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Marijuana Use and the Risk of Early Ischemic Stroke: The Stroke Prevention in Young Adults Study.

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Abstract

Background and Purpose: Few studies have examined the dose-response and temporal relationships between marijuana use and ischemic stroke while controlling for important confounders, including amount of tobacco smoking. The purpose of our study was to address these knowledge gaps.

Methods: A population-based case-control study with 1,090 cases and 1,152 controls was used to investigate the relationship of marijuana use and early-onset ischemic stroke. Cases were first-ever ischemic stroke between the ages of 15 and 49 identified from 59 hospitals in the Baltimore-Washington region. Controls obtained by random digit dialing from the same geographic region were frequency-matched to cases by age, sex, region of residence and, except for the initial study phase, race. After excluding subjects with cocaine and other vasoactive substance use, the final study sample consisted of 751 cases and 813 controls. All participants underwent standardized interviews to characterize stroke risk factors and marijuana use. Unconditional logistic regression analysis was used to assess the relationships between marijuana use and risk of ischemic stroke, adjusting for age, sex, race, study phase, the amount of current tobacco smoking, current alcohol use, hypertension, and diabetes mellitus.

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DISCLOSURES
None.

SUPPLEMENTAL MATERIALS
Supplementary Methods.

Results: After adjusting for other risk factors, including the amount of current tobacco smoking, marijuana use was not associated with ischemic stroke, regardless of the timing of use in relationship to the stroke, including ever use, use within 30 days, and use within 24 hours. There was a non-significant trend towards increased stroke risk among those who smoked marijuana at least once a week (OR=1.9, 95%CI=0.8–4.9).

Conclusions: These analyses do not demonstrate an association between marijuana use and an increased risk of early-onset ischemic stroke, although statistical power was limited for assessing the association among very heavy users.

Keywords

ischemic stroke; stroke in the young; marijuana; cannabis

Subject Codes:

[66] Risk Factors for Stroke; [135] Risk Factors; [68] Stroke in Children and the Young; [13] Cerebrovascular disease/stroke; [127] Behavioral/psychosocial – stroke

INTRODUCTION

The incidence of stroke in young adults is increasing[1,2,3] and is the eighth leading cause of death in 25–45 year-olds in the United States.[4] In this age-group drug use is one of the most common modifiable risk factors for stroke prevention. Though tobacco smoking[5,6] and cocaine[7,8] are known risk factors for ischemic stroke, the role of marijuana use as a causative or contributing factor remains unclear. Notably, marijuana use is on the rise in the United States, particularly among those age 18–25.[9] Derived from cannabis, marijuana exerts a variety of effects on the cardiovascular system, some of which are dose-dependent, and has been shown to influence thrombosis, inflammation, and development of atherosclerosis.[10] Marijuana use has been implicated in numerous cardiovascular pathologies,[11] particularly in healthy young males without other known vascular risk factors[12,13,14] and is the subject of a recent scientific statement focused on cardiovascular health issued by the American Heart Association.[15] Numerous case series and reports[16,17,18] have suggested an association between marijuana use and acute ischemic stroke, further supported by a recent analysis of the National Inpatient Sample Dataset[19] demonstrating a significant increase in hospitalizations for acute ischemic stroke among cannabis users, particularly among males and African-Americans. However, few epidemiologic studies have evaluated this association[20] and some reports have demonstrated conflicting findings indicating no association with stroke risk.[21,22] Additionally, some studies suggest a potential temporal relationship between use and ischemic stroke occurrence.[14,18,23] The possibility of a dose-response effect has also been suggested.[18,24] Disparate results among prior epidemiological studies may reflect a lack of control for illicit sympathomimetic drugs, including cocaine, and inadequate control for concurrent tobacco use, which itself has a known dose-response relationship with ischemic stroke risk among young adults.[5,6,22] In light of ongoing legislation legalizing marijuana use in some states, expanding indications for medical use, and increasing recreational use, clarifying the relationships between marijuana use and ischemic stroke is of great importance, particularly for younger

adults.[15,25,26] We therefore sought to evaluate whether self-reported marijuana use was associated with early-onset ischemic stroke using a large population-based case-control study of ischemic stroke in young adults, controlling for several common stroke risk factors, including quantity of current tobacco use, and evaluating for dose-response and the temporal relationship between marijuana use and stroke.

METHODS

Study Population

The Stroke Prevention in Young Adults (SPYA) Study was designed as a population-based case–control study of young onset ischemic stroke. During three study periods between 1992 and 2008, cases with a first-ever ischemic stroke ages 15 to 49 years were identified by discharge surveillance from 59 non-federal acute care hospitals in the greater Baltimore/Washington, DC area and by direct referral from regional neurologists. In the initial study period, only women were recruited, the upper age limit was 44 years, and controls were in a 2:1 ratio to cases and were frequency-matched to cases by age, sex, region of residence. Women were recruited in the second study period and men in the third study period. In the last two study periods, the upper age limit was 49 years, and controls were in a 1:1 ratio to cases and were additionally matched for race. Details of the study design have been previously described,[27,28,29] with additional details in the Supplementary Methods (download available online).

Assessment of Exposures

All exposure information was collected by self-report through a standardized face-to-face interview, less a small subset of cases by proxy interview. To assess the use of illicit drug use, including marijuana, participants were asked to recall whether, prior to the reference date, they had ever used drugs, pills or medications for non-medical or recreational reasons or to “get high”. For the purposes of this analysis, marijuana use also included hashish use. The name(s), route(s) and timing(s) of drug use were also collected. The reference date was defined as the date of stroke onset for cases and for controls, the date of interview (initial study period) or the day of week that the stroke occurred in the matched case (last two study periods). Participants were shown cards with the names, routes of use and duration of use of various illicit drugs. In order to minimize potential discomfort associated with disclosing sensitive information, participants indicated their responses using codes printed on the cards rather than naming the drug or route of use directly. In addition, participants were informed that their responses were protected by a Federal Confidentiality Certificate.

Information on traditional stroke risk factors (e.g. history of hypertension, diabetes mellitus, current smoking status and alcohol consumption) and demographic variables (e.g. age, sex, and race) was also obtained by a standardized face-to-face or proxy interview. Current smoking status was defined as use within 30 days prior to the stroke, or for controls, prior to the reference date. Amount of current smoking was based on the average number of cigarettes smoked per day over the 30 days prior to the stroke. Current alcohol consumption was defined as having a drink of wine, beer or hard liquor in the year prior to the stroke or, for controls, prior to the reference date.

Statistical Analysis

Statistical analyses were performed using the Statistical Analysis System Software package (version 9.3; SAS Institute, Inc., Cary, N.C.). Cases and controls were compared for differences in means using t-tests (for continuous variables) or differences in proportions by $\chi 2$ tests (for categorical variables) to obtain the unadjusted two-sided p-values. Unconditional logistic regression with case/control status as the outcome and study characteristics as predictors was used to obtain the age-, sex- and ethnicity-adjusted p-values.

Assessment of the association between marijuana use and ischemic stroke was performed using an unconditional logistic regression model with case/control status as outcome and marijuana variable as the predictor after adjusting for the effect of age, sex, race, study phase, and other stroke risk factors. The odds ratios for marijuana use were estimated in comparison to those who had never used marijuana previously (reference group).

Assessments of the temporal link to marijuana use with stroke (years-ago, months-ago, 1–30 days, within 24 hours), as well as the dose-response nature of marijuana use with stroke (occasional:<1x/week, moderate:1x/week ≥ amount < 7x/week, daily:≥ 7x/week) were evaluated using unconditional logistic regression models with case/control status as outcome and marijuana variable as the predictor after adjusting for the effect of age, sex, race, study phase, and other stroke risk factors. The odds ratios for marijuana use were estimated in comparison to those who had never used marijuana previously (reference group).

Lastly, in a post-hoc analyses we evaluated the clinical characteristics of the strokes among daily marijuana users to evaluate for the presence of reversible cerebral vasoconstriction syndrome (RCVS).

The study was approved by the University of Maryland at Baltimore Institutional Review Board and all participants gave informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request from investigators with appropriate institutional assurances of confidentiality.

RESULTS

A total of 1,090 cases and 1,152 controls from 59 hospitals were enrolled. Cases and controls reporting a history of vasoactive drugs associated with stroke risk, including cocaine, amphetamine derivatives (MDMA aka “ecstasy”, “ice”, and “speed”) were excluded from the primary analysis. Those reporting use of substances without known association with ischemic stroke, such as heroin, were not excluded. Following exclusions, the final study population consisted of a total of 751 cases and 813 controls.

The 751 ischemic stroke cases were older and were significantly more likely to have hypertension, diabetes mellitus, and report current tobacco when compared to the 813 controls (Table 1). Controls were significantly more likely to report current alcohol use.

Among controls, ever use of marijuana was more often reported among men than women and among whites than blacks (Table 2). There were no significant differences in rates of diabetes mellitus and hypertension between ever and never users of marijuana. However, marijuana users were more likely to be current cigarette smokers and users of alcohol.

There were similar rates of ever marijuana use among the stroke cases and controls (36.1% vs. 38.4% respectively, Table 3). Ever use of marijuana use did not show an association with stroke after adjusting for age, sex, race, the amount of current smoking, current alcohol use, hypertension, and diabetes mellitus. There was no significant stroke association with timing of last marijuana use after adjusting for demographic and vascular risk factors. The odds ratio for use within 24 hours was 0.98 (95% CI 0.29–3.27).

Among those reporting marijuana use at least once a week, the odds ratio for stroke was 1.9 but was not statistically significant (95% CI 0.8–4.9) (Table 4). A specific evaluation of the eleven cases who were daily marijuana users did not disclose a particular stroke pattern or vasoactive syndrome, including RCVS (Table 5). All daily user cases were also current tobacco smokers. Interestingly, the 8 control subjects using marijuana daily were also current tobacco smokers.

As a secondary analysis, we analyzed our entire study population inclusive of those using vasoactive drugs and, again, found no association between marijuana use and stroke. Lastly, we excluded cases completed by proxy (total n=26; within subset excluding vasoactive drug use n=18) and reanalyzed the data demonstrating no change in our results (results not shown).

DISCUSSION

Our study did not demonstrate a significant association between marijuana use and ischemic stroke in young adults. Our findings are consistent with several smaller studies that evaluated stroke risk when controlling for tobacco use. A urine drug screen study in New Zealand[21] of 160 consecutive cases of ischemic stroke or transient ischemic ages 18–55 and age-, sex-, and ethnicity-matched controls hospitalized for other reasons found an odds ratio of 2.3 (95% CI 1.08–5.08), but the association did not remain significant after adjusting for current tobacco use. Similarly, a prospective study of Swedish men,[22] born between 1949 and 1951, identified 192 cases of ischemic stroke before age 45 demonstrated an odds ratio of 1.5 (95% CI 0.6–4.1) among those who had used marijuana more than 50 times at baseline. However, after adjustment for smoking the odds ratio was reduced to 0.9 (95% CI 0.3–2.6). Further, no dose-response relationship between marijuana use at baseline and subsequent stroke risk was identified.[22] A recent retrospective observational study[30] of adults ages ≥18 hospitalized over a two-year period, and for whom urine toxicology screen was performed, assessed for an association between marijuana use and ischemic stroke. After excluding those with hemorrhagic stroke or transient ischemic attack, as well as those testing positive for cocaine and amphetamines, 1643 individuals testing positive for cannabinoids remained in the analysis. After controlling for established stroke risk factors, including current and former smoking (assessed separately), no association with acute

ischemic stroke was found. However, this study was limited by the fact that information about marijuana dose, chronicity, and frequency were not available.

In contrast, a study based on administrative data from Texas hospitals[31] identified 998 ischemic stroke cases ages 18–44 years from over 3 million discharges and found an odds ratio of 1.8 (95% CI 1.2–2.7), but while they did adjust for smoking and other illicit drug use, they did not adjust for the amount of current cigarette smoking. Another study reviewed data from the United States Nationwide Inpatient Sample (2004–2011)[32] for patients age 15–54 with a primary diagnosis of acute ischemic stroke and documentation of current marijuana use based on ICD-9-CM diagnosis code, demonstrating the incidence of stroke was significantly greater in current marijuana users as compared to non-users (RR 1.13, 95% CI 1.11–1.15 entire group, RR 2.26, 95% CI 2.13–2.38 for ages 25–34). In this study, although marijuana users were significantly more likely to smoke tobacco and use other substances including cocaine, alcohol, and amphetamines, the association between marijuana and acute ischemic stroke persisted even after adjustment in the multivariable analysis for potential confounders, including tobacco and cocaine use (OR 1.17, 95% CI 1.15–1.20). Additionally, another report[19] suggest that marijuana users are at an increased risk for hospitalization related to ischemic stroke. Information from over 3.3 million hospitalizations obtained from the United States National Inpatient Sample Dataset from 2007–2014 found a 16% increased risk of young-onset stroke-related hospitalizations among cannabis users during this time-period, and a 41% higher risk of hospitalization specifically for acute ischemic stroke (OR 1.31, 95% CI 1.31–1.51), this after adjusting for baseline comorbidities, including current or prior smoking and concurrent use of vasoactive drugs.

Some reports have suggested a temporal link between the timing of marijuana use in relation to stroke onset. Data analyzed from a longitudinal patient cohort collected for the Australian Personality and Total Health Study[24] found that individuals reporting use of cannabis in the past year (as compared to those who did not) were 3.3 times as likely to develop a stroke or transient ischemic attack (95% CI 1.8–6.3), with risk persisting after adjustment for covariates, including smoking tobacco (IRR 2.3, 95% CI 1.1–4.5). Increased risk was seen only in those using cannabis at least weekly (IRR 4.7, 95%CI 2.1–10.7), while less frequent use was not significantly associated with development of ischemic stroke or transient ischemic attack. A systematic review[15] of case-reports on marijuana and ischemic stroke or transient ischemic attack, identified 64 cases, of whom 81% presented with symptoms within 24 hours of last use, and 22% had recurrent stroke in the setting of re-exposure to marijuana. Another systematic review[14] evaluated published case-reports of individuals presenting with cerebrovascular disease or transient ischemic attack in the setting of cannabinoid use, and specifically, those without known cardiovascular risk factors (n=18). The vast majority were young males and demonstrated a likely temporal correlation with timing of last use. Similarly, another review[18] including 85 individuals with stroke and/or transient ischemic attack following cannabis use (age range 15–63, mean 32.3) noted a strong temporal relationship with use. Of note, 81% were described as chronic cannabis users and approximately two-thirds used tobacco concurrently. However, it is important to note, that case report data provide limited evidence due to the strong likelihood of publication bias, and any results should be interpreted in lei of this consideration.

Our study did not demonstrate a temporal link between self-reported marijuana use and ischemic stroke, although the number of individuals reporting use within 24 hours was small. Our post-hoc analysis of the 11 daily marijuana users did not demonstrate a particular pattern of infarct to suggest a consistent mechanism, such as RCVS. However, marijuana use has been reported in a significant number of RCVS cases[33] and reported in several systematic reviews of ischemic stroke cases in the context of marijuana use.[16,18,34] Not all series have reported this pattern though, including one series of predominantly young male patients with ischemic stroke in the context of very recent marijuana use, most of whom demonstrated no evidence of vasculopathy on imaging.[23]

Several limitations should be considered in the interpretation of our study. First and most importantly, we had relatively few weekly or daily marijuana users in our study population, thereby limiting our statistical power to assess risk in these groups. Nevertheless, among the individuals that used marijuana at least once per week we had 80% power to detect an odds ratio of 2.7. For those using marijuana within 24 hours of stroke we had 80% power to detect an odds ratio of 3.6. Second, information regarding marijuana use was obtained via self-report, which is subject to recall bias and under-reporting. Differential recall bias with more under-reporting by cases is possible due to the variable interval between the stroke and the interview. However, it seems unlikely that daily marijuana use would be forgotten. In addition, a similar analysis of cocaine use in our study did find a strong temporal association with stroke,[8] suggesting against a strong effect of recall bias in our cases. Third, since subjects were interviewed, there may have been selection bias with under-representation of severe cases. If marijuana use were preferentially associated with severe strokes, this could have biased our results towards the null. Fourth, our study looked only at ischemic stroke and does not address possible risk for strokes due to intracerebral or subarachnoid hemorrhage. Fifth, there may be inadequate control for the covariates used in the analysis. Particularly among young adults, hypertension may have been present but not diagnosed. In addition, although any alcohol use was included in our models, we did not control for variation in the amount of alcohol or binge drinking. In order for these factors to bias our results towards the null, these stroke risk factors would need to be strongly under-represented in cases who used marijuana. We believe that this is unlikely. Lastly, as with all observational studies, it is possible that our results are biased due to unmeasured confounders.

Our study has several strengths. First, this is the largest case-control study to date evaluating the association between marijuana use and ischemic stroke risk. Second, we were able to assess the frequency and timing marijuana use in relationship to stroke risk. Third, we were able to exclude individuals reporting prior use of vasoactive illicit drugs known to influence stroke risk, namely cocaine and amphetamines. Lastly, our analyses were adjusted for other vascular risk factors, and most importantly, for the amount of concurrent tobacco cigarette use.

CONCLUSION

Although we did not demonstrate an association between marijuana use and an increased risk of early-onset ischemic stroke, our statistical power was limited for assessing the

association among very heavy users. The issue of whether high frequency or high dose of use is associated with stroke risk is increasingly important as marijuana use becomes more widespread. At present, the epidemiologic literature, including our study, does not provide evidence that marijuana use is causally associated with stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

SPYA	Stroke Prevention in Young Adults Study
MDMA	3,4-Methyl enedioxy methamphetamine
RCVS	reversible cerebral vasoconstriction syndrome

REFERENCES

1. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, et al.Age at stroke: Temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79:1781–7. doi:10.1212/WNL.0b013e318270401d. [PubMed: 23054237]
2. Ekker MS, Verhoeven JI, Vaartjes I, Van Nieuwenhuizen KM, Klijn CJM, De Leeuw FE. Stroke incidence in young adults according to age, subtype, sex, and time trends. Neurology. 2019;92:e2444–e2454. doi:10.1212/WNL.0000000000007533. [PubMed: 31019103]
3. George MG, Tong X, Bowman BA. Prevalence of cardiovascular risk factors and strokes in younger adults. JAMA Neurol. 2017;74:695–703. doi: 10.1001/jamaneurol.2017.0020. [PubMed: 28395017]
4. Centers for Disease Control. 10 Leading Causes of Death by Age Group, United States-2017. 2018. https://www.cdc.gov/injury/images/lccharts/leading_causes_of_death_by_age_group_2017_1100w850h.jpg Last accessedSeptember 23, 2020.
5. Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-Response Relationship Between Cigarette Smoking and Risk of Ischemic Stroke in Young Women. Stroke. 2008;39:2439–2443. doi: 10.1161/STROKEAHA.107.510073. [PubMed: 18703815]
6. Markidan J, Cole JW, Cronin CA, Merino JG, Phipps MS, Wozniak MA, Kittner SJ. Smoking and Risk of Ischemic Stroke in Young Men. Stroke. 2018;49:1276–1278. doi: 10.1161/STROKEAHA.117.018859. [PubMed: 29674522]
7. Levine SR, Brust JC, Futrell N, Ho KL, Blake D, Millikan CH, Brass LM, Fayad P, Schultz LR, Selwa JF, et al.Cerebrovascular complications of the use of the “crack” form of alkaloidal cocaine. N Engl J Med. 1990913;323:699–704. doi: 10.1056/NEJM199009133231102. [PubMed: 2388668]

8. Cheng YC, Ryan KA, Qadwai SA, Shah J, Sparks MJ, Wozniak MA, Stern BJ, Phipps MS, Cronin CA, Magder LS, et al.Cocaine Use and Risk of Ischemic Stroke in Young Adults. Stroke. 2016;47:918–922. doi:10.1161/STROKEAHA.115.011417. [PubMed: 26965853]
9. Substance Abuse and Mental Health Services Administration. The National Survey on Drug Use and Health. 2018. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/Assistant-Secretary-nsduh2018_presentation.pdf AccessedJanuary 28, 2021.
10. Latif Z, Garg N. The Impact of Marijuana on the Cardiovascular System: A Review of the Most Common Cardiovascular Events Associated with Marijuana Use. J Clin Med. 2020;9:1925. doi: 10.3390/jcm9061925.
11. DeFilippis EM, Baja NS, Singh A, Malloy R, Givertz MM, Blankstein R, Bhatt DL, Vaduganathan M. Marijuana use in patients with cardiovascular disease. J Am Coll Cardiol. 2020;75:320–332. doi: 10.1016/j.jacc.2019.11.025 [PubMed: 31976871]
12. Goyal H, Awad HH, Ghali JK. Role of cannabis in cardiovascular disorders. J Thorac Dis. 2017l;9:2079–2092. doi: 10.21037/jtd.2017.06.104. [PubMed: 28840009]
13. Singh A, Saluja S, Kumar A, Agrawal S, Thind M, Nanda S, Shirani J. Cardiovascular Complications of Marijuana and Related Substances: A Review. Cardiol Ther. 2018;7:45–59. doi: 10.1007/s40119-017-0102-x. [PubMed: 29218644]
14. Gómez Ochoa SA. Stroke and cannabis use in patients with no cardiovascular risk factors: a systematic review of case reports. Neurologia. 20171222:S0213–4853(17)30362–6. English, Spanish. doi: 10.1016/j.nrl.2017.09.016.
15. Page RL 2nd, Allen LA, Kloner RA, Carriker CR, Martel C, Morris AA, Piano MR, Rana JS, Saucedo JF; American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research. Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation. 2020;142:e131–e152. doi: 10.1161/CIR.0000000000000883. [PubMed: 32752884]
16. Wolff V, Armspach JP, Lauer V, Rouyer O, Bataillard M, Marescaux C, Geny B. Cannabis-related stroke: myth or reality?Stroke. 2013;44:558–563. doi:10.1161/STROKEAHA.112.671347. [PubMed: 23271508]
17. Hackam DG. Cannabis and stroke: systematic appraisal of case reports. Stroke. 2015;46:852–856. doi: 10.1161/STROKEAHA.115.008680 [PubMed: 25700287]
18. Wolff V, Jouanjus E. Strokes are possible complications of cannabinoids use. Epilepsy Behav. 2017;70(Pt B):355–363. doi: 10.1016/j.yebeh.2017.01.031.Epub 2017 Feb 23. [PubMed: 28237318]
19. Desai R, Singh S, Patel K, Goyal H, Shah M, Mansuri Z, Patel S, Mahuwala ZK, Goldstein LB, Qureshi AI. Stroke in young cannabis users (18–49 years): National trends in hospitalizations and outcomes. Int J Stroke. 2020;15:535–539. doi: 10.1177/1747493019895651. [PubMed: 31870242]
20. Ravi D, Ghasemiesfe M, Korenstein D, Cascino T, Keyhani S. Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. Ann Intern Med. 2018;168:187–194. doi: 10.7326/M17-1548. [PubMed: 29357394]
21. Barber PA, Pridmore HM, Krishnamurthy V, Roberts S, Spriggs DA, Carter KN, Anderson NE. Cannabis, ischemic stroke, and transient ischemic attack: a case-control study. Stroke. 2013;44:2327–2329. doi: 10.1161/STROKEAHA.113.001562. [PubMed: 23696547]
22. Falkstedt D, Wolff V, Allebeck P, Hemmingsson T, Danielsson AK. Cannabis, tobacco, alcohol use, and the risk of early stroke: a population-based cohort study of 45 000 Swedish Men. Stroke. 2017;48:265–270. doi: 10.1161/STROKEAHA.116.015565. [PubMed: 28028147]
23. Singh NN, Pan Y, Muengtaweeponsa S, Geller TJ, Cruz-Flores S. Cannabis-related stroke: case series and review of literature. J Stroke Cerebrovasc Dis. 2012;21:555–60. doi: 10.1016/j.jstrokecerebrovasdis.2010.12.010. [PubMed: 21367621]
24. Hemachandra D, McKetin R, Cherbuin N, Anstey KJ. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. Aust N Z J Public Health. 2016;40:226–30. doi: 10.1111/1753-6405.12477. [PubMed: 26558539]

25. Parekh T, Pemmasani S, Desai R. Marijuana Use Among Young Adults (18–44 Years of Age) and Risk of Stroke: A Behavioral Risk Factor Surveillance System Survey Analysis. Stroke. 2020;51:308–310. doi:10.1161/STROKEAHA.119.027828. [PubMed: 31707926]
26. Aparicio HJ, Himali JJ, Satizabal CL, Pase MP, Romero JR, Kase CS, Beiser AS, Seshadri S. Temporal Trends in Ischemic Stroke Incidence in Younger Adults in the Framingham Study. Stroke. 2019;50:1558–1560. doi:10.1161/STROKEAHA.119.025171. [PubMed: 31084341]
27. Johnson CJ, Kittner SJ, McCarter RJ, Sloan MA, Stern BJ, Buchholz D, Price TR. Interrater reliability of an etiologic classification of ischemic stroke. Stroke. 1995;26:46–51. [PubMed: 7839396]
28. Kittner SJ, Stern BJ, Wozniak M, Buchholz DW, Earley CJ, Feeser BR, Johnson CJ, Macko RF, McCarter RJ, Price TR, et al.Cerebral infarction in young adults: The Baltimore-Washington cooperative young stroke study. Neurology. 1998;50:890–894. [PubMed: 9566368]
29. Hamedani AG, Cole JW, Cheng Y, Sparks MJ, O'Connell JR, Stine OC, Wozniak MA, Stern BJ, Mitchell BD, Kittner SJ. Factor V leiden and ischemic stroke risk: the Genetics of Early Onset Stroke (GEOS) study. J Stroke Cerebrovasc Dis. 2013;22:419–423. doi:10.1016/j.jstrokecerebrovascdis.2011.10.007. [PubMed: 22100829]
30. San Luis CV, O'Hana S Nobleza C, Shekhar S, Sugg R, Villareal DJ, Mehta T, Gangadhara S. Association between recent cannabinoid use and acute ischemic stroke. Neurol Clin Pract. 2020;10:333–339. doi: 10.1212/CPJ.0000000000000888. [PubMed: 32983613]
31. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. Arch Gen Psychiatry. 2007;64:495–502. doi:10.1001/archpsyc.64.4.495. [PubMed: 17404126]
32. Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. J Neurol Sci. 2016;364:191–6. doi: 10.1016/j.jns.2016.01.066. [PubMed: 26874461]
33. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain. 2007;130(Pt 12):3091–101. doi: 10.1093/brain/awm256. [PubMed: 18025032]
34. Wolff V, Lauer V, Rouyer O, Sellal F, Meyer N, Raul JS, Sabourdy C, Boujan F, Jahn C, Beaujeux R, Marescaux C. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: a prospective study in 48 consecutive young patients. Stroke. 2011;42:1778–80. doi: 10.1161/STROKEAHA.110.610915. [PubMed: 21512186]

Table 1.

Comparison of Cases and Controls for Selected Factors.

	Cases (n=751)	Controls (n=813)	P-value*
Age, mean	40.5	37.9	<0.001
Male, %	47.3	41.9	0.03
Self-reported race, %			0.03
Whites	49.8	56.6	
Blacks	43.7	37.8	
Others	6.5	5.7	
History of Hypertension, %	41.7	17.4	<0.001
History of Diabetes Mellitus, %	17.2	4.4	<0.001
Current Tobacco Use, %	35.3	19.7	<0.001
Current Alcohol Use, %	54.0	63.5	<0.001

*For age, sex and race, p-values were adjusted for the other variables and study phase. For other risk factor variables p-values were adjusted for age, sex, race, and study phase.

Table 2.

Comparison of Ever vs. Never Marijuana Users for Selected Factors among Controls.

	Ever Used Marijuana (n=312)	Never Used Marijuana (n=501)	P-Value*
Age, Mean	39.0	37.3	0.002
Male, %	48.7	37.7	0.002
Self-Reported Race, %			0.02
Whites	62.8	52.7	
Blacks	32.7	40.9	
Others	4.5	6.4	
History of Diabetes Mellitus, %	4.2	4.6	0.61
History of Hypertension, %	18.3	16.8	0.96
Current Smokers, %	29.5	13.6	<0.001
Current Alcohol Users, %	78.9	53.9	<0.001

*For age, sex and race, p-values were adjusted for the other variables and study phase. For other risk factor variables p-values were adjusted for age, sex, race, and study phase.

Table 3.

Association between Marijuana Use and Ischemic Stroke by Time of Last Use.

	Stroke Cases (n=751) n (%)	**Controls (n=813) n (%)**	**Adjusted OR* (95% CI)**	**P-Value***
Never Users of Marijuana	480 (63.9)	501 (61.6)	Reference Group	
Ever Users of Marijuana	271 (36.1)	312 (38.4)	0.86 (0.68–1.08)	0.19
Timing of Last Use				
Years-ago	216 (28.8)	266 (32.7)	0.82 (0.64, 1.04)	0.11
Months-ago	27 (3.6)	18 (2.2)	1.46 (0.73, 2.92)	0.29
1–30 days	21 (2.8)	22 (2.7)	0.87 (0.44, 1.73)	0.70
Within 24 Hours	7 (0.9)	6 (0.7)	0.98 (0.29, 3.27)	0.97

*Adjusted for age, sex, race, study phase, amount of tobacco use, hypertension status, diabetes mellitus status, and current alcohol use. All analyses were performed using individuals who had never used marijuana as reference group.

Table 4.

Association between Marijuana Use and Ischemic Stroke by Frequency of Use in Last 0–30 Days.

	Case (n=508)	Control (n=529)	Adjusted OR* (95% CI)	p-value*
Never Used	480	501	Reference Group	
Occasional Use (amount < 1x/week)	7	16	0.5 (0.2–1.4)	0.20
Moderate Use (1x/week ≥ amount < 7x/week)	10	4	3.1 (0.6–16.4)	0.18
Daily Use (amount ≥ 7x/week)	11	8	1.5 (0.5–4.6)	0.51
Moderate and Daily Use Groups Combined	21	12	1.9 (0.8–4.9)	0.17

*Adjusted for age, sex, race, study phase, the amount of current tobacco use, hypertension status, diabetes mellitus status, and alcohol use. All analyses were performed using individuals who had never used marijuana as reference group.

Table 5.

Clinical characteristics of Case Daily Marijuana Users.*

Age/sex	Current Tobacco Use	Alcohol (shots/ day)	Other stroke risk factors	Stroke Location and Distribution	Modified Rankin Scale at time of hospital discharge
36F	Yes	3	None	Left PCA and Left MCA	2
17M	Yes	5	None	Bilateral Temporal/Parietal and Left Frontal	1
42M	Yes	None	Mitral valve vegetation	Left MCA and Right Frontal	3
43M	Yes	None	HTN, DM2	Left Thalamic and Left Internal Capsule	1
43M	Yes	None	Mitral valve vegetation, HTN, ESRD	Multifocal Left Hemisphere	1
49F	Yes	None	HTN	Right Basal Ganglia	0
41F	Yes	None	HTN, DM2	_	1
43M	Yes	2	Apical cardiac akinesia, Lupus	Right Thalamus and Right Parietal	0
44M	Yes	None	HTN, DM2	Left Internal Capsule	1
43M	Yes	8	HTN	Left Cerebellum	2
22F	Yes	None	Marfan syndrome	Left Cerebellum	1

*Route of marijuana use was smoking among all listed subjects.

HTN = hypertension, DM = diabetes mellitus, MCA = middle cerebral artery, PCA = posterior cerebral artery