges were granted to the authors.

Competing interests

JRBD is a former board member for a major cannbis company. JGH has worked as a paid advisor and speaker for Canadian Cannabis Clinics. JRBD has a financial interest in Aurora Cannabis Inc. DTE and JRBD hold a Mitacs Grant with Aurora as a partner. AZ is a former Mitacs/Aurora post-doctoral fellow. Mitacs is a national, not-for-profit organization that works with universities, private companies, and both federal and provincial governments, to build partnerships and administer research funding that supports industrial and social innovation in Canada. AZ and DTE do not have any past or present financial interest in the companies involved. CL, JM, and EH have no conflicts of interest to declare. Moreover, the above mentioned entities, research funders and companies listed were not involved in any aspect of the design or write-up of the study and all analysis was performed independent from the funders and companies.

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Patient and Public Involvement

Patients was not involved in the design, conduct and reporting of this research project as it was not applicable to this project.

Authors' Contributorship Statement

DTE, AZ, JRBD, JGH, EH designed the study and DTE and JRBD acquired the data. AZ analyzed the data. CL, AZ, and JM drafted the manuscript. All other authors revised it critically for important intellectual content and approved the final version to be published. All authors are accountable for the work and integrity of the work. The corresponding author and guarantor accepts full responsibility of the work and/or conduct of the study, had access to the data and controlled the decision to publish. AZ attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Transparency Declaration

AZ affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and if relevant) have been explained.

References

1. Montero-Oleas N, Arevalo-Rodriguez I, Nuñez-González S, Viteri-García A, Simancas-Racines D. Therapeutic use of cannabis and cannabinoids: an evidence mapping and appraisal of systematic reviews. BMC Complement Med Ther. 15 janv 2020;20(1):12.
2. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 23 juin 2015;313(24):2456-73.
3. MacDonald E, Adams A. The Use of Medical Cannabis with Other Medications: A Review of Safety and Guidelines - An Update [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019. (CADTH Rapid Response Reports).Available at: http://www.ncbi.nlm.nih.gov/books/NBK549545/
4. Moussouttas M. Cannabis use and cerebrovascular disease. The Neurologist. janv 2004;10(1):47-53.
5. Wolff V, Armspach J-P, Lauer V, Rouyer O, Bataillard M, Marescaux C, et al. Cannabis-related stroke: myth or reality? Stroke. févr 2013;44(2):558-63.
6. Sachs J, McGlade E, Yurgelun-Todd D. Safety and Toxicology of Cannabinoids. Neurotherapeutics. oct 2015;12(4):735-46.
7. Jouanjus E, Raymond V, Lapeyre-Mestre M, Wolff V. What is the Current Knowledge About the Cardiovascular Risk for Users of Cannabis-Based Products? A Systematic Review. Curr Atheroscler Rep. 21 avr 2017;19(6):26.
8. Choi S-H, Mou Y, Silva AC. Cannabis and cannabinoid biology in stroke: controversies, risks, and promises. Stroke. sept 2019;50(9):2640-5.
9. Deusch E, Kress HG, Kraft B, Kozek-Langenecker SA. The procoagulatory effects of delta-9-tetrahydrocannabinol in human platelets. Anesth Analg. oct 2004;99(4):1127-30, table of contents.
10. Ravi D, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. Ann Intern Med. 06

2018;168(3):187-94.

11. Richards JR, Bing ML, Moulin AK, Elder JW, Rominski RT, Summers PJ, et al. Cannabis use and acute coronary syndrome. Clin Toxicol Phila Pa. oct 2019;57(10):831-41.
12. Goyal H, Awad HH, Ghali JK. Role of cannabis in cardiovascular disorders. J Thorac Dis. juill 2017;9(7):2079-92.
13. Reis JP, Auer R, Bancks MP, Goff DC, Lewis CE, Pletcher MJ, et al. Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Public Health. avr 2017;107(4):601-6.
14. Falkstedt D, Wolff V, Allebeck P, Hemmingsson T, Danielsson A-K. Cannabis, Tobacco, Alcohol Use, and the Risk of Early Stroke: A Population-Based Cohort Study of 45 000 Swedish Men. Stroke. 2017;48(2):265-70.
15. Canada's Medical Cannabis Clinics | Canadian Cannabis Clinics [Internet]. Available at: www.cannabisclinics.ca
16. Accuracy Of Ontario Health Administrative Databases Identifying Patients With Rheumatoid Arthritis | Institute of Health Policy, Management and Evaluation [Internet].available at: https://ihpme.utoronto.ca/document/accuracy-of-ontario-health-administrative-databases-identifying-patients-with-rheumatoid-arthritis/
17. Apply for OHIP and get a health card [Internet]. Ontario.ca. 2017. Available at: https://www.ontario.ca/page/apply-ohip-and-get-health-card
18. Desai R, Fong HK, Shah K, Kaur VP, Savani S, Gangani K, et al. Rising Trends in Hospitalizations for Cardiovascular Events among Young Cannabis Users (18-39 Years) without Other Substance Abuse. Med Kaunas Lith. 5 août 2019;55(8).
19. Patel RS, Manocha P, Patel J, Patel R, Tankersley WE. Cannabis Use Is an Independent Predictor for Acute Myocardial Infarction Related Hospitalization in Younger Population. J Adolesc Health. 1 janv 2020;66(1):79-85.
20. Mukhopadhyay P, Mohanraj R, Bátkai S, Pacher P. CB1 cannabinoid receptor inhibition: promising approach for heart failure? Congest Heart Fail Greenwich Conn. déc 2008;14(6):330-4.
21. Piotrowska Ż, Niezgoda M, Łebkowski W, Filipek A, Domian N, Kasacka I. Sex differences in distribution of cannabinoid receptors (CB1 and CB2), S100A6 and CacyBP/SIP in human ageing hearts. Biol Sex Differ. 27 2018;9(1):50.
22. Barber PA, Pridmore HM, Krishnamurthy V, Roberts S, Spriggs DA, Carter KN, et al. Cannabis, ischemic stroke, and transient ischemic attack: a case-control study. Stroke. août 2013;44(8):2327-9.
23. SG-Cannabis-report-Nov-23.pdf [Internet]. Available at: https://bccewh.bc.ca/wp-content/uploads/2019/11/SG-Cannabis-report-Nov-23.pdf
24. Duerr GD, Heinemann JC, Suchan G, Kolobara E, Wenzel D, Geisen C, et al. The endocannabinoid-CB2 receptor axis protects the ischemic heart at the early stage of cardiomyopathy. Basic Res Cardiol. juill 2014;109(4):425.

25. Mukhopadhyay P, Rajesh M, Bátkai S, Patel V, Kashiwaya Y, Liaudet L, et al. CB1 cannabinoid receptors promote oxidative stress and cell death in murine models of doxorubicin-induced cardiomyopathy and in human cardiomyocytes. Cardiovasc Res. 1 mars 2010;85(4):773-84.

Supplementary Materials

Supplemental Tables are not available with this version.

Figures

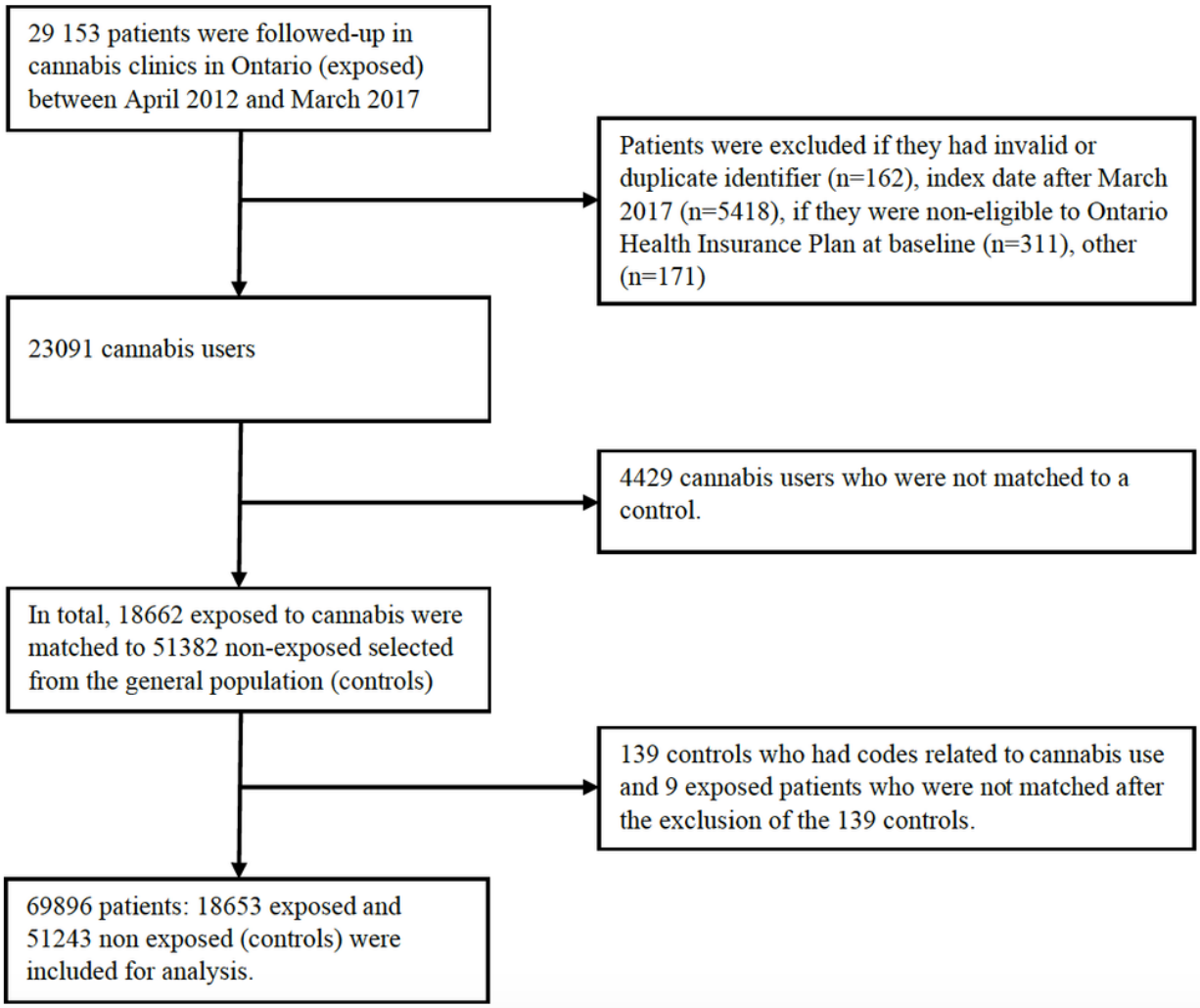

Figure 1

Selection of study population

Supplementary Files

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