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ORIGINAL ARTICLE

The association between regular cannabis use, with and without tobacco co-use, and adverse cardiovascular outcomes: cannabis may have a greater impact in non-tobacco smokers

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ABSTRACT

Background: Understanding the potential impact of cannabis use on cardiovascular health is increasingly important as cannabis use rises in the U.S.

Objectives: This study evaluated the associations between regular cannabis use, with and without tobacco co-use, and cardiovascular outcomes.

Methods: Analysis of a limited dataset obtained through IBM Watson Health Explorys, a platform integrating electronic health record data. Matched controls using Mahalanobis distance within propensity score calipers were defined for: 1) cannabis-using patients (n = 8,944; 43% female); and subgroups of cannabis-using patients: 2) with an encounter diagnosis for tobacco use disorder (TUD; n = 4,682); and 3) without a TUD diagnosis (non-TUD; n = 4,262). Patients had ≥1 blood pressure measurement and blood chemistry lab result in the MetroHealth System (Cleveland, Ohio). Cannabis-using patients had an encounter diagnosis of cannabis abuse/dependence and/or ≥2 cannabis-positive urine drug screens. Control patients, with no cannabis-use-documentation, were matched to the cannabis-using patients on demographics, residential zip code median income, body mass index, and, for the total sample, TUD-status. Outcomes were encounter diagnosis (yes/no) of cerebrovascular accident (CVA), heart arrhythmia, myocardial infarction, subarachnoid hemorrhage (SAH), and all-cause mortality.

Results: TUD-patients had the greatest prevalence of cardiovascular disease, regardless of cannabis-use indication. In the total sample and non-TUD subgroup, regular cannabis use was significantly associated with greater risk for CVA, arrhythmia, SAH, and mortality. In the TUD subgroup, regular cannabis use was significantly associated with greater risk for arrhythmia and SAH.

Conclusions: Cannabis use is associated with significantly greater risk of adverse cardiovascular diagnoses and overall death, particularly in non-tobacco users.

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Introduction

Cannabis use in U.S. adults has increased significantly in recent years (1,2). There is a dearth of high-quality research on the effects of cannabis use on health (3) and, in the absence of scientific evidence, there is a tendency to perceive cannabis as being harmless or even helpful (4,5); this is important since research has found that the perception of no risk from cannabis use is associated with increased use (6). As more U.S. states legalize cannabis, it becomes increasingly important to understand the potential impact of cannabis use on health so that adults can make informed choices about its use.

Heart disease is the leading cause of death in the U.S (7). Animal and in vitro research suggests that cannabis may have a negative impact on cardiovascular functioning (3,8,9). Recent reviews of the clinical literature have concluded that existing research is insufficient for evaluating the association between cannabis use and adverse cardiovascular outcomes (3,8). Limitations of past research include reliance on self-reported cannabis use, the use of cross-sectional rather than longitudinal designs, failure to control for potential confounding factors, the use of study samples in which harm is less likely to be detected (i.e., younger participants, infrequent cannabis users) (8), and the failure to disentangle the

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effects of cannabis from tobacco smoking (3,10). The latter is of importance since tobacco smoking is a primary cause of cardiovascular disease (11) and there is a high prevalence of tobacco smoking among people with cannabis use disorder (CUD), which has been estimated to be 47% (12).

The present study evaluated the association between regular cannabis use, with and without tobacco co-use, and cardiovascular outcomes using a method that addresses many of the limitations of past research (13). This approach included using EHR data, rather than self-report measures, of cannabis use and adverse cardiovascular outcomes, use of a multi-year dataset, which allows detection of effects that may take several years to develop, large sample sizes, and the use of rigorous matching and analytic procedures to control for potential confounding factors (e.g., age, race, ethnicity, socioeconomic status, other substance use, etc.). We predicted that a positive association would be found between regular cannabis use, with or without tobacco-co-use, and adverse cardiovascular outcomes.

Methods

Setting

The study data were derived from the Explorys (IBM Watson Health; Cleveland, OH) technology platform, which utilizes a health data gateway server behind the firewall of each participating healthcare organization. The server collects data from a variety of health information systems (e.g., EHR, billing systems, lab/tests systems, etc.). The data are then de-identified and passed into the Explorys data grid, which is a private cloud-based data store, and are standardized and normalized (14). The Explorys dataset has been validated in past research (14,15). Our analytic approach, in which substance-using patients are "matched" to patients without evidence of substance use to decrease the possibility of study confounds (13), requires a limited dataset available to us only from the MetroHealth System Explorys dataset. MetroHealth is an integrated healthcare system in Northeast Ohio that consists of one tertiary care academic medical center, four emergency departments, and over 24 ambulatory clinics, seeing approximately 25,000 inpatients per year, with over 1.2 million outpatient visits annually. A data use agreement between the MetroHealth System and the University of Cincinnati (UC) was established to allow the use of limited datasets. This study was deemed not to be human subjects research by the UC institutional review board.

Study population

The Explorys Cohort Discovery tool was used to identify adult patients (age ≥18) in the MetroHealth System who received a medical evaluation as evidenced by having at least one recorded blood pressure measurement and at least one blood chemistry lab result. At the time of Explorys query, the MetroHealth System included 410,484 patients meeting these criteria and contained up to 18 years of patient data on these patients.

Cannabis-use group

The a priori definition of the cannabis-using group, which was designed to identify regular cannabis users, was patients having: 1) at least one encounter diagnosis code for cannabis abuse or dependence (see Supplement, Table S1 for ICD-9/10 codes), indicating CUD; and/or 2) at least two urine drug screens (UDSs) results positive for cannabinoids. The rationale for this definition is that having at least one CUD diagnosis is evidence that a patient is very likely a regular cannabis user. On the other hand, a single positive UDS could occur for an infrequent cannabis user. Our consensus was that two or more such positive results are indicative of regular use (i.e., on multiple separate occasions, a clinician ordered this testing to be done, and it was positive at least twice). The cannabis-use group included 8,944 patients. To further elucidate the potential impact of cannabis use, with and without tobacco use, the cannabis-using group was divided into patients who had at least one encounter diagnosis code for tobacco use disorder or nicotine dependence (see Supplement, Table S1 for ICD-9/10 codes), referred to as the tobacco use disorder (TUD) subgroup (n = 4,682) and patients who did not have a TUD diagnosis, referred to as the non-TUD subgroup (n = 4,262).

Control groups

For each of the three groups (total sample, TUD subgroup, non-TUD subgroup), a control group was identified. To be included as a potential control participant, a patient could not have any encounter diagnoses with a cannabis-related ICD-9/10 code and could not have any cannabinoid-positive UDS results; 7,940 patients had a single cannabinoid-positive UDS result and were thus excluded. The potential control group included 393,600 patients. Because cannabis-using patients may differ from patients without evidence of

cannabis use on a variety of factors that could impact cardiovascular health, we created a control group that was matched to the cannabis-use group. Matching variables included: age, sex, race, ethnicity, median income of zip code of residence, and body mass index (BMI), and, for the total sample, TUD status (yes/no).

The Ohio Valley Node (OVN) matching programs, which are SAS macros (version 9.4; Cary, NC) created by one of the authors (DL), were used; they are open-source and can be used free of charge (13). The OVN matching program uses Mahalanobis Distance within Propensity Score Calipers as the distance measure (16) and allows for two matching methods: "optimal" and "greedy". For this study, we utilized optimal matching, which matches patients from the cohort of interest (e.g., cannabis-use group) to respective control patients so as to minimize the sum of the distances over all pairs (17).

Cardiovascular outcomes

The cardiovascular outcomes were selected a priori and defined by ICD-9/10 encounter diagnoses. Four cardiovascular outcomes were evaluated: 1) cerebrovascular accident (CVA); 2) heart arrhythmia; 3) myocardial infarction (MI); and 4) subarachnoid hemorrhage (SAH). The ICD-9/10 codes used for each outcome, along with the number of patients having each code, are provided in the supplementary material (Table S2). While the data are correlational in nature (i.e., patients are not randomized to cannabis-use and control groups), our approach helped to ensure that the outcome encounter diagnoses occurred after the patient's first indication of cannabis use (i.e., either CUD diagnosis or positive UDS) and, thus, that cannabis use could have played a role in developing the condition. To this end, patients were scored as: 1) positive for the condition if the initial outcome encounter diagnosis date was later than the initial cannabis-use indication date (controls were assessed using the initial cannabis-use indication date of their respective matched cannabis-use patient); 2) negative for the condition if they did not have the outcome encounter diagnosis; or 3) missing if the initial outcome encounter diagnosis date was not later than the initial cannabis-use indication date. The rationale for using the missing code is based on the potential for patients to have a condition prior to it being entered into the EHR. For example, a patient could be using cannabis for years before a UDS is completed. Hence, there is no way to ascertain whether an outcome diagnosis preceding the initial cannabis-use indication date reflects the outcome actually preceding the patient using cannabis or simply reflects the outcome diagnosis preceding the cannabis-use indication being added to the EHR. The missing code reflects the unknown temporal relationship.

All-Cause Mortality (ACM)

Social Security Death Index data is linked to Explorys patient information, and the Explorys system provides a patient's year of death, if applicable. Mortality, unlike the morbidity outcomes described above, does not have the potential problems of temporal order (i.e., if a patient has died, we presume that all the encounter diagnoses of interest were made prior to the death). Patients with no indication of death were assumed to be alive at the time of data retrieval.

Data analysis

All analyses were completed using SAS, Version 9.4. Statistical tests were defined a priori and were conducted at an α level of 0.05 (two-tail) for all measures. Logistic generalized mixed-model regressions (with a random effect to account for matched patient pairs) were used to evaluate whether cannabis-using status was significantly associated with each of the cardiovascular outcomes. For each planned regression, all possible models (i.e., all combinations of covariates) were estimated. The covariates considered for inclusion were other substance use disorders (opioid, cocaine, and alcohol; see Supplement, Table S3 for ICD 9/10 codes) and the matching covariates; the variable indicating cannabis-use group vs. control group was included in all models. The model with the covariates resulting in the best corrected Akaike Information Criterion (AIC-C) was selected; Tables S4-S6 list the covariates included in each regression. The proportion of data coded as missing (i.e., when initial outcome encounter diagnosis date was not later than the initial cannabis-use indication date) ranged from a minimum of 0.3% (SAH) to 7.1% (heart arrhythmia). The median proportion of missing data was 1.1%.

Results

As can be seen in Table 1, the matching procedure created very comparable matched groups, with no significant difference on demographics. Table 2 displays the results of the comparisons between the cannabis-use group and its matched control for each of the evaluated outcomes. The crude odds ratio (OR) results were yielded by the comparison of the cannabis-use group with its matched control

Table 1. Demographics for cannabis use and matched control cohorts for the total, tobacco use disorder (TUD), and non-TUD samples.

Total Sample	Control (n = 8944)	Cannabis Use (n = 8944)	Test statistic (*p*-value)*
Age, m (sd)	42.4 (13.5)	42.3 (13.6)	W = 0.2 (*p* = .85)
Female n (%)	3866 (43.2%)	3866 (43.2%)	χ^2 (1) = 0.0 (*p* = 1.00)
Race n (%)			χ^2 (2) = 0.0 (*p* = 1.00)
Black/African American	4123 (46.1%)	4127 (46.1%)	
White	4058 (45.4%)	4053 (45.3%)	
Other †	763 (8.5%)	764 (8.5%)	
Hispanic n (%)	238 (2.7%)	238 (2.7%)	χ^2 (1) = 0.0 (*p* = 1.00)
Median income for the zip code of residence m (sd)	$36325.9 (13965.5)	$36363.3 (14087.2)	W = 0.1 (*p* = .91)
Tobacco Use Disorder n (%)	4682 (52.3%)	4682 (52.3%)	χ^2 (1) = 0.0 (*p* = 1.00)
Average BMI m (sd)	28.1 (7.3)	28.1 (7.4)	W = 0.0 (*p* = .98)
Tobacco Use Disorder Subgroup	**Control (n = 4682)**	**Cannabis Use (n = 4682)**	**Test statistic (*p*-value)***
Age, m (sd)	45.1 (13.2)	45.0 (13.3)	W = 0.2 (*p* = .84)
Female n (%)	2118 (45.2%)	2120 (45.3%)	χ2 (1) = 0.0 (*p* = .97)
Race n (%)			χ2 (2) = 0.0 (*p* = .99)
Black/African American	2102 (44.9%)	2108 (45.0%)	
White	2241 (47.9%)	2234 (47.7%)	
Other †	339 (7.2%)	340 (7.3%)	
Hispanic n (%)	117 (2.5%)	117 (2.5%)	χ2 (1) = 0.0 (*p* = 1.00)
Median income for the zip code of residence m (sd)	$35622.6 (12940.7)	$35708.3 (13230.5)	W = 0.1 (*p* = .88)
Average BMI m (sd)	28.3 (7.2)	28.3 (7.4)	W = −0.1 (*p* = .91)
Non-Tobacco Use Disorder Subgroup	**Control (n = 4262)**	**Cannabis Use (n = 4262)**	**Test statistic (*p*-value)***
Age, m (sd)	39.4 (13.3)	39.3 (13.3)	W = 0.1 (*p* = .93)
Female n (%)	1746 (41.0%)	1746 (41.0%)	χ2 (1) = 0.0 (*p* = 1.00)
Race n (%)			χ2 (2) = 0.0 (*p* = 1.00)
Black/African American	2019 (47.4%)	2019 (47.4%)	
White	1819 (42.7%)	1819 (42.7%)	
Other †	424 (9.9%)	424 (9.9%)	
Hispanic n (%)	121 (2.8%)	121 (2.8%)	χ2 (1) = 0.0 (*p* = 1.00)
Median income for the zip code of residence m (sd)	$37067.8 (14887.8)	$37082.8 (14940.4)	W = 0.0 (*p* = .97)
Average BMI m (sd)	27.9 (7.4)	27.9 (7.5)	W = 0.0 (*p* = .96)

*Quantitative measures were tested either with Wilcoxon rank-sum test (W) or Student's t-test (T), depending on whether cohort variances tested significantly different; Categorical measures were tested with Pearson's chi-square test of independence (χ^2 (degrees of freedom)). †: "Other" race includes: American Indian/Alaska Native, Asian, Multiracial, Native Hawaiian/Pacific Islander, and "missing" (i.e., no race data available).

without controlling for additional variables (i.e., other substance use disorders including opioid, cocaine and alcohol; time since the earliest observation/diagnosis in the EHR; and demographics including age, sex, race, ethnicity, median income of zip code of residence, and BMI). The adjusted odds ratio (aOR) reflects the results from a logistic regression comparing the cannabis-use group with its matched control using AIC-C to determine inclusion of additional variables. Discrepancies between the OR and aOR results may reflect the more precise control provided by the logistic regression analysis and/or may reflect complicating factors such as the relatively low prevalence of an outcome and the number of variables selected by AIC-C in the statistical model; for example, the low prevalence of SAH in the present study may have resulted in inflated aORs. The most conservative interpretation of the findings is to consider a cannabis-use-control group comparison to be significant based on the results of the logistic regression (i.e., as indicated by the aOR column in Table 2) and to judge the degree to which the difference is clinically meaningful based on the aOR or crude OR value, whichever is closer to 1.0 (shaded in Table 2); the summary of findings in this section reflects this conservative approach.

Total sample

Characteristics

The total sample was approximately 57% male and 46% African American, and participants were a mean age of 42 years. The average number of years of EHR data available for all patients was 15.4 years (SD = 8.0). The average number of years of EHR data available following initial cannabis-use indication was 7.5 (SD = 5.0) in the cannabis-use patients. The prevalence of cannabis use disorder (CUD) within the cannabis-use group was 76.8%; the remainder of the cannabis-use group met the cannabinoid-positive UDS criterion described in Methods.

Outcomes

Table 2 provides the total sample logistic regression results, which revealed significantly higher prevalence in the cannabis-use, compared to control, group for

Table 2. Outcome diagnosis prevalence in cannabis-using vs. matched control cohort and cannabis-use ORs for total, tobacco use disorder (TUD), and non-TUD samples.

Sample†	Prevalence*	Odds Ratio (95% CI), *p*-value	aOR (95% CI), *p*-value
a. Cerebrovascular accident			
Total Sample (N = 17,888)	1.9% vs 1.3%	**1.42 (1.12–1.80), *p* = .0037**	**1.62 (1.05–2.50), *p* = .0282**
TUD‡ Subgroup (N = 9,364)	2.9% vs 2.4%	1.19 (0.92–1.54), *p* = .1756	0.90 (0.57–1.40), *p* = .6292
Non-TUD‡ Subgroup (N = 8,524)	0.8% vs 0.5%	1.56 (0.91–2.66), *p* = .1050	**3.62 (1.30–10.05), *p* = .0136**
b. Heart arrhythmia			
Total Sample (N = 17,888)	19.4% vs. 12.8%	**1.64 (1.51–1.79), *p* < .0001**	**1.38 (1.25–1.52), *p* < .0001**
TUD‡ Subgroup (N = 9,364)	26.6% vs 17.9%	**1.65 (1.49–1.83), *p* < .0001**	**1.37 (1.22–1.54), *p* < .0001**
Non-TUD‡ Subgroup (N = 8,524)	11.7% vs 7.2%	**1.71 (1.47–1.99), *p* < .0001**	**1.48 (1.23–1.77), *p* < .0001**
c. Myocardial Infarction			
Total Sample (N = 17,888)	1.7% vs 1.4%	1.25 (0.98–1.59), *p* = .0736	1.25 (0.80–1.95), *p* = .3225
TUD‡ Subgroup (N = 9,364)	2.5% vs 2.2%	1.18 (0.90–1.55), *p* = .2294	1.01 (0.61–1.66), *p* = .9855
Non-TUD‡ Subgroup (N = 8,524)	0.8% vs 0.6%	1.34 (0.79–2.28), *p* = .2787	2.12 (0.76–5.94), *p* = .1521
d. Subarachnoid hemorrhage			
Total Sample (N = 17,888)	0.5% vs 0.3%	**1.79 (1.11–2.87), *p* = .0146**	**5.66 (2.23–14.39), *p* = .0003**
TUD‡ Subgroup (N = 9,364)	0.7% vs 0.4%	1.70 (0.96–3.00), *p* = .0660	**4.41 (1.52–12.79), *p* = .0064**
Non-TUD‡ Subgroup (N = 8,524)	0.4% vs 0.1%	**2.68 (1.05–6.85), *p* = .0326**	**158.59 (9.25–2718.99), *p* = .0005**
e. All-cause Mortality			
Total Sample (N = 17,888)	4.7% vs 4.0%	**1.18 (1.02–1.37), *p* = .0227**	**1.50 (1.14–1.98), *p* = .0040**
TUD‡ Subgroup (N = 9,364)	4.7% vs 4.2%	1.12 (0.92–1.37), *p* = .2503	1.22 (0.87–1.71), *p* = .2579
Non-TUD‡ Subgroup (N = 8,524)	4.6% vs 3.4%	**1.39 (1.11–1.73), *p* = .0034**	**3.26 (2.05–5.19), *p* < .0001**

† Total Sample: N = 17,888 (n = 8,944 in Cannabis and 8,944 in Control group); TUD Subgroup: N = 9,364 (n = 4,682 in Cannabis and 4,682 in Control group); Non-TUD sample: N = 8,524 (n = 4,262 in Cannabis and n = 4,262 in Control group). *Prevalence is the prevalence of the diagnosis in the cannabis-using versus matched control cohorts. aOR = adjusted Odds Ratio; bold = statistically significant ($p < 0.05$) effect. ‡ Tobacco Use Disorder.

CVA (1.9% vs. 1.3%, OR = 1.42 (1.12–1.80)), heart arrhythmia (19.4% vs. 12.8%, aOR = 1.38 (1.25–1.52)), and SAH (0.5% vs. 0.3%, OR = 1.79 (1.11–2.87)). There was no significant difference in prevalence of MI (1.7% vs. 1.4%. aOR = 1.25 (0.80–1.95)). The regression results revealed significantly higher prevalence of ACM in the cannabis-use, compared to control, group (4.7% vs. 4.0%, OR = 1.18 (1.02–1.37)).

TUD subgroup

Characteristics

The TUD subgroup was approximately 55% male and 45% African American, and participants were a mean age of 45 years. The average number of years of EHR data available for TUD patients was 16.4 years (SD = 8.4). The average number of years of EHR data available following initial cannabis-use indication was 7.6 (SD = 4.9) in the cannabis-use patients. The prevalence of CUD within the cannabis-using TUD subgroup was 79.8%.

Outcomes

Table 2 provides the TUD subgroup logistic regression results, which revealed significantly higher prevalence in the cannabis-use, compared to control, group for heart arrhythmia (26.6% vs. 17.9%, aOR = 1.37 (1.22–1.54)), and SAH (0.7% vs. 0.4%, OR = 1.70 (0.96–3.00)). There was no significant difference in prevalence of CVA (2.9% vs. 2.4%, aOR = 0.90 (0.57–1.40)), MI (2.5% vs. 2.2%. aOR = 1.01 (0.61–1.66)), or ACM (4.7% vs. 4.2%, aOR = 1.22 (0.87–1.71)) among the TUD subgroup.

Non-TUD subgroup

Characteristics

The non-TUD subgroup was approximately 59% male and 47% African American, and participants were a mean age of 39 years. The average number of years of EHR data available for non-TUD patients was 14.3 years (SD = 7.4). The average number of years of EHR data available following initial cannabis-use indication was 7.5 (SD = 5.2) in the cannabis-use patients. The prevalence of CUD within the cannabis-using non-TUD subgroup was 73.7%.

Outcomes

Table 2 provides the non-TUD subgroup logistic regression results, which revealed significantly higher prevalence in the cannabis-use, compared to control, group for CVA (0.8% vs. 0.5%, OR = 1.56 (0.91–2.66)), heart arrhythmia (11.7% vs. 7.2%, aOR = 1.48 (1.23–1.77)), and SAH (0.4% vs. 0.1%, OR = 2.68 (1.05–6.85)). There was no significant difference in prevalence of MI (0.8% vs. 0.6%. aOR = 2.12 (0.76–5.94)). The regression results also revealed significantly higher prevalence of ACM in the cannabis-use, compared to control, group (4.6% vs. 3.4%, OR = 1.39 (1.11–1.73)).

Discussion

With the increasing use of cannabis by adults in the U.S., it is important to understand the potential impact of cannabis use on health. The present study used an approach designed to address some of the limitations of past research. This approach included utilizing multi-

year EHR data to evaluate the associations between documented cannabis use and cardiovascular outcomes and all-cause mortality using a rigorous procedure to define matched controls. Controls were matched to a sample of cannabis-using patients and subgroups of cannabis-using patients with and without tobacco use disorder (TUD). The results suggest that cannabis use is associated with a significantly greater risk of some adverse cardiovascular outcomes (CVA, heart arrhythmia, and SAH) and overall death. The associations were generally stronger among the non-TUD subgroup than in the TUD subgroup.

The present analyses evaluating adverse cardiovascular events revealed significantly worse outcomes for cannabis-using, relative to control, participants on three of the four outcomes evaluated: CVA, heart arrhythmia, and SAH. The present results revealed that CVA was significantly more prevalent in cannabis-using, relative to control, patients in the total sample, which controlled for TUD status (crude OR = 1.42), and in the non-TUD subgroup (OR = 1.56) – but not the TUD subgroup. This pattern of subgroup results may suggest that, within the context of tobacco use, any additional impact of comorbid cannabis use on CVA is relatively minor whereas among non-tobacco-users, cannabis use was discernibly associated with CVA. Past research evaluating the association between cannabis use and stroke have produced mixed findings, with some studies finding a significant association (18–20) and others failing to do so (21–23). The level of cannabis use may account for the discrepant findings, in that studies finding a significant association have utilized samples with heavier cannabis users. The present finding of greater heart arrhythmia in cannabis-using patients, in the total sample, and TUD and non-TUD subgroups, is consistent with a study finding a higher rate of arrhythmia in drivers who were positive for cannabis, relative to control drivers (24). In contrast, a study in patients with heart failure revealed lower rates of atrial fibrillation in cannabis-using, compared to control, participants (25); the discrepancy in findings may be due to the difference in the patient samples, with the present study including patients not selected for heart failure or other cardiovascular conditions and the present evaluation of arrhythmia as opposed to atrial fibrillation.

The present finding of no significant differences in rates of MI in cannabis-using patients is consistent with the results from past studies which also failed to find an association between cannabis-use and MI (21,26). The present results are discrepant with a study by Desai and colleagues that found a significant association between cannabis use and MI (27). It is important to note that while Desai and colleagues controlled for tobacco use through regression adjustment, they did not match the patient samples on tobacco use (27). While the use of regressions to control for potential confounding variables is a valid approach, it may be insufficient when groups are particularly unbalanced on the confounding variable (17). Given the high prevalence of tobacco use in cannabis users, relative to the general population (12), regression adjustment may not sufficiently control for tobacco use. For comparison, we conducted an analysis with the present dataset in which we controlled for tobacco use using regression adjustment but did not match on TUD and, like Desai et al. (27), found that cannabis use was significantly associated with MI (data not shown). Thus, the discrepant results are likely the result of the different analytic approaches taken in the two studies, with a more rigorous approach utilized in the present study. The present results are also discrepant with results from a study by Mittleman and colleagues (28), which is likely due to the difference in time-frames assessed, with Mittleman et al. evaluating cannabis use in the hour before an MI (28) and the present trial evaluating the potential impact of regular chronic use over multiple years.

The present finding of increased SAH in cannabis-using patients, in the total sample, and TUD and non-TUD subgroups, is consistent with the results of a study finding that cannabis-using patients were more likely to experience a subarachnoid hemorrhage relative to control patients (29). The present results revealed that all-cause mortality was significantly more prevalent in cannabis-using, relative to control, patients in the total sample, which controlled for TUD status (OR = 1.18), and in the non-TUD subgroup (OR = 1.39) but not in the TUD subgroup. This pattern of subgroup results may suggest that, within the context of tobacco use, any additional impact of comorbid cannabis use on mortality is relatively minor whereas among non-tobacco-users, cannabis use was significantly associated with mortality. The finding of an association between cannabis use and mortality is consistent with past research finding an elevated mortality rate in cannabis users (30–32).

The present study contributes needed evidence for understanding the potential associations between cannabis use and cardiovascular health. Although our study was not designed to directly evaluate the effect of TUD on cardiovascular disease, it should be noted that TUD-patients had the greatest prevalence of cardiovascular problems and mortality, regardless of cannabis-use indication. However, it should also be noted that the TUD subgroup was significantly older than the non-

TUD subgroup (data not shown); thus, the increased prevalence of cardiovascular problems and mortality could be due, in part, to age. Of note, this study avoided many of the limitations of past research in this area (8). First, the definition of the cannabis-using group was based on documentation in the EHR and, thus, was not open to recall bias. Second, a longitudinal design was utilized, which allows the detection of effects that may take years to develop. Moreover, the sample of cannabis-users included heavier users, in whom potential health effects are more likely to be seen, with 77% of the sample having a diagnosis of cannabis abuse or dependence. Additional strengths include a large sample size (N = 17,888) and the use of rigorous matching and analytic approaches.

This study also has important limitations. First, the findings are correlational in nature and, thus, cause and effect determinations cannot be made. Second, while the sample size was large, the sample was limited to patients being treated in the MetroHealth System, located in Northeast Ohio, and the extent to which the results are generalizable to the rest of the U.S. and other countries is unknown. Third, while the Explorys dataset has been validated in past research (14,15) there is still the potential for data quality issues. For example, as is the case with medical conditions generally, the under-diagnosis, misclassification, or under-coding of substance use disorder by clinicians is possible (33). The CUD prevalence in our full, unmatched, sample of potential patients was 1.7%, which is similar to the national estimate of 1.5% for CUD (6). Similarly, the prevalence of TUD in the cannabis-use patients was 52%, which is consistent with the 47% prevalence found in past research with individuals with cannabis use disorder (12). Still, some "control" participants may have been cannabis users despite not having had a positive UDS or cannabis diagnosis in the EHR; this would serve to weaken the associations observed in this study and, thus, the reported associations may be overly conservative. In addition, some cigarette smokers may not have been given a TUD diagnosis and, thus, classified as nonsmokers; such misclassification could reduce the accuracy of the subgroup-specific estimates. Finally, there may have been other potential confounding factors that were not accounted for in the statistical models. With these limitations in mind, the present results suggest that regular cannabis use is associated with a significantly greater risk of adverse cardiovascular diagnoses and overall death, particularly in non-tobacco users. Future research to understand the potential impact of cannabis use on cardiovascular health seems warranted.

Declarations of interest

TW, JT, and DL declare no conflicts of interest. DCK is the Chief Medical Informatics Officer of the MetroHealth System. In exchange for contributing de-identified data to the Explorys network, the MetroHealth System receives access to the Explorys Cohort Discovery tool, which was used to conduct this study. Neither DCK nor the MetroHealth System have any direct financial ties to Explorys (IBM Watson Health).

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