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Cumulative Marijuana Use and Carotid Intima-Media Thickness at Middle Age:

The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Running Head: *Marijuana and Carotid Intima-Media Thickness*

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Abstract

Background: Long-term cardiovascular health effects of marijuana are understudied. Future cardiovascular disease is often indicated by subclinical atherosclerosis, for which carotid intima-media thickness is an established parameter.

Methods: Data from the CARDIA Study, a cohort of 5,115 Black and white women and men at Year 20 visit. We studied the association between carotid intima-media thickness in mid-life and lifetime exposure to marijuana (1 marijuana year = 365 days-of-use) and tobacco smoking (1 packyear = 20 cigarettes/day for 365 days). We measured carotid intima-media thickness by ultrasound and defined high carotid intima-media thickness at the threshold of the 75th percentile

of all examined participants. We fit logistic regression models stratified by tobacco smoking exposure, adjusting for demographics, cardiovascular risk factors, and other drug exposures.

Results: Data was complete for 3,257 participants; 2,722 (84%) reported ever marijuana use; 374 (11%) were current users; 1,539 (47%) reported ever tobacco smoking; 610 (19%) were current smokers. Multivariable adjusted models showed no association between cumulative marijuana exposure and high carotid intima-media thickness in never or ever tobacco smokers, odds ratio (OR) 0.87 (95% CI: 0.63 to 1.21) at 1 marijuana-year among never smokers and OR 1.11 (95% CI: 0.85 to 1.45) among ever tobacco smokers. Cumulative exposure to tobacco was strongly associated with high carotid intima-media thickness, OR 1.88 (95%CI: 1.20 to 2.94) for 20 pack-years of exposure.

Conclusions: This study adds to the growing body of evidence that there might be no association between the average population level of marijuana use and subclinical atherosclerosis.

Significance – 69 words

- In a middle-aged population, lifetime cumulative marijuana use was not associated with Carotid Intima-Media Thickness, a marker of subclinical atherosclerosis.
- This adds to the growing body of evidence that a moderate level of marijuana use and cardiovascular disease and markers of subclinical atherosclerosis might be unassociated.

- Using marijuana extensively might cause as much harm as tobacco cigarettes because exposition to combustion constituents would then be similar.

Background

Marijuana, made of dried cannabis flowers, is used by between 7.5% and 9.4% of the United States population, and by 6% of the population aged older than 55 years.[1-3] Increasing legalization for recreational and medical use has been accompanied by concern about its possible health effects.[4] Cardiovascular health is a special concern, since case reports from the early 2010s suggested that marijuana may trigger heart attacks in healthy adults.[5-7] Smoking tobacco is a major cause of premature death worldwide, including cardiovascular disease[8] and tobacco and marijuana smoke share many constituents.[9] The recent statement from the American Heart Association on medical marijuana, recreational cannabis, and cardiovascular health highlighted the lack of rigorously performed studies. Authors stated that carefully designed prospective short- and long-term studies regarding cannabis use and cardiovascular safety are needed. [4,10,11]

No association between incident cardiovascular disease (stroke or transient ischemic attacks, coronary heart disease, or cardiovascular mortality) and marijuana use was identified in large observational studies (5,000 to 65,000 participants) in the USA, Sweden and Belgium published from the late 90's through the late 2010's.[4,10,12-15] Cumulative marijuana use was not associated with coronary and abdominal calcium score, a marker of subclinical atherosclerosis in earlier analyses of data from the Coronary Artery Disease Risk of the Young (CARDIA) study, a longitudinal study of over 5,000 participants with up to 30-year follow-up in the USA.[16]

Since CARDIA follows a relatively young cohort into early middle age, participants may be too young to exhibit signs of cardiovascular disease. An increase in future cardiovascular risk could be captured by measuring carotid intima-media thickness with vascular ultrasound, a widely used subclinical atherosclerosis measure.[17-21] Carotid intima-media thickness is associated with traditional cardiovascular risk factors like blood lipids, hypertension, and tobacco smoking.[22-25] Carotid intima-media thickness predicts atrial fibrillation, myocardial infarction, and cerebrovascular events.[26-29] We found no studies that evaluated the association between marijuana use and carotid intima-media thickness.

We thus set out to test the association between cumulative marijuana or tobacco exposure and carotid intima-media thickness in multivariable adjusted logistic regression models stratified by tobacco smoking exposure.

Methods

Design and participants. We used data from the CARDIA study, a cohort of 5,115 self-identified Black and white women and men, aged 18 to 30 years at baseline, from four study sites in the USA (Birmingham, AL, Chicago, IL, Minneapolis, MI, Oakland, CA) followed over 30 years. The study strove for equal distribution of race, sex, education, and age at each site. We used data from seven visits, up to Year 20 (2005-2006) because carotid intima-media thickness measures were available. Each attending participant received non-monetary incentives and monetary reimbursement to cover travel expenses for the exam. All participants gave informed consent before entering the study and at each follow-up exam. The study was approved by institutional review boards for each site.

Measures: Marijuana and tobacco exposure. Marijuana use variables were available for all visits up through year 20 (baseline, and follow-up Years 2, 5, 7, 10, 15 and 20). Current marijuana use was assessed with the following survey question: "During the last 30 days, on how many days did you use marijuana?" We defined daily use as 30 days of use in the last 30 days. Direct self-reported lifetime exposure was assessed with the question, "About how many times in your lifetime have you used marijuana?" We used current use and baseline lifetime use to compute marijuana-years as in previous analyses; 1 year of exposure was equivalent to 365 days of marijuana use.[30,31] We assumed current use at each visit (the number of days of using marijuana during the month before each visit) reflected the average number of days of use in the months before and after each visit. We estimated cumulative lifetime use by adding the total number of days using marijuana during follow-up. We adjusted our estimate upwards whenever participants self-reported higher lifetime use than we computed for each visit (eMethods, Supporting information). Marijuana use was illegal in these jurisdictions at the time.

Cigarette smoking was evaluated at each in-person CARDIA exam and at yearly phone follow-up between CARDIA exams.[32] We used these data to estimate cumulative lifetime exposure to cigarettes in pack-years: one pack-year of exposure was equivalent to 7,300 cigarettes (1 year×365 days/y×1 pack/d×20 cigarettes/pack).[31]

Outcome measures: carotid intima-media thickness. High-resolution B-mode ultrasonography (Logiq 700; General Electric Medical Systems, Waukesha, Wis) was used to capture images of the common carotid and internal carotid arteries, and of the carotid bulbs at the Year 20 exam. Four images (1 longitudinal image of the common carotid and 3 longitudinal images of the internal carotid / carotid bulb) were acquired each on the left and right sides. Maximal carotid intima-media thickness was measured at a central reading center by readers blinded to all clinical information, and defined as the mean measure of the near and far wall on both the left and right sides. We averaged all measures of common carotid, internal carotid, and carotid bulb separately, and computed the composite maximal carotid intima-media thickness as the mean of common carotid, internal carotid, and carotid bulb. We derived a normalized composite maximal carotid intima-media thickness measure by standardizing the averages of common carotid, internal carotid, and carotid bulb each (by subtracting the mean and dividing by the SD) and averaging these standardized measures.[33]

Measures: Covariables. We estimated lifetime alcohol consumption in 'drink-years'. We defined 1 drink-year as the amount of alcohol consumed by a person in 1 year of drinking one drink/day[32]. We defined acute heavy exposure to alcohol (bingeing) as four (women) or five (men) or more drinks consumed on one occasion, and we estimated total lifetime bingeing episodes. We estimated total exposure to passive smoking (eMethods, Supporting information).[32] The highest educational grade attained at Year 20 for each participant was the measure of education. We measured physical activity with the CARDIA physical activity history questionnaire.[34]

Our cardiovascular risk factor measurements included blood pressure, blood cholesterol [total, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol and triglycerides], fasting glucose and body mass index (BMI), which were collected at each CARDIA exam.[32]

Statistical Analyses. We used descriptive statistics to compare participants with different levels of marijuana and tobacco exposure at Year 20. We described unadjusted associations between lifetime marijuana use or tobacco smoking and high carotid intima-media thickness. We defined high carotid intima-media thickness as a score over the 75th percentile.[35] Because tobacco and marijuana smoking are frequently co-occurring behaviors, we stratified all results and analyses by history of tobacco smoking.[16,32]

We fit unadjusted and multivariable adjusted models, controlling for variables to achieve balanced sampling in CARDIA (age, race, sex, study site and years of education) and for variables potentially associated with marijuana use or tobacco smoking and subclinical atherosclerosis (passive smoking, alcohol, cocaine, amphetamines and heroin exposures, cardiovascular risk factors, physical activity, BMI, and diabetes). We used restricted cubic splines with three knots at the quartiles of their distributions to flexibly model marijuana-years and pack-years of exposure. To account for deaths and potential informative censoring, we used inverse probability of attrition weights (IPAWs, eMethods, Supporting information).[36,37] We used Last Observation Carried Forward and Backward (LOCFB) imputation for missing covariables, because we have information on co-variables in previous and following visit in most of the missing cases. We tested whether sex and race interacted with the main predictors. We tested sensitivity of the results to alternate modelling techniques: (1) a set of multivariable regressions that enabled us to model measures of carotid intima-media thickness as continuous measures, and (2) a multivariable adjusted model that included an interaction term between history of exposure to tobacco smoking and cumulative exposure to marijuana.

Tests of statistical significance were two-tailed; alpha level was 0.05. Analyses were conducted with Stata version 14.2 (StataCorp LP, College Station, TX, USA).

Results:

At Year 20, 3,549 participants were examined; 3,257 (92%) had data on carotid intima-media thickness; 2,722 (84%) reported ever marijuana use; 374 (11%) were current users; 1,539 (47%) reported ever tobacco smoking, 610 (19%) were current smokers. Ever marijuana users had a mean cumulative exposure of 1.6 marijuana-years. Ever tobacco smokers had a mean cumulative exposure of 10 pack-years. Among those who never smoked tobacco, 73% (n=1,250) were ever marijuana users; among ever tobacco smokers, 96% (n=1472) were ever marijuana users (Table 1).

The distribution of high normalized composite carotid intima-media thickness, composite carotid intima-media thickness, and common carotid, carotid bulb, and internal carotid intima-media thickness varied between never and ever tobacco smokers (Table 2). Among those who never smoked tobacco, cumulative marijuana-years were not associated with any carotid intima-media thickness measure in unadjusted or multivariable adjusted models (Table 3, Figure 1 Panel A). Among ever tobacco smokers, cumulative marijuana-years was associated with high common carotid intima-media thickness measures in unadjusted models, but not after multivariable adjustment (Table 3 Figure 1 Panel B). Among ever tobacco smokers, cumulative pack-years were significantly associated with almost all carotid intima-media thickness measures in unadjusted and multivariable adjusted models: multivariable unadjusted OR of 10 pack-years and

high normalized composite carotid intima-media thickness was 1.57 (95%CI: 1.08 to 2.27, Table 3, Figure 1 Panel C). The strength of association increased with higher cumulative exposures to tobacco.

Results were comparable in analyses modelling carotid intima-media thickness as continuous measure (Appendix Table 1 and 2).

Sensitivity analyses showed no evidence of interactions by race or sex (all p-values>0.1, Appendix Table 3). Results were similar when we included an interaction term between history of exposure to tobacco smoking and cumulative exposure to marijuana instead of stratifying the results (results not shown).

Discussion

In this community-based cohort of young adults followed for 20 years, most participants had been exposed to marijuana during their lifetime, but few had more than 365 days of cumulative exposure in total (one marijuana-year) and few used it daily. Almost half of participants reported past tobacco smoking; mean lifetime exposure was 10 pack-years. Cumulative marijuana use in never tobacco smokers was not associated with any carotid intima-media thickness measure. Among ever tobacco users, after multivariate adjustment, cumulative marijuana use was not associated with measures of carotid intima-media thickness, except for common carotid intima-media thickness when modelled as a continuous outcome. Pack-years of tobacco smoking were associated with

markedly elevated carotid intima-media thickness measures and the measures of association increased with higher exposures, suggesting a dose-dependent association. Having smoked 10 pack-years of tobacco cigarettes was associated with almost 60% higher odds of a high normalized composite CIMT.

The recent statement from the American Heart Association on medical marijuana, recreational cannabis, and cardiovascular health highlighted the lack of rigorously performed studies.[4] Previous analyses of CARDIA participants showed no association between marijuana use and cardiovascular events or mortality overall.[12,14] But the study population was only around 50 years old, so participants had not yet reached the age at which cardiovascular disease usually occurs. Therefore, we used markers of subclinical atherosclerosis as indications of increased future cardiovascular risk. We identified no previous studies on marijuana and carotid intima-media thickness and only two studies that tested the association between abdominal artery and coronary artery calcium and cumulative marijuana use.[16,38] Our results align with the results of both these studies, especially the strong expected association between cumulative tobacco exposures and markers of subclinical atherosclerosis. These studies did not report an association between cumulative marijuana use and subclinical atherosclerosis either.

The single association between marijuana-years in ever tobacco smokers and CC IMT modelled as a continuous variable might be explained by residual confounding from tobacco smoking, since tobacco smoking and marijuana use are associated.[9,16] It may also be a chance finding because we ran multiple analyses that used varying definitions of CIMT. In the CARDIA cohort, cumulative marijuana exposure was low among users—much lower than cumulative tobacco exposure among ever users. One marijuana-year is equivalent to smoking one or more joints per day for a year, while one pack-year of

tobacco is equivalent to smoking 20 cigarettes each day for a year. Our null findings among never smokers might thus be explained by the low intensity of marijuana use in our cohort. It is possible that smoking many joints of marijuana every day for many years could cause as much harm as smoking tobacco cigarettes because users would be exposed to the combustion constituents in marijuana smoke at a level close to tobacco smokers. Future studies should test if such high-intensity marijuana use is associated with markers of subclinical atherosclerosis and cardiovascular disease.

Besides the risks associated with repeated use of an inhaled combustible agent, acute exposure to marijuana might also have negative effects on the heart. In case reports, scientists suspected marijuana to increase heart rate and suggested it may trigger arrhythmias, possibly leading to myocardial infarction.[7,39] The acute effect of marijuana might explain one study's finding of a surge in myocardial infarctions just after marijuana use.[7] The absence of evidence of an increase in subclinical atherosclerosis in our study and the absence of significant association in previous analyses in CARDIA [14,40] suggest that even if marijuana can trigger an acute myocardial infarction, it does not seem to increase the atherosclerotic process that leads to myocardial infarction when used at intensities typical in the general population.

The extensive data set of covariables, including a wide range of potential confounders and detailed data on tobacco smoking and other drug exposures strengthened our study. We used advanced modelling to adjust for multiple CVRFs and IPCW to address potential informative censoring. The proportion of participants followed up to the Year 20 exam was high (69%). Ultrasound measurement was standardized, assessed by professionals blinded to clinical

outcomes; they observed various segments of the carotid artery on both sides and of the near and far wall into account, with multiple measurements, giving us precise results.

Our study has some limitations. We found that cumulative marijuana use was not associated with carotid intima-media thickness among never tobacco smokers but found that there was an association with common carotid intima-media thickness modelled as a continuous outcome in ever tobacco smokers, even after multivariable adjustment that accounted for past cumulative and current tobacco smoking and for passive smoking. We cannot rule out residual confounding by tobacco smoking.[9,16,30] It is possible that tobacco smokers who use marijuana are more likely to smoke a mix of tobacco and marijuana ('mulling') and not report this as tobacco smoking.[41] Unfortunately, CARDIA did not ask participants if they were 'mulling', but future studies should do so. We had to rely on participant self-reports and could not validate the assessment of exposure to marijuana. Since marijuana use was illegal throughout the study, we cannot exclude social desirability bias; CARDIA participants may have been less likely to report their marijuana use. We believe this possibility was mitigated by the trust participants placed in study personnel, as evidenced by the fact that 84% percent of participants reported past marijuana use. Information on intensity and frequency of marijuana use in the month prior to a visit was collected every 2-5 years. We extrapolated exposure of the past month to the whole period between visits, and our estimates are thus imprecise. Though the cohort we studied was racially diverse and spanned 20 years, our analysis was limited mainly to a middle-aged population of self-reported Black and white participants in the US—an age when cardiovascular disease is uncommon. Our results apply mainly to occasional, recreational users of marijuana whose exposure is low, overall. Larger studies with longer follow-up and higher intensity marijuana use are needed to confirm the absence or presence of association between marijuana and subclinical atherosclerosis and cardiovascular disease.

Conclusion:

Cumulative marijuana use was not associated with normalized composite or mean carotid intima-media thickness in a middle-aged population of self-reported Black and white participants in the US, but our study confirms the strong association between tobacco smoking and increased carotid intima-media thickness. Since most of the study population occasionally used marijuana, in line with the typical frequency of use in the general population, future studies are needed in populations who engage in high-intensity marijuana use. Though the broader public health implications of high prevalence of tobacco use among marijuana users is alarming, this study adds to the growing body of evidence that there is no association between a moderate level of marijuana use and cardiovascular disease and markers of subclinical atherosclerosis.

Conflicts of interest: None.

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Table 1: Characteristics of 3,257 CARDIA participants with CIMT measurement at Year 20 exam, overall and by never/ever tobacco smoking.

	Never Tobacco Smoker N= 1,718 (53%)			Ever Tobacco Smoker N= 1,539 (47%)			p-value[i]
	No marijuana use	>0 to <1 marijuana-years[h]	≥1 marijuana-years[h]	No marijuana use	>0 to <1 marijuana-years[h]	≥1 marijuana-years[h]	
N	468	1,043	207	67	853	619	
Demographics							<0.001
Age, mean (Q1; Q3), y	45 (41; 48)	45 (42; 48)	46 (43; 48)	45 (42; 48)	45 (43; 49)	46 (43; 49)	
Race/sex, N (col %)[a]							
- Black women	175 (37)	284 (27)	30 (14)	28 (42)	266 (31)	131 (21)	<0.001
- Black men	72 (15)	146 (14)	58 (28)	14 (21)	112 (13)	176 (28)	

- White women	116 (25)	333 (32)	41 (20)	14 (21)	310 (36)	122 (20)	
- White men	105 (22)	280 (27)	78 (38)	11 (16)	165 (19)	188 (30)	
Education, median (Q1; Q3), years	16 (14; 18)	17 (15; 19)	16 (14; 18)	15 (12; 18)	16 (14; 17)	15 (13; 16)	<0.001
Study center, N (col %)							
- Birmingham, AL	204 (44)	203 (20)	26 (12)	37 (55)	198 (23)	102 (17)	<0.001
- Chicago, IL	131 (28)	244 (23)	34 (17)	12 (18)	218 (25)	146 (24)	
- Minneapolis, MI	74 (16)	197 (19)	51 (25)	8 (12)	219 (26)	188 (30)	
- Oakland, CA	59 (13)	399 (38)	96 (47)	10 (15)	218 (26)	183 (29)	
Substance use exposure							
Marijuana use category, N (col %)[b]							
- Never used marijuana	468 (100)	-	-	67 (100)	-	-	<0.001
- Past marijuana use	-	1,024 (98)	130 (63)	-	833 (98)	361 (58)	
- Current marijuana use	-	19 (2)	77 (37)	-	20 (2)	258 (42)	
Tobacco smoking, N (col %)							
- Never smoker	468 (100)	1,043 (100)	207 (100)	-	-	-	<0.001
- Former smoker	-	-	-	49 (73)	567 (66)	313 (51)	
- Current smoker	-	-	-	18 (27)	286 (34)	306 (49)	
Lifetime tobacco exposure among ever smokers, median (Q1; Q3), pack-years[c]	-	-	-	6 (0; 8)	9 (1; 13)	12 (2; 19)	<0.001

Alcohol use							
- Cumulative alcohol use among ever drinkers, median (Q1, Q3), drink-years[d]	6 (1; 8)	10 (2; 14)	19 (6; 24)	10 (2; 12)	15 (4; 19)	28 (9; 38)	<0.001
Binge drinking days, cumulative use, N (col %)[e]							
- never reported bingeing							
- ≤ 250 days	391 (83)	639 (61)	58 (28)	43 (64)	358 (42)	130 (21)	<0.001
- > 250 days	59 (13)	286 (27)	75 (36)	18 (27)	300 (35)	198 (32)	
	18 (4)	118 (11)	74 (36)	6 (9)	195 (23)	291 (47)	
Physical activity							<0.001
Physical activity score, median (Q1; Q3)[f]	270 (88; 381)	355 (129; 517)	419 (187; 577)	226 (81; 313)	319 (121; 469)	363 (157; 523)	
Anthropomorphic variable	31 (7)	29 (8)	30 (7)	29 (7)	29 (7)	29 (6)	<0.001
BMI, mean (SD)[g]							
Cardiovascular risk factors							
Systolic blood pressure, mean (SD), mmHg	117 (16)	115 (14)	119 (13)	118 (16)	117 (17)	119 (15)	<0.001
Diastolic blood pressure, mean (SD), mmHg	74 (12)	72 (11)	74 (10)	76 (12)	73 (12)	75 (12)	<0.001
LDL-Cholesterol, mean (SD), mg/dl	112 (33)	110 (30)	115 (34)	109 (34)	109 (32)	109 (33)	0.3
HDL-Cholesterol, mean (SD), mg/dl	53 (15)	55 (16)	51 (16)	52 (15)	56 (18)	53 (18)	<0.001
Triglycerides, mean (Q1; Q3), mg/dl	102 (59; 123)	102 (59; 125)	118 (66; 139)	113 (66; 151)	108 (63; 126)	121 (69; 143)	<0.001
Diabetes mellitus, N (%)	33 (7)	82 (8)	17 (8)	4 (6)	72 (8)	39 (3)	0.7

Abbreviations: BMI, body mass index (weight in kilograms divided by height in meters squared); CARDIA, Coronary Artery Risk Development in Young Adults study; dy, drink-years; LDL, low density lipoprotein; HDL, high-density lipoprotein; N, number of participants; py, pack-years; Q1, Q3: 1st and 3rd quartile (percentile 25 and 75); SD, standard deviation; py, pack-years

SI conversion factors: To convert LDL and HDL to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

[a] The CARDIA study sampled roughly equal numbers of self-identified white men, white women, Black men, and Black women.[1]

[b] Based on the answer to these questions: "**Have you ever used marijuana?**" and "**During the last 30 days, on how many days did you use marijuana?"**

[c] Cumulative lifetime tobacco smoking in pack-years: 1 pack-year of exposure equivalent to 7300 cigarettes (1 year x 365 days/y x 1 pack/d x 20 cigarettes/pack).[2]

[d] Cumulative alcohol use in terms of drink-years: 1 drink-year is the total amount of ethanol consumed by a person who had 1 alcoholic drink per day for 1 year (1 drink-year = 17.24 ml of ethanol/drink x 1 drink/d x 365 days/y = 6292.6 ml of ethanol).

[e] Binge drinking days defined as 5 or more drinks per day. If bingeing were constant over 25 years in one individual, 250 binge drinking days would correspond to 10 days of bingeing per year over 25 years.

[f] Physical activity measured with the CARDIA Physical Activity History questionnaire, which asks how much time per week was spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months.[3]

[g] Calculated as weight in kilograms divided by height in meters squared.

[h] Cumulative lifetime marijuana use in marijuana-years: 1 marijuana-year of exposure is equivalent to 365 days of marijuana use (1 year x 365 days per year).[2]

[i] P-values are from Kruskal-Wallis rank test for age, years of education, pack-years, number of cigarettes per day, number of marijuana-days per month, drink-years, physical activity, triglycerides, and BMI, and from a $\chi 2$ test for race and sex, study site, current smoking status, CES-D, cumulative binge drinking categories, illicit drug use categories, and current alcohol use categories.

Table 2: High CIMT by categories of cumulative marijuana use, stratified by ever smoking exposure

IMT measure	Never Tobacco Smoker N = 1718 (53%)			Ever Tobacco Smoker N= 1539 (47%)			
	No marijuana use	>0 to <1 marijuana-years	≥1 marijuana-years	No marijuana use	>0 to <1 marijuana-years	≥1 marijuana-years	P-value[f]
Total N	468	1,043	207	67	853	619	
Normalized composite CIMT at ≥75th percentile, N, (%)[a]	127 (27)	225 (22)	54 (26)	18 (27)	207 (24)	183 (30)	0.010
Composite CIMT at ≥75th percentile, N, (%)[b]	132 (28)	217 (21)	53 (26)	17 (25)	219 (26)	176 (28)	0.006
Mean of CC IMT at ≥75th percentile, N, (%)[c]	119 (25)	226 (22)	52 (25)	20 (30)	195 (23)	201 (32)	<0.001
Mean of CB IMT at ≥75th percentile, N, (%)[d]	131 (28)	222 (21)	54 (26)	17 (25)	205 (24)	166 (27)	0.06
Mean of IC IMT at ≥75th percentile, N, (%)[e]	116 (25)	226 (22)	55 (27)	8 (12)	203 (24)	161 (26)	0.08

Abbreviations: CIMT, carotid intima-media thickness; 1 marijuana-year equivalent to 365 days of marijuana use; CC, common carotid artery; IC, internal carotid artery; CB, carotid bulb.

Distribution of all CARDIA participants examined (≥75th percentile) to define high standardized CC at ≥75th percentile. [4]

[a] Normalized composite measure of the maximal CIMT. First, we built the arithmetic average of all IC and bulb measurements, and the arithmetic average of all CC measures. Second, we standardized these averages separately by subtracting the mean and dividing by the SD. Finally, we averaged these standardized measures.[4]

[b] Mean of averages of CC; IC, and IC CIMT

[c] Average of the maximal CC IMT records (1-4 measurements)

[d] Average of the maximal CB IMT records (1-8 measurements)

[e] Average of the maximal IC IMT records (1-8 measurements)

[f] P-values are from a $\chi 2$ test.

Table 3: Association between cumulative marijuana use or cumulative tobacco smoking and high CIMT, stratified by ever smoking exposure

| | | Never tobacco smoker N= 1,718 (53%) | | | | Ever tobacco smoker N= 1,539 (47%) | | | |
| | | Unadjusted | | Multivariable adjusted[f] | | Unadjusted | | Multivariable adjusted[f] | |
Category of CIMT	Cumulative exposure to marijuana	Odds Ratio (CI)	P-value[g]	Odds Ratio (CI)	P-value[g]	Odds Ratio (CI)	P-value[g]	Odds Ratio (CI)	P-value[g]
Normalized composite CIMT at ≥ 75th percentile[a]	At 0.5 marijuana-years	1.06 (0.93 to 1.21)	0.68	0.93 (0.77 to 1.12)	0.46	1.09 (0.97 to 1.22)	0.10	1.06 (0.91 to 1.23)	0.38
	At 1 marijuana-year	1.11 (0.88 to 1.40)		0.87 (0.63 to 1.21)		1.16 (0.95 to 1.42)		1.11 (0.85 to 1.45)	
	At 5 marijuana-years	1.18 (0.79 to 1.77)		0.70 (0.38 to 1.29)		1.41 (1.00 to 1.99)		1.31 (0.81 to 2.10)	
	At 10 marijuana-years	1.08 (0.61 to 1.91)		0.63 (0.30 to 1.33)		1.48 (1.02 to 2.15)		1.45 (0.86 to 2.42)	
Composite CIMT at ≥ 75th percentile[b]	At 0.5 marijuana-years	1.06 (0.92 to 1.20)	0.72	0.94 (0.78 to 1.12)	0.36	1.09 (0.98 to 1.22)	0.24	1.02 (0.87 to 1.19)	0.97
	At 1 marijuana-year	1.10 (0.87 to 1.39)		0.89 (0.64 to 1.22)		1.17 (0.96 to 1.44)		1.03 (0.79 to 1.36)	
	At 5 marijuana-years	1.13 (0.75 to 1.71)		0.69 (0.38 to 1.27)		1.35 (0.95 to 1.92)		1.06 (0.64 to 1.75)	
	At 10 marijuana-years	1.00 (0.56 to 1.80)		0.56 (0.26 to 1.24)		1.30 (0.89 to 1.90)		1.04 (0.62 to 1.75)	
Mean of CC IMT at ≥ 75th percentile[c]	At 0.5 marijuana-years	1.13 (0.99 to 1.29)	0.16	1.00 (0.82 to 1.21)	0.21	1.15 (1.03 to 1.29)	0.002	1.10 (0.95 to 1.27)	0.06
	At 1 marijuana-year	1.24 (0.98 to 1.57)		0.98 (0.70 to 1.38)		1.29 (1.05 to 1.58)		1.20 (0.92 to 1.55)	
	At 5 marijuana-years	1.26 (0.84 to 1.89)		0.74 (0.39 to 1.38)		1.78 (1.25 to 2.55)		1.56 (0.99 to 2.45)	

	At 10 marijuana-years	0.88 (0.45 to 1.69)		0.46 (0.19 to 1.12)		1.95 (1.34 to 2.85)		1.79 (1.10 to 2.90)	
Mean of CB IMT at ≥75th percentile[d]	At 0.5 marijuana-years	1.06 (0.94 to 1.21)	0.53	0.94 (0.79 to 1.12)	0.71	1.09 (0.99 to 1.22)	0.23	1.02 (0.87 to 1.19)	0.97
	At 1 marijuana-year	1.12 (0.89 to 1.40)		0.90 (0.66 to 1.23)		1.17 (0.95 to 1.43)		1.04 (0.79 to 1.37)	
	At 5 marijuana-years	1.26 (0.85 to 1.86)		0.79 (0.45 to 1.40)		1.36 (0.95 to 1.94)		1.07 (0.64 to 1.78)	
	At 10 marijuana-years	1.25 (0.72 to 2.18)		0.77 (0.40 to 1.50)		1.34 (0.91 to 1.98)		1.06 (0.62 to 1.81)	
Mean of IC IMT at ≥75th percentile[e]	At 0.5 marijuana-years	1.10 (0.96 to 1.25)	0.17	0.99 (0.84 to 1.17)	0.10	1.07 (0.95 to 1.20)	0.54	0.95 (0.82 to 1.11)	0.61
	At 1 marijuana-year	1.17 (0.93 to 1.48)		0.97 (0.72 to 1.32)		1.12 (0.91 to 1.39)		0.92 (0.70 to 1.20)	
	At 5 marijuana-years	1.08 (0.71 to 1.65)		0.71 (0.40 to 1.26)		1.20 (0.83 to 1.72)		0.81 (0.50 to 1.31)	
	At 10 marijuana-years	0.70 (0.36 to 1.37)		0.42 (0.19 to 0.97)		1.08 (0.72 to 1.60)		0.77 (0.46 to 1.29)	
Category of CIMT	**Cumulative exposure to tobacco**								
Normalized composite CIMT at ≥75th percentile[a]	At 5 pack-years	-	-	-	-	1.40 (1.17 to 1.69)	<0.001	1.29 (1.03 to 1.60)	0.016
	At 10 pack-years					1.85 (1.36 to 2.51)		1.57 (1.08 to 2.27)	
	At 20 pack-years					2.43 (1.71 to 3.45)		1.88 (1.20 to 2.94)	
	At 40 pack-years					2.93 (1.83 to 4.70)		2.07 (1.11 to 3.85)	
Composite CIMT at ≥75th percentile[b]	At 5 pack-years	-	-	-	-	1.46 (1.22 to 1.74)	<0.001	1.33 (1.08 to 1.65)	0.010
	At 10 pack-years					1.95 (1.44 to 2.64)		1.66 (1.16 to 2.38)	
	At 20 pack-years					2.50 (1.76 to 3.56)		1.97 (1.27 to 3.05)	
	At 40 pack-years					2.68 (1.67 to 4.32)		1.94 (1.07 to 3.52)	

Mean of CC IMT at ≥75th percentile[c]	At 5 pack-years	-	-	-	-	1.17 (0.97 to 1.40)	0.001	1.05 (0.85 to 1.30)	0.36
	At 10 pack-years					1.33 (0.98 to 1.81)		1.10 (0.77 to 2.59)	
	At 20 pack-years					1.63 (1.16 to 2.30)		1.23 (0.79 to 1.90)	
	At 40 pack-years					2.24 (1.40 to 3.57)		1.52 (0.86 to 2.68)	
Mean of CB IMT at ≥75th percentile[d]	At 5 pack-years	-	-	-	-	1.31 (1.09 to 1.58)	<0.001	1.20 (0.98 to 1.49)	0.15
	At 10 pack-years					1.63 (1.20 to 2.22)		1.39 (0.97 to 1.99)	
	At 20 pack-years					2.02 (1.41 to 2.89)		1.55 (0.99 to 2.41)	
	At 40 pack-years					2.32 (1.43 to 3.77)		1.53 (0.85 to 2.77)	
Mean of IC IMT at ≥75th percentile[e]	At 5 pack-years	-	-	-	-	1.35 (1.12 to 1.63)	<0.001	1.37 (1.10 to 1.70)	0.004
	At 10 pack-years					1.70 (1.24 to 2.33)		1.75 (1.21 to 2.54)	
	At 20 pack-years					2.07 (1.44 to 2.97)		2.18 (1.37 to 3.46)	
	At 40 pack-years					2.17 (1.36 to 3.47)		2.37 (1.28 to 4.39)	

Abbreviations: CIMT, carotid intima-media thickness; 1 marijuana-year equivalent to 365 days of marijuana use; CC, common carotid artery; IC, internal carotid artery; CB, carotid bulb

Distribution of all CARDIA participants examined (≥75th percentile) to define high standardized CC at ≥75th percentile. [4]

[a] Normalized composite measure of the maximal CIMT. First, we built the arithmetic average of all IC and bulb measurements, and the arithmetic average of all CC measures. Second, we standardized these averages separately by subtracting the mean and dividing by the SD. Finally, we averaged these standardized measures.[4]

[b] Mean of averages of CC; IC, and IC CIMT

[c] Average of the maximal CC IMT records (1-4 measurements)

[d] Average of the maximal CB IMT records (1-8 measurements)

[e] Average of the maximal IC IMT records (1-8 measurements)

[f] Multivariable adjusted: sex, race, age, education years, center, current and cumulative alcohol use, passive smoking exposure, total physical activity score, BMI, cardiovascular risk factors (systolic and diastolic blood pressure, LDL, HDL, TRG), diabetes, illicit drug use. To account for potential informative censoring during follow-up, we used inverse probability of censoring weights in the multivariable adjusted model.

[g] P-values came from a Wald test.

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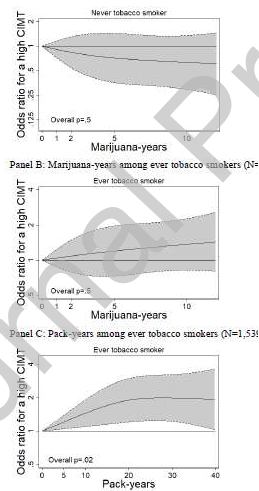
Figure 1: Odds Ratio of high CIMT by cumulative marijuana use (marijuana-years) or cumulative

tobacco smoking (pack-years), multivariable adjusted Panel A: Marijuana-years among never tobacco

smokers (N=1,718)

Abbreviations: CIMT, carotid intima-media thickness. Figures showing marijuana-years are stratified by tobacco smoking exposure because there was a positive interaction between never- and ever- tobacco users when we examined the association of cumulative marijuana use and CIMT (p=0.02). P-values are from a χ2 test. Normalized composite measure of the maximal CIMT: First, we built the arithmetic average of all IC and bulb measurements, and the arithmetic average of all CC measures. Second, we standardized these averages separately by subtracting the mean and dividing by the SD. Finally, we averaged these standardized measures.[1] Distribution of all CARDIA participants examined, >75th percentile to define high IMT. [1] Multivariable adjusted: sex, race, age, education years, center, current and cumulative alcohol use, passive smoking exposure, total physical activity score, BMI, cardiovascular risk factors (systolic and diastolic blood pressure, LDL, HDL, TRG), diabetes, illicit drug use. To account for potential informative censoring during follow-up, we used inverse probability of censoring weights in the multivariable adjustedmodel.

References:

1. Reis, J.P., et al., *Coffee, decaffeinated coffee, caffeine, and tea consumption in young adulthood and atherosclerosis later in life: the CARDIA study.* Arterioscler Thromb Vasc Biol, 2010. **30**(10): p. 2059-66.