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RESEARCH REPORT

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Cannabis use disorder and adverse cardiovascular outcomes: A population-based retrospective cohort analysis of adults from Alberta, Canada

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Abstract

Aim: To measure the association between cannabis use disorder (CUD) and adverse cardiovascular disease (CVD) outcomes.

Design and Setting: We conducted a matched, population-based retrospective cohort study involving five linked administrative health databases from Alberta, Canada.

Participants: We identified participants with CUD diagnosis codes and matched them to participants without CUD codes by gender, year of birth and time of presentation to the health system. We included 29 764 pairs (n = 59 528 individuals in total).

Measurements: CVD events were defined by at least one incident diagnostic code within the study period (1 January 2012–31 December 2019). Covariates included comorbidity, socio-economic status, prescription medication use and health service use. Using mortality-censored Poisson regression models, we computed survival analyses for time to incident CVD stratified by CUD status. In addition, we calculated crude and stratified risk ratios (RRs) across various covariates using the Mantel–Haenszel technique.

Findings: The overall prevalence of documented CUD was 0.8%. Approximately 2.4% and 1.5% of participants in the CUD and unexposed groups experienced an incident adverse CVD event (RR = 1.57; 95% confidence interval = 1.40–1.77). CUD was significantly associated with reduced time to incident CVD event. Individuals who appeared to have greater RRs for incident CVD were those without mental health comorbidity, who had not used health-care services in the previous 6 months, who were not on prescription medications and who did not have comorbid conditions.

Conclusions: Canadian adults with cannabis use disorder appear to have an approximately 60% higher risk of experiencing incident adverse cardiovascular disease events than those without cannabis use disorder.

KEYWORDS
adult, Canada, cardiovascular diseases/myocardial infarction/peripheral vascular diseases, humans, marijuana use/cannabis, substance-related disorders

INTRODUCTION

Globally, more than 200 million people report using cannabis [1], and the harmful effects associated with cannabis have become a serious global problem [2]. Of these, cannabis use disorder (CUD) impacts between 27 and 34% of people who use cannabis [3, 4]. As there are no approved medications for the treatment of CUD [5] and limited access to behavioral interventions [6], CUD has become an increasingly significant public health priority [7]. Furthermore, with increasing cannabis legalization in many parts of the world, there are concerns that this may lead to a greater prevalence of cannabis use, CUD and cannabis-related harms [8]. For example, after Canada became just the second country to legalize cannabis in 2018 [9], there was a 5% increase in reported cannabis use—from 22% in 2018 to 27% in 2020 [10]. However, data regarding cannabis-related harms have been limited, and there are no available data on CUD since 2012, when the life-time and past-year prevalences of CUD were 6.9 and 1.3% [11].

Mounting epidemiological, clinical and laboratory research suggests that regular cannabis use is associated with many adverse health outcomes [12]. However, an inadequately explored area is the intersection between cannabis and cardiovascular disease (CVD). Available data indicate rising CV events among young people who consume cannabis [13], particularly in the absence of tobacco [14]. Cannabis has been linked to serious CV events, including myocardial infarction, stroke, cardiomyopathies, atherosclerosis and cardiac arrhythmias [15–21]. Although the exact mechanisms by which cannabis use may induce CVD events are unknown, it appears to be through activation of the endogenous cannabinoid system, consisting of endocannabinoids, their receptors and complex downstream signaling pathways [18, 22–25]. When cannabinoids enter systemic circulation they activate G-protein-coupled cannabinoid receptors—CB1 and CB2 [17]—which trigger several downstream effects, such as tachycardia, vasoconstriction, platelet aggregation, vascular inflammation and cardiac myocyte changes, among others [26,27]. In addition, some cannabinoids can inhibit hepatic enzymatic processes, causing subtherapeutic levels of cardiac medications, such as anticoagulants and antiplatelet agents [25], which can exacerbate pre-existing CVD.

However, despite the considerable amount of research on the topic, notable limitations persist and a consensus on the actual relationship between CUD and CVD remains elusive in the existing literature, with some studies reporting a positive association [16, 18, 20, 21, 25–31], others reporting a negative association [32, 33] and others reporting no or an unclear association [23, 34]. These limitations may be attributed to several issues prevalent in previous studies. First, the measurement of outcomes, such as the types of CVD events considered, varies across studies, leading to inconsistent findings. Secondly, only a few previous studies have directly examined the association between CUD and CVD, with most focusing solely upon retrospectively assessed cannabis use among individuals with pre-existing CVD disease. Furthermore, these studies often lack proper control for potential confounding factors, such as other substance use disorders, age or gender. Additionally, the scarcity of longitudinal data restricts the generalizability of findings to the broader population, and there has been a lack of studies conducted specifically in Canada.

To address these gaps and inconsistencies in the existing literature, we conducted a comprehensive population-based retrospective cohort study using Alberta data. By examining the relationship between CUD and adverse CVD outcomes at a population level, we aimed to provide a more robust understanding of these risks. Our study design considers the limitations of previous research and controls for key confounding factors, allowing us to contribute valuable insights into the association between CUD and CVD. By doing so, we hope to significantly add to the literature and enhance our understanding of this complex and nuanced relationship.

METHODS

The analysis was not pre-registered and the results should be considered exploratory. We obtained institutional approval from the Conjoint Health Research Ethics Board of the University of Calgary on 22 December 2020 (REB20-1845). The present report adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting observational studies [35].

Study population and data sources

Alberta, Canada, has a diverse, multicultural population (approximately 4.5 million people as of 2022), and virtually all Albertans have access to universal, publicly funded physician services and hospital care via the Alberta Ministry of Health. Our analyses are population-based, as health administrative data are collected on all Alberta residents through the province's single-payer public health insurance plan. All Alberta residents enrolled in the Alberta Health Care Insurance Plan were included. Multiple health-related databases were linked by the Alberta Ministry of Health using unique personal health numbers (PHN). We used the following population-based health administrative databases between 1 January 2012 and 31 December 2019.

1. The Discharge Abstract Database (DAD) [36] captures detailed administrative, demographic, clinical and diagnostic information for all hospitalizations to regular beds and hospital discharges, including deaths, sign-outs and transfers in Alberta since 2002. For each admitted patient, trained professionals assign one primary and up to 24 secondary diagnostic codes (a total of 25 diagnosis fields) using the International Classification of Diseases, 10th revision (ICD-10) [36].
2. The National Ambulatory Care Reporting System (NACRS, since 2010) [37] captures detailed administrative, demographic, clinical and diagnostic information for hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics and emergency departments in Alberta. Coverage of emergency visits is almost 100%, but other forms of

ambulatory care coverage are less extensive. Like the DAD, NACRS records relevant dates, a primary diagnosis and up to nine secondary diagnoses coded using ICD-10 (total of 10 diagnosis fields), coded by trained professionals using national guidelines [37].

3. The Alberta Practitioner Claims Database contains detailed information on fee-for-service and shadow billing claims submitted by physicians and other providers for insured services covered by the Alberta Health Care Insurance Plan [38]. For each service, up to three diagnostic codes are assigned using the International Classification of Diseases, 9th revision (ICD-9). Claims Data facilitates physician remuneration but has been commonly used for health research studies [39–41].
4. The Alberta Provincial Population Registry [38] contains basic demographic information, including date of death and geographic information on all Alberta residents since 1993.
5. The Pharmaceutical Information Network (PIN) [42] is a pharmacy-based drug information system implemented in Alberta in 2008, which records all prescriptions filled in pharmacies within the province.

Exposure and index date definitions

The DAD, NACRS and Practitioner Claims databases were used to identify individuals with CUD (exposure), and the date each patient was first diagnosed with CUD was their index date. NACRS has 10 diagnosis fields, DAD has 25 diagnosis fields and CLAIMS has three diagnosis fields. All diagnosis fields were used to identify CUD exposure. A participant was considered to have CUD if, during the study period, they had at least one hospital record with an eligible corresponding ICD-10 code; at least one emergency department record with an eligible corresponding ICD-10 CUD code; or at least three physician claims on different days within a single fiscal year, with an eligible corresponding ICD-9 CUD code. See Supporting information, Appendix S1 for a comprehensive list of the ICD-9 and ICD-10 codes defining CUD previously used and validated in the literature [43–48]. Administrative diagnostic codes for substance use disorders generally show a high specificity exceeding 95% [49–51] but have lower sensitivity, ranging from 9 to 78% [52, 53]. Each participant with CUD exposure was matched—by age, gender and time of year of health service utilization at index date—to one unexposed patient, defined as having no previously documented code relating to CUD during the study period; this method has been previously applied in administrative health service studies [54–57]. The index date for each case was assigned to that case's matched control. In addition, we added time of year to the matching criteria to help control for unmeasurable confounding that may have contributed to health service utilization [58].

Cardiovascular outcomes

Our primary outcome was an incident CVD event, which we defined as the first occurrence of at least one ICD-9 or ICD-10 code for acute myocardial infarction, unstable angina, other ischemic heart disease, ischemic stroke, heart failure, cardiac dysrhythmias or peripheral vascular disease (see Supporting information, Appendix S1 for a comprehensive list of the codes considered). As per previous studies [59, 60], if a patient had at least one of these CVD diagnostic codes across the NACRS, DAD or Claims within the study period, they were considered to have had a composite CVD event (yes/no). We excluded individuals with a previous history of CVD events (i.e. prevalent cases) by examining a 2-year look-back window for any CVD-related codes.

Follow-up period

The follow-up period for each patient was the time at risk of developing a CVD from the index date until the exit date, which was defined as the earliest of the study end date (31 December 2019), the last date of data collection in the event of death or a move out of province, the date of an incident CVD event (our primary outcome) or the date of death.

Covariates

The covariates we adjusted for in analyses were selected because of their independent association with the development of CUD and CVD disease [21, 28, 61–63]. These covariates were:

- Charlson comorbidity index (CCI): we calculated the CCI [64] for each participant with a 2-year look-back window in NACRS, DAD and claims from the year of index enrolment, which allowed measurement of established CV risk factors, such as hypertension, diabetes, hepatitis C, renal disease and dyslipidemia. A 2-year look-back for CCI is standard within analytical research at AHS. However, it has also been shown that more than 1 year of a look-back does not significantly increase performance with the Quan algorithm employed [65]. Finally, 2 years is the limit for our emergency department database NACRS as it only has data from 2010.
- Material and social deprivation indices (MDI and SDI): the MDI and SDI are area-based indices derived using postal code data from the year of index enrolment and linking to the 2016 Pampalon deprivation indices, in turn, generated from census data characterizing those geographical areas [66]. Deprivation was separated into quintiles, one being the least and five being the most deprived.
- Anatomical therapeutic chemical (ATC) subgroup count: the number of distinct ATC subgroup classification codes was used to identify the number of medications participants were prescribed 6 months before a participant's index enrolment [67]. For our 6-month medication look-back window, we concluded that prescriptions would be filled regularly enough that a longer time-frame would not be necessary to determine the number of different ATC code pharmacological subgroups prescriptions participants were filling.

- Health-care utilization: we captured the number of ED, inpatient and physician visits 6 months before a participant's index enrolment to measure participant health-care utilization. The number of visits was collected by aggregating the times a study participant appeared in the databases (NACRS for ED visits, DAD for inpatient visits and Claims for physician visits).
- Mental health comorbid diagnoses: patients were considered to have co-occurring mental health or addiction-related problems if, within a 6-month retrospective window from their index enrolment in the study time-frame, they had had a relevant ICD-9/10 code for any mental health or addiction-related problem, including mood, anxiety, psychotic, substance use, personality, cognitive or developmental disorders. For mental health comorbid diagnosis, a 6-month look-back window allowed us to capture sufficient time to observe any significant mental health events immediately preceding enrolment into our study. As many mental health diagnoses can be transitory states, looking further back than this would increase the likelihood of including diagnoses no longer relevant to the participant's current state on enrolment into the study.

Statistical methods

We used a matched, retrospective cohort study design to assess the association between CUD and incident CVD events. A dedicated data scientist (J.H.) within Alberta Health Services accessed identifiable, line-level data and conducted our analyses in SAS Enterprise Guide, version 8.3 [68]. Afterwards, data were aggregated, downloaded as an Excel summary sheet (Microsoft, Redmond, WA, USA) and distributed to co-authors. We used the mid-year Alberta population in 2012 to calculate CUD point prevalence. We used percentages, raw counts (*n*), medians and interquartile ranges (IQR) and 95% confidence intervals (CI) in descriptive statistics. We conducted survival analysis using the Kaplan–Meier method. We used a log-rank test to quantify the overall association between CUD and CVD, accounting for such factors as censoring due to mortality. The remainder of the analyses were based on stratified analyses with Rate ratios (RRs) that ignored censoring by mortality. For these, we computed crude RRs by dividing the risk of a CVD event in the CUD population by that of the controls and computing CIs for the RR estimates [69]. These estimates were stratified by levels of the various covariates included in the study, and the stratum-specific RRs and 95% CIs were calculated. When the stratum-specific estimates were similar, we used the Mantel–Haenszel (MH) technique to pool those estimates, producing an adjusted RR. If the confidence intervals for each stratum-specific RR overlapped with those of the other strata, this was interpreted as an indication that differences between the stratified estimates could arise from sampling variability in each case. Decisions about the homogeneity of each set of stratified estimates were also supported by inspecting the point estimates and their associated 95% CIs and calculating the *P*-values for the MH test of homogeneity; *P*-values less than 0.05 were suggestive of effect modification (i.e. that the stratum-specific RR estimates were significantly heterogeneous). Finally, in circumstances of homogeneity, these adjusted RRs were compared to the crude RRs to assess confounding by the specified variable. All statistical tests were two-sided, with the criterion for statistical significance set at $\alpha = 0.05$.

Exploratory analyses

Exploratory analyses were undertaken to estimate if 'dose–response' relationships existed between the number of CUD diagnostic codes and the number of CVD events. For example, some patients' CUD and CVD count was quite high due to how physicians entered diagnosis data into their systems. Therefore, rather than treat the number codes as continuous variables, we created a category from the total count of CUD and CVD diagnoses among NACRS, DAD and Claims events during the study period separated into one, two to four and five or more records. A higher number of diagnoses were used as a surrogate for CUD and CVD severity, respectively.

E-values

We quantified potential unmeasured confounding using E-values, and the minimum RR and unmeasured confounder would need to have with CUD and CVD events to fully explain a specific association, conditional on the measured covariate [70, 71]. Large E-values help to quantify the potential impact of unmeasured confounding. An E-value is the strength of association between a covariate and exposure and covariate and disease for an unmeasured confounder that could account for a RR associated with the exposure. Conversely, small E-values imply that an unmeasured covariate weakly associated with the exposure and outcome could account for an observed association, providing evidence of low robustness [70, 71]. The E-values were computed using the following formula: $RR + \sqrt{RR * (RR - 1)}$. The E-value of the CI is one if the lower limit (LL) of the CI is ≤ 1; or the E-value for the 95% CI equals $LL + \sqrt{LL * (LL - 1)}$. In this study, the E-value should be interpreted as the effect size an unmeasured confounder will probably have on the exposure (CUD) and outcome (incident CVD). For all RR estimates, the E-value was greater than the observed RR, indicating that the effect size of a possible unmeasured confounder would need to exceed the measured effect sizes, even after adjustment for covariates. We supply E-values for RR estimates in Supporting information, Appendix S2.

RESULTS

We included 29 764 pairs (*n* = 59 528 individuals total) matched on gender, year of birth and year and month of presentation to the health system in the analysis (Figure 1). The overall prevalence of documented CUD was 24 161/3875000 (2012 Alberta population), or approximately 0.8%. In total, 1435 participants had missing data.

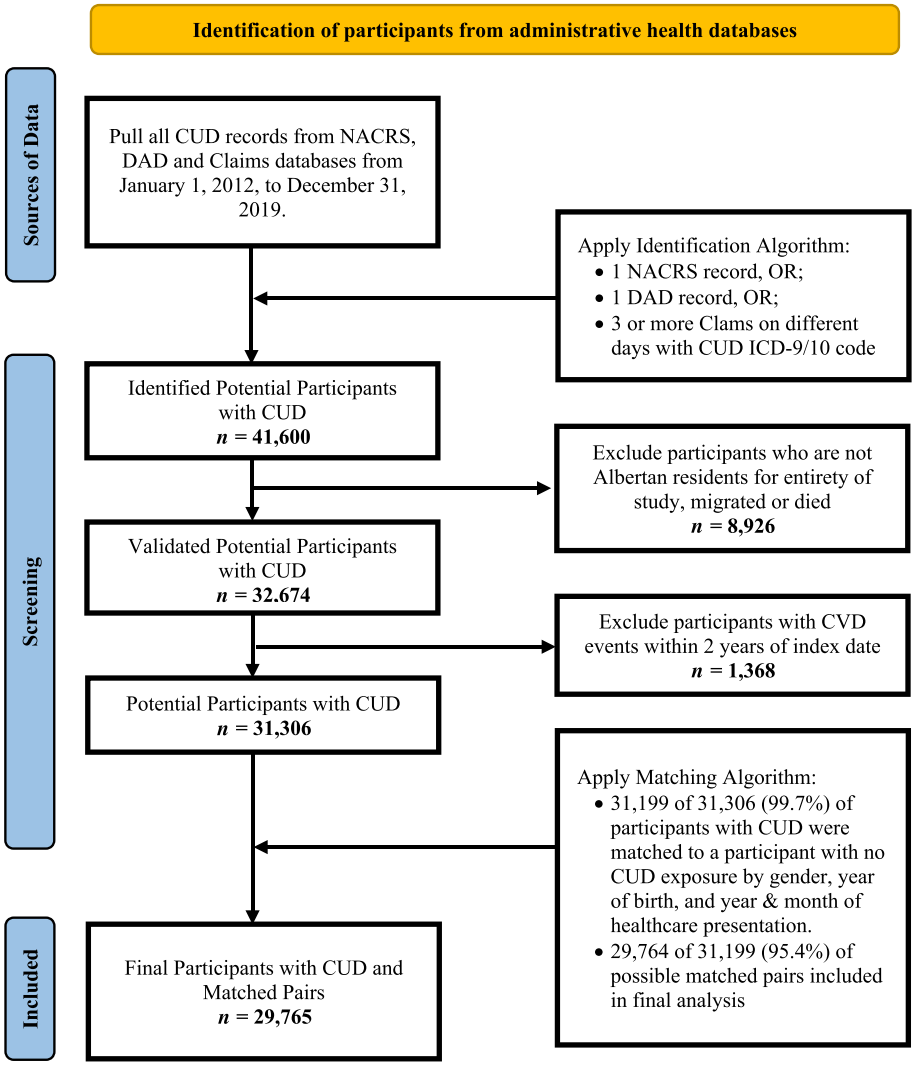

FIGURE 1 Participant flow diagram. *Note*: Flow diagram adapted from the PRISMA 2020 guidelines [72].

TABLE 1 Baseline covariates values for cannabis use disorder (CUD) and control group, respectively.

	CUD (median, IQR; mean, SD)[a]	Control (median, IQR; mean, SD)[a]
n	29 764	29 764
Charlson comorbidity index	0 (0–0); 0.3 (0.8)	0 (0–0); 0.1 (0.5)
Material deprivation index	4 (2–5); 3.3 (1.4)	3 (2–4); 3.1 (1.4)
Social deprivation index	4 (2–5); 3.5 (1.4)	3 (2–4); 3.1 (1.4)
Number of distinct prescriptions	2 (0–4); 2.9 (3.6)	1 (0–2); 1.4 (2.1)
Health-care utilization[b]	5 (2–11); 8.8 (11.8)	1 (0–3); 2.6 (4.1)
Number of mental health comorbidities	1 (0–2); 1.4. (1.8)	0 (0–0); 0.2 (0.5)

Abbreviations: IQR = interquartile range; SD = standard deviation.
[a]IQR 1368 participants had missing data.
[b]The number of ED, inpatient and physician visits 6 months before a participant's index enrolment was used to measure participant health-care utilization.

Baseline covariates

The median CCI was 0 in both the CUD and unexposed groups. The median material deprivation index (MDI) and social deprivation index (SDI) values were both 4 in the CUD group and 3 in the unexposed group, respectively. According to the MDI and SCI scores, people with CUD were less likely to be in the least deprived quartiles and more likely to be in the most deprived quartiles (Table 1). The median number of prescription medications (organized by the ATC Code Pharmacological Subgroup) 6 months before index enrolment was two in the CUD group and one in the unexposed group. The median number of ED, inpatient and practitioner visits 6 months before index enrolment was five (IQR = 2–11) and one (0–3) in the CUD and unexposed groups, respectively.

Association between CUD and incident CVD events

Overall, the proportion of participants experiencing at least one incident adverse CVD event was 2.4% in the CUD group and 1.5% in

the unexposed group (RR = 1.57, 95% CI = 1.40–1.77; Table 2). The log-rank test for the overall association between CUD and incident CVD was significant (χ^2 = 59.7890; *P*-value < 0.001); a Kaplan–Meier curve for the corresponding survival analyses is provided in Supporting information, Appendix S3.

Sensitivity analysis: relationship between CUD severity and CVD risk

By CUD severity (defined as the number of CUD codes), we saw a 'dose-dependent' increase in the strength of association, with larger effect sizes for adverse CVD events with higher CUD severity (Table 3). For example, for individuals with just one CUD diagnostic code, the strength of association was RR = 1.32 (95% CI = 1.22–1.43). For those with two to four CUD diagnostic codes the strength of association was RR = 2.47 (95% CI = 2.28–2.68) and for those with five or more codes was RR = 2.64 (95% CI = 2.40–2.91).

Stratum-specific estimates for confounder variables

For each stratum of confounding variables, we calculated the stratum-specific RR for the strength of association between CUD and incident adverse CVD events (Table 4). In most cases, the confidence intervals for each stratum-specific RR overlapped with those of the other strata, indicating that differences between the stratified estimates could arise from sampling variability in each case. However, the *P*-values for Mantel–Haenszel homogeneity tests were significant for three variables—Charlson index (*P*-value = 0.0037), number of different prescriptions (*P*-value = 0.0116) and health-care utilization (*P*-value = 0.0149)—suggestive of effect modification for these three covariates (see Table 3). Specifically, the RR estimates were higher among those with no medical comorbidities, who were not on any prescriptions and who had had fewer than five visits to health services during the last 6 months.

E-values

We calculated E-values based on VanderWeel & Ding's seminar paper, as described in the Methods section. For all reported RR estimates in Tables 2–4, we list the E-values for the overall and covariate-specific RR estimates alongside the E-value for the 95% CI for the RR (Supporting information, Appendix S2). While there was variation in our effect sizes and E-values, most RR estimates were approximately 1.5–2 or between 1.0 and 1.5; one RR was below 1. Therefore, the analysis could not exclude the possibility that an unmeasured confounder, such as cigarette smoking, could account for the association observed.

DISCUSSION

Summary of key findings

In this population-based retrospective cohort study of Albertans, adults with CUD had a 60% higher risk of experiencing incident adverse CVD events than people of the same age and sex but without CUD. This study's main contribution to the field is in helping to quantify the extent of the association of CUD with CVD risk. The study confirms that apparently healthy people, in terms of their medical and

TABLE 2 Cardiovascular disease (CVD) events by cannabis use disorder (CUD) exposure, *n* = 59 528.

	CVD event				
CUD exposure	Yes	No	Total	% CVD outcome	RR (95% CI)
Unexposed	458	29 306	29 764	1.5%	1.57 (1.40–1.77)
Exposed	721	29 043	29 764	2.4%	
Total	1179	58 349	59 528	2.0%	

Abbreviations: CI = confidence interval; RR = risk ratio.

TABLE 3 Cardiovascular disease (CVD) events by cannabis use disorder (CUD) severity, *n* = 59 528.

		CVD events					
CUD exposure	CUD severity	0	1	2–4	5+	Total	RR (95% CI)
Unexposed	0	29 306	159	146	153	29 764	Ref.
Exposed	1	17 356	192	98	109	17 755	1.48 (1.30–1.69)
	2–4	7591	116	50	47	7804	1.80 (1.53–2.11)
	5+	4096	53	33	23	4205	1.71 (1.39–2.10)
Total		58 349	520	327	332	59 528	1.57 (1.40–1.77)

Abbreviations: CI = confidence interval; RR = risk ratio.

TABLE 4 Stratum-specific estimates for confounder variables.

Variable	Crude RR (95% CI)	Stratum	Stratum-specific RR (95% CI)	Combined RR (95% CI)	*P*-value for homogeneity test
CCI	1.57 (1.40–1.77)	CCI = 0	1.49 (1.29–1.73)	1.32 (1.17–1.48)	**0.0037**
		CCI = 1+	1.05 (0.86–1.27)		
MDI	1.57 (1.40–1.77)	MDI = 1	1.56 (1.17–2.10)	1.55 (1.37–1.75)	0.4561
		MDI = 2	1.36 (1.00–1.84)		
		MDI = 3	1.63 (1.22–2.18)		
		MDI = 4	1.35 (1.05–1.73)		
		MDI = 5	1.80 (1.43–2.28)		
SDI	1.57 (1.40–1.77)	SDI = 1	1.19 (0.83–1.71)	1.50 (1.33–1.69)	0.1148
		SDI = 2	1.06 (0.75–1.48)		
		SDI = 3	1.61 (1.22–2.12)		
		SDI = 4	1.69 (1.33–2.14)		
		SDI = 5	1.63 (1.30–2.04)		
ATC	1.57 (1.40–1.77)	ATC = 0	1.68 (1.34–2.11)	1.22 (1.08–1.37)	**0.0116**
		ATC = 1	1.06 (0.75–1.50)		
		ATC = 2–3	1.18 (0.91–1.52)		
		ATC = 4+	1.04 (0.87–1.26)		
HCU	1.57 (1.40–1.77)	HCU = 0–1	1.44 (1.12–1.86)	1.18 (1.05–1.34)	**0.0149**
		HCU = 2–4	1.38 (1.10–1.74)		
		HCU = 5+	0.98 (0.82–1.17)		
MH	1.57 (1.40–1.77)	MH = 0	1.65 (1.43–1.91)	1.53 (1.35–1.74)	0.1326
		MH = 1	1.26 (0.92–1.73)		
		MH = 2+	1.13 (0.70–1.82)		

Note: Bold data indicates statistically significant.

Abbreviations: ATC, anatomical therapeutic chemical; CCI, Charlson comorbidity index; CI, confidence interval; HCU, health-care utilization; MDI, material deprivation index; MH, mental health; RR, risk ratio; SDI, social deprivation index.

medication history, are at increased risk of CVD if they have CUD. However, the study cannot causally attribute the elevated risk to CUD.

The reported prevalence of 0.8% may appear slightly lower than the prevalence estimate of 1.3% cited previously, corresponding to the past-year prevalence of CUD in Canada from the 2012 Canadian Community Health Survey (CCHS). The difference in prevalence may be that the lower prevalence we captured represents more severe cases and, possibly, treatment-seeking individuals. The disparity in these estimates may also be attributed to the distinct methodologies used to ascertain them. For example, the 1.3% estimate was based on computer-assisted telephone interviews utilizing the Composite International Diagnostic Instrument (CIDI), which employs DSM-IV criteria for cannabis abuse or cannabis dependence. In contrast, our study utilized clinician-diagnosed CUD that appeared in administrative data sets, aligning more with the DSM-5 criteria. Furthermore, it is worth noting that few previous provincial estimates for CUD prevalence, whether derived from surveys or administrative data, exist. However, this highlights opportunities for future research to explore and address the variations in prevalence estimation methods throughout provinces. By doing so we can more clearly understand CUD prevalence at a regional level and its implications for public health and policy.

Comparison with previous studies

Throughout the extant literature, mounting evidence shows that cannabis use is associated with a more problematic CV risk profile, including increased mortality from acute cardiovascular events [73–76]. Furthermore, frequent cannabis smoking is associated with a higher risk of stroke, myocardial infarction, coronary artery disease, heart failure and premature CVD [13, 44, 46, 47, 54, 62, 77, 78].

However, findings from prospective studies have been inconsistent, with the coronary artery risk development in young adults (CARDIA), one of the largest prospective studies of its kind, finding that neither cumulative life-time nor recent use of cannabis is associated with the incidence of CVD in middle age [79]. However, long-term prospective studies can be plagued by recall bias, inadequate exposure assessment, minimal cannabis exposure and low-risk cohorts, which may affect the ability to detect an association [21]. Other sources of inconsistency in the findings across the extant literature include over-reliance upon small, cross-sectional samples; the lack of longitudinal data; disparate definitions of CVD; and heterogeneity in definitions of cannabis use. Also, by studying cannabis use, this study combined CUD with potentially infrequent recreational use of cannabis.

Interestingly, only two prior studies have examined the association between CVD and CUD, and these have had more consistent findings than those that examine cannabis use alone. For example, Auger *et al*. found that parous women with ICD-9 or ICD-19 documented CUD diagnoses had a nearly 50% higher risk for incident CV hospitalization than those without CUD [hazard ratio (HR) = 1.48; 95% CI = 1.27–1.72] [43]. Auger *et al*. also found that a concurrent CUD diagnosis (HR = 1.84; 95% CI = 1.53–2.21) had a stronger association with CVD than CUD alone (HR = 1.30; 95% CI = 0.99–1.72). Similarly, Patel *et al*. found that CUD (diagnosed using ICD-9 codes) was associated with higher odds of arrhythmia hospitalization among young adults, including in 15–24-year-olds [odds ratio (OR) = 1.28; 95% CI = 1.23–1.35] and 25–34-year-olds (OR = 1.52; 95% CI = 1.47–1.58) [55].

Strengths and limitations

This project has several strengths. It is one of the first Canadian studies to examine the association between CUD and adverse CVD outcomes. The main contribution of this study is its quantification of the size of the association of CUD with CVD events at the population level. For example, an approximately 60% increased CVD risk among individuals with CUD suggests potential value in using CUD as a basis for targeting preventive interventions, as occurs with other risk factors. This might include increased testing, screening or surveillance for CVD in CUD populations. Additional research is needed to clarify the underlying mechanisms and to guide specific preventive strategies. If a causal mechanism is confirmed, the treatment of CUD may have preventive benefits for cardiovascular health. The base rates of cannabis use and CUD were high in Alberta, with 22% of Albertans reporting cannabis use in the past 3 months—higher than the national average of 20% [10]—in the last quarter of 2020, as per the National Cannabis Survey. Approximately 1% have a diagnosed CUD per this study. However, limitations exist as our project relied heavily upon linked, observational data from several health administrative sources.

First, a wealth of epidemiological data indicates a bidirectional relationship between cannabis and tobacco co-use [50, 80–85]. While we could not directly control for confounding caused by tobacco smoking (as the data available via administrative sources were not reliable enough to serve as a control for the study), we measured E-values to quantify unmeasured confounding. These E-values exceeded the strengths of association established by a previous study by Winhusen *et al*., which showed that the RR values between TUD and CUD in the context of CVD were less than 2 [14]. These E-values indicate that our study findings are potentially robust and unrelated to unmeasured confounding, but additional confirmatory evidence is needed. We also controlled for several other indicators, including socio-economic status, comorbidity and medication use. Hence, the possibility of a pathway independent of several of these markers associated with CUD and CVD is less likely. These results should motivate a general strategy to intervene in cardiovascular risk factors in this group, even if a causal relationship cannot yet be confirmed. In addition, future studies will confirm how much of the increased risk is attributed directly to cannabis and how much of this risk can be reduced by preventing CUD as opposed to other strategies, such as tobacco smoking cessation.

Secondly, we did not have a direct measure of CUD severity or quantity of cannabis use and instead used the number of times a person had been diagnosed with CUD as a proxy for the severity of CUD. However, while severity is probably associated with the number of diagnoses, misclassification may have occurred. Future population-based cohort studies should examine the impact of these variables on the strength of the association between CUD and CVD outcomes. For example, a study could measure the impact of DSM-5-based measures of CUD severity, calculated per the number of symptoms endorsed by the individual (e.g. two or three symptoms constitute mild CUD, four to five as moderate and six or more as severe). Other studies could look at the specific contributions of cannabis use variables, including the type consumed (e.g. hybrid, Indica, Sativa), mode of consumption (e.g. smoked, ingested, vaporized), frequency and duration of use.

Thirdly, our study presumed that people with CUD continue to use cannabis consistently, and we expected that CVD events are related to recent use. As it is more difficult to establish an association if the window of exposure between a CUD diagnosis and CVD outcomes is long, this may have led to a non-differential misclassification bias, as future CVD events would not affect the likelihood of CUD. However, this might have diluted the observed effect of CUD on CVD. Although former cigarette smokers continue to have elevated CVD risk even after quitting, it is unclear if this relationship applies to cannabis use [86]. Future studies could collect data on former, current and never users of cannabis and apply this to the measurement of CVD risk associated with cannabis use.

Fourthly, the sensitivity and specificity of CUD diagnosis in administrative data are unclear, and we do not know how many people with CUD were missed. However, available data suggest that CUD is underdiagnosed, as individuals who use cannabis in Alberta were previously shown to be less likely to receive a formal CUD diagnosis than individuals who consume alcohol or multiple substances [87]. While some people with CUD may have been misclassified as unexposed, it is unlikely that misclassification of CUD would dilute the effect size toward the null as those formally diagnosed and recorded as having CUD are likely to be more severe cases and cases with higher service utilization. Ultimately, this points to further refining and validating case definitions for CUD.

Nevertheless, given that our findings were statistically significant, the study provides evidence of association. However, the vulnerability to misclassification bias suggests the strength of the association may have been underestimated, and the public health implications may be more pronounced than the estimates would otherwise suggest.

Finally, although our findings do not establish a causal link between CUD and CVD events, there is still a descriptive value to

the project, particularly for applications such as screening individuals who use cannabis for CVD, as it helps to establish the base rates of CVD in this population. Nevertheless, the generalizability of our study's main finding—that individuals diagnosed with CUD are at higher risk of experiencing CVD events—to cannabis use in the absence of diagnosed CUD will need to be confirmed using other data sources in future studies. In addition, although we cannot claim a causal connection between CUD and CVD events, our study determined that people with CUD have an approximately 57% increased risk of experiencing cardiovascular morbidity. Consequently, individualized preventive interventions are of potential value in preventing CVD among people with diagnosed CUD. However, it is beyond this study's scope to determine if someone's cardiovascular risk profile will return to baseline if they stop cannabis use.

CONCLUSIONS

This study indicates that individuals with CUD are at higher risk for adverse cardiovascular health effects. Importantly, this evidence suggests that cannabis use may place a healthier population at increased risk of major cardiovascular events. As a result, our study points to the importance of educating our patients about the potential risks associated with cannabis use and CUD.

AUTHOR CONTRIBUTIONS

Anees Bahji: Formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Josh Hathaway:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (equal); visualization (equal); writing—review and editing (equal). **Denise Adams:** Conceptualization (equal); funding acquisition (equal); project administration (equal); resources (equal); writing—review and editing (equal). **David Crockford:** Conceptualization (equal); supervision (equal); writing—review and editing (equal). **E. Jennifer Edelman:** Conceptualization (equal); writing—review and editing (equal). **Michael D. Stein:** Conceptualization (equal); writing—review and editing (equal). **Scott B. Patten:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); visualization (equal); writing—review and editing (equal).

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DECLARATION OF INTERESTS

A.B. receives a small honorarium for teaching undergraduate and postgraduate medical trainees in the Cumming School of Medicine at the University of Calgary. In addition, A.B. is an unpaid member of the Canadian Network for Mood and Anxiety Treatments (CANMAT) editorial committee, the International Society of Addiction Journal Editors (ISAJE), the Canadian Society of Addiction Medicine (CSAM) policy committee and the Addiction Psychiatry section of the Canadian Psychiatric Association (CPA). A.B. is also an unpaid associate editor of the Canadian Journal of Addiction (CJA) and a mental health educator for TED-Ed, where he receives a small honorarium for supporting online educational content. Finally, A.B. does not report royalties, licenses, consulting fees, payment or honoraria for lectures or presentations, speaker's bureaux, manuscript writing, expert testimony, patents or participation on other boards. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

No data are available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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