Hypertension

ORIGINAL ARTICLE

Lifetime Cannabis Use and Incident Hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Jamie Corroon, Ryan Bradley, Igor Grant, Michael P. Bancks, Julian Jakob, Reto Auer, Jared P. Reis, Norrina Allen, Kuan-Hung Yeh, Matthew A. Allison

BACKGROUND: Observational evidence investigating associations between cannabis use and hypertension is inconsistent.

METHODS: The association between cumulative lifetime cannabis use (cannabis-years) and incident hypertension was examined over 35 years in a sample of CARDIA study (Coronary Artery Risk Development in Young Adults) participants free of cardiovascular disease at baseline. Marginal structural models with inverse probability weighting were used to adjust for potential time-dependent confounding and censoring. Hazard ratios and 95% CIs were estimated using Cox proportional hazards regression. Sensitivity analyses included modeling cannabis-years using restricted cubic splines, stratifying the primary analyses by sex, race, alcohol and cigarette smoking, and evaluating an additional exposure measure (days of use in the past month).

RESULTS: The analytic sample consisted of 4328 participants at baseline and 2810 (64.9%) at year 35. Median cannabis-years increased minimally and remained low across visits: 0.0 (Q1–Q3, 0.0–0.3) at baseline and 0.2 (Q1–Q3, 0.0–0.7) by year 35. There were 2478 cases of incident hypertension over 88 292 person-years (28.1 cases per 1000 person-years). Cannabis-years were not significantly associated with incident hypertension (adjusted hazard ratio, 0.99 [95% CI, 0.97–1.00]; *P*=0.18). The association remained unchanged in sensitivity analyses.

CONCLUSIONS: In a cohort of Black and White young adults with 35 years of follow-up, no association was found between cumulative lifetime use of cannabis and risk of incident hypertension. This finding was robust to restricted cubic spline analyses, analyses stratified by sex, race, alcohol use and tobacco cigarette smoking, and an additional measure of exposure (days of use in the past month). ***(Hypertension.* 2025;82:1641–1652. DOI: 10.1161/HYPERTENSIONAHA.125.25005.)** • **Supplement Material**.

Key Words: blood pressure ■ cannabis ■ cardiovascular diseases ■ hypertension ■ marijuana

The increasing legalization of *Cannabis sativa* L. (cannabis, marijuana) for both medicinal and recreational purposes has contributed to decreasing public perception of harms and increasing use,[1] yet there remains limited understanding of its long-term cardiovascular effects. While cannabinoids, particularly delta-9-tetrahydrocannabinol, have been shown to produce various cardiovascular effects in acute administration studies, the impact of regular, long-term cannabis use on blood pressure (BP) and the risk of developing hypertension is a subject of ongoing debate.

Cardiovascular effects of cannabis are primarily mediated through interactions between phytocannabinoids and cannabinoid receptors (CB1R [cannabinoid receptor

Correspondence to: Jamie Corroon, Department of Psychiatry, Center for Medicinal Cannabis Research, University of California, San Diego, 220 Dickinson Street, Suite B, MC8231, San Diego, CA 92103-8231. Email jcorroon@health.ucsd.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.125.25005.

For Sources of Funding and Disclosures, see page 1650.

Hypertension is available at www.ahajournals.org/journal/hyp

ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

This study is the first to examine the association between cumulative lifetime cannabis use—quantified as cannabis-years—and incident hypertension over 35 years of follow-up. It leverages a longitudinal design with repeated exposure assessments to allow for marginal structural modeling to address time-varying confounding and mediation.

What Is Relevant?

Despite acute hemodynamic effects of cannabis, our study did not find a significant association between long-term use and incident hypertension. These results contrast with some prior studies that relied on cross-sectional or retrospective data and noncumulative exposure measures.

Clinical/Pathophysiological Implications?

The absence of an association reported in our study suggests that long-term cannabis use may not meaningfully contribute to long-term hypertension risk. This challenges the assumption that repeated activation of CB1R (cannabinoid receptor type 1) receptors leads to deleterious long-term changes in vascular health vis-à-vis blood pressure. These findings may inform clinical risk assessment and public health guidance, particularly as cannabis use becomes more widespread.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
CARDIA	Coronary Artery Risk Development in Young Adults
CB1R	cannabinoid receptor type 1
CB2R	cannabinoid receptor type 2
DBP	diastolic blood pressure
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MESA	Multiethnic Study of Atherosclerosis
NHANES	National Health and Nutrition Examination Survey
RCS	restricted cubic spline
SBP	systolic blood pressure

type 1] and CB2R [cannabinoid receptor type 2]) in the cardiovascular and nervous systems. These involve both direct cardiac effects and indirect autonomic effects. These effects are complex, variable, and typically include net increases in heart rate, myocardial contractility, and changes in vascular resistance ranging from vasodilatation to vasoconstriction, potentially resulting in altered BP.[2–4]

For BP and hypertension, several cross-sectional studies have reported associations between recent (past month) cannabis use, frequency of recent use (days of use in the past month), and elevated systolic BP (SBP)[5,6] but not diastolic BP (DBP) or prevalent hypertension.[7] Studies investigating recent use, however, fail to consider long-term exposure, which may be expected to influence the development of chronic disease, including hypertension. Prospective research on this topic is limited, and has not reported associations with greater SBP, DBP (in the CARDIA study [Coronary Artery Risk Development in Young Adults]),[8] or incident hypertension.[9]

Since most epidemiological studies evaluating the relationships between cannabis use and BP outcomes have relied on case reports, case series, and cross-sectional designs, and because hypertension is a major risk factor for incident clinical cardiovascular events, it is critical to understand the potential relationship between cumulative lifetime cannabis use and hypertension. Further, few studies have assessed cannabis use starting in young adulthood and followed participants for long durations to assess incident hypertension. Thus, the current analysis aimed to explore longitudinal associations over 35 years between lifetime cannabis use, measured in cannabis-years , and the development of hypertension. We hypothesized that cumulative lifetime cannabis use would not be associated with greater risk of incident hypertension. Our focus was on incident diagnosable hypertension, given findings from a previous CARDIA publication that reported no association between quantiles of cannabis-years and either SBP or DBP,[8] as well as our prior work in the National Health and Nutrition Examination Survey (NHANES)[10] and Multiethnic Study of Atherosclerosis (MESA),[11] in which we found no association between duration of regular cannabis use and either SBP or DBP.

METHODS

Data Availability

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers

trained in human subject confidentiality protocols may be sent to the CARDIA Coordinating Center at coc@uab.edu.

Study Population

The CARDIA study is a multicenter observational cohort study focused on the development of coronary artery disease risk factors in young adults. Briefly, in 1985 to 1986, 5115 Black and White adults aged 18 to 30 years were recruited from 4 US urban communities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Study recruitment was designed to achieve approximate balance across age (<25 years and ≥25 years), sex, race (self-identified Black and White), and education (≤ high school graduation and > high school education). In-person examinations occurred at baseline, and at 2, 5, 7, 10, 15, 20, 25, 30, and 35 (2020–2021) years after baseline, with annual telephone interviews that updated health status and contact information. Participation rates at follow-up examinations ranged from 90% (year 2 follow-up) to 64% (year 35 follow-up) of the surviving cohort. Institutional review boards at each study center approved research protocols, and participants provided written informed consent at each examination. Additional details of the study design are published elsewhere.[12]

Independent Variables

Cannabis Use

Self-reported cannabis use was evaluated at each in-person CARDIA examination. Cumulative lifetime use, quantified as cannabis-years (as previously described),[8] was calculated using responses to the following questions: During the last 30 days, on how many days did you use marijuana? and How many times in your lifetime have you used marijuana? Recent use at each examination (the number of days of reported use during the month preceding each examination) was assumed to approximate the average number of days of use during the months before and after the examination. The question During the last 30 days, on how many days did you use marijuana? was used as a measure of recent use (past month use). Recent use was defined as >1 day of use in the past 30 days.

Cannabis-years are cumulative and summed as the total number of days of self-reported cannabis use over the follow-up period, where 1 cannabis-year is equivalent to 365 days of use. If the calculated value of cannabis-years was less than the value of lifetime use (categorical: How many times in your lifetime have you used marijuana?) at a given examination, the value of self-reported lifetime use was used as the value for cannabis-years.

Covariates

Using an interviewer-administered questionnaire, self-reported age, sex, race, highest education level achieved, alcohol use, tobacco cigarette smoking, and illicit substance use were collected at each in-person CARDIA examination. Alcohol use was categorized as no daily consumption, ≤1 drink per day or >1 drink per day. A continuous variable of drink-years was also calculated, where 1 drink-year is equivalent to 1 drink per day for 365 days[13] (see Alcohol Exposure in Supplemental Methods). Tobacco cigarette smoking was categorized as never, former, or current. Estimated lifetime exposure to tobacco cigarettes was calculated as pack-years, as previously described.[14] Substance use (eg, cocaine/crack, amphetamine, and heroin) was categorized as yes or no based on the question Have you ever used (substance)? Family history of hypertension at baseline was categorized as yes or no based on self-report. Psychiatric medication use was dichotomized (yes/no) according to participants' self-reported use of medications commonly prescribed for the 5 most prevalent psychiatric conditions: Major Depressive Disorder, Anxiety Disorders, Bipolar Disorder, Schizophrenia, and attention-deficit/hyperactivity disorder, as outlined in the Supplemental Methods.

Physical activity was measured using the CARDIA Physical Activity History Questionnaire, which asks the amount of time per week spent in 13 categories of vigorous and moderate-intensity leisure, occupational, and household physical activities over the past 12 months. A total physical activity (self-reported moderate-to-vigorous physical activity) score was derived using a computer-based algorithm, which combined the frequency, intensity, and a duration-weighting factor for each activity. The final score, expressed in exercise units, represents the sum of these weighted values across all reported activities.[15,16]

Starting at year 5, depression was categorized as yes or no and measured every 5 years using the Center for Epidemiological Studies Depression Scale (<16=not depressed; ≥16=depressed)[17] (see Cardiovascular Risk Factors in Supplemental Methods).

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Clinical biomarkers, including total cholesterol (mg/dL), LDL (low-density lipoprotein) cholesterol (mg/dL),[18] HDL (high-density lipoprotein) cholesterol (mg/dL), triglycerides (mg/dL), and fasting blood glucose (mg/dL), were objectively measured at each examination (see Cardiovascular Risk Factors in Supplemental Methods). Dyslipidemia was defined as a total cholesterol to HDL ratio >5.0 or self-reported use of lipid-lowering medication (available starting at year 5). Diabetes was defined as a fasting blood glucose level ≥126 mg/dL or self-reported use of oral antiglycemic medication or insulin (hemoglobin A1C was not available for all examinations).

Dependent Variables

Clinic BP Measurements

At each examination, SBP and DBP were measured following a standardized protocol by trained and certified staff. During the baseline, and at the year 2, 5, 7, 10, and 15 examinations, BP was measured using a Hawksley random-zero sphygmomanometer (W.A. Baum Co., Copiague, NY). At the year 20, 25, 30, and 35 examinations, BP was recorded using a standard automated BP measurement monitor (Omron model HEM907XL; Omron Healthcare, Inc, Lake Forest, IL). To ensure comparability between the 2 methods, BP measurements at the year 20 and 25 examinations were calibrated to random-zero sphygmomanometer values based on simultaneous readings from both devices using a Y connector on a subset of participants (n=906).[19]

The arm circumference of each participant was measured at the midpoint between the acromion and olecranon of the right arm to determine the appropriate cuff size. Participants were asked to sit quietly in a comfortable position with their feet flat on the floor for at least 5 minutes before their BP was measured. Three readings, each separated by at least 30 seconds, were taken with the participant's right arm positioned at heart level. Each BP measurement was rounded to the

nearest even number and recorded. The average of the second and third readings was used to define SBP and DBP at each examination.

Hypertension

Incident hypertension was defined by the first examination at which a participant met the definition for hypertension. In 2017, clinical guidelines for managing elevated BP in adults were updated from the 2014 JNC 8 threshold (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or use of antihypertensive medication)[20] to the American College of Cardiology/American Heart Association threshold (SBP ≥130 mm Hg, DBP ≥80 mm Hg, or use of antihypertensive medication).[21] In the analysis, the updated hypertension thresholds were applied to ensure consistency with contemporary clinical guidelines and enhance the relevance of findings to current medical practice.

Statistical Methods

Analytic Sample

The analytic sample (n=4328) was limited to CARDIA participants who had data for the primary exposure (cannabis-years) and were free of hypertension at baseline.

Descriptive statistics included means and standard deviations for normally distributed continuous variables; medians and 25th and 75th percentiles for nonnormally distributed continuous variables; and counts and percentages for categorical variables. Incidence rates were calculated per 1000 person-years. Follow-up time was calculated as the difference between the baseline examination date and the event date, or the date of last contact, whichever came first.

The primary analysis tested the association between cannabis-years (a time-dependent measure of self-reported lifetime cannabis use) and incident hypertension. Secondary analyses evaluated the robustness of this association using restricted cubic spline (RCS) analyses, analyses stratified by sex, race, alcohol use, and tobacco cigarette smoking status, and an additional exposure measure (days used in the past month).

A marginal structural model analysis was used to account for potential time-dependent confounding and mediation. Standard regression methods may yield biased estimates when exposure and covariates vary over time, especially when past confounders influence both future exposure and the outcome. A marginal structural model addresses this issue by using Inverse Probability of Treatment Weights and Inverse Probability of Censoring Weights to balance covariates at each time point, thereby creating a pseudo-population that minimizes confounding. While the marginal structural model relies on the assumption that the model used to estimate treatment probabilities is correctly specified, this assumption is supported by the inclusion of all covariates deemed relevant to self-reported cannabis use. As such, study center, sex, and race (White, Black), and family history of hypertension (yes/no) at enrollment were modeled as time-independent covariates. Age, education, cigarette pack-years, alcohol drink-years, cocaine, speed, or heroin use (yes/no), physical activity, BMI, depression (yes/no), dyslipidemia (yes/no), diabetes (yes/no), antilipidemic medications (yes/no), antiglycemic medications (yes/no), and psychiatric medications (yes/no) were modeled as time-dependent covariates.

To limit the influence of extreme weights, Inverse Probability of Treatment Weights and Inverse Probability of Censoring Weights were truncated at the 1st and 99th percentiles of their respective distributions. These calculated weights were applied in Cox proportional hazards regression models to estimate hazard ratios and 95% CIs for the primary (cannabis-years; time-dependent) and secondary analyses (days of use in the past month; time-dependent).

To further explore potential nonlinearity in the association between cannabis-years and incident hypertension, we modeled cannabis-years using a RCS function within the marginal structural Cox proportional hazards framework. Knots were placed at the 5th, 50th, and 95th percentiles of cannabis-years and days of use in the past month among participants with values greater than zero, respectively. Global Wald tests were used to assess whether nonlinear spline terms improved fit over the linear model.

We designed a series of multivariable regression models. Model 1 was an unadjusted model. Model 2 adjusted for sociodemographic factors, including age, sex, race/ethnicity, education level, and study center. Model 3 further adjusted for behavioral risk factors, including tobacco cigarette smoking (pack-years), cumulative alcohol use (drink-years), illicit drug use (cocaine, speed, and heroin), and physical activity. Model 4 included all covariates from Models 2 and 3, as well as additional cardiovascular risk factors, including BMI, family history of hypertension, depression, dyslipidemia, diabetes, and use of antilipidemic, antiglycemic and psychiatric medications.

Multiple imputation (5 imputed data sets) was used to impute missing values using multiple imputation by chained equations with predictive mean matching implemented in the MICE package in R. The Nelson-Aalen estimator was applied to handle censored survival data during the imputation process. Each data set was analyzed separately, and results from the 5 analyses were combined using the rules of Little and Rubin.

Assessment of collinearity between independent variables was performed in the final multivariate-adjusted model using the Variance Inflation Factor and Tolerance. Tests of statistical significance were 2-tailed, with statistical significance set at $P<0.05$. Statistical analyses were performed using SAS On-Demand for Academics (Copyright© 2014 SAS Institute, Cary, NC) and R (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

Stratified Analyses (Effect Modification)

Stratified analyses were used to assess differences between cannabis-years and incident hypertension in subgroups defined by biologic sex, race, alcohol use per day, alcohol drink-years, tobacco cigarette smoking status, and tobacco cigarette pack-years. Multiplicative first-order interactions were constructed for each subgroup variable in the final model. Interaction terms were considered significant in the final multivariable-adjusted model if $P<0.10$.

RESULTS

The study sample consisted of 4328 participants at baseline (year 0), with retention rates of 72.1% (n=3121) at year 15 and 64.9% (n=2810) at year 35 (Table 1). The median age of participants was 25.0 years at baseline, increasing to 40.0 years by year 15 and 62.0 years by year 35. The proportion of female participants increased

Table 1. Characteristics Participants With Self-Reported Cannabis Use and Blood Pressure Data in the CARDIA Study, 1985–2021

Characteristic	Year 0	Year 15	Year 35
n (% of sample)	4328 (100.0)	3121 (72.1)	2810 (64.9)
Lost to follow-up	0 (0.0)	1207 (27.9)	1518 (35.1)
Socio-demographics			
Age, y; median (Q1–Q3)	25.0 (22.0, 28.0)	40.0 (37.0, 43.0)	62.0 (58.0, 64.0)
Female, n (%)	2517 (58.2)	1864 (59.7)	1729 (61.5)
White, n (%)	2122 (49.0)	1664 (53.3)	1530 (54.5)
Education, n (%)			
High school or less	1716 (39.7)	692 (22.2)	418 (18.6)
Some college	1425 (33.0)	959 (30.8)	734 (32.7)
College graduate or above	1184 (27.4)	1460 (46.9)	1090 (48.6)
Study center, n (%)			
Birmingham, AL	999 (23.1)	732 (23.5)	707 (25.2)
Chicago, IL	982 (22.7)	721 (23.1)	623 (22.2)
Minneapolis, MI	1174 (27.1)	832 (26.7)	729 (25.9)
Oakland, CA	1173 (27.1)	836 (26.8)	751 (26.7)
Substance use exposure			
Tobacco use			
Cigarette smoking status, n (%)			
Never	2380 (55.3)	1838 (59.0)	1259 (67.0)
Former	589 (13.7)	591 (19.0)	439 (23.4)
Current	1332 (31.0)	687 (22.1)	181 (9.6)
Pack-years, median (Q1–Q3)*	0.0 (0.0–2.3)	0.0 (0.0–5.6)	0.0 (0.0–6.0)
Alcohol use			
No daily consumption, n (%)	1726 (40.0)	853 (34.5)	439 (29.8)
≤1 drink/d	1770 (40.9)	1085 (43.8)	655 (44.5)
>1 drink/d	827 (19.1)	538 (21.7)	379 (25.7)
Drink-years, median (Q1–Q3)†	0.5 (0.0–1.7)	0.0 (0.0–6.0)	0.5 (0.0–1.7)
Cannabis use			
Past month, n (%)	1214 (28.6)	367 (16.9)	343 (23.7)
Days of use (past month), mean (SD)‡	0.0 (0.0–1.0)	1.7 (5.5)	3.7 (8.8)
Cannabis-years, median (Q1–Q3)§	0.0 (0.0–0.3)	0.2 (0.0–0.4)	0.2 (0.0–0.7)
Cocaine/crack use (Ever), n (%)	NA	311 (10.0)	666 (30.2)
Amphetamine use (Ever), n (%)	NA	752 (24.2)	375 (17.0)
Heroin (Ever), n (%)	NA	158 (5.1)	74 (3.4)
Physical activity score, median exercise units (Q1–Q3), min/week¶	357.0 (196.0–576.0)	283.0 (144.0–496.0)	250.0 (96.0–446.5)
Body mass index, kg/m; median (Q1–Q3)	23.2 (21.0–26.0)	27.1 (23.8–31.8)	29.0 (25.4–34.1)
Cardiometabolic medical history			
Systolic blood pressure, mm Hg; mean (SD)	108.0 (9.1)	111.4 (13.7)	122.5 (17.1)
Diastolic blood pressure, mm Hg; mean (SD)	66.3 (7.7)	73.1 (10.8)	73.0 (10.6)
LDL cholesterol, mg/dL; mean (SD)	108.0 (30.8)	112.5 (31.9)	117.8 (36.5)
HDL cholesterol, mg/dL; mean (SD)	53.5 (13.1)	51.4 (14.7)	55.7 (15.6)
Total cholesterol, mg/dL; mean (SD)	175.4 (32.8)	184.2 (35.3)	194.9 (43.1)
Triglycerides, mg/dL; median (Q1–Q3)	60.0 (45.0–82.0)	80.0 (58.0–118.0)	93.0 (70.0–126.0)
Hypertension, n (%)	0 (0.0)	1169 (37.5)	1751 (65.6)
Dyslipidemia, n (%)	356 (8.2)	598 (19.2)	825 (29.4)
Diabetes, n (%)	23 (0.5)	106 (3.5)	488 (24.1)
Antihypertensive medication, n (%)	0 (0.0)	174 (5.6)	1125 (42.9)

(*Continued*)

Table 1. Continued

Characteristic	Year 0	Year 15	Year 35
Antilipidemic medication, n (%)	NA	81 (2.3)	672 (26.6)
Antiglycemic medication, n (%)	10 (0.2)	60 (1.9)	248 (8.8)
Depression, n (%)	NA	510 (16.6)	601 (27.5)
Psychiatric medication, n (%)	0 (0.0)	40 (1.3)	91 (3.2)

BMI indicates body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and NA, not available.

*Cumulative lifetime exposure to tobacco cigarettes in terms of pack-years; 1 pack-year of exposure is equivalent to 7300 tobacco cigarettes (365 d×1 pack per day×20 cigarettes per pack).

†Drink-years in those who reported ever drinking alcohol. Drink-year was defined as the total amount of ethanol consumed by someone who had 1 alcoholic drink per day for 1 y (1 drink-year=17.24 mL of ethanol per drink×1 drink per day×365 d=6292.6 mL of ethanol).

‡Mean reported instead of median, despite significant right skew.

§Cumulative lifetime exposure to marijuana joints in cannabis-years; 1 cannabis-year of exposure is equivalent to 365 d of marijuana use.

¶Physical activity measured with the CARDIA Physical Activity History questionnaire, which asks the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 mo and reported as exercise units.

from 58.2% at baseline to 61.5% at year 35. Racial distribution showed a relatively stable percentage of White participants, with 49.0% at baseline, 53.3% at year 15, and 54.5% at year 35.

Tobacco cigarette smoking declined, with the proportion of participants reporting current tobacco cigarette smoking decreasing from 31.0% at baseline to 9.6% at year 35. Alcohol consumption patterns shifted in the opposite direction, with the proportion of participants consuming more than 1 drink per day increasing from 19.1% at baseline to 25.7% at year 35.

A general trend toward decreasing physical activity and increasing body mass was observed over time. The median weekly physical activity score declined from 357 minutes at baseline to 283 minutes at year 15 and 250 minutes at year 35. Concurrently, median BMI steadily increased from 23.2 kg/m^2 at baseline to 27.1 kg/m^2 at year 15 and 29.0 kg/m^2 by year 35.

The prevalence of hypertension, dyslipidemia, and diabetes increased notably throughout the follow-up period. Hypertension prevalence increased from 0.0% at baseline to 37.5% at year 15 and 65.6% at year 35. The use of antihypertensive, antilipidemic, and antiglycemic medications rose sharply, with 42.9%, 26.6%, and 8.8% of participants using such medications by year 35, respectively.

Characteristics of Cannabis Use

Given the right skew and large number of zero values for the 75th percentile, both means and medians are reported in Table 2 for continuous cannabis measures.

Table 2. Self-Reported Cannabis Use Characteristics by Exam Year in the CARDIA Study (Coronary Artery Risk Development in Young Adults), 1985–2021

	Year 0	Year 2	Year 5	Year 7	Year 10	Year 15	Year 20	Year 25	Year 30	Year 35
Characteristic	**1985–1986**	**1987–1988**	**1990–1991**	**1992–1993**	**1995–1996**	**2000–2001**	**2005–2006**	**2010–2011**	**2015–2016**	**2020–2021**
n (% of sample)	4328 (1.0)	3917 (90.5)	3680 (85.0)	3461 (80.0)	3353 (77.5)	3121 (72.1)	3025 (69.9)	3008 (69.5)	2886 (66.7)	2810 (64.9)
Ever use (yes), n (%)	3040 (70.3)	2844 (73.4)	2647 (72.6)	2456 (71.5)	2351 (71.0)	2182 (70.1)	2089 (70.0)	2113 (70.7)	1969 (69.7)	1459 (65.8)
Past month use (yes), n (%)	1214 (28.6)	938 (33.0)	582 (22.0)	528 (21.5)	462 (19.7)	367 (16.9)	344 (17.1)	347 (16.4)	399 (20.4)	343 (23.7)
Days of use (past month)										
Mean (SD)	2.7 (6.5)	3.0 (6.6)	1.7 (5.1)	1.7 (5.2)	1.9 (5.7)	1.7 (5.5)	1.9 (5.9)	2.0 (6.3)	2.6 (7.1)	3.7 (8.8)
Median (Q1–Q3)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Lifetime use, n (%)										
0×	1282 (29.6)	1031 (26.3)	999 (27.2)	981 (28.3)	959 (28.6)	929 (29.8)	897 (29.7)	878 (29.2)	857 (29.7)	757 (26.9)
1–10 ×	1035 (23.9)	958 (24.5)	911 (24.8)	875 (25.3)	1522 (45.4)	1400 (44.9)	1353 (44.7)	1335 (44.4)	1245 (43.1)	889 (31.6)
11–99×	1015 (23.5)	926 (23.6)	902 (24.5)	798 (23.1)	421 (12.6)	390 (12.5)	351 (11.6)	358 (11.9)	346 (12.0)	257 (9.2)
≥100×	969 (22.4)	956 (24.4)	831 (22.6)	779 (22.5)	405 (12.1)	388 (12.4)	372 (12.3)	420 (14.0)	374 (13.0)	311 (11.1)
Cannabis-years										
Mean (SD)	0.2 (0.3)	0.4 (0.8)	0.6 (1.4)	0.8 (1.8)	1.0 (2.3)	1.3 (2.8)	1.8 (3.6)	2.0 (4.0)	2.4 (4.5)	2.7 (4.8)
Median (Q1–Q3)	0.0 (0.0–0.3)	0.1 (0.0–0.3)	0.2 (0.0–0.4)	0.2 (0.0–0.6)	0.2 (0.0–0.8)	0.2 (0.0–1.0)	0.3 (0.0–1.6)	0.3 (0.0–2.1)	0.3 (0.0–2.5)	0.6 (0.2–3.4)

Mean cannabis-years rose consistently from 0.2 at baseline to 2.7 by year 35. Median cannabis-years also increased but slightly and remained relatively low, starting at 0.0 (Q1–Q3, 0.0–0.3) at baseline and increasing to 0.6 (Q1–Q3, 0.2–3.4) by year 35. The proportion of participants who reported using cannabis in the past month decreased from 28.6% at baseline to 16.9% by year 15, before slightly rebounding to 23.7% by year 35. The number of days of self-reported past-month cannabis use followed a similar trend, decreasing from a mean of 2.7 days at baseline to 1.7 days at year 15, before increasing to 3.7 days by year 35.

Patterns of self-reported lifetime cannabis use (categorical) demonstrated a shift in frequency across categories and exam years. The percentage of participants reporting having used cannabis 1 to 10 times increased from 23.9% at baseline to 31.6% at year 35, while those reporting ≥100 lifetime uses decreased from 22.4% at baseline to 11.1% by year 35.

Incident Hypertension

There were 2478 cases of hypertension over 88 292 person-years, resulting in an incidence rate of 28.1 cases per 1000 person-years.

In the primary analysis, cannabis-years were not significantly associated with incident hypertension in the unadjusted model (Figure 1). Adjusting for sociodemographic factors resulted in no change of the hazard ratio (adjusted hazard ratio, 0.99 [95% CI, 0.97–1.01]; *P*=0.27). Further adjustment for behavioral and lifestyle factors (Model 3) and cardiometabolic factors (Model 4) did not materially change this finding, with adjusted hazard ratios of 0.98 (95% CI, 0.95–1.01; *P*=0.23) and 0.98 (95% CI, 0.95–1.01; *P*=0.21) for Models 3 and 4, respectively.

In secondary analyses, self-reported recent cannabis use (measured as the imputed median of 5 days of use in the past month) was not significantly associated with incident hypertension in the final model (adjusted hazard ratio, 1.03 [95% CI, 1.00–1.07], *P*=0.06; Figure 1).

Post hoc RCS analyses revealed a significant nonlinear dose-response for cannabis-years (global Wald test: *P*=0.04), whereas the association for days of use in the past month showed no evidence of nonlinearity (*P*=0.66). For cannabis-years, a modest increase in hypertension risk was observed at the highest cumulative lifetime exposures, with uncertainty increasing at greater exposures due to fewer observations (Figure 2A). For past-month use, risk rose modestly with ≈1 to 10 days of use, declined after about 15 days (Figure 2B).

Effect Modification

No significant effect modification was observed for sex, race, alcohol consumption per day, drink-years, cigarette

Model	HR (95% CI)	P-value
Model 1 (Unadjusted)		
Cannabis-years (per 1 yr.)*	0.99 (0.97-1.01)	0.18
Days of Use (per 5 days, median; past month)*	1.04 (1.01-1.08)	0.02
Model 2 (Sociodemographic)**		
Cannabis-years	0.99 (0.97-1.01)	0.27
Days of Use (past month)	1.04 (1.01-1.08)	0.01
Model 3 (Behavioral & Lifestyle)***		
Cannabis-years	0.98 (0.95-1.01)	0.23
Days of Use (past month)	1.03 (1.00-1.07)	0.06
Model 4 (Cardiometabolic)****		
Cannabis-years	0.98 (0.95-1.01)	0.21
Days of Use (past month)	1.03 (1.00-1.07)	0.06

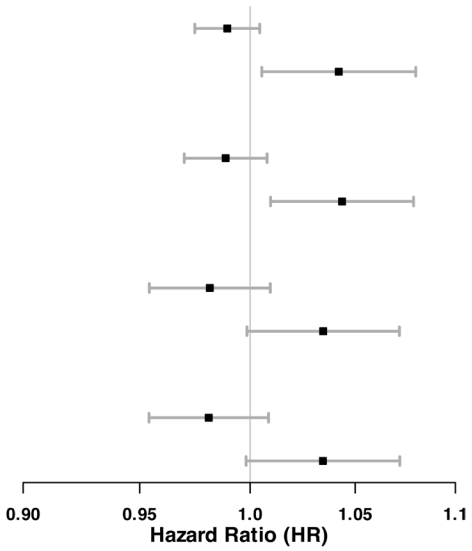

Figure 1. Self-reported cannabis use patterns and incident hypertension in the CARDIA study (Coronary Artery Risk Development in Young Adults; 1985–2021).

*Hazard ratios calculated per additional cannabis-year and per 5 days of use in the past month (imputed median among past-month users). **Model 2: age, sex, race/ethnicity, educational, study center. ***Model 3: Model 2+tobacco use (pack-years), alcohol use (drink-years), other illicit substance use (cocaine, crack, speed (methamphetamine), or opioids; yes/no), body mass index (BMI), physical activity (total intensity score as exercise units). ****Model 4: Model 3 + family history of hypertension (yes/no)+depression (yes/no), dyslipidemia (yes/no), diabetes (yes/no), and use of antilipidemic (yes/no), antiglycemic (yes/no) and psychiatric (yes/no) medications. Notes: No. of events=2478.

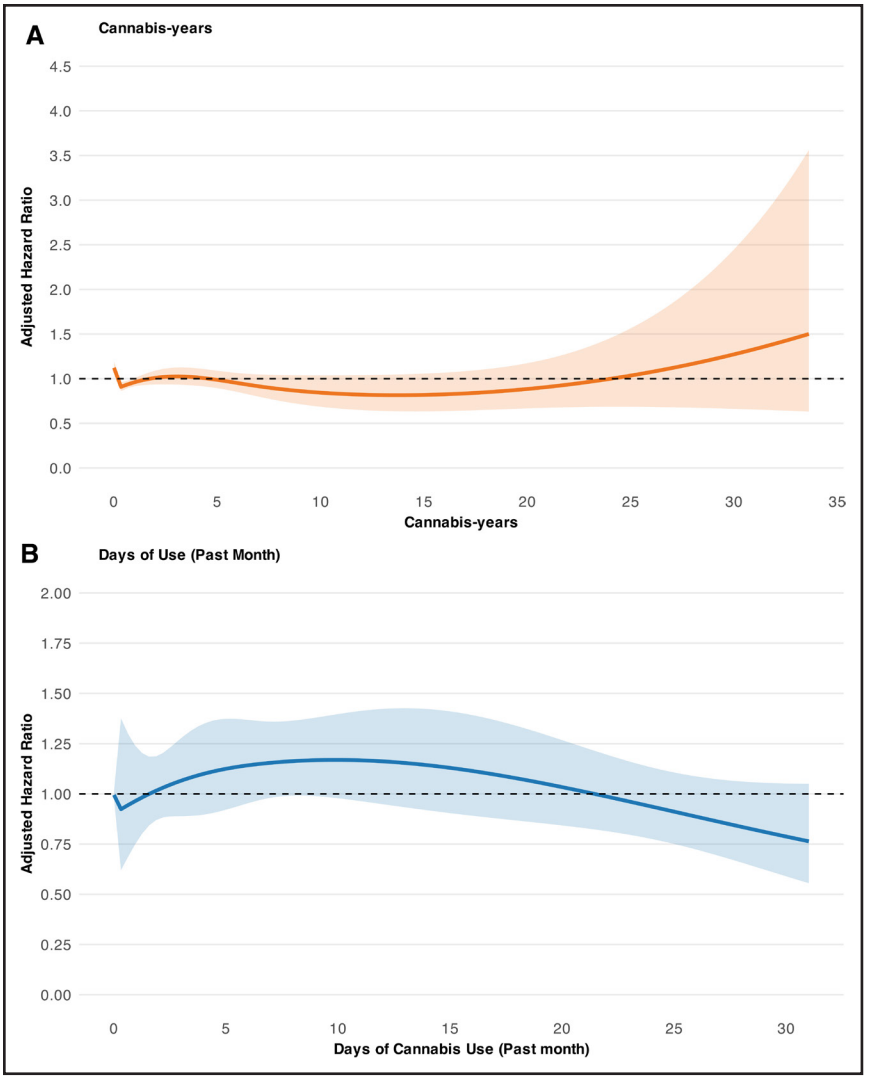

Figure 2. Self-reported cannabis use patterns and incident hypertension using restricted cubic splines, the CARDIA study (Coronary Artery Risk Development in Young Adults; 1985–2021).
Results from restricted cubic spline (RCS) analyses of model 4 with knots at the 5th, 50th, and 95th percentiles of cannabis-years and days of use in the past month, respectively, among participants with values greater than zero. Model 4 includes age, sex, race/ethnicity, education, study center, tobacco use (pack-years), alcohol use (drink-years), other illicit substance use (cocaine, crack, speed (methamphetamine), or opioids; yes/no), body mass index (BMI), physical activity (total intensity score), family history of hypertension (yes/no), depression (yes/no), dyslipidemia (yes/no), diabetes (yes/no), and use of antilipidemic (yes/no), antiglycemic (yes/no), and psychiatric (yes/no) medications.

smoking status, or cigarette pack-years at baseline (Figure 3).

DISCUSSION

In this analysis of CARDIA participants, no association was found between cumulative lifetime use of cannabis, measured as cannabis-years, and incident hypertension over 35 years of follow-up in a cohort of relatively young Black and White adults free of cardiovascular disease at baseline. This finding was consistent across sensitivity analyses, including post hoc RCS analyses, analyses stratified by sex, race, alcohol use, and tobacco cigarette smoking, and an additional measure of exposure (days of use in the past month).

Previous research examining cannabis-related cardiovascular effects has reported inconsistent findings due to varied study designs, exposure assessments, and methodological quality. Case reports and case series, while suggestive of potential associations with acute events like myocardial infarction and stroke[22–25] are limited by inherent biases and lack of controls. Similarly, cross-sectional and retrospective studies have yielded conflicting results, partly due to inadequate exposure assessment and limited ability to establish temporality.[10,11,26,27] Some suggest no association, while others report a greater risk of myocardial infarction,[28] including among young and middle-aged adults.[29,30] In contrast, prospective cohort studies with more rigorous exposure assessments and a clearer temporal relationship between exposure and outcome, have generally reported no association between lifetime cannabis use and cardiovascular outcomes. For example, prior analyses of CARDIA data have consistently reported no evidence to support associations with CVD risk factors (ie, BMI, BP, total cholesterol, HDL cholesterol, triglycerides, and fasting blood glucose),[8] incident CVD in middle age,[31] subclinical atherosclerosis,[32] abdominal adiposity,[33] markers of systemic inflammation,[34] electrocardiographic abnormalities,[35] carotid intima-media thickness,[36] heart rate,[35] and BMI.[37] Other studies have suggested a more favorable cardiometabolic profile among cannabis users compared with nonusers.[10,11,26,27,38,39]

Variable	HR (95% CI)	P-value
Main Effect (per 1 cannabis-yr.)*	0.98 (0.95-1.01)	0.21
By Sex		**0.87**
Male	0.97 (0.94-0.99)	0.06
Female	0.98 (0.96-1.00)	0.12
By Race		**0.77**
Black	0.96 (0.94-0.98)	0.02
White	0.98 (0.96-1.01)	0.16
By Alcohol Use		**0.33**
No daily consumption	0.96 (0.93-0.99)	0.06
<=1 drink/day	0.98 (0.95-1.00)	0.07
>1 drink/day	0.99 (0.96-1.02)	0.42
Alcohol drink-years (baseline)	1.00 (1.00-1.00)	0.59
By Tobacco Smoking		**0.65**
Never	0.98 (0.96-1.00)	0.14
Former	0.97 (0.93-1.01)	0.21
Current	0.98 (0.95-1.00)	0.20
Cigarette pack-years (baseline)	1.00 (1.00-1.00)	0.33

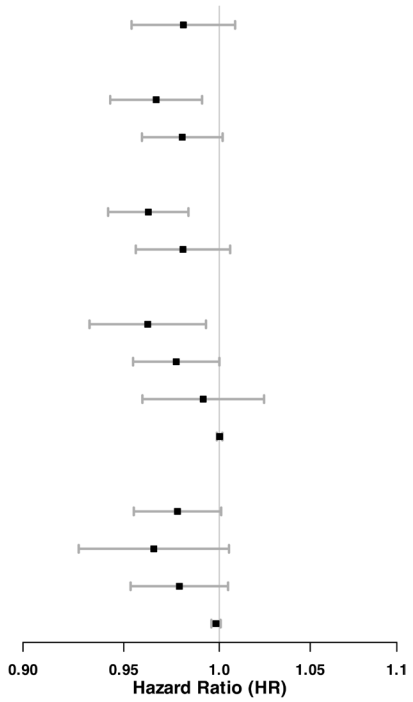

Figure 3. Effect modification of self-reported cannabis-years on incident hypertension in the CARDIA study (Coronary Artery Risk Development in Young Adults; 1985–2021).

*Potential effect modifier was added as an interaction term with cannabis-years to model 4 (4 separate models, each with 1 interaction term). Model 4 includes age, sex, race/ethnicity, education, study center, tobacco use (pack-years), alcohol use (drink-years), other illicit substance use (cocaine, crack, speed [methamphetamine], or opioids; yes/no), body mass index (BMI), physical activity (total intensity score), family history of hypertension (yes/no), depression (yes/no), dyslipidemia (yes/no), diabetes (yes/no), and use of antilipidemic (yes/no), antiglycemic (yes/no), and psychiatric (yes/no) medications. *P* values derived from Wald tests.

Our previous investigations using data from the NHANES (2009–2018) and the Multiethnic Study of Atherosclerosis (2016–2017),[10,11] reported no associations between a history of regular cannabis smoking, including duration of regular smoking, and greater SBP, DBP, or prevalent hypertension.[10,11] An earlier NHANES study using data from 2017 to 2018 reported similar findings for hypertension.[7] Conversely, a large cross-sectional study (n=91 161) utilizing data from the UK Biobank, a population-based study of around 500 000 volunteers in the UK, noted lower SBP, DBP, and pulse pressure among heavy lifetime cannabis users (>100× in a lifetime).[40] A previously published longitudinal study using data from Waves 1 (2001/2002) and 2 (2004/2005) of the National Epidemiological Survey on Alcohol and Related Conditions[9] also reported a lack of association between lifetime cannabis use (and other measures) and incident hypertension.

Compared with NHANES and MESA, this CARDIA sample features the highest levels of self-reported cannabis use in terms of duration and recency of use. In NHANES from 2009 to 2018, 25.0% of middle-aged respondents reported a history of regular use (ie, monthly use for more than a year). Among those respondents, just over 37% reported past-month use (slightly >11% of all respondents). In MESA from 2016 to 2018 (mean age, 74.2 years), slightly >9% of participants reported smoking ≥100 joints or pipes in their lifetime, and 7.4% of all respondents reported a history of regular use (ie, at least once per month). Among participants with a history of regular use, almost 34% reported past-month use. Notably, in MESA, only participants with a history of regular use were asked about past-month use. In the CARDIA study, at baseline (1985–1986), 32.5% of participants reported more than 100 lifetime uses of cannabis, increasing to over 42% by 2020–2021. Of the overall cohort, 28.9% reported past-month use at baseline, which decreased to 23.8% by 2020–2021. Therefore, this current study's higher prevalence of self-reported cannabis use, along with its extensive 35 years of longitudinal data and stronger analytical approach, provides more robust and comprehensive insights compared with our previous cross-sectional studies in NHANES and MESA.

The absence of an association in our study seems paradoxical given preclinical evidence indicating cannabinoids can contribute to cardiovascular pathology through mechanisms involving CB1R-mediated oxidative stress, inflammation, fibrosis and endothelial dysfunction.[41–43] Moreover, despite differences in chemical

composition and patterns of use, cannabis smoke contains many of the same toxic byproducts of combustion as tobacco smoke.[44,45] In contrast, activation of CB2R, upregulated in the presence of inflammation, may exert protective, antiinflammatory effects potentially counteracting the deleterious effects of CB1R activation.[42,46,47] In addition, tolerance from regular use through CB1R receptor downregulation might mitigate adverse effects associated with CB1R activation.[2] Given these complexities, further research is needed to clarify these complex interactions and their long-term impact on cardiovascular health.

The strengths of our study include a prospective design with extensive follow-up (unique to CARDIA), robust adjustment for confounding via time-dependent covariates, and the use of cumulative lifetime exposure as cannabis-years. Limitations involve potential inaccuracies from self-reported cannabis use (due to recall bias and social desirability bias); inability to capture changes in usage patterns between assessments; lack of detailed cannabis usage methods, cannabinoid profiling, or dosage information; and uncertainty in causal interpretation due to untestable assumptions of complete covariate adjustment in marginal structural models.

CONCLUSIONS

No association was found between cumulative lifetime use of cannabis, measured as cannabis-years, and incident hypertension over 35 years of follow-up in a cohort of relatively young Black and White adults free of cardiovascular disease at baseline. This finding was consistent across sensitivity analyses, including post hoc RCS analyses, analyses stratified by sex, race, alcohol use, and tobacco cigarette smoking, and an alternative measure of cannabis exposure (days of use in the past month).

PERSPECTIVES

This study contributes to a growing body of longitudinal evidence suggesting that cumulative lifetime cannabis use is not associated with the development of hypertension. With 35 years of follow-up in a well-characterized cohort, our findings challenge prior findings suggesting adverse long-term hypertensive effects of cannabis use. These results are particularly relevant as cannabis legalization continues to expand and rates of use increase among older adults.

Given that hypertension is a major modifiable risk factor for cardiovascular disease, understanding whether cannabis use contributes to developing this risk factor is critical for clinical guidance, public health messaging, and policy decisions. Our findings suggest that cannabis use, even when accumulated over decades, may not independently elevate hypertension risk. However, the nuanced physiological effects of cannabinoids, mediated through direct pathways (cannabinoid receptor activation in cardiovascular tissues) and indirect pathways (activation within tissues of the autonomic nervous and immune systems), warrant continued investigation, particularly with respect to long-term vascular health and potential interactions with other risk factors.

Future research may consider exploring heterogeneity of effects by route of administration, cannabinoid composition (eg, delta-9-tetrahydrocannabinol versus cannabidiol), and frequency and intensity of use. Additionally, the integration of objective biomarkers and pharmacological data with epidemiological analyses will be relevant to exploring causal mechanisms. As cannabis products and patterns of use continue to evolve, updated prospective studies and surveillance systems will be essential to inform clinical and public health recommendations.

ARTICLE INFORMATION

Received March 18, 2025; accepted July 10, 2025.

Affiliations

Center for Medicinal Cannabis Research, Department of Psychiatry (J.C., I.G.), and Herbert Wertheim School of Public Health and Human Longevity Science (R.B.), University of California, San Diego. Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, NC (M.P.B.). Institute of Primary Health Care (BIHAM), University of Bern, Switzerland (J.J., R.A.). Department of Pediatrics, University Hospital Bern, Switzerland (J.J.). University General Medicine and Public Health Centre (Unisanté), Lausanne, Switzerland (R.A.). National Heart, Lung, and Blood Institute (J.P.R.). Northwestern University Feinberg School of Medicine, Chicago, IL (N.A.). Division of Biomedical Informatics, Department of Medicine, University of California San Diego (K.-H.Y.). Department of Family Medicine, University of California San Diego (M.A.A.).

Acknowledgments

The CARDIA study (Coronary Artery Risk Development in Young Adults) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (75N92023D00002 and 75N92023D00005), Northwestern University (75N92023D00004), University of Minnesota (75N92023D00006), and Kaiser Foundation Research Institute (75N92023D00003). This article has been reviewed by CARDIA for scientific content. The funding organizations were independent of the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation of the article. Before submission for publication, the article was reviewed and approved by the CARDIA P&P committee. The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services.

Sources of Funding

This study was supported by National Institutes of Health grants T32HL079891 and K24AT011568, and the Center for Medicinal Cannabis Research at University of California, San Diego (State of California award no. 6440-520-3314).

Disclosures

Dr Corroon is a compensated member of the Board of Directors of CV Sciences, Inc, a manufacturer of hemp-derived cannabidiol products. The other authors report no conflicts.

Supplemental Material

Supplementary Methods
Supplementary Results
Tables S1–S4
Figures S1–S3

REFERENCES

1. National Academies of Sciences Engineering, Medicine. *Cannabis Policy Impacts Public Health and Health Equity*. The National Academies Press; 2024.
2. Pacher P, Steffens S, Haskó G, Schindler TH, Kunos G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol*. 2018;15:151–166. doi: 10.1038/nrcardio.2017.130
3. Benowitz NL, Jones RT. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *J Clin Pharmacol*. 1981;21(S1):214S–223S. doi: 10.1002/j.1552-4604.1981.tb02598.x
4. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol*. 2002;42(S1):64S–70S. doi: 10.1002/j.1552-4604.2002.tb06005.x
5. Alshaarawy O, Elbaz HA. Cannabis use and blood pressure levels: United States National Health and Nutrition Examination Survey, 2005-2012. *J Hypertens*. 2016;34:1507–1512. doi: 10.1097/HJH.0000000000000990
6. Vidot DC, Powers M, Gonzalez R, Jayaweera DT, Roy S, Dong C, Messiah SE. Blood pressure and marijuana use: results from a decade of NHANES data. *Am J Health Behav*. 2019;43:887–897. doi: 10.5993/AJHB.43.5.2
7. Shah RM, Patel S, Shah S, Doshi S, Li A, Diamond JA. Sustained cannabis use does not predispose clinical hypertension: findings from a national survey. *J Clin Hypertens (Greenwich)*. 2023;25:47–52. doi: 10.1111/jch.14623
8. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S; Coronary Artery Risk Development in Young Adults (CARDIA) Study. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *Am J Cardiol*. 2006;98:478–484. doi: 10.1016/j.amjcard.2006.03.024
9. Haleem A, Hwang YJ, Elton-Marshall T, Rehm J, Imtiaz S. The longitudinal relationship between cannabis use and hypertension. *Drug Alcohol Rev*. 2021;40:914–919. doi: 10.1111/dar.13266
10. Corroon J, Grant I, Bradley R, Allison MA. Trends in cannabis use, blood pressure and hypertension in middle-aged adults: findings from NHANES, 2009–2018. *Am J Hypertens*. 2023;36:651–659. doi: 10.1093/ajh/hpad068
11. Corroon J, Bradley R, Allison MA, Grant I. Blood pressure and hypertension in older adults who regularly smoke cannabis: findings from the multi-ethnic study of atherosclerosis (MESA). *Front Cardiovasc Med*. 2024;11:1432923. doi: 10.3389/fcvm.2024.1432923
12. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. Cardia: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41:1105–1116. doi: 10.1016/0895-4356(88)90080-7
13. 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;161:423–433. doi: 10.1093/aje/kwi062
14. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, Lin F, Kertesz S. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307:173–181. doi: 10.1001/jama.2011.1961
15. Bild DE, Jacobs DR Jr, Sidney S, Haskell WL, Anderssen N, Oberman A. Physical activity in young black and white women. The CARDIA study. *Ann Epidemiol*. 1993;3:636–644. doi: 10.1016/1047-2797(93)90087-k
16. National Cholesterol Education Program. Expert Panel on Detection, Treatment of High Blood Cholesterol in Adults. *Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III)*. The Program; 2002.
17. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385–401. doi: 10.1177/014662167700100306
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
19. Gunderson EP, Chiang V, Lewis CE, Catov J, Quesenberry CP Jr, Sidney S, Wei GS, Ness R. Long-term blood pressure changes measured from before to after pregnancy relative to nonparous women. *Obstet Gynecol*. 2008;112:1294–1302. doi: 10.1097/AOG.0b013e31818da09b
20. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, et al. 2014 Guideline for Management of High Blood Pressure. *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427
21. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 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 (Dallas, Tex: 1979)*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
22. Kumar B, Chawla O, Nigam A, Singh PK, Singh A. Interaction of cannabis cultural use and health: a case of acute myocardial infarction following consumption of cannabis beverage (Bhang). *Toxicol Rep*. 2024;13:101755. doi: 10.1016/j.toxrep.2024.101755
23. Padda I, Mahtani AU, Farid M, Fabian D, Nigussie B, Piccione G, Kavarthapu A, Sethi Y, Htyte N. Marijuana-induced ST-elevation myocardial infarction in adolescents and young adults: a case report and comprehensive review of literature. *Curr Probl Cardiol*. 2024;49:102225. doi: 10.1016/j.cpcardiol.2023.102225
24. Aissaoui H, Boulouiz S, El-Azrak M, Bouchlarhem A, Elouafi N, Bazid Z. Cannabis-induced myocardial infarction in a 27-year-old man: case report. *Ann Med Surg*. 2022;80:104054. doi: 10.1016/j.amsu.2022.104054
25. Levinger U, Hadar S, Habib G. Stroke following cannabis overuse. *Isr Medi Assoc J*. 2021;23:55–56.
26. Corroon J, Bradley R, Grant I, Daniels MR, Denenberg J, Bancks MP, Allison MA. Regular cannabis smoking and carotid artery calcification in the multi-ethnic study of atherosclerosis (MESA). *Vasc Med*. 2024;29:621–631. doi: 10.1177/1358863x241287690
27. Corroon J, Grant I, Allison MA, Bradley R. Associations between monthly cannabis use and myocardial infarction in middle-aged adults: NHANES 2009 to 2018. *Am J Cardiol*. 2023;204:226–233. doi: 10.1016/j.amjcard.2023.07.065
28. Jeffers AM, Glantz S, Byers AL, Keyhani S. Association of cannabis use with cardiovascular outcomes among US adults. *J Am Heart Assoc*. 2024;13:e030178. doi: 10.1161/JAHA.123.030178
29. Ladha KS, Mistry N, Wijeysundera DN, Clarke H, Verma S, Hare GMT, Mazer CD. Recent cannabis use and myocardial infarction in young adults: a cross-sectional study. *CMAJ*. 2021;193:E1377–E1384. doi: 10.1503/cmaj.202392
30. Mahtta D, Ramsey D, Krittanawong C, Al Rifai M, Khurram N, Samad Z, Jneid H, Ballantyne C, Petersen LA, Virani SS. Recreational substance use among patients with premature atherosclerotic cardiovascular disease. *Heart (British Cardiac Society)*. 2021;107:650–656. doi: 10.1136/heartjnl-2020-318119
31. 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. doi: 10.2105/AJPH.2017.303654
32. Auer R, Sidney S, Goff D, Vittinghoff E, Pletcher MJ, Allen NB, Reis JP, Lewis CE, Carr J, Rana JS. Lifetime marijuana use and subclinical atherosclerosis: the coronary artery risk development in young adults (CARDIA) study. *Addiction (Abingdon, England)*. 2018;113:845–856. doi: 10.1111/add.14110
33. Bancks MP, Auer R, Carr JJ, Goff DC, Kiefe C, Rana JS, Reis J, Sidney S, Terry JG, Schreiner PJ. Self-reported marijuana use over 25 years and abdominal adiposity: the coronary artery risk development in young adults (CARDIA) study. *Addiction (Abingdon, England)*. 2018;113:689–698. doi: 10.1111/add.14097
34. Alshaarawy O, Sidney S, Auer R, Green D, Soliman EZ, Goff DC, Anthony JC. Cannabis use and markers of systemic inflammation: the coronary artery risk development in young adults study. *Am J Med*. 2019;132:1327–1334.e1. doi: 10.1016/j.amjmed.2019.04.045
35. Jakob J, Stalder O, Syrogiannouli L, Pletcher MJ, Vittinghoff E, Ning H, Tal K, Rana JS, Sidney S, Lloyd-Jones DM, et al. Association between marijuana use and electrocardiographic abnormalities by middle age: the coronary artery risk development in young adults (CARDIA) study. *Addiction (Abingdon, England)*. 2021;116:583–595. doi: 10.1111/add.15188
36. Jakob J, von Wyl R, Stalder O, Pletcher MJ, Vittinghoff E, Tal K, Rana JS, Sidney S, Reis JP, Auer R. Cumulative marijuana use and carotid intima-media thickness at middle age: the CARDIA study. *Am J Med*. 2021;134:777–787.e9. doi: 10.1016/j.amjmed.2020.11.026
37. Jakob J, Schwerdtel F, Sidney S, Rodondi N, Pletcher MJ, Reis JP, Muniyappa R, Clair C, Tal K, Bancks MP, et al. Associations of cannabis use and body mass index–The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Eur J Intern Med*. 2024;129:41–47. doi: 10.1016/j.ejim.2024.07.007
38. 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. doi: 10.1136/bmjopen-2011-000494
39. 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;58:2736–2744. doi: 10.1007/s00125-015-3740-3
40. Vallée A. Association between cannabis use and blood pressure levels according to comorbidities and socioeconomic status. OriginalPaper. *Sci Rep*. 2023;13:1–13. doi: 10.1038/s41598-022-22841-6
41. Weresa J, Pędzińska-Betiuk A, Mińczuk K, Malinowska B, Schlicker E. Why do marijuana and synthetic cannabimimetics induce acute myocardial infarction in healthy young people? *Cells*. 2022;11:1142. doi: 10.3390/cells11071142
42. Singla S, Sachdeva R, Mehta JL. Cannabinoids and atherosclerotic coronary heart disease. *Clin Cardiol*. 2012;35:329–335. doi: 10.1002/clc.21962
43. Mohammadi L, Navabzadeh M, Jiménez-Téllez N, Han DD, Reagan E, Naughton J, Zhou LY, Almeida R, Castaneda LM, Abdelaal SA, et al. Association of endothelial dysfunction with chronic marijuana smoking and THC-Edible use. *JAMA Cardiol*. 2025. doi: 10.1001/jamacardio.2025.1399
44. Moir D, Rickert WS, Levasseur G, Larose Y, Maertens R, White P, Desjardins S. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol*. 2008;21:494–502. doi: 10.1021/tx700275p
45. Page RL, 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
46. Rajesh M, Mukhopadhyay P, Bátkai S, Hasko G, Liaudet L, Huffman JW, Csiszar A, Ungvari Z, Mackie K, Chatterjee S, et al. CB2-receptor stimulation attenuates TNF-α-induced human endothelial cell activation, transendothelial migration of monocytes, and monocyte-endothelial adhesion. *Am J Physiol Heart Circ Physiol*. 2007;293:H2210–H2218. doi: 10.1152/ajpheart.00688.2007
47. Zhao Y, Yuan Z, Liu Y, Xue J, Tian Y, Liu W, Zhang W, Shen Y, Xu W, Liang X, et al. Activation of cannabinoid CB2 receptor ameliorates atherosclerosis associated with suppression of adhesion molecules. *J Cardiovasc Pharmacol*. 2010;55:292–298. doi: 10.1097/FJC.0b013e3181d2644d