Cannabis Use and Electrocardiographic Myocardial Injury

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Multiple observational studies have demonstrated an association with cannabis use and acute myocardial infarction, especially among young adults. However, little is known about the connection with subclinical or electrocardiographic myocardial injury. We hypothesized that cannabis use would be associated with an increased risk of myocardial injury as defined by the cardiac infarction and/or injury score (CIIS). This analysis included 3,634 (age 48.0 ± 5.9 years, 47.1% male, 68.7% Caucasians) participants from the Third National Health and Examination Survey. Cannabis use was defined by self-report. Those with history of cardiovascular disease were excluded. Myocardial injury was defined as electrocardiographic CIIS ≥ 10. Multivariable logistic regression was used to examine the association between cannabis use and myocardial injury. The consistency of this association was tested among subgroups stratified by race, gender, tobacco smoking status, and comorbidities. About 26.0% (n = 900) of participants were ever-cannabis users and 15.5% (n = 538) had myocardial injury. In a model adjusted for potential confounders, ever-cannabis users had 43% increased odds of myocardial injury compared to never users (Odds ratio (95% confidence interval): 1.43 (1.14, 1.80); p = 0.002). This association was stronger among participants with a history of hypertension versus those without (Odds ratio (95% confidence interval): 1.83 (1.36, 2.47) vs 1.17 (0.83, 1.64), respectively; interaction p value 0.04). Cannabis use is associated with an increased risk of myocardial injury among those without cardiovascular disease with effect modification by co-existent hypertension. These novel findings underscore the harmful effects of cannabis use on cardiovascular health and also merit a personalized risk assessment when counseling patients with hypertension on its use. **(Am J Cardiol 2021;151:100−104)**

Cannabis is the most commonly used illegal drug in the United States.[1] Multiple observational studies have demonstrated an association between cannabis use and acute myocardial infarction, especially among young adults.[2-4] Cannabis use has also been linked to a range of other cardiovascular (CV) diseases, including stroke, arrhythmias, peripheral arterial disease, cardiomyopathy, and various metabolic aberrations.[5] Its use is most common among younger age groups; approximately 35.1% of high school seniors and 34.4% of college students reported cannabis use in the prior year.[6] The recent changes in the legalization of cannabis for both medical and recreational use have made cannabis consumption nearly as conventional as tobacco use.[7] This makes understanding the long−term effects of cannabis, whether harmful or beneficial, imperative. Despite its popularity, however, few studies have examined the long-term CV effects of cannabis. To date, no studies have examined the connection between cannabis use and subclinical or electrocardiographic myocardial injury. Subclinical myocardial injury, defined by the cardiac infarction and/or injury score (CIIS), has been identified as a risk factor for cardiovascular mortality.[8-12] We hypothesized that cannabis use would also be associated with electrocardiographic myocardial injury as defined by the CIIS among those free from CV disease.

Methods

The Third National Health and Nutrition Examination Survey (NHANES-III) is a survey of a representative sample of the civilian U.S. population that estimates disease prevalence and overall health.[13] Data in NHANES-III were collected from 1988-1994 through an in-home interview process and a subsequent appointment at a mobile examination center.

For this analysis, we excluded participants < 18 years of age and those with missing data elements. Only those with electrocardiographic data and responses to the cannabis use questions were included. Participants with a history of CV disease defined by composite history of myocardial infarction, heart failure, or stroke, were excluded. Age, gender, race (Caucasian, African-American, or other), and tobacco smoking status (never, former, or current) were defined by self-report. Former cannabis users were defined as

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participants who reported ever using but had not used cannabis in the last month. Among those who reported cannabis use in the previous month, they were classified as either current light users (≤ 4 days per month) or current heavy users (≥ 5 days per month) as has been done in prior studies.[14,15] Current users were defined as a composite of light or heavy users.

Diabetes was defined as fasting serum glucose ≥ 126 mg/dL, hemoglobin A1c ≥ 6.5%, or use of an antihyperglycemic medication. Hypertension was defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg or use of an antihypertensive medication according to American Heart Association/American College of Cardiology guidelines.[16] Hyperlipidemia was defined as total cholesterol ≥ 200 mg/dL, serum triglycerides ≥ 150 mg/dL, or use of lipid-lowering medications. Obesity was defined as body mass index ≥ 30 kg/m^2.

A total of 12-lead electrocardiograms were obtained by trained technicians with a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, WI) during mobile examination visits. Electrocardiograms were automatically processed in a centralized core laboratory after being visually inspected by a trained technician. The cardiac infarction/injury score is a scoring scheme for visual and computer classification that uses various continuous and discrete features.[9] Raw calculated scores were multiplied by 10 in NHANES-III to avoid decimal places. Myocardial injury was defined as cardiac infarction and/or injury scores ≥ 10, which is the minimum limit for an abnormal value.[9]

Population characteristics were compared based on cannabis use. Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as frequency and percentage. A student's t-test was used to compare continuous variables and a chi-square test was used to compare categorical variables.

Multivariable logistic regression was used to estimate the association between cannabis use and myocardial injury. Two models were used: model 1 was adjusted for age, gender, and race and model 2 was adjusted for model 1 plus hypertension, obesity, diabetes, hyperlipidemia, and tobacco smoking status.

To examine the consistency of the results among subgroups, the association between cannabis use and myocardial injury was evaluated in subgroups stratified by race (Caucasian vs. non-Caucasian), gender, hypertension, obesity, diabetes, hyperlipidemia, and tobacco smoking status. Interaction was tested for using variables similar to those in model 2 with addition of the interaction term between ever-cannabis use and subgroup stratification.

All statistical analyses were conducted using RStudio version 1.3.1093 (Boston, MA) and p-values were considered significant if < 0.05.

Results

A total of 3,464 participants (age 48.0 ± 5.9 years, 47.1% male, 68.7% whites) were included in the analysis. About 26.0% (n = 900) of participants were ever-cannabis users and 15.5% (n = 538) had myocardial injury. Population characteristics stratified by cannabis use status are depicted in Table 1. Compared to never users, ever-cannabis users were more likely to be younger, male, African-American, and tobacco users. Ever-users were less likely to have hyperlipidemia. Former cannabis users were more likely to have myocardial injury. Former cannabis users were less likely to have hypertension or diabetes. Heavy current users were less likely to be obese.

Table 1
Population characteristics

Characteristics	Cannabis user status			
	Never	Former	Light current	Heavy current
(Mean ± SD or n (%))	2564 (74.0%)	785 (22.7%)	70 (2.0%)	45 (1.3%)
Age (years)	49.1 ± 5.8	45.1 ± 4.9*	44.3 ± 4.2*	44.0 ± 3.8*
Men	1074 (41.9%)	478 (60.9%)*	50 (71.4%)*	31 (68.9%)*
Race				
White	1842 (71.8%)	493 (62.8%)*	28 (40.0%)*	18 (40.0%)*
Black	633 (24.5%)	262 (33.4%)*	38 (54.2%)*	26 (57.8%)*
Other	89 (3.5%)	30 (3.8%)*	4 (5.7%)*	1 (2.2%)*
Hypertension	1361 (53.1%)	373 (47.5%)*	37 (52.9%)	26 (57.8%)
Obesity	838 (32.7%)	236 (30.1%)	15 (21.4%)	5 (11.1%)*
Diabetes mellitus	327 (12.8%)	66 (8.4%)*	7 (10.0%)	1 (2.2%)
Hyperlipidemia	1814 (70.8%)	523 (66.6%)*	41 (58.6%)*	24 (53.3%)*
Smoker				
Never	1273 (49.7%)	217 (27.6%)*	10 (14.3%)*	6 (13.3%)*
Former	657 (25.6%)	279 (35.5%)*	13 (18.9%)*	9 (20.0%)*
Current	634 (24.7%)	289 (36.8%)*	47 (67.1%)*	30 (66.7%)*
Electrocardiographic Myocardial Injury	380 (14.8%)	142 (18.1%)*	9 (12.9%)	7 (15.6%)

* $p < 0.05$ compared with never users.
Light current = cannabis use ≤4 days in prior month.
Heavy current = cannabis use ≥5 days in prior month.
Obesity = body mass index ≥30kg/m^2.
Hyperlipidemia = total cholesterol ≥200 mg/dL, serum triglycerides ≥150 mg/dL, or use of lipid-lowering medications.

Table 2
Association of cannabis use and electrocardiographic myocardial injury

Cannabis use	Reference level	Model 1		Model 2	
		Odds Ratio (95% CI)	p *value*	Odds Ratio (95% CI)	p *value*
Ever User	Never User	1.46 (1.17 − 1.82)	<0.001	1.43 (1.14 − 1.80)	0.002
Former User	Never User	1.51 (1.20 − 1.89)	<0.001	1.49 (1.18 − 1.88)	<0.001
Current User	Never User	1.12 (0.64 − 1.95)	0.69	1.03 (0.59 − 1.81)	0.91
Light User	Never User	1.02 (0.50 − 2.10)	0.96	0.92 (0.44 − 1.90)	0.81
Heavy User	Never User	1.28 (0.56 − 2.92)	0.56	1.23 (0.53 − 2.83)	0.63

Model 1 adjusted for age, gender, and race.
Model 2 adjusted for model 1 plus hypertension, obesity, diabetes, hyperlipidemia, and tobacco smoking status.

In a logistic regression model adjusted for demographic and comorbid covariates, ever-cannabis use was associated with 43% increased odds of myocardial injury (Odds Ratio: 1.43, 95% CI: 1.14 to 1.80, p value = 0.002) when compared to never users. Former users had 49% increased odds of myocardial injury (Odds Ratio: 1.49, 95% CI: 1.18 to 1.88, p value < 0.001) when compared to never users. There was no significant association with current users, light current users, or heavy current users compared to never users. These results are summarized in Table 2.

Table 3 shows the association of ever-cannabis users and myocardial injury across sub-groups when compared to never users. A significant effect modification by hypertension was observed with a stronger association among those with versus those without hypertension (interaction p value = 0.04). Results were consistent among the other subgroups when stratified by race, gender, obesity, diabetes, hyperlipidemia, and tobacco smoking status.

Discussion

In this racially diverse examination of cannabis users without CV disease, we observed an association between ever-cannabis use and myocardial injury. This relationship appeared to be stronger among participants with co-existent hypertension. Hypertension has the strongest evidence for causation of coronary artery disease and a high prevalence in the general population.[17] Thus, patients with hypertension represent a high-risk group that is more susceptible to the adverse CV effects of cannabis use. Our observed association of cannabis use with myocardial injury persisted despite adjustment for multiple known risk factors for coronary artery disease.[18] The clinical implications of these findings support cannabis use as an emerging risk factor for cardiovascular disease and also suggest that those with hypertension are at higher risk of these deleterious effects.

Table 3
Association of ever cannabis use and electrocardiographic myocardial injury among sub-groups

Sub-group		Model 1† Odds Ratio *(95% CI)*	Model 2† Odds Ratio *(95% CI)*	*Interaction* p *value**
Race	*Non-white*	1.38 (0.93 − 2.02)	1.40 (0.94 − 2.07)	0.58
	White	1.56 (1.18 − 2.06)	1.62 (1.22 − 2.15)	
Gender	*Men*	1.61 (1.19 − 2.18)	1.62 (1.19 − 2.20)	0.43
	Women	1.29 (0.92 − 1.80)	1.32 (0.94 − 1.85)	
Hypertension	*Present*	1.78 (1.32 − 2.39)	1.83 (1.36 − 2.47)	0.04
	Absent	1.17 (0.83 − 1.65)	1.17 (0.83 − 1.64)	
Obesity	*Present*	1.58 (1.09 − 2.28)	1.63 (1.12 − 2.38)	0.09
	Absent	1.40 (1.05 − 1.85)	1.42 (1.07 − 1.88)	
Diabetes	*Present*	1.73 (0.91 − 3.31)	1.76 (0.92 − 3.39)	0.41
	Absent	1.45 (1.14 − 1.84)	1.48 (1.16 − 1.88)	
Hyperlipidemia	*Present*	1.51 (1.15 − 1.97)	1.56 (1.19 − 2.05)	0.92
	Absent	1.39 (0.93 − 2.07)	1.41 (0.94 − 2.10)	
Tobacco Smoking Status	*Never*	1.31 (0.85 − 2.00)	1.37 (0.89 − 2.11)	0.82
	Former	1.37 (0.90 − 2.08)	1.41 (0.92 − 2.17)	
	Current	1.44 (1.01 − 2.06)	1.43 (1.00 − 2.05)	

95% CI = 95% Confidence Interval.
Model 1 adjusted for age, gender, and race.
Model 2 adjusted for model 1 plus hypertension, obesity, diabetes, hyperlipidemia, and tobacco smoking status.
† Comparison of ever cannabis users to never users.
* Interaction p-value calculated from model 2.

As cannabis legalization is gaining more acceptance among the general population for both recreational and medical uses, it is becoming increasingly important to recognize the possible health consequences of its use. Its current status as a federally-classified Schedule I drug makes it illegal to conduct rigorous controlled trials in the United States.[5] Therefore, most of the data behind its health effects are based on weak evidence such as case reports and observational studies.

The connection of cannabis use to the risk of acute myocardial infarction currently has the most evidence. A systematic review by Richards and colleagues revealed a positive association between cannabis use and acute myocardial infarction in multiple observational studies.[4] There are several possible explanations for the risk of myocardial injury (or infarction) with cannabis use. Cannabis smoking and tobacco smoking share many of the same cardiotoxic chemical constituents,[19] and smoking is a major risk factor for cardiovascular disease.[20] Besides, cannabis and tobacco are often used in parallel, so there may also be a component of concurrent toxicity.[5] Further, similar mechanisms such as platelet activation, sympathetic nervous system activation, pro-inflammatory cytokine release, and increased low-density lipoprotein formation are thought to play a role in its pathogenesis.[5]

However, contradictory evidence also exists regarding the connection between cannabis use and CV disease. The CARDIA study examined a longitudinal cohort of 5113 adults in middle-age and no significant association was observed based on cumulative lifetime or recent cannabis use.[21] A case-crossover analysis of the Determinants of Myocardial Infarction Study showed an elevated risk of myocardial infarction in the 60 minutes following use; after this period, the risk of myocardial infarction rapidly declined to baseline levels.[22] Finally, an analysis of the Multicenter AIDS Cohort Study failed to show any significant association between long-term cannabis use and subclinical atherosclerosis as measured by CT angiography of coronary artery calcium.[23]

Our study does suffer from several limitations. The cross-sectional design of the analysis lends itself to temporality and residual confounding issues. As such, our findings are hypothesis-generating and cannot support definitive conclusions. Also, cannabis use was defined by self-report only and is therefore subject to reporting and recall bias, and thus the prevalence may have been underestimated.[24] While we do have categories of "light" and "heavy" cannabis use, we do not have any data regarding the dosage of cannabis, route of administration, or time when users quit. To this point, our data did not demonstrate any association between current cannabis use and myocardial injury. However, only ~3.3% of our study population were current users, so this small proportion likely lacked statistical power for robust conclusions. Further, we do not have any data regarding the specific type of cannabis used; cannabis is a heterogenous species that comes in a wide variety of potencies.[25] Hence, varying composition of cannabis may also influence its CV effects. A final limitation is that our population may have been subjected to the cohort effect since those that use cannabis may have other predispositions towards myocardial injury. However, we attempted to control for this by adjusting our regression model for known risk factors of cardiovascular disease. Despite these limitations, our study provides a novel link between cannabis use and an objective measure of myocardial injury among participants without CV disease. Other strengths include a racially diverse population and large sample size.

Among individuals free from CV disease, cannabis use is independently associated with increased risk of myocardial injury with possible effect modification by co-existent hypertension. This is a novel finding that underscores the harmful effects of cannabis use on CV health and highlights the need for further, controlled studies regarding cannabis and CV disease as the drug becomes more accepted by the general population. Additionally, the finding of effect modification by co-existent hypertension merits a personalized risk assessment when counseling patients on cannabis use.

Authors' Contribution

Travis Skipina: Software, formal analysis, data curation, writing − original draft, visualization

Elsayed Soliman: Conceptualization, methodology, writing − review and editing, supervision

Bharathi Upadhya: Conceptualization, methodology, writing − review and editing, supervision

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1. The CBHSQ Report. *Rockville (MD)*. 2013.
2. Patel RS, Manocha P, Patel J, Patel R, Tankersley WE. Cannabis use is an independent predictor for acute myocardial infarction related hospitalization in younger population. *J Adolesc Health* 2020;66:79–85.
3. Chami T, Kim CH. Cannabis abuse and elevated risk of myocardial infarction in the young: a population-based study. *Mayo Clin Proc* 2019;94:1647–1649.
4. Richards JR, Bing ML, Moulin AK, Elder JW, Rominski RT, Summers PJ, Laurin EG. Cannabis use and acute coronary syndrome. *Clin Toxicol (Phila)* 2019;57:831–841.
5. DeFilippis EM, Bajaj NS, Singh A, Malloy R, Givertz MM, Blankstein R, Bhatt DL, Vaduganathan M. Marijuana use in patients with cardiovascular disease: JACC review topic of the week. *J Am Coll Cardiol* 2020;75:320–332.
6. National Institute on Drug Abuse., University of Michigan. *Institute for Social Research. Monitoring the future, national survey results on drug use NIH publication*. Bethesda, Md.: National Institute on Drug Abuse, U.S. Dept. of Health and Human Services, National Institutes of Health; 2000 volumes.
7. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* 2015;110:19–35.
8. O'Neal WT, Shah AJ, Efird JT, Rautaharju PM, Soliman EZ. Subclinical myocardial injury identified by cardiac infarction/injury score and the risk of mortality in men and women free of cardiovascular disease. *Am J Cardiol* 2014;114:1018–1023.
9. Rautaharju PM, Warren JW, Jain U, Wolf HK, Nielsen CL. Cardiac infarction injury score: an electrocardiographic coding scheme for ischemic heart disease. *Circulation* 1981;64:249–256.
10. Dekker JM, Schouten EG, Pool J, Kok FJ. Cardiac Infarction Injury Score predicts cardiovascular mortality in apparently healthy men and women. *Br Heart J* 1994;72:39–44.
11. Dekker JM, Schouten EG, Kromhout D, Klootwijk P, Pool J. The cardiac infarction injury score and coronary heart disease in middle-aged and elderly men: the Zutphen Study. *J Clin Epidemiol* 1995;48:833–840.

12. Richardson K, Engel G, Yamazaki T, Chun S, Froelicher VF. Electrocardiographic damage scores and cardiovascular mortality. *Am Heart J* 2005;149:458–463.
13. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. *Vital Health Stat* 1994;1:1–407.
14. Rajavashisth TB, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, Friedman TC. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open* 2012;2:e000494.
15. Smit E, Crespo CJ. Dietary intake and nutritional status of US adult marijuana users: results from the Third National Health and Nutrition Examination Survey. *Public Health Nutr* 2001;4:781–786.
16. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71:1269–1324.
17. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension* 2020;75:285–292.
18. Hajar R. Risk factors for coronary artery disease: historical perspectives. *Heart Views* 2017;18:109–114.
19. Henry JA, Oldfield WL, Kon OM. Comparing cannabis with tobacco. *BMJ* 2003;326:942–943.
20. rd, Roy A, Rawal I, Jabbour S, Prabhakaran D. Tobacco and cardiovascular disease: a summary of evidence eds. In: Prabhakaran D, Anand S, Gaziano TA, Mbanya JC, Wu Y, Nugent R, eds. Cardiovascular. Washington (DC): Respiratory, and Related Disorders; 2017.
21. Reis JP, Auer R, Bancks MP, Goff DC, Lewis CE, Pletcher MJ, Rana JS, Shikany JM, Sidney S. Cumulative lifetime marijuana use and incident cardiovascular disease in middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Public Health* 2017;107:601–606.
22. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001;103:2805–2809.
23. Kelly SG, Plankey M, Post WS, Li X, Stall R, Jacobson LP, Witt MD, Kingsley L, Cox C, Budoff M, Palella FJ. Associations between Tobacco, Alcohol, and Drug Use with Coronary Artery Plaque among HIV-Infected and Uninfected Men in the Multicenter AIDS Cohort Study. *PLoS One* 2016;11:e0147822.
24. Macleod J, Hickman M, Smith GD. Reporting bias and self-reported drug use. *Addiction* 2005;100:562–563.
25. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. *Biol Psychiatry* 2016;79:613–619.