Schizophrenia Research 264 (2024) 534–542

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Medical cannabis authorization and risk of emergency department visits and hospitalization due to psychotic disorders: A propensity score-matched cohort study

Cerina Dubois [a], Carlotta Lunghi [b,c,d], Dean T. Eurich [a], Jason R.B. Dyck [e], Elaine Hyshka [a], John G. Hanlon [f,g], Arsene Zongo [d,h,*]

[a] School of Public Health, University of Alberta, Edmonton, Alberta, Canada
[b] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[c] Department of Health Sciences, Université du Québec à Rimouski, Lévis, Quebec, Canada
[d] Population Health and Optimal Health Practices Research Unit, CHU de Québec, Université Laval Research Centre, Quebec City, Quebec, Canada
[e] Cardiovascular Research Centre, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[f] St. Michael's Hospital Department of Anesthesia, Ontario, Canada
[g] Department of Anesthesiology and Pain Medicine, University of Toronto, Ontario, Canada
[h] Faculty of Pharmacy, Université Laval, Quebec City, Quebec, Canada

ARTICLE INFO

Keywords:
Psychosis
Psychotic disorder
Schizophrenia
Medical cannabis
Epidemiology

ABSTRACT

Despite evidence showing that recreational cannabis use is associated with a higher risk of psychotic disorders, this risk has not been well characterized for patients using medical cannabis. Therefore, this study assessed the risk of emergency department (ED) visits and hospitalization for psychotic disorders (the study outcome) among adult patients authorized to use medical cannabis. We performed a retrospective cohort study on patients authorized to use medical cannabis in a group of Ontario cannabis clinics between 2014 and 2019. Using clinical and health administrative data, each patient was matched by propensity scores to up to 3 population-based controls. Conditional Cox proportional hazards regressions were used to assess the risk. Among 54,006 cannabis patients matched to 161,265 controls, 39 % were aged ≤50 years, and 54 % were female. Incidence rates for psychotic disorders were 3.00/1000 person-years (95%CI: 2.72–3.32) in the cannabis group and 1.88/1000 person-years (1.75–2.03) in the control group. A significant association was observed, with an adjusted hazard ratio of 1.38 (95%CI: 1.19–1.60) in the total sample and 1.63 (1.40–1.91) in patients without previous psychotic disorders. The results suggest that cannabis authorization should include a benefit-risk assessment of psychotic disorders to minimize the risk of events requiring emergency attention.

1. Introduction

Psychosis is a common symptom of many mental health conditions including schizophrenia that has severe effects on patients' physical, mental, and social well-being (Calabrese and Al Khalili, 2022) and psychosis is one of the leading cause of disability worldwide (Chong et al., 2016). In Canada and the United States, psychosis and psychotic disorders have been described as one of the costliest mental disorders in the healthcare system (De Oliveira et al., 2016).

Known risk factors of psychosis include childhood trauma, emotional abuse, the use of psychoactive substances (e.g., tobacco, amphetamines, cannabis), and having one or more affected close relatives with the disorder (Calabrese and Al Khalili, 2022). The risk of psychosis associated with cannabis use has been demonstrated in individuals who mainly use cannabis for recreational purposes (Hasan et al., 2020, Patel and Khan, 2020) Indeed, a review of reviews published in 2020 including 26 systematic reviews with 15 reviews that conducted meta-analyses reported that heavy (frequent) cannabis users and those with cannabis dependency or cannabis use disorders are at higher risk of psychosis, pre-existing psychosis exacerbation, higher risk of relapse, and high risk of emergency department visits or hospitalization for psychosis (Hasan et al., 2020; Gilman et al., 2022). Cannabis use at

* Corresponding author at: CHU de Quebec Research Centre, Population Health and Optimal Health Practices Research Unit, 1050 Chemin Ste-Foy (office J1-14B), Quebec City, Quebec G1S 4L8, Canada.
E-mail address: arsene.zongo@pha.ulaval.ca (A. Zongo).

https://doi.org/10.1016/j.schres.2024.01.029
Received 13 March 2023; Received in revised form 8 January 2024; Accepted 22 January 2024

younger age (in adolescence) is also associated with a higher risk of adult psychosis (Arseneault et al., 2002; Hall and Degenhardt, 2008) while cannabis use in general is associated with an earlier age of psychosis onset compared to non-users (Large et al., 2011).

Although evidence supports the risk of psychosis associated with recreational cannabis use, it is important to note that some cannabinoids including cannabidiol (CBD) and delta-9 tetrahydrocannabinol (THC) have been assessed for their potential therapeutic benefits to treat symptoms of psychotic disorders with non-conclusive results at date (Sarris et al., 2020, Mcguire et al., 2018, Sami and Bhattacharyya, 2018) (Ahmed et al., 2021, D'souza et al., 2004). Some mechanisms have been suggested to support the possible therapeutic effects of CBD on psychotic symptoms including hyperlocomotion, and pre-pulse inhibition (Davies and Bhattacharyya, 2019). It is also suggested that a lower dose of THC may provide benefit on psychosis symptoms while higher doses of THC potentially contribute to worsen psychosis symptoms (Ahmed et al., 2021, Whitfield-Gabrieli et al., 2018) Taken together, these data suggest that the risk of psychosis associated with cannabis use could differ between recreational and medical cannabis users as they differ in their characteristics and their patterns of cannabis use (Sznitman, 2017; Subbaraman and Kerr, 2018; Roy-Byrne et al., 2015). For example, compared to medical cannabis users, recreational cannabis users are more likely to be alcohol users (Lin et al., 2016; Gunn et al., 2019; Subbaraman and Kerr, 2018) have drug use disorders (Roy-Byrne et al., 2015) less frequently use cannabis (Turna et al., 2020) be younger (Sznitman, 2017) or have less psychiatric symptomatology (Turna et al., 2020).

Beyond the differences in the characteristics of the two groups of cannabis users, the conditions for medical cannabis access and the motivated reasons make the medical cannabis users a unique population compared to the recreational users. In Canada, access to cannabis for medical use was authorized since 2001 and is regulated by federal laws, making the conditions of access similar across all the provinces. Based on the cannabis federal laws that were modified over the years, only patients, with no age restriction, who received an authorization from a healthcare provider can access cannabis to treat a health condition (Government of Canada, 2022b). However, the legislation does not specify the specific health conditions that can be treated with cannabis. In practice, the most prevalent health conditions for which patients are seeking cannabis for healthcare in Canada include pain, anxiety, depression, and sleep disorders (Lee et al., 2021). In Ontario (Canada), as in other provinces, clinics that are specialized in consult for medical use of cannabis, known as cannabis clinics, are the main care facilities where the patients can obtain cannabis authorization. Patients can be referred to the cannabis clinics by other healthcare professionals but self-reference (i.e., patients who feel that their health conditions can be treated with cannabis) is common (Lee et al., 2021). Following the authorization/after receiving a medical authorization, patients should buy their cannabis from a federally licensed medical cannabis seller according to the regulation. However, with the legalization of cannabis for recreational purposes in Canada in October 2018, some patients may opt to buy their cannabis in legal non-medical cannabis stores that offers cannabis products with the same regulatory quality standards. Cannabis products sold for medical use by licensed sellers include CBD-rich extracts (i.e., products that contain very low amounts of other cannabinoids), THC and CBD extract with variable ratios of the two cannabinoids, THC-rich extract, whole plants parts, etc. Patients can also choose to grow their cannabis for medical use following their medical assessment and cannabis authorization (Government of Canada, 2022b). The authorized cannabis products can be ingested, smoked, vaped, vaporized, or used in topical forms (Lee et al., 2021).

Being followed by a healthcare professional for their cannabis use, medical cannabis users benefit from a closer monitoring including cannabis product choice and doses titration that may minimize the risk of acute adverse events (Government of Canada, 2022b). Canadian surveys data showed that some patients seeking medical cannabis may also combine recreational use and have usually tried other unsuccessful therapies before seeking cannabis for treatment (Shim et al., 2023). A significant proportion of medical cannabis users also use other medications for their conditions including opioids, anti-depressants, benzodiazepines, etc. (Rampakakis et al., 2023). In Ontario, over 122,000 patients were registered with a federally licensed cannabis seller as of December 2022 for medical cannabis use (Statista, 2022). However, this number does not well represent the whole population of cannabis users for medical reason as many may opt to buy their cannabis directly from legal recreational cannabis stores not requiring a registration while other may directly opt for self-medication (Government of Canada, 2022a).

Considering that cannabis is being increasingly used for medical care including patients with mental health conditions and in light with the evidence suggesting that the recreational use of cannabis is associated with an increased risk of psychosis, it has become important to fully clarify the risk of psychosis in patients who specifically use cannabis for medical care.

Therefore, this study aims to address the evidence gap on the association between medical cannabis authorization and the risk of emergency department (ED) visits or hospitalization due to a psychosis event or psychosis disorders. From the existing literature which associates cannabis use with higher risk of psychosis, our research hypothesis is that medical cannabis use will be associated with an increased risk of psychotic disorders.

2. Methods

2.1. Study design

This is a retrospective longitudinal cohort study of adult patients who have been medically authorized to use cannabis for medical care (the exposure) between June 19, 2014 and January 28, 2019. These patients were matched to controls selected from the general population of Ontario using propensity scores (details are provided below).

2.2. Data sources

Two sources of data were used for this study including electronic medical records (EMR) that were linked to the Ontario health administrative data. The EMR data were provided by *Canadian Cannabis Clinics* (https://www.cannabisclinics.ca/), which is a group of cannabis clinics providing cannabis-related care in the Canadian province of Ontario. These EMR data included sociodemographic variables, medical diagnoses, and information on cannabis authorization and follow-up, and covered period from June 19, 2014, to January 28, 2019 (Eurich et al., 2019). We used these data to select the patients authorized to use cannabis (cannabis cohort) and to assess their clinical characteristics. The Ontario administrative health data were provided by the Ontario Institute for Clinical Evaluative Sciences (ICES), covering the period between January 1, 2011 and January 31, 2020. For practical and administrative reasons, the EMR data were directly sent by the cannabis clinics to ICES who proceeded to the data linkage, controls selection and the propensity score matching. The administrative data of the total population of Ontario ($n = 14{,}284{,}221$) was used to select the controls and to assess the study' outcomes and co-variates for both exposed patients and controls (Zongo et al., 2022; Eurich et al., 2020). These data included individual data files for each beneficiary, inpatient files, physician billings and prescription drug claims. The National Ambulatory Care Reporting System (NACRS) and the Discharge Abstract Database (DAD) includes respectively information on emergency department visits and hospitalizations. In these datasets, for each visit, up to 25 possible diagnoses are registered following the tenth revision of International Classification of Diseases system (ICD-10), including the primary diagnosis. The Ontario Health Insurance Plan (OHIP) includes data on physician services, with diagnostic codes based on the ICD-9

classification. All data were de-identified and released in a secured virtual data analysis platform from ICES.

2.3. Study population

The study population were adults authorized to use medical cannabis (18 years or older) attending the cannabis clinics between June 19, 2014, to January 28, 2019. These patients were assessed during their baseline and follow-up visits in the cannabis clinics. Consent was obtained by the clinics to collect and use their data (sociodemographic and clinical data) for research purposes. Patients who already reported cannabis use during their baseline visit at the cannabis clinics were excluded from the current study (Fig. 1). We also excluded patients under 18 years old, patients who were not eligible for the Ontario Health Insurance Plan, and patients with invalid or duplicate identifiers.

Controls with cannabis-related diagnostic codes during the study period, i.e., ICD-10 codes T407 (poisoning by cannabis) and F12 (Cannabis related disorders) were excluded. The cannabis authorization date was defined as the exposed index date. A random index date was assigned to each patient eligible to be selected as control so that the distribution of the eligible controls index dates would be similar to that of the cannabis patients.

2.4. Propensity score calculation and matching

Up to three controls were randomly selected from the general population of Ontario (using the Ontario administrative data) and matched to each exposed patient using propensity scores to control for confounding. Propensity scores were calculated using sociodemographic variables (age, sex, nearest census-based neighborhood income quintile and area of residence (rural versus urban), Local Health Integration Network (LHIN) and other potential confounders (anxiety and mood disorders comorbidity, asthma, COPD, behavioral disorders, cancer, diabetes, congestive heart failure, pain, musculoskeletal disorders, fatigue, neurological disorders, and metabolic disorders). The Caliper method was used for matching using Peter Austin's standard 0.2 caliper width (Austin, 2011). Standardized differences between the exposed and controls characteristics were calculated before and after matching. A difference of >10 % was considered as unbalanced (Williamson and Forbes, 2014).

2.5. Outcomes

The primary outcome was defined as an ED visit or hospitalization with primary diagnosis codes for psychotic disorders. This primary outcome aimed to capture potentially serious events that require an immediate medical attention through an ED visit or a hospitalization, and that could result from the worsening of an existing psychotic disorder, a relapse, or a new psychotic episode. As such defined, we included for analysis, patients with and without a diagnosis code for psychotic disorders before their index date. This definition includes ICD-10 codes F20 to F25, F28, F29 and other codes presented in Appendix A1 (Davis et al., 2016). These codes were previously used to identify psychotic and other mental disorders within the Ontario administrative data (Morin et al., 2020).

A secondary outcome was defined as incident psychotic disorder in patients with no prior diagnosis code for psychotic disorders. It was defined as an ED visit, or a hospitalization for psychotic disorders (the

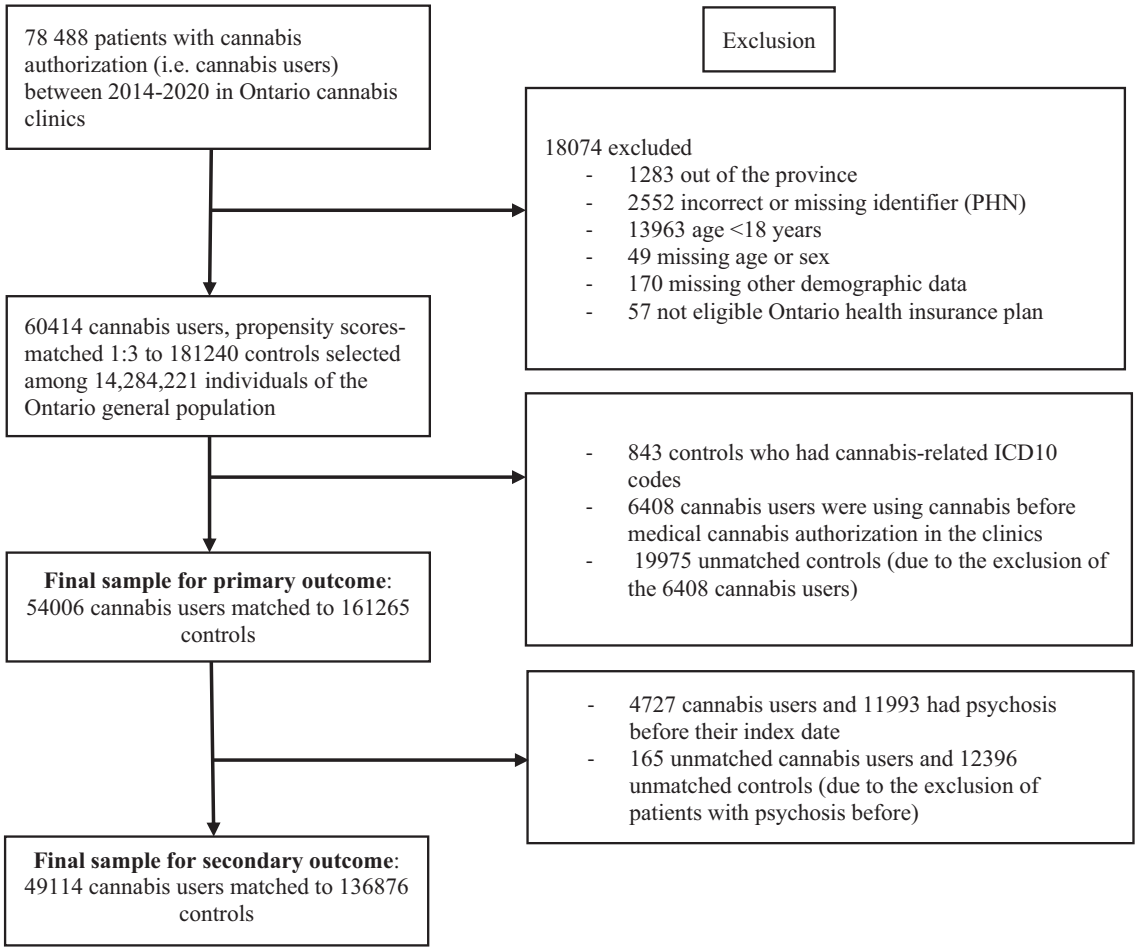

Fig. 1. Selection of study population.

same definition used for the first primary outcome), or a physician claim for psychotic disorders (ICD-9 codes for psychosis: 290–299 in Appendix A2) capturing outpatient cases. All patients with a diagnostic code for a psychotic disorder before their index date were therefore excluded for this secondary outcome analysis.

For each outcome, cannabis-authorized patients and their matched controls were followed from their index date until the occurrence of the event of interest, censoring (death or moved out of province), or the end of the study (March 31st, 2019), whichever occurred first.

2.6. Other variables

Demographic variables included in this study for both exposed and unexposed patients were age at index, sex, nearest census-based neighborhood income quintile and area of residence (rural versus urban). We also considered patients' existing health conditions including diabetes, congestive heart failure, chronic obstructive pulmonary disease, asthma, cancer, musculoskeletal issues, pain, neurologic disorders, fatigue, metabolic disease, mental health, and behavioral issues (ICD-10: F00-F99.x), liver disorders, and chronic kidney disease for up to 5-year prior to the index date. Finally, we specifically assessed prior ER visits or hospitalization for 1) psychotic disorders; and 2) any mental disorder before the index date using both primary and secondary diagnosis codes (identified as history of psychosis or mental health). Specific to the exposed medical cannabis group, we also assessed their characteristics based on the data collected in the clinics during their baseline visits.

2.7. Statistical analyses

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

Table 1A
Characteristics of the study population.**

Characteristic	Exposed to medical cannabis (n=54006) n (%)	Unexposed to medical cannabis (n=161265) n (%)	Total sample n (%)
Age			
≤20	410 (0.76)	2042 (1.27)	2452 (1.14)
21 to 30	4039 (7.48)	11934 (7.40)	15973 (7.42)
31 to 40	8095 (14.99)	22151 (13.74	30246 (14.05)
41 to 50	9659 (17.89)	25642 (15.90)	35301 (16.40)
51 to 60	13097 (24.25)	35640 (22.10)	48737 (22.64)
61 to 70	10352 (19.17)	30437 (18.87)	40789 (18.95)
71 to 80	5696 (10.55)	19461 (12.07)	25157 (11.69)
>80	2658 (4.92)	13958 (8.66)	16616 (7.72)
Female	29419 (54.47)	87827 (54.46)	117246 (54.46)
Census Based Neighbourhood Income Quintile (low to high)			
1	11448 (21.20)	34532 (21.41)	45980 (21.36)
2	11300 (20.92)	34398 (21.33)	45698 (21.23)
3	10700 (19.81)	31813 (19.73)	42513 (19.75)
4	10319 (19.11)	30530 (19.93)	40849 (18.98)
5	10239 (18.96)	29992 (18.60)	40231 (18.69)
Rural (yes)	5973 (11.06)	18219 (11.30)	24192 (11.24)
Anxiety and/or mood disorders	9065 (16.79)	26315 (16.32)	35380 (16.44)
Asthma	12494 (23.13)	36346 (22.54)	48840 (22.69)
Chronic obstructive pulmonary disease	10007 (18.53)	29774 (18.46)	39781 (18.48)
Mental and behavioural disorders	11791 (21.83)	34395 (21.33)	46186 (21.45)
Cancer	6529 (12.09)	19320 (11.98)	25849 (12.01)
Congestive heart failure	2200 (4.07)	6018(3.73)	8218 (3.82)
Diabetes	9243 (17.11)	27605 (17.12)	36848 (17.12)
Metabolic disorders	12654 (23.43)	36911 (22.89)	49565 (23.02)
Fatigue	2928 (5.42)	7152 (4.43)	10080 (4.68)
Musculoskeletal disorders	26244 (48.59)	80163(49.71)	106407 (49.43)
Neurological disorders	11811 (21.87)	34356 (21.30)	46167 (21.45)
Pain	4501 (8.33)	10487(6.50)	14988 (6.96)
ED visits or hospitalization for psychotic disorders	1464 (2.71)	3148 (1.95)	4612 (2.14)
Any psychotic diorder*	4727 (8.75)	11993 (7.44)	16720 (7.76)
ED visits or hospitalization for mental health disorder	4841 (8.96)	12635 (7.83)	17476 (8.12)
Any mental disorder	32135 (59.50)	59222 (36.72)	91357 (42.44)

*Defined as an ER visit or hospitalization with a primary and secondary diagnostic code for psychosis or a physician claim for psychotic disorder.
**Following the PS matching that was performed by ICES for the whole cohort, we excluded patients who reported cannabis use at baseline for the present analysis. The pre- and post-matching characteristics of the whole cohort and the standardized differences are presented in Supplemental Table 1.

rates for the outcome per 1000 person-years were calculated for each group. Conditional Cox proportional hazard regressions, that accounted for the propensity score matching were used to assess the association between medical cannabis authorization and the risk of each outcome. The conditional models were further adjusted for age, sex, and history of mental health.

For the primary outcome (i.e., ED visits and hospitalization for psychotic disorders), in sensitivity analyses, we restricted the study sample to patients without ED visits or hospitalizations for psychosis (primary and secondary diagnosis codes) before the index date. For this analysis, unmatched exposed and controls in the restricted sample were excluded. We also tested the interaction between age and sex and the exposure. We stratified the analysis according to age (≤ 40 years, 41–60, ≥61) and sex. We also excluded the unmatched exposed individuals and controls in each age and sex-specific stratum. For all analyses, a $P < 0.05$ was considered as statistically significant. The analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Our study included 54,006 patients authorized to use cannabis, and 161,265 matched controls for analysis (Fig. 1). The majority of exposed and non-exposed patients were aged 31 to 60 years and 54 % were female (Table 1A and Supplemental Table 1). The most prevalent morbidities were respectively musculoskeletal disorders (49.3 %), asthma (22.7 %), behavioral disorders (21.5 %), and neurological disorders (21.3 %) (Table 1B). History of an ED visit or hospitalization due to psychosis (primary or secondary diagnostic code for psychosis) was observed in 2.7 % of exposed and 1.9 % of controls. History of any psychotic disorder was observed in 8.7 % of exposed and 7.4 % of controls (Table 1A).

Based on the clinical data (exposed patient group only), 39.1 % of cannabis-authorized patients reported during the baseline visit that they had a mental health disease, 24.6 % anxiety, 15.7 % depression, and 75.8 % used cigarettes. The median follow-up for the primary outcome was 2.29 (Q1-Q3:1.52–3.24) years in the exposed group and 2.25 (1.54–3.13) in the unexposed group. The incidence rate for ED visits or hospitalizations for psychotic disorders (primary outcome) in the cannabis group was 3.00 (95 % CI: 2.72–3.32) per 1000 person-years and 1.88 (95 % CI: 1.85–2.03) per 1000 person-years in the control group (Table 2). A Kaplan-Meier survival plot is presented in Supplemental Fig. 1.

For the secondary outcome, 49,114 patients with cannabis authorization and 136,876 matched controls were included (Fig. 1). The incidence rate for the outcome was 29.48 (95%CI: 28.52–30.48) per 1000 person-years in the exposed group and 17.71 (95%CI: 17.26–18.17) in the control group (Table 2). A Kaplan-Meier survival plot for this outcome is presented in Supplemental Fig. 2.

In our Cox models for the primary outcome, medical cannabis patients had a significant risk of ED visit or hospitalization for psychotic disorders in comparison to unexposed patients (Table 3): adjusted hazard ratio (aHR) was 1.38 (95 % CI: 1.19–1.60) for the model further adjusted for age, sex, and prior mental health disorders. Likewise, a similar risk was observed among those who had no history of a prior ED visits or hospitalization for psychotic event (aHR: 1.63 (95 % CI: 1.40–1.91)) (Table 3). When stratified by sex, the incidence rates for psychotic disorders and the corresponding HRs were similar among males and females. The interaction between age and exposure was significant ($p = 0.0085$) and the stratification of the analysis by age (Table 3), showed that younger age (i.e., ≤ 40 years) were significantly more likely to visit the ED or being hospitalized for a psychotic disorder than patients aged 41–60 years. Patients aged 61 years or older had also a significant risk of the outcome but not statistically different from the age group ≤40 years.

For the secondary outcome (assessed among patients with no prior psychotic event), medical cannabis authorization was also associated with an increased risk of psychotic disorders (HR: 1.64; 95%CI: 1.56–1.72) (Table 3).

Table 1B
Characteristics of the cannabis cohort based on data collected in the cannabis clinics (n = 54,006).

Characteristic	N (%)
Annual mean income (CAD $)	
< 45,000	22,963 (42.52)
45,000–59,999	24,359 (45.10)
60,000–99,999	6188 (11.46)
≥ 100,000	496 (0.91)
Cigarette smoking	40,405 (74.82)
Alcohol use	11,182 (20.71))
Cocaine use	368 (0.68)
Use of other medications	27,218 (50.40)
Legal issues	2316 (4.29)
Morbidities	
Any pain	41,439 (76.73)
Non-cancer pain*	39,474 (73.09)
Musculoskeletal pain	36,977 (68.47)
Back pain	22,089 (40.90)
Neck pain	6572 (12.17)
Hip pain	5990 (11.09)
Knee pain	7359 (13.63)
Fibromyalgia	5549 (10.27)
Migraine/headache	4869 (9.02)
Nerve pain	3464 (6.41)
Arthritis	12,742 (23.59)
Any mental health disease	21,117 (39.10)
Depression	8477 (15.70)
Bipolar disorder	1124 (2.08)
Anxiety	13,307 (24.64)
Post-traumatic stress disorder	2076 (3.84)
Attention deficit hyperactivity disorder	794 (1.47)
Panic disorder	1816 (3.36)
Sleep problems	12,908 (23.90)
Insomnia	5149 (9.53)
Fatigue	1518 (2.81)
Cancer	5468 (10.12)
Neurological disorders	4301 (7.96)
Seizure	980 (1.81)
Schizophrenia	291 (0.54)
Neuropathy	1795 (3.32)
Diabetes	1106 (2.05)
COPD	836 (1.55)
Appetite disorders	1879 (3.48)
Osteoporosis	2788 (5.16)
Fracture	1691 (3.13)
Glaucoma	267 (0.49)
Nausea	2443 (4.52)

* The list is non-exhaustive.

4. Discussion

Overall, this cohort study found that medical cannabis patients had an increased risk of psychotic disorders following cannabis authorization. Notably, there was a significant interaction between age and the exposure on the risk of ED visit or hospitalization for psychotic disorders, and patients ≤40 years and those ≥61 years had higher risk compared to the patients aged 41 to 60 years. Our findings align with evidence specific to recreational cannabis users, which suggest that frequent cannabis use, is associated with an increased risk of psychosis (Hasan et al., 2020). Although we did not account for the frequency of cannabis use in our cohort, previous studies have reported that medical cannabis users tend to consume cannabis more frequently than recreational cannabis users (Turna et al., 2020) potentially increasing the risk of psychotic disorders as observed with frequent recreational cannabis users (Hasan et al., 2020). Alongside this, other studies have reported that individuals having access to medical cannabis may have higher risk for cannabis dependence, and no actual therapeutic benefits in anxiety, depression, or other mental health condition which could potentially

Table 2
Incidence rates of the primary outcome (i.e., emergency department (ED) visits or hospitalizations for psychosis) and the secondary outcome (i.e., any psychotic event) among patients who received medical cannabis authorization (exposed) and their matched controls (unexposed).

Population	Medical cannabis authorization	Total N	Number of events	Total person-years	Incidence rate per 1000 person-years (95 %CI)
Primary outcome					
Total sample 1	Exposed	54,006	390	129,820.50	3.00 (2.72–3.32)
	Unexposed	161,264	722	383,403.15	1.88 (1.75–2.03)
No prior psychosis*,#	Exposed	53,774	326	129,311.32	2.52 (2.26–2.81)
	Unexposed	159,871	494	380,538.50	1.30 (1.19–1.42)
No prior mental health*,#	Exposed	48,955	224	117,618.90	1.90 (1.67–2.17)
	Unexposed	137,558	248	330,675.54	0.75 (0.66–0.85)
Male#	Exposed	22,990	210	57,816.91	3.63 (3.17–4.16)
	Unexposed	61,452	288	147,443.07	1.95 (1.74–2.19)
Female#	Exposed	28,324	148	65,850.82	2.25 (1.91–2.64)
	Unexposed	75,955	274	182,204.20	1.50 (1.34–1.69)
Age ≤ 40#	Exposed	11,171	149	29,870.46	4.99 (4.25–5.85)
	Unexposed	30,737	190	74,939.57	2.53 (2.20–2.92)
Age 41 to ≤60#	Exposed	20,344	128	51,594.79	2.48 (2.09–2.95)
	Unexposed	53,717	228	131,544.78	1.73 (1.52–1.97)
Age ≥ 61#	Exposed	17,944	51	37,486.28	1.36 (1.03–1.79)
	Unexposed	47,715	84	111,041.08	0.76 (0.61–0.94)
Secondary outcome					
Total sample 2	Exposed	49,114	3348	113,553.57	29.48 (28.52–30.48)
	Unexposed	136,876	5698	321,823.25	17.71 (17.26–18.17)

* Defined as an ED visit or hospitalization with a primary and secondary diagnostic code for psychosis (or mental health) before the cannabis authorization date (or controls assigned index date)).

Unmatched IDs were excluded for each stratum.

Table 3
Association between the medical cannabis authorization and the risk of the primary outcome (i.e., emergency department visit or hospitalization for psychosis event) and the secondary outcome (i.e., any psychotic event).

Analytic sample	Hazard ratio (95 %confidence interval)	
	Model 1: conditional Cox model*	Model 1 further adjusted**
Primary outcome		
Total sample 1	1.43 (1.26–1.64)	1.38 (1.19–1.60)
No prior psychosis¥	1.74 (1.50–2.03)	1.63 (1.40–1.91)
No prior mental health¥	2.18 (1.78–2.67)	2.12 (1.71–2.61)
Male	1.62 (1.33–1.97)	1.63 (1.32–2.01)
Female	1.23 (0.99–1.53)	1.27 (0.995–1.63)
Age ≤ 40	1.90 (1.50–2.40)	1.84 (1.44–2.36)
Age 41 to ≤60	1.08 (0.85–1.37)	1.11 (0.86–1.43)
Age ≥ 61	1.47 (1.02–2.13)	1.62 (1.08–2.44)
Secondary outcome		
Total sample 2	1.64 (1.56–1.72)	1.55 (1.48–1.64)***

Note: Interaction between sex and exposure: p-value = 0.1312.
Interaction between age and exposure: p-value =0.0085.

* These Cox regression models accounted for the propensity scores matching and were, therefore, fully adjusted models.

** These models were further adjusted (if applicable) for sex, age, and history of an ED visit or hospitalization for mental health disorders (primary and secondary diagnostic codes).

*** further adjusted for age, sex and any non-psychotic mental health disorder before.

¥ « No prior psychosis» (or no prior mental health including psychosis) was defined as no ED visit or hospitalization with a primary and secondary diagnostic code for psychosis (or any mental health) before the cannabis authorization date (or controls assigned index date).

increase their risk for psychotic disorders (Gilman et al., 2022).

Our finding of a significant interaction between age and cannabis exposure on the risk of psychosis, particularly with younger aged patients (≤40 years) being more likely to experience ED visit or hospitalization for psychosis than older, is also concordant with other studies (Ksir and Hart, 2016). Indeed, the frequent use of cannabis in younger ages is suggested to be a risk factor for developing a psychotic illness (Hasan et al., 2020). However, it is also important to note that our results are more relevant to patients with severe psychotic disorders that require emergency medical attention. At the same time, there is mixed evidence that does suggest that younger people with psychotic illnesses who use cannabis, are more likely to have severe symptoms than older patients (Hasan et al., 2020; Koskinen et al., 2010). While a systematic review (Hasan et al., 2020) of studies on cannabis and mental health in older adults did not provide evidence of an association between medical cannabis use and the risk of psychosis, our results showed that older adults (≥ 61 years) who used medical cannabis are at higher risk of psychosis compared to non-users (Brendel and Stern, 2005). The interaction between cannabis and other psychosis risk factors that could be more prevalent in older adults such as dementia could have contributed to the high risk of ED visit and hospitalization for psychosis in this age group. It is also known that cannabis intoxication, which could be more prevalent in older adults, can induce a temporary psychotic episode that is associated with developing psychotic disorders later (NIDA, 2023). Ingestion as a method of cannabis use that is highly prevalent in older adults using cannabis for medical reasons is associated with a high risk of intoxication compared to inhalation (Tumati et al., 2022). This is due to the long time it takes cannabis to produce its effect by ingestion compared to inhalation (Schlienz et al., 2020) that may lead the patients to use additional doses in very short time intervals thus increasing the risk of intoxication, particularly considering the reduced capacities of drug metabolism of older adults. Authorization of cannabis for the older patients should thus be preceded by a careful assessment of existing risk factors as well as a proper titration of cannabis and an adapted treatment plan. Lastly, regarding sex, our analyses did not show its interaction with cannabis authorisation on the risk of psychosis. In previous studies, no clear effect of sex on the risk of psychosis associated with cannabis use could be observed (Hasan et al., 2020).

The strengths of our study include the large sample size and the strength in the opportunity to link the EMR data with administrative data, which allowed for the selection of population-based controls and the adjustment of relevant potential confounders. Notably, no large studies such as this one has been carried out specifically in the Canadian population. In terms of limitations, our results are subject to residual confounding as some potential confounders that were not available

within the administrative data could not be addressed (e.g., alcohol and illicit drug use, some prescribed medications, data on drug dispensation are only available for a subset of the sample). Our study may not have been able to capture all individuals (in both exposed and non-exposed groups) who experienced psychosis or psychotic disorder-related events but are not seen in the ED or hospitalized. This non-differential detection bias may have led to an underestimation of the true association between medical cannabis exposure and psychosis. There was also a possibility that controls and/or exposed group individuals may have used cannabis (recreationally or for self-medication), which may have led to a misclassification bias and an underestimation of the effect of medical cannabis on psychotic disorders in our study. As literature has shown recreational cannabis has been associated with higher risk for psychosis, recreational use may have increased individuals' risk for psychosis-related ED visit/hospitalization; however, the extent of this risk is unknown. Furthermore, our study did not include individuals younger than 18 years of age. As early-age cannabis use has been associated with high risk of adulthood psychosis, excluding this subgroup did not allow a full assessment of cannabis exposure and differing age groups. It is also important to note that approximately 75 % of medically authorized cannabis patients reported smoking cigarettes, a known risk factor of psychosis (Quigley and Maccabe, 2019) that may have contributed to the higher risk of psychotic events in the cannabis cohort. The lack of data on tobacco use for the controls did not allow us to account for this variable in the analysis. Lastly, a full measurement of cannabis exposure was not possible as we did not have full information regarding cannabis products contents (THC, CBD, etc.), dose, frequency of use, and route of administration.

5. Conclusion

Overall, this study suggests that there is an association between medical cannabis authorization and psychosis. In particular, the risk seems higher for patients under the age of 40. The results of this study have important clinical and policy implications as cannabis is increasingly considered as an alternative treatment for a variety of health conditions. Medical cannabis prescribers should carefully communicate and assess potential risks for all patients seeking medical cannabis.

Abbreviations

aHR	adjusted hazard ratio
CBD	cannabidiol
DAD	Discharge Abstract Database
ED	emergency department
HR	hazard ratio
ICES	Ontario Institute for Clinical Evaluative Sciences
LHIN	Local Health Integration Network
NACRS	The National Ambulatory Care Reporting System
OHIP	Ontario Health Insurance Plan
THC	tetrahydrocannabinol

Contributors

This study made use of de-identified data from the Ontario administrative data, which are managed by the Institute for Clinical Evaluative Sciences (ICES) 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 the Canadian Institute of Health Information. However, the analyses, conclusions, opinions and statements expressed herein are only those of the authors.

Role of the funding source

This study was funded by a Canadian Institutes of Health Research Project grant (CIHR PS 159668). 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.

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.

Funding

This study was funded by a Canadian Institutes of Health Research Project grant (CIHR PS 159668).

Ethics

Research ethics approval was obtained from the University of Alberta Health Research Ethics Board (PRO 00083651), Veritas Research Ethics Board (Ontario) (16111-13:21:103-01-2017), and from the CHU de Quebec Research Center Research Ethics Board (#CER: 2022-5999).

CRediT authorship contribution statement

Cerina Dubois: Writing – review & editing, Writing – original draft, Project administration. **Carlotta Lunghi:** Validation, Methodology, Formal analysis, Data curation. **Dean T. Eurich:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Jason R.B. Dyck:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization. **Elaine Hyshka:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **John G. Hanlon:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization. **Arsene Zongo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

JRBD is a former member on the board of directors of Aurora Cannabis Inc., which is a for-profit, company licensed for the cultivation and sale of medical cannabis. In the past, JGH has worked as a paid advisor and speaker for Canadian Cannabis Clinics, but currently has no ties with the CCCs. JRBD has a financial interest in Aurora Cannabis Inc. DTE, JRBD, and AZ (as a postdoctoral fellow) held a Mitacs Grant with Aurora Cannabis as a partner. 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. DTE and AZ do not have any past or present financial interest in the companies involved. CL, CaLu, 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.

Data availability

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.

Acknowledgements

This study is part of large project designed by DTE, JRBD, AZ, JH to assess the health outcomes of the medical use of cannabis. The present sub-study was designed by AZ, CL, CaLu, and DTE. AZ analyzed the data. CL, AZ and DTE 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 its integrity. The corresponding author and guarantor accept full responsibility of the work and/or conduct of the study, had access to the data and controlled the decision to publish. AZ, the corresponding author, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

AZ also 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.

Appendix A

Appendix A1
International Classification of Diseases – Tenth Revision (ICD-10) codes for psychotic disorders.

Conditions	ICD-10 codes
Schizophrenia Spectrum and Related Disorders	
Schizophrenia	F20
Schizotypal disorder	F21
Delusional disorder	F22
Brief psychotic disorder	F23
Shared psychotic disorder	F24
Schizoaffective disorders	F25
Other psychotic disorder not due to a substance or known physiological condition	F28
Unspecified psychosis not due to a substance or known physiological condition	F29
Mania with psychotic symptoms	F30.2
Bipolar disorder with psychotic features	F31.2; F31.5; F31.64
Depressive disorder with psychotic features	F.32.3; F33.3
Substance-induced psychotic episode	F10.15; F10.25; F10.95; F11.15; F11.25; F11.95; F12.15; F12.25; F12.95; F13.15; F13.25; F13.95; F14.15; F14.25; F14.95; F15.15; F15.25; F15.95; F16.15; F16.25; F16.95; F18.15; F18.25; F18.95; F19.15; F19.25; F19.95

The codes were based on Morin KA, Eibl JK, Gauthier G, et al. A cohort study evaluating the association between concurrent mental disorders, mortality, morbidity, and continuous treatment retention for patients in opioid agonist treatment (OAT) across Ontario, Canada, using administrative health data. Harm Reduct J. Jul 23 2020;17(1):51. doi:https://doi.org/10.1186/s12954-020-00396-x.

Appendix A2
International Classification of Diseases – ninth Revision (ICD-9) codes for psychotic disorders.

Conditions	ICD-9 codes
Senile and pre-senile psychotic conditions	290
Transient organic psychotic conditions	293
Other organic psychotic conditions	294
Alcohol-induced psychosis	291
Drug-induced psychoses	292
Schizophrenia	295
Affective psychoses	296
Paranoid states	297
Other nonorganic psychoses	298
Psychoses with origin specific to childhood	299

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.01.029.

References

Ahmed, S., Roth, R.M., Stanciu, C.N., Brunette, M.F., 2021. The impact of THC and CBD in schizophrenia: a systematic review. Frontiers in Psychiatry 12.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T.E., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 325, 1212–1213.

Austin, P.C., 2011. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm. Stat. 10, 150–161.

Brendel, R.W., Stern, T.A., 2005. Psychotic symptoms in the elderly. Prim Care Companion J Clin Psychiatry 7, 238–241.
Calabrese, J., Al Khalili, Y., 2022. Psychosis. StatPearls, Treasure Island (FL).
Chong, H.Y., Teoh, S.L., Wu, D.B., Kotirum, S., Chiou, C.F., Chaiyakunapruk, N., 2016. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr. Dis. Treat. 12, 357–373.
Davies, C. & Bhattacharyya, S. (2019). Cannabidiol as a potential treatment for psychosis. *Ther Adv Psychopharmacol,* 9, 2045125319881916.
Davis, K.A.S., Sudlow, C.L.M., Hotopf, M., 2016. Can mental health diagnoses in administrative data be used for research? A systematic review of the accuracy of routinely collected diagnoses. BMC Psychiatry 16.
De Oliveira, C., Cheng, J., Rehm, J., Kurdyak, P., 2016. The economic burden of chronic psychotic disorders in Ontario. J. Ment. Health Policy Econ. 19, 181–192.
D'souza, D.C., Perry, E., Macdougall, L., Ammerman, Y., Cooper, T., Wu, Y.T., Braley, G., Gueorguieva, R., Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29, 1558–1572.
Eurich, D.T., Hanlon, J.G., Boisvenue, J.J., Meng, H., Dyck, J.R.B., 2019. A description of the medical cannabis use in Ontario, Canada. Cannabis and Cannabinoid Research 4.
Eurich, D., Lee, C., Zongo, A., Minhas-Sandhu, J.K., Hanlon, J.G., Hyshka, E., Dyck, J., 2020. Cohort study of medical cannabis authorisation and healthcare utilisation in 2014-2017 in Ontario, Canada. J. Epidemiol. Community Health 74, 299–304.
Gilman, J.M., Schuster, R.M., Potter, K.W., Schmitt, W., Wheeler, G., Pachas, G.N., Hickey, S., Cooke, M.E., Dechert, A., Plummer, R., Tervo-Clemmens, B., Schoenfeld, D.A., Evins, A.E., 2022. Effect of medical marijuana card ownership on pain, insomnia, and affective disorder symptoms in adults: a randomized clinical trial. JAMA Netw. Open 5, e222106.
Government of Canada, 2022a. Canadian Cannabis Survey 2022: Summary.
Government of Canada, 2022b. Cannabis for Medical Purposes Under the Cannabis Act: Information and Improvements.
Gunn, R., Jackson, K., Borsari, B., Metrik, J., 2019. A longitudinal examination of daily patterns of cannabis and alcohol co-use among medicinal and recreational veteran cannabis users. Drug Alcohol Depend. 205, 107661.
Hall, W., Degenhardt, L., 2008. Cannabis use and the risk of developing a psychotic disorder. World Psychiatry 7, 68–71.
Hasan, A., Von Keller, R., Friemel, C.M., Hall, W., Schneider, M., Koethe, D., Leweke, F. M., Strube, W., Hoch, E., 2020. Cannabis use and psychosis: a review of reviews. Eur. Arch. Psychiatry Clin. Neurosci. 270, 403–412.
Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., Miettunen, J., 2010. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. Schizophr. Bull. 36, 1115–1130.
Ksir, C., Hart, C.L., 2016. Cannabis and psychosis: a critical overview of the relationship. Curr. Psychiatry Rep. 18, 12.
Large, M., Sharma, S., Compton, M.T., Slade, T., Nielssen, O., 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch. Gen. Psychiatry 68, 555–561.
Lee, C., Round, J.M., Klarenbach, S., Hanlon, J.G., Hyshka, E., Dyck, J.R.B., Eurich, D.T., 2021. Gaps in evidence for the use of medically authorized cannabis: Ontario and Alberta. Canada. Harm Reduct J 18, 61.
Lin, L.A., Ilgen, M.A., Jannausch, M., Bohnert, K.M., 2016. Comparing adults who use cannabis medically with those who use recreationally: results from a national sample. Addict. Behav. 61, 99–103.
Mcguire, P., Englund, A., Bhattacharyya, S., 2018. Commentary on "the potential of cannabidiol treatment for cannabis users with recent-onset psychosis". Schizophr. Bull. 44, 18–19.
Morin, K.A., Eibl, J.K., Gauthier, G., Rush, B., Mushquash, C., Lightfoot, N.E., Marsh, D. C., 2020. A cohort study evaluating the association between concurrent mental disorders, mortality, morbidity, and continuous treatment retention for patients in opioid agonist treatment (OAT) across Ontario, Canada, using administrative health data. Harm Reduct. J. 17, 51.
NIDA, 2023. Is there a Link between Marijuana Use and Psychiatric Disorders?.
Patel, S., Khan, S., M,S. & Hamid, P. (2020). The association between cannabis use and schizophrenia: causative or curative? A systematic review. Cureus, 12, e9309.
Quigley, H., Maccabe, J.H., 2019. The relationship between nicotine and psychosis. Ther Adv Psychopharmacol 9, 2045125319859969.
Rampakakis, E., Thorne, C., Cesta, A., Movahedi, M., Li, X., Mously, C., Ahluwalia, V., Brophy, J., Ciaschini, P., Keystone, E., Lau, A., Major, G., Pavlova, V., Pope, J.E., Bombardier, C., 2023. Medical cannabis use by rheumatology patients in routine clinical care: results from The Ontario Best Practices Research Initiative. Clin. Exp. Rheumatol. 41, 118–125.
Roy-Byrne, P., Maynard, C., Bumgardner, K., Krupski, A., Dunn, C., West, Ii, Donovan, D., Atkins, D.C., Ries, R., 2015. Are medical marijuana users different from recreational users? The view from primary care. Am. J. Addict. 24, 599–606.
Sami, M.B., Bhattacharyya, S., 2018. Are cannabis-using and non-using patients different groups? Towards understanding the neurobiology of cannabis use in psychotic disorders. J. Psychopharmacol. 32, 825–849.
Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., Firth, J., 2020. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry 20, 24.
Schlienz, N.J., Spindle, T.R., Cone, E.J., Herrmann, E.S., Bigelow, G.E., Mitchell, J.M., Flegel, R., Lodico, C., Vandrey, R., 2020. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. Drug Alcohol Depend. 211, 107969.
Shim, M., Nguyen, H., Grootendorst, P., 2023. Lessons from 20 years of medical cannabis use in Canada. PLoS One 18, e0271079.
Statista, 2022. Number of Medical Marijuana Clients Registered in Canada as of December 2022, by Province.
Subbaraman, M.S., Kerr, W.C., 2018. Alcohol use and risk of related problems among cannabis users is lower among those with medical cannabis recommendations, though not due to health. J. Stud. Alcohol Drugs 79, 935–942.
Sznitman, S.R., 2017. Do recreational cannabis users, unlicensed and licensed medical cannabis users form distinct groups? Int. J. Drug Policy 42, 15–21.
Tumati, S., Lanctot, K.L., Wang, R., Li, A., Davis, A., Herrmann, N., 2022. Medical cannabis use among older adults in Canada: self-reported data on types and amount used, and perceived effects. Drugs Aging 39, 153–163.
Turna, J., Balodis, I., Munn, C., Van Ameringen, M., Busse, J., Mackillop, J., 2020. Overlapping patterns of recreational and medical cannabis use in a large community sample of cannabis users. Compr. Psychiatry 102, 152188.
Whitfield-Gabrieli, S., Fischer, A.S., Henricks, A.M., Khokhar, J.Y., Roth, R.M., Brunette, M.F., Green, A.I., 2018. Understanding marijuana's effects on functional connectivity of the default mode network in patients with schizophrenia and co-occurring cannabis use disorder: a pilot investigation. Schizophr. Res. 194, 70–77.
Williamson, E.J., Forbes, A., 2014. Introduction to propensity scores. Respirology 19, 625–635.
Zongo, A., Lee, C., Dyck, J.R.B., El-Mourad, J., Hyshka, E., Hanlon, J.G., Eurich, D.T., 2022. Incidence and predictors of cannabis-related poisoning and mental and behavioral disorders among patients with medical cannabis authorization: a cohort study. Subst. Use Misuse 57, 1633–1641.