Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Jared P. Reis, PhD, Reto Auer, MD, MAS, Michael P. Bancks, PhD, MPH, David C. Goff Jr, MD, PhD, Cora E. Lewis, MD, MSPH, Mark J. Pletcher, MD, MPH, Jamal S. Rana, MD, PhD, James M. Shikany, DrPH, and Stephen Sidney, MD, MPH

Objectives. To investigate the effects of marijuana in the development of incident cardiovascular and cerebrovascular outcomes.

Methods. Participants were 5113 adults aged 18 to 30 years at baseline (1985–1986) from the Coronary Artery Risk Development in Young Adults study, who were followed for more than 25 years. We estimated cumulative lifetime exposure to marijuana using repeated assessments collected at examinations every 2 to 5 years. The primary outcome was incident cardiovascular disease (CVD) through 2013.

Results. A total of 84% (n = 4286) reported a history of marijuana use. During a median 26.9 years (131 990 person-years), we identified 215 CVD events, including 62 strokes or transient ischemic attacks, 104 cases of coronary heart disease, and 50 CVD deaths. Compared with no marijuana use, cumulative lifetime and recent marijuana use showed no association with incident CVD, stroke or transient ischemic attacks, coronary heart disease, or CVD mortality. Marijuana use was not associated with CVD when stratified by age, gender, race, or family history of CVD.

Conclusions. Neither cumulative lifetime nor recent use of marijuana is associated with the incidence of CVD in middle age. (*Am J Public Health.* 2017;107:601–606. doi:10.2105/AJPH.2017.303654)

Marijuana is the most frequently used illicit drug in the United States. Its use is greatest among young adults, with as many as 35.1% of high school seniors and 34.4% of college students reporting having used marijuana during the preceding year.[1] Despite its popularity, however, few studies have examined the long-term cardiovascular effects of marijuana.

The acute cardiovascular effects of marijuana include a substantial dose-dependent increase in heart rate, a mild increase in blood pressure, and orthostatic hypotension.[2–4] However, it is unknown whether these immediate effects heighten the risk for chronic cardiovascular conditions because tolerance is known to develop within several days to a few weeks of use.[5] Case reports have suggested possible links between marijuana use and myocardial infarction,[6,7] stroke,[8,9] and cardiac arrthythmias.[10,11] One study, using a case–crossover design in which cases served as their own controls, showed that marijuana use during the hour before symptom onset was associated with a higher risk of triggering myocardial infarction.[12]

Evidence suggests that marijuana may have opposing effects on the long-term development of atherosclerosis and cardiovascular disease (CVD).[13] The main components of marijuana are the cannabinoids, the active ingredients of marijuana. Cannabinoid receptors CB1 and CB2 are widely distributed in the cardiovascular system.[14] In mice, activating the CB2 receptor has been shown to suppress the inflammatory response[15]; therefore, this might protect marijuana smokers from developing atherosclerosis. Activating the CB1 receptor, conversely, might increase atherosclerosis, because inhibiting CB1 may protect against atherosclerosis.[16]

Despite these potential mechanisms, weak and inconsistent associations have been observed between cumulative marijuana use and subclinical atherosclerosis.[17] Contrary to the previously cited retrospective studies and case reports that claim that marijuana may be an acute trigger of myocardial infarction and other cardiovascular outcomes, longitudinal prospective studies have failed to detect adverse effects of marijuana use on cardiovascular risk factors,[18,19] hospitalizations for cardiovascular conditions,[20] or mortality.[21,22] However, these few available prospective studies have generally been limited by only a single assessment and crude classification of

ABOUT THE AUTHORS

Jared P. Reis and David C. Goff Jr are with the Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD. Reto Auer is with the Institute of Primary Health Care, University of Bern, Bern, Switzerland. Michael P. Bancks is with the Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL. Cora E. Lewis and James M. Shikany are with the Division of Preventive Medicine, Department of Medicine, University of Alabama, Birmingham. Mark J. Pletcher is with the Department of Epidemiology and Biostatistics, University of California, San Francisco. Jamal S. Rana and Stephen Sidney are with the Division of Research, Kaiser Permanente Northern California, Oakland.

Correspondence should be sent to Stephen Sidney, MD, MPH, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA, 94612 (e-mail: steve.sidney@kp.org). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted December 30, 2016.

doi: 10.2105/AJPH.2017.303654

marijuana use (e.g., current or former user) or the absence of carefully conducted clinical cardiovascular or cerebrovascular event collection, adjudication, and classification.

We investigated the recent and long-term effects of marijuana use in the development of multiple incident cardiovascular and cerebrovascular outcomes in middle age among a population-based sample of participants with marijuana use typical of the communities in which they live. We estimated both the recent frequency and cumulative lifetime exposure to marijuana using repeated measurements beginning in young adulthood.

METHODS

Participants were Black and White adults recruited in 1985–1986 as part of the Coronary Artery Risk Development in Young Adults (CARDIA) study. CARDIA is a multicenter, community-based, longitudinal cohort study of the development and determinants of CVD over time in 5115 young adults who were aged 18 to 30 years in 1985–1986. Adults were recruited from 4 geographic locations of the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA), with population-based samples approximately balanced within center by gender, age (18–24 years vs 25–30 years), race (White vs Black), and education (≤ high school graduate vs > high school graduate).

To date, participants have been reexamined 2, 5, 7, 10, 15, 20, and 25 years after baseline. Participation rates across these examinations were 91%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively, of the surviving cohort. Additionally, 94% of the surviving cohort were contacted by telephone or examination from 2009 to 2014.

Measurements

Standardized protocols for data collection were used across study centers and examinations. Participants were asked to fast for at least 12 hours before each examination and to avoid smoking or engaging in heavy physical activity for at least 2 hours.

Recent marijuana use was assessed at each in-person CARDIA examination (at baseline and after 2, 5, 7, 10, 15, 20, and 25 years of follow-up) using the following survey question: "During the last 30 days, on how many days did you use marijuana?" Direct self-reported lifetime exposure was also assessed at each examination using the question "About how many times in your lifetime have you used marijuana?" We used recent and lifetime use to compute marijuana-years, with 1 year of exposure equivalent to daily marijuana use.[23] We assumed that recent use at each examination (i.e., the number of days of using marijuana during the month before each examination) reflected the average number of days of use during the months before each examination.

We estimated cumulative lifetime use by adding the total number of days using marijuana during follow-up up until the examination immediately preceding the date of the clinical cardiovascular event, date of death, or last date of contact. We adjusted our estimate upward whenever self-reported lifetime marijuana use reported at baseline and each follow-up examination was higher than our computed estimate.[23] We defined recent marijuana use as recent use as of the examination immediately before the date of the clinical cardiovascular event, date of death, or last date of contact. We classified cumulative lifetime and recent marijuana use into previously defined categories, including never, 1 day to less than 0.5 marijuana-years, 0.5 to less than 2.0 marijuana-years, 2.0 to less than 5.0 marijuana-years, and 5.0 or more marijuana-years, and none, 1 to 9 days, 10 to 19 days, and 20 or more days, respectively.[24]

We recorded new cardiovascular and cerebrovascular events from the baseline examination through August 2013. During scheduled study examinations and yearly telephone interviews, each participant or designated proxy was asked about interim hospital admissions, outpatient procedures, and deaths. Designated proxies did not participate in the examination. We requested medical records for participants who had been hospitalized or received an outpatient revascularization procedure. Vital status was assessed every 6 months; we requested medical and other death records after consent had been obtained from the next of kin.

Two physician members of the Endpoints Committee blinded to participant marijuana use independently reviewed medical records and recorded information to adjudicate each possible cardiovascular or cerebrovascular event or underlying cause of death using specific definitions and a detailed manual of operations (http://www.cardia.dopm.uab.edu). If disagreement occurred between the primary reviewers, the full committee reviewed the case. The primary composite outcome was incident CVD, which included coronary heart disease ([CHD] myocardial infarction, acute coronary syndrome, or CHD death, including fatal myocardial infarction), stroke, transient ischemic attack (TIA), hospitalization for heart failure, intervention for peripheral arterial disease, or death from cardiovascular causes. Secondary cause-specific outcomes included stroke or TIA, CHD, and CVD mortality.

We measured education as the maximum educational grade attained. We measured physical activity with the CARDIA Physical Activity History questionnaire, which asks about the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months. Body mass index was calculated at each examination as weight in kilograms (measured to the nearest 0.5 kg using a balance beam scale) divided by height in meters (measured with a vertical ruler to the nearest 0.5 cm) squared. We used cigarette smoking behavior, collected at each examination, to estimate cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to smoking 1 pack of cigarettes per day for a year.[23]

We estimated cumulative lifetime alcohol consumption in drink-years, defining 1 drink-year as the amount of alcohol consumed in 1 year by a person consuming 1 drink per day.[25] We defined acute heavy exposure to alcohol (bingeing) as reporting 5 or more drinks on 1 occasion, and we estimated total cumulative lifetime episodes. We estimated total number of cumulative lifetime exposures to cocaine (including other forms of cocaine, e.g., crack, powder, and free base), amphetamines (speed, uppers, methamphetamines), and opioids for nonmedical reasons (including heroin) based on repeat assessments.[26] History of myocardial infarction or stroke in a first degree male or female relative was queried at baseline and years 5, 10, and 25.

We defined hypertension at each examination as a systolic blood pressure of ≥ 140 millimeter of mercury, of diastolic blood

pressure 90 millimeter of mercury or greater, or antihypertensive medication use.[27] We determined diabetes from a combination of measured fasting glucose levels (≥ 7.0 mmol/L; ≥ 126 mg/dL) at baseline and years 7, 10, 15, 20, and 25; self-report of oral hypoglycemic medications or insulin (all examinations); a 2-hour postload glucose of 11.1 millimole per liter or greater (≥ 200 mg/dl) at years 10, 20, and 25; or a glycated hemoglobin A_{1c} of 6.5% or greater at years 20 and 25.[28] Self-reported depression was measured every 5 years starting at year 5 using the Center for Epidemiologic Studies Depression scale. We defined depression as a Center for Epidemiologic Studies Depression scale score of 16 or greater. Dyslipidemia at each examination was defined as a low high-density lipoproteins cholesterol (< 40 mg/dL for men; < 50 mg/dL for women), high low-density lipoproteins cholesterol (≥ 160 mg/dL), high triglycerides (≥ 200 mg/dL), or lipid-lowering medication use.[29]

Statistical Analysis

We described participant characteristics overall and by cumulative lifetime use of marijuana using means, medians, and proportions as appropriate. We conducted descriptive analyses using linear regression models and χ^2 analyses for continuous and categorical variables, respectively. We calculated incidence rates per 1000 person-years overall and according to marijuana use. We calculated follow-up time as the difference between the baseline examination date and the event date, date of death, or the date of last contact (whichever came first).

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for our primary (total CVD) and secondary (stroke or TIA, CHD, and CVD mortality) outcomes. We included marijuana use as a time-dependent variable in 1 of 2 exposure forms: cumulative lifetime use or recent use.

We adjusted our model for sociodemographic characteristics (i.e., age, gender, race, educational attainment), study center, and factors potentially associated with marijuana use and CVD selected a priori, including family history of cardiovascular disease and time-varying physical activity (average self-reported exercise units), body mass index (average kg/m^2), high blood pressure, diabetes, dyslipidemia, depression, smoking (pack-years), cumulative alcohol use (drink-years), cumulative binge drinking episodes, and cumulative use of other illicit drugs (cocaine, crack, speed, methamphetamine, or opioids).

We performed tests for a linear trend by entering the categorical marijuana use variable into the models as a continuous term. We assessed potential effect modification by age, gender, race, and family history of CVD by testing multiplicative interaction. To evaluate the potential for informative censoring, we estimated sub-HRs and 95% CIs for our primary and secondary outcomes in a Fine–Gray competing risk model, in which the competing event was mortality from causes other than CVD.[30] Power calculations demonstrated greater than 80% power to detect extreme category HRs (i.e., for the comparison of never any marijuana use with ≥ 5 marijuana-years) greater than 1.61.

We used multiple imputation (5 times) to impute missing examination values using the sequential regression imputation approach that is implemented in the software package IVEware version 0.2 (Institute for Social Research, University of Michigan, Ann Arbor, MI).[31] We analyzed each data set separately and combined results from the 5 analyses using the rules of Little and Rubin.[32] Tests of statistical significance were 2-tailed, with an α level of 0.05. We used SAS version 9.4 (SAS Institute, Cary, NC) to perform all statistical analyses.

RESULTS

Of the 5115 participants, we excluded 1 who reported having had a myocardial infarction at the baseline examination and another who withdrew consent for study participation. Of the remaining 5113 participants, most (n = 4286; 84%) reported having used marijuana before or during follow-up, but most had relatively few cumulative lifetime years of exposure. Median cumulative lifetime marijuana use was 0.51 (interquartile range = 0.02–2.40) marijuana-years. Cumulative lifetime marijuana use was associated with male gender, Black race, less educational attainment, greater physical activity, other substance use, and a positive family history of CVD (Table A, available as a supplement to the online version of this article at http://www.ajph.org). Marijuana use was not associated with other risk factors for CVD, including age, body mass index, depression, hypertension, diabetes, or dyslipidemia (Table A).

During a median 26.9 years of follow-up (interquartile range = 26.7, 27.0; 131 990 person-years), we identified 215 total CVD events (1.63 per 1000 person-years), including 62 strokes or TIAs (0.47 per 1000 person-years), 104 cases of CHD (0.78 per 1000 person-years), and 50 CVD deaths (0.38 per 1000 person-years). Table 1 shows the number of incident events; incidence rates; and adjusted HRs for total CVD, stroke or TIA, CHD, and CVD mortality according to cumulative lifetime marijuana use. In multivariable-adjusted analyses, cumulative lifetime marijuana use was not associated with incident CVD. Likewise, cumulative lifetime marijuana use showed no associations with stroke or TIA, CHD, or CVD mortality in adjusted analyses.

Table 2 displays the number of incident events; incidence rates; and adjusted HRs for total CVD, stroke or TIA, CHD, and CVD mortality according to recent marijuana use, which was reported by 18.8% (n = 960) of the cohort. Compared with no recent use, categories of recent marijuana use showed no evidence for a higher or lower risk for incident CVD, stroke or TIA, CHD, or CVD mortality in adjusted analyses. Tables B and C (available as supplements to the online version of this article at http://www.ajph.org) display the adjusted HRs for total CVD according to cumulative lifetime and recent marijuana use, respectively, within strata of participants defined by age, gender, race, and family history of CVD. We found no consistent evidence that cumulative lifetime (Table B) or recent (Table C) marijuana use was associated with incident CVD events within these strata of participants.

Tables D and E (available as supplements to the online version of this article at http://www.ajph.org) display the adjusted HRs for total CVD, stroke or TIA, CHD, and CVD mortality according to cumulative lifetime and recent marijuana use, respectively, from a Fine–Gray competing risk model in which the competing event was mortality from

TABLE 1—Cumulative Lifetime Marijuana Use Effect on Incident Total Cardiovascular Disease, Stroke or Transient Ischemic Attack, Coronary Heart Disease, and Cardiovascular Disease Mortality: CARDIA, United States, 2014

Variable	Never (n = 827)	1.0 Days to < 0.5 Marijuana-Years (n = 1775)	0.5 to < 2.0 Marijuana-Years (n = 1,120)	2.0 to < 5.0 Marijuana-Years (n = 705)	≥ 5.0 Marijuana-Years (n = 686)	*P* for Trend
Total cardiovascular disease						
No. of events	45	60	51	36	23	
Event rate[a]	2.11	1.31	1.78	1.98	1.29	
AHR (95% CI)[b]	1 (Ref)	0.66 (0.41, 1.09)	0.80 (0.43, 1.49)	0.84 (0.45, 1.58)	0.72 (0.35, 1.50)	.86
Stroke or transient ischemic attack						
No. of events	14	21	12	8	6	
Event rate[a]	0.65	0.46	0.42	0.46	0.35	
AHR (95% CI)[b]	1 (Ref)	0.73 (0.32, 1.68)	0.62 (0.21, 1.81)	0.57 (0.17, 1.93)	0.65 (0.16, 2.66)	.76
Coronary heart disease						
No. of events	20	28	24	19	13	
Event rate[a]	0.95	0.61	0.84	1.08	0.73	
AHR (95% CI)[b]	1 (Ref)	0.65 (0.32, 1.33)	0.74 (0.25, 2.19)	1.05 (0.38, 2.93)	0.84 (0.28, 2.51)	.43
Cardiovascular disease mortality						
No. of events	7	13	11	12	7	
Event rate[a]	0.33	0.29	0.39	0.66	0.37	
AHR (95% CI)[b]	1 (Ref)	1.04 (0.36, 3.04)	1.01 (0.28, 3.68)	1.47 (0.36, 6.07)	0.95 (0.20, 4.59)	.87

Note. AHR = adjusted hazard ratio; CARDIA = the Coronary Artery Risk Development in Young Adults study; CI = confidence interval. The sample size was n = 5113. Cumulative lifetime exposure to marijuana is shown in terms of marijuana-years, with 1 marijuana-year of exposure equivalent to 365 d marijuana use (1 y × 365 d/y) up to the examination immediately before the date of the clinical cardiovascular event, date of death, or the last date of contact.

[a]Per 1000 person-years.

[b]Adjusted for age, gender, race, educational attainment, and study center as well as family history of cardiovascular disease and time-varying physical activity, body mass index, high blood pressure, diabetes, dyslipidemia, depression, smoking (pack-years), cumulative alcohol use, cumulative binge drinking episodes, and cumulative use of other illicit drugs (cocaine, crack, speed, methamphetamine, or opioids).

causes other than CVD. The sub-HRs for total CVD, stroke or TIA, CHD, and CVD mortality according to cumulative lifetime (Table D) and recent (Table E) marijuana use were similar to the HRs without considering competing risk from other causes of death (Tables 1 and 2, respectively).

DISCUSSION

In this community-based cohort of young adults followed for more than 25 years, we found no evidence to suggest that cumulative lifetime or recent marijuana use, at levels typical of most recreational, occasional users of marijuana in the United States, affects risk of future CVD events through middle age. Furthermore, we found no significant associations between CVD risk and cumulative lifetime or recent marijuana use in subgroups defined by age, gender, race, or family history of CVD (Tables B and C). In addition, there was no suggestion that these null results were attributable to competing risks of death from other causes (Tables D and E).

We believe this is the first long-term study of cumulative lifetime marijuana use and incidence of fatal and nonfatal CVD events later in life. Our results are consistent with a recent case–control study of ischemic stroke or TIA patients that observed no evidence for an association with marijuana use.[33] Similarly, in a cohort study conducted in a large health maintenance organization, Sidney et al.[20] found no evidence that currently or ever using marijuana influenced the risk of death from CVD or hospitalization for myocardial infarction, CHD, stroke, or CVD during follow-up. Likewise, among a cohort of myocardial infarction survivors, marijuana use in the year before symptom onset was not associated with long-term CVD mortality.[21,34] Our findings are also consistent with a limited number of studies of marijuana use, subclinical atherosclerosis,[17] and risk factors for CVD,[18,19] including an earlier report from CARDIA that showed no evidence for an association of cumulative marijuana use over a 15-year period with systolic blood pressure, fasting glucose levels, lipids, or adiposity.[18]

By contrast, many case reports have implicated marijuana in the occurrence of clinical CVD events.[6–11] However, whereas case reports are useful in suggesting possible links between an exposure, such as marijuana use, and outcomes, they do not establish an etiologic role, because of the absence of a comparison group. Nevertheless, there is evidence that marijuana may be a rare trigger of acute ischemic CHD.

In a case–crossover design among 3882 patients hospitalized after acute myocardial infarction, Mittleman et al.[12] showed that marijuana use during the hour before symptom onset increased risk of myocardial

TABLE 2—Recent Marijuana Use Effect on Incident Total Cardiovascular Disease, Stroke or Transient Ischemic Attack, Coronary Heart Disease, and Cardiovascular Disease Mortality: CARDIA, United States, 2014

Variable	None (n = 4153)	1–9 Days (n = 573)	10–19 Days (n = 148)	≥ 20 Days (n = 239)	*P* for Trend
Total cardiovascular disease					
No. of events	156	34	11	14	
Event rate[a]	1.44	2.43	2.98	2.46	
AHR (95% CI)[b]	1 (Ref)	1.05 (0.69, 1.50)	1.36 (0.60, 3.09)	0.88 (0.42, 1.82)	.78
Stroke or transient ischemic attack					
No. of events	43	10	5	4	
Event rate[a]	0.39	0.73	1.38	0.67	
AHR (95% CI)[b]	1 (Ref)	1.25 (0.51, 3.07)	2.77 (0.83, 9.24)	1.03 (0.22, 4.78)	.69
Coronary heart disease					
No. of events	78	14	5	8	
Event rate[a]	0.72	0.96	1.46	1.43	
AHR (95% CI)[b]	1 (Ref)	0.85 (0.40, 1.79)	1.30 (0.43, 3.95)	1.01 (0.38, 2.65)	.97
Cardiovascular disease mortality					
No. of events	30	12	4	5	
Event rate[a]	0.27	0.84	1.04	0.87	
AHR (95% CI)[b]	1 (Ref)	1.60 (0.67, 3.85)	1.91 (0.55, 6.61)	1.20 (0.23, 6.16)	.84

Note. AHR = adjusted hazard ratio; CARDIA = the Coronary Artery Risk Development in Young Adults study; CI = confidence interval. The sample size was n = 5113. We assessed the number of participants who used marijuana over the last 30 d during the examination immediately before the date of the clinical cardiovascular event, date of death, or the last date of contact.

[a]Per 1000 person-years.

[b]Adjusted for age, gender, race, educational attainment, and study center as well as family history of cardiovascular disease and time-varying physical activity, body mass index, high blood pressure, diabetes, dyslipidemia, depression, smoking (pack-years), cumulative alcohol use, cumulative binge drinking episodes, and cumulative use of other illicit drugs (cocaine, crack, speed, methamphetamine, or opioids).

infarction by 4.8 times over the baseline risk (95% CI = 2.4, 9.5) and decreased it rapidly thereafter. This finding was derived from only 9 (0.2%) exposed cases. Additional evidence that marijuana may be a rare trigger of ischemic CHD has come from double-blind experimental studies conducted among patients with chronic stable angina. In these studies, Aronow and Cassidy[35,36] determined that exercise time until the onset of angina decreased significantly more by smoking 1 marijuana cigarette than by smoking a placebo marijuana cigarette or a high-nicotine cigarette. Although we were unable to test the hypothesis that marijuana may acutely increase the risk of CHD, we found no indication for an association according to recent use.

One potential explanation for our observed lack of an association between marijuana use and CVD events in later life is the relatively low lifetime dose compared with other CVD risk factors. Although most participants reported a history of marijuana use, total marijuana-years were low, consistent with the observation that a typical marijuana user smokes less than 1 marijuana cigarette per day and generally quits using marijuana early in adulthood.[37] Another potential reason for the lack of an association of marijuana use and CVD events is the opposing cardiovascular effects of cannabinoids, via cannabinoid receptors CB1 and CB2.[13,14] Activation of CB1 receptors has been shown in mouse models to promote a proathergenic profile,[16] whereas activation of CB2 receptors may suppress the inflammatory response,[15] thereby reducing the progression of atherosclerosis.

Strengths and Limitations

Study strengths include a community-based sampling method as opposed to a clinic-based sample; repeated assessments of and extensive data on marijuana use and potential confounding factors beginning early in adulthood; adjudication of suspected cardiovascular outcomes by a panel of physicians using detailed evaluation criteria; a biracial cohort; a relatively large sample size well balanced with respect to age, gender, race, and education that increased precision and permitted simultaneous adjustment and stratification by multiple variables; high retention; and the standardized data collection protocols and rigorous quality control of the CARDIA study.

At least 3 limitations deserve mention. First, our measures of marijuana use lacked information on the exact dosage and were derived from self-report, which may not always be reliable, especially for an illicit substance. This may have contributed to our null findings. However, repeat assessments of marijuana use were incorporated into our measure of cumulative lifetime exposure, our questionnaire was self-administered rather than interviewer administered, the survey was completed in a research clinic as opposed to a government agency or employer facility, and confidentiality was ensured at each examination.

Second, we relied, at least initially, on participant self-report of cardiovascular-related hospitalizations or procedures performed in an outpatient setting before medical record adjudication, which may not be reliable among long-term or heavy marijuana users.[38] However, we confirmed null associations in analyses of marijuana use and CVD mortality, an outcome independent of participant self-report.

Third, the relatively small number of outcomes and somewhat few recent marijuana users limited the precision of our estimates, particularly in analyses of our secondary cause-specific outcomes. Thus, our results should be confirmed in studies of large cohorts with high cumulative marijuana use.

Conclusions

With the increasing use of marijuana and decreasing perceived harmfulness, evaluation

of the potential cardiovascular effects of marijuana has become a public health priority. In this long-term follow-up study of predominately occasional, recreational users of marijuana, neither cumulative lifetime nor recent use of marijuana was associated with the incidence of CVD in middle age. Even though our results were consistently null, it seems prudent at this time to inform potential users at high risk for CHD about the acutely increased risk of myocardial infarction that may occur immediately after exposure to marijuana. AJPH

CONTRIBUTORS

J. P. Reis originated the study concept and design and was responsible for data analysis. C. E. Lewis and S. Sidney acquired the data. All authors were involved in data interpretation, article development, and providing substantive feedback on all drafts of the article.

ACKNOWLEDGMENTS

The Coronary Artery Risk Development in Young Adults (CARDIA) study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (grants HHSN268201300025C and HHSN268201300026C), Northwestern University (grant HHSN268201300027C), the University of Minnesota (grant HHSN268201300028C), the Kaiser Foundation Research Institute (grant HHSN268201300029C), and the Johns Hopkins University School of Medicine (grant HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intraagency agreement between NIA and NHLBI (agreement AG0005).

The authors thank the staff and participants of the CARDIA study for their important contributions.

Note. The views expressed in this article are those of the authors and do not necessarily represent the views of the NHLBI, the National Institutes of Health, or the US Department of Health and Human Services.

HUMAN PARTICIPANT PROTECTION

Institutional review boards from each field center and the coordinating center approved the study annually. All participants provided written informed consent.

REFERENCES

1. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. *Monitoring the Future. National Survey Results on Drug Use: 1975–2014. 2015 Overview: Key Findings on Adolescent Drug Use*. Ann Arbor, MI: Institute for Social Research, the University of Michigan; 2015.

2. Benowitz NL, Rosenberg J, Rogers W, Bachman J, Jones RT. Cardiovascular effects of intravenous delta-9-tetrahydrocannabinol: autonomic nervous mechanisms. *Clin Pharmacol Ther*. 1979;25(4):440–446.

3. Beaconsfield P, Ginsburg J, Rainsbury R. Marihuana smoking. Cardiovascular effects in man and possible mechanisms. *N Engl J Med*. 1972;287(5):209–212.

4. Merritt JC, Cook CE, Davis KH. Orthostatic hypotension after delta 9-tetrahydrocannabinol marihuana inhalation. *Ophthalmic Res*. 1982;14(2):124–128.

5. Benowitz NL, Jones RT. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *J Clin Pharmacol*. 1981;21(8–9 suppl):214S–223S.

6. Charles R, Holt S, Kirkham N. Myocardial infarction and marijuana. *Clin Toxicol*. 1979;14(4):433–438.

7. Collins JS, Higginson JD, Boyle DM, Webb SW. Myocardial infarction during marijuana smoking in a young female. *Eur Heart J*. 1985;6(7):637–638.

8. Marinella MA. Stroke after marijuana smoking in a teenager with factor V Leiden mutation. *South Med J*. 2001;94(12):1217–1218.

9. White D, Martin D, Geller T, Pittman T. Stroke associated with marijuana abuse. *Pediatr Neurosurg*. 2000; 32(2):92–94.

10. Akins D, Awdeh MR. Marijuana and second-degree AV block. *South Med J*. 1981;74(3):371–373.

11. Kosior DA, Filipiak KJ, Stolarz P, Opolski G. Paroxysmal atrial fibrillation in a young female patient following marijuana intoxication—a case report of possible association. *Med Sci Monit*. 2000;6(2):386–389.

12. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation*. 2001;103(23):2805–2809.

13. Singla S, Sachdeva R, Mehta JL. Cannabinoids and atherosclerotic coronary heart disease. *Clin Cardiol*. 2012; 35(6):329–335.

14. Franz CA, Frishman WH. Marijuana use and cardiovascular disease. *Cardiol Rev*. 2016;24(4):158–162.

15. Steffens S, Veillard NR, Arnaud C, et al. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature*. 2005;434:782–786. [Erratum in Karsak M. *Nature*. 2005;435(7041):528]

16. Liu J, Gao B, Mirshahi F, et al. Functional CB1 cannabinoid receptors in human vascular endothelial cells. *Biochem J*. 2000;346(pt 3):835–840.

17. Kelly SG, Plankey M, Post WS, et al. 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(1):e0147822.

18. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *Am J Cardiol*. 2006; 98(4):478–484.

19. Bancks MP, Pletcher MJ, Kertesz SG, Sidney S, Rana JS, Schreiner PJ. Marijuana use and risk of prediabetes and diabetes by middle adulthood: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetologia*. 2015;58(12):2736–2744.

20. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol*. 2002;42(11 suppl):64S–70S.

21. Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman MA. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J*. 2013;165(2):170–175.

22. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *Am J Public Health*. 1997;87(4):585–590.

23. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307(2):173–181.

24. Auer R, Vittinghoff E, Yaffe K, et al. Association between lifetime marijuana use and cognitive function in middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *JAMA Intern Med*. 2016; 176(3):352–361.

25. Pletcher MJ, Varosy P, Kiefe CI, Lewis CE, Sidney S, Hulley SB. Alcohol consumption, binge drinking, and early coronary calcification: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Epidemiol*. 2005;161(5):423–433.

26. Kertesz SG, Pletcher MJ, Safford M, et al. Illicit drug use in young adults and subsequent decline in general health: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Drug Alcohol Depend*. 2007; 88(2–3):224–233.

27. Levine DA, Lewis CE, Williams OD, et al. Geographic and demographic variability in 20-year hypertension incidence: the CARDIA study. *Hypertension*. 2011;57(1):39–47.

28. Reis JP, Hankinson AL, Loria CM, et al. Duration of abdominal obesity beginning in young adulthood and incident diabetes through middle age: the CARDIA study. *Diabetes Care*. 2013;36(5):1241–1247.

29. Sarzynski MA, Schuna JM Jr, Carnethon MR, et al. Association of fitness with incident dyslipidemias over 25 years in the Coronary Artery Risk Development in Young Adults study. *Am J Prev Med*. 2015;49:745–752.

30. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999; 94(446):496–509.

31. Raghunathan TE, Lepkowski JM, VanHoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol*. 2001;27(1):85–95.

32. Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. New York, NY: Wiley-Interscience; 2002.

33. Barber PA, Pridmore HM, Krishnamurthy V, et al. Cannabis, ischemic stroke, and transient ischemic attack: a case–control study. *Stroke*. 2013;44(8):2327–2329.

34. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J*. 2008;155(3):465–470.

35. Aronow WS, Cassidy J. Effect of marihuana and placebo-marihuana smoking on angina pectoris. *N Engl J Med*. 1974;291(2):65–67.

36. Aronow WS, Cassidy J. Effect of smoking marihuana and of a high-nicotine cigarette on angina pectoris. *Clin Pharmacol Ther*. 1975;17(5):549–554.

37. *Results From the 2013 National Survey on Drug Use and Health: Summary of National Findings*. Rockville, MD: US Department of Health and Human Services; 2014.

38. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev*. 2008;1(1):81–98.