



# Cumulative Marijuana Use and Carotid Intima-Media Thickness at Middle Age: The CARDIA Study

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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:** Using the data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort of 5115 Black and white women and men at Year 20 visit, we studied the association between carotid intima-media thickness in midlife and lifetime exposure to marijuana (1 marijuana year = 365 days of use) and tobacco smoking (1 pack-year = 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 3257 participants; 2722 (84%) reported ever marijuana use; 374 (11%) were current users; 1539 (47%) reported ever tobacco smoking; 610 (19%) were current smokers. Multi-variable 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% confidence interval [CI]: 0.63-1.21) at 1 marijuana-year among never smokers and OR 1.11 (95% CI: 0.85-1.45) among ever tobacco smokers. Cumulative exposure to tobacco was strongly associated with high carotid intima-media thickness, OR 1.88 (95%CI: 1.20-2.94) 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.

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**KEYWORDS:** Carotid intima-media thickness; Cumulative exposure; Marijuana; Subclinical atherosclerosis; Tobacco

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## BACKGROUND

Marijuana, made of dried cannabis flowers, is used by between 7.5% and 9.4% of the US population and by 6% of the population ages older than 55 years.<sup>1-3</sup> Increasing legalization for recreational and medical use has been accompanied by concern about its possible health effects.<sup>4</sup> Cardiovascular health is a special concern because case reports from the early 2010s suggested that marijuana may trigger heart attacks in healthy adults.<sup>5-7</sup> Smoking tobacco is a major cause of premature death worldwide, including cardiovascular disease,<sup>8</sup> and tobacco and marijuana smoke share many constituents.<sup>9</sup> 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.<sup>4,10,11</sup>

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 (5000 to 65,000 participants) in the United States, Sweden, and Belgium published from the late 1990s through the late 2010s.<sup>4,10,12-15</sup> Cumulative marijuana use was not associated with coronary and abdominal calcium score, a marker of subclinical atherosclerosis in previous analyses of data from the Coronary Artery Risk Development in Young Adult (CARDIA) study, a longitudinal study of more than 5000 participants with up to 30-years follow-up in the United States.<sup>16</sup>

Because 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.<sup>17-21</sup> Carotid intima-media thickness is associated with traditional cardiovascular risk factors like blood lipids, hypertension, and tobacco smoking.<sup>22-25</sup> Carotid intima-media thickness predicts atrial fibrillation, myocardial infarction, and cerebrovascular events.<sup>26-29</sup> 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 5115 self-identified Black and white women and men, ages 18 to 30 years at baseline, from 4 study sites in the United States (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; Oakland, California) followed over 30 years. The study strove for equal distribution of race, sex, education, and age at each site. We used data from 7 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 examination. All participants gave informed consent before entering the study and at each follow-up examination. The study was approved by institutional review boards for each site.

## PERSPECTIVES VIEWPOINTS

- 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 exposure to combustion constituents would then be similar.

### 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.<sup>30,31</sup> 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 upward whenever participants self-reported higher lifetime use than we computed for each visit (eMethods, available online). Marijuana use was illegal in these jurisdictions at the time.

Cigarette smoking was evaluated at each in-person CARDIA examination and at yearly phone follow-up between CARDIA examinations.<sup>30</sup> We used these data to estimate cumulative lifetime exposure to cigarettes in pack-years: 1 pack-year of exposure was equivalent to 7300

cigarettes (1 year  $\times$  365 days/y  $\times$  1 pack/d  $\times$  20 cigarettes/pack).<sup>31</sup>

## Outcome Measures: Carotid Intima-Media Thickness

High-resolution B-mode ultrasonography (Logiq 700; General Electric Medical Systems, Waukesha, Wisc.) was used to capture images of the common carotid and internal carotid arteries and of the carotid bulbs at the year 20 examination. 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 standard deviation) and averaging these standardized measures.<sup>32</sup>

## 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 1 drink/d.<sup>30</sup> We defined acute heavy exposure to alcohol (bingeing) as 4 (women) or 5 (men) or more drinks consumed on 1 occasion, and we estimated total lifetime bingeing episodes. We estimated total exposure to passive smoking (eMethods, available online).<sup>30</sup> 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.<sup>33</sup>

Our cardiovascular risk factor measurements included blood pressure, blood cholesterol (total cholesterol, low-density lipoprotein [LDL]- and high-density lipoprotein [HDL]-cholesterol, and triglycerides), fasting glucose, and body mass index (BMI), which were collected at each CARDIA examination.<sup>30</sup>

## 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.<sup>34</sup> Because tobacco and marijuana smoking are frequently co-occurring behaviors, we stratified all results and analyses by history of tobacco smoking.<sup>16,30</sup>

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 3 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, available online).<sup>35,36</sup> We used Last Observation Carried Forward and Backward (LOCFB) imputation for missing covariables because we have information on covariables 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 2-tailed; alpha level was 0.05. Analyses were conducted with Stata version 14.2 (StataCorp LP, College Station, Tex.).

## RESULTS

At year 20, 3549 participants were examined; 3257 (92%) had data on carotid intima-media thickness; 2722 (84%) reported ever marijuana use; 374 (11%) were current users; 1539 (47%) reported ever tobacco smoking; and 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 = 1250) 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 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 1B). 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 odds ratio (OR)

**Table 1** Characteristics of 3257 CARDIA Participants with CIMT Measurement at Year 20 Examination, Overall, and by Never/Ever Tobacco Smoking

	Never Tobacco Smoker N = 1718 (53%)			Ever Tobacco Smoker N = 1539 (47%)			P Value†
	No marijuana use	>0 to <1 marijuana-years*	≥1 marijuana-years*	No marijuana use	>0 to <1 marijuana-years*	≥1 marijuana-years*	
N	468	1043	207	67	853	619	
Demographics							<.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 %) <sup>‡</sup>							
- Black women	175 (37)	284 (27)	30 (14)	28 (42)	266 (31)	131 (21)	<.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)	<.001
Study center, N (col %)							
- Birmingham, AL	204 (44)	203 (20)	26 (12)	37 (55)	198 (23)	102 (17)	<.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 %) <sup>§</sup>	468 (100)	—	—	67 (100)	—	—	<.001
- Never used marijuana	—	1024 (98)	130 (63)	—	833 (98)	361 (58)	
- Past marijuana use	—	19 (2)	77 (37)	—	20 (2)	258 (42)	
- Current marijuana use	—	—	—	—	—	—	
Tobacco smoking, N (col %)							
- Never smoker	468 (100)	1043 (100)	207 (100)	—	—	—	<.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 <sup>  </sup>	—	—	—	6 (0; 8)	9 (1; 13)	12 (2; 19)	<.001
Alcohol use							
- Cumulative alcohol use among ever drinkers, median (Q1, Q3), drink-years <sup>¶</sup>	6 (1; 8)	10 (2; 14)	19 (6; 24)	10 (2; 12)	15 (4; 19)	28 (9; 38)	<.001
Binge drinking days, cumulative use, N (col %) <sup>**</sup>	391 (83)	639 (61)	58 (28)	43 (64)	358 (42)	130 (21)	<.001
- never reported bingeing	59 (13)	286 (27)	75 (36)	18 (27)	300 (35)	198 (32)	
- ≤250 days	18 (4)	118 (11)	74 (36)	6 (9)	195 (23)	291 (47)	
- >250 days	—	—	—	—	—	—	
Physical activity							<.001
Physical activity score, median (Q1; Q3) <sup>††</sup>	270 (88; 381)	355 (129; 517)	419 (187; 577)	226 (81; 313)	319 (121; 469)	363 (157; 523)	<.001
Anthropomorphic variable							<.001
BMI, mean (SD) <sup>‡‡</sup>	31 (7)	29 (8)	30 (7)	29 (7)	29 (7)	29 (6)	<.001

**Table 1 (Continued)**

	Never Tobacco Smoker N = 1718 (53%)			Ever Tobacco Smoker N = 1539 (47%)			P Value <sup>†</sup>
	No marijuana use	>0 to <1 marijuana-years*	≥1 marijuana-years*	No marijuana use	>0 to <1 marijuana-years*	≥1 marijuana-years*	
Cardiovascular risk factors							
Systolic blood pressure, mean (SD), mm Hg	117 (16)	115 (14)	119 (13)	118 (16)	117 (17)	119 (15)	<.001
Diastolic blood pressure, mean (SD), mm Hg	74 (12)	72 (11)	74 (10)	76 (12)	73 (12)	75 (12)	<.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)	<.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)	<.001
Diabetes mellitus, N (%)	33 (7)	82 (8)	17 (8)	4 (6)	72 (8)	39 (3)	0.7

BMI = body mass index (weight in kilograms divided by height in meters squared); CARDIA = Coronary Artery Risk Development in Young Adults study; CES-D = Center for Epidemiological Studies- Depression; LDL = low-density lipoprotein; HDL = high-density lipoprotein; N = number of participants; Q1, Q3 = 1st and 3rd quartile (percentile 25 and 75); SD = standard deviation.

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.

\*Cumulative lifetime marijuana use in marijuana-years: 1 marijuana-year of exposure is equivalent to 365 days of marijuana use (1 year × 365 days per year).<sup>31</sup>

†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.

‡The CARDIA study sampled roughly equal numbers of self-identified white men, white women, Black men, and Black women.<sup>41</sup>

§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?"

||Cumulative lifetime tobacco smoking in pack-years: 1 pack-year of exposure equivalent to 7300 cigarettes (1 year × 365 days/y × 1 pack/d × 20 cigarettes/pack).<sup>31</sup>

¶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 × 1 drink/d × 365 days/y = 6292.6 mL of ethanol).

\*\*Binge drinking days defined as 5 or more drinks per day. If bingeing were constant for more than 25 years in 1 individual, 250 binge drinking days would correspond to 10 days of bingeing per year over 25 years.

††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.<sup>33</sup>

‡‡Calculated as weight in kilograms divided by height in meters squared.

**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%)			P Value*
	No marijuana use	>0 to <1 marijuana-years	≥1 marijuana-years	No marijuana use	>0 to <1 marijuana-years	≥1 marijuana-years	
Total N	468	1043	207	67	853	619	
Normalized composite CIMT at ≥75th percentile, N, (%) <sup>†</sup>	127 (27)	225 (22)	54 (26)	18 (27)	207 (24)	183 (30)	.010
Composite CIMT at ≥75th percentile, N, (%) <sup>‡</sup>	132 (28)	217 (21)	53 (26)	17 (25)	219 (26)	176 (28)	.006
Mean of CC IMT at ≥75th percentile, N, (%) <sup>§</sup>	119 (25)	226 (22)	52 (25)	20 (30)	195 (23)	201 (32)	<.001
Mean of CB IMT at ≥75th percentile, N, (%) <sup>  </sup>	131 (28)	222 (21)	54 (26)	17 (25)	205 (24)	166 (27)	.06
Mean of IC IMT at ≥75th percentile, N, (%) <sup>¶</sup>	116 (25)	226 (22)	55 (27)	8 (12)	203 (24)	161 (26)	.08

CB = carotid bulb; CC = common carotid artery; CIMT = carotid intima-media thickness; IC = internal carotid artery; SD = standard deviation. One marijuana-year equivalent to 365 days of marijuana use.

Distribution of all CARDIA participants examined (≥75th percentile) to define high standardized CC at ≥75th percentile.<sup>32</sup>

\*P values are from a  $\chi^2$  test.

<sup>†</sup>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.<sup>32</sup>

<sup>‡</sup>Mean of averages of CC, IC, and IC CIMT.

<sup>§</sup>Average of the maximal CC IMT records (1-4 measurements).

<sup>||</sup>Average of the maximal CB IMT records (1-8 measurements).

<sup>¶</sup>Average of the maximal IC IMT records (1-8 measurements).

of 10 pack-years and high normalized composite carotid intima-media thickness was 1.57 (95% confidence interval: 1.08-2.27, Table 3, Figure 1C). The strength of association increased with higher cumulative exposures to tobacco.

Results were comparable in analyses modeling carotid intima-media thickness as continuous measure (Appendix Tables 1 and 2, available online).

Sensitivity analyses showed no evidence of interactions by race or sex (all P values >.1, Appendix Table 3, available online). 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 (1 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 modeled 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 an almost 60% higher odds of a high normalized composite carotid intima-media thickness.

The recent statement from the American Heart Association on medical marijuana, recreational cannabis, and cardiovascular health highlighted the lack of rigorously performed studies.<sup>4</sup> Previous analyses of CARDIA participants showed no association between marijuana use and cardiovascular events or mortality overall.<sup>12,14</sup> 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 2 studies that tested the association between abdominal artery and coronary artery calcium and cumulative marijuana use.<sup>16,37</sup> 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.

**Table 3** Association Between Cumulative Marijuana Use or Cumulative Tobacco Smoking and High CIMT, Stratified by Ever-Smoking Exposure

		Never tobacco smoker N = 1718 (53%)				Ever tobacco smoker N = 1539 (47%)			
		Unadjusted		Multivariable adjusted*		Unadjusted		Multivariable adjusted*	
Category of CIMT	Cumulative exposure to	OR (CI)	P Value†	OR (CI)	P Value†	OR (CI)	P Value†	OR (CI)	P Value†
Normalized composite CIMT at ≥75th percentile‡	At 0.5 marijuana-years	1.06 (0.93-1.21)	.68	0.93 (0.77-1.12)	.46	1.09 (0.97-1.22)	.10	1.06 (0.91-1.23)	.38
	At 1 marijuana-year	1.11 (0.88-1.40)		0.87 (0.63-1.21)		1.16 (0.95-1.42)		1.11 (0.85-1.45)	
	At 5 marijuana-years	1.18 (0.79-1.77)		0.70 (0.38-1.29)		1.41 (1.00-1.99)		1.31 (0.81-2.10)	
	At 10 marijuana-years	1.08 (0.61-1.91)		0.63 (0.30-1.33)		1.48 (1.02-2.15)		1.45 (0.86-2.42)	
Composite CIMT at ≥75th percentile§	At 0.5 marijuana-years	1.06 (0.92-1.20)	.72	0.94 (0.78-1.12)	.36	1.09 (0.98-1.22)	.24	1.02 (0.87-1.19)	.97
	At 1 marijuana-year	1.10 (0.87-1.39)		0.89 (0.64-1.22)		1.17 (0.96-1.44)		1.03 (0.79-1.36)	
	At 5 marijuana-years	1.13 (0.75-1.71)		0.69 (0.38-1.27)		1.35 (0.95-1.92)		1.06 (0.64-1.75)	
	At 10 marijuana-years	1.00 (0.56-1.80)		0.56 (0.26-1.24)		1.30 (0.89-1.90)		1.04 (0.62-1.75)	
Mean of CC IMT at ≥75th percentile	At 0.5 marijuana-years	1.13 (0.99-1.29)	.16	1.00 (0.82-1.21)	.21	1.15 (1.03-1.29)	.002	1.10 (0.95-1.27)	.06
	At 1 marijuana-year	1.24 (0.98-1.57)		0.98 (0.70-1.38)		1.29 (1.05-1.58)		1.20 (0.92-1.55)	
	At 5 marijuana-years	1.26 (0.84-1.89)		0.74 (0.39-1.38)		1.78 (1.25-2.55)		1.56 (0.99-2.45)	
	At 10 marijuana-years	0.88 (0.45-1.69)		0.46 (0.19-1.12)		1.95 (1.34-2.85)		1.79 (1.10-2.90)	
Mean of CB IMT at ≥75th percentile¶	At 0.5 marijuana-years	1.06 (0.94-1.21)	.53	0.94 (0.79-1.12)	.71	1.09 (0.99-1.22)	.23	1.02 (0.87-1.19)	.97
	At 1 marijuana-year	1.12 (0.89-1.40)		0.90 (0.66-1.23)		1.17 (0.95-1.43)		1.04 (0.79-1.37)	
	At 5 marijuana-years	1.26 (0.85-1.86)		0.79 (0.45-1.40)		1.36 (0.95-1.94)		1.07 (0.64-1.78)	
	At 10 marijuana-years	1.25 (0.72-2.18)		0.77 (0.40-1.50)		1.34 (0.91-1.98)		1.06 (0.62-1.81)	
Mean of IC IMT at ≥75th percentile**	At 0.5 marijuana-years	1.10 (0.96-1.25)	.17	0.99 (0.84-1.17)	.10	1.07 (0.95-1.20)	.54	0.95 (0.82-1.11)	.61
	At 1 marijuana-year	1.17 (0.93-1.48)		0.97 (0.72-1.32)		1.12 (0.91-1.39)		0.92 (0.70-1.20)	
	At 5 marijuana-years	1.08 (0.71-1.65)		0.71 (0.40-1.26)		1.20 (0.83-1.72)		0.81 (0.50-1.31)	
	At 10 marijuana-years	0.70 (0.36-1.37)		0.42 (0.19-0.97)		1.08 (0.72-1.60)		0.77 (0.46-1.29)	
Category of CIMT	Cumulative exposure to tobacco								
Normalized composite CIMT at ≥75th percentile‡	At 5 pack-years	—	—	—	—	1.40 (1.17-1.69)	<.001	1.29 (1.03-1.60)	.016
	At 10 pack-years					1.85 (1.36-2.51)		1.57 (1.08-2.27)	
	At 20 pack-years					2.43 (1.71-3.45)		1.88 (1.20-2.94)	
	At 40 pack-years					2.93 (1.83-4.70)		2.07 (1.11-3.85)	
Composite CIMT at ≥75th percentile§	At 5 pack-years	—	—	—	—	1.46 (1.22-1.74)	<.001	1.33 (1.08-1.65)	.010
	At 10 pack-years					1.95 (1.44-2.64)		1.66 (1.16-2.38)	
	At 20 pack-years					2.50 (1.76-3.56)		1.97 (1.27-3.05)	
	At 40 pack-years					2.68 (1.67-4.32)		1.94 (1.07-3.52)	
Mean of CC IMT at ≥75th percentile	At 5 pack-years	—	—	—	—	1.17 (0.97-1.40)	.001	1.05 (0.85-1.30)	.36
	At 10 pack-years					1.33 (0.98-1.81)		1.10 (0.77-2.59)	
	At 20 pack-years					1.63 (1.16-2.30)		1.23 (0.79-1.90)	
	At 40 pack-years					2.24 (1.40-3.57)		1.52 (0.86-2.68)	

Table 3 (Continued)

		Never tobacco smoker N = 1718 (53%)				Ever tobacco smoker N = 1539 (47%)			
		Unadjusted		Multivariable adjusted*		Unadjusted		Multivariable adjusted*	
Mean of CB IMT at $\geq 75^{\text{th}}$ percentile <sup>¶</sup>	At 5 pack-years	—	—	—	—	1.31 (1.09-1.58)	<.001	1.20 (0.98-1.49)	.15
	At 10 pack-years					1.63 (1.20-2.22)		1.39 (0.97-1.99)	
	At 20 pack-years					2.02 (1.41-2.89)		1.55 (0.99-2.41)	
	At 40 pack-years					2.32 (1.43-3.77)		1.53 (0.85-2.77)	
Mean of IC IMT at $\geq 75^{\text{th}}$ percentile**	At 5 pack-years	—	—	—	—	1.35 (1.12-1.63)	<.001	1.37 (1.10-1.70)	.004
	At 10 pack-years					1.70 (1.24-2.33)		1.75 (1.21-2.54)	
	At 20 pack-years					2.07 (1.44-2.97)		2.18 (1.37-3.46)	
	At 40 pack-years					2.17 (1.36-3.47)		2.37 (1.28-4.39)	

BMI = body mass index; CB, carotid bulb; CC = common carotid artery; CI = confidence interval; CIMT = carotid intima-media thickness; HDL = high-density lipoprotein; IC = internal carotid artery; LDL = low-density lipoprotein; OR = odds ratio; TRG = triglycerides.

One marijuana-year equivalent to 365 days of marijuana use.

Distribution of all CARDIA participants examined ( $\geq 75^{\text{th}}$  percentile) to define high standardized CC at  $\geq 75^{\text{th}}$  percentile. [4]

\*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.

†P values came from a Wald test.

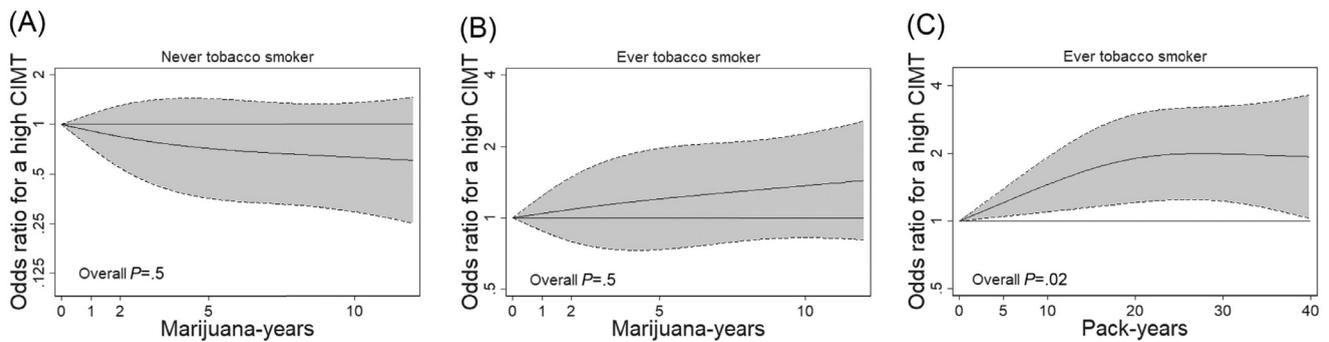
‡Normalized composite measure of the maximal CIMT. First, we built the arithmetic average of all IC and bulb measurements, and the arithmetic average of all CC measures. Second, we standardized these averages separately by subtracting the mean and dividing by the SD. Finally, we averaged these standardized measures.<sup>32</sup>

§Mean of averages of CC, IC, and IC CIMT.

||Average of the maximal CC IMT records (1-4 measurements).

¶Average of the maximal CB IMT records (1-8 measurements).

\*\*Average of the maximal IC IMT records (1-8 measurements).



**Figure 1** Odds ratio of high CIMT by cumulative marijuana use (marijuana-years) or cumulative tobacco smoking (pack-years), multivariable adjusted (A) Marijuana-years among never tobacco smokers (N = 1718). (B) Marijuana-years among ever tobacco smokers (N = 1539). (C) Pack-years among ever tobacco smokers (N = 1539). 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 ( $P = .02$ ). P values are from a  $\chi^2$  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.<sup>41</sup> Distribution of all CARDIA participants examined, >75th percentile to define high IMT.<sup>41</sup> 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.<sup>32</sup> BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; CC = common carotid artery; CIMT = carotid intima-media thickness; HDL = high-density lipoprotein; IC = internal carotid artery; IMT = intima-media thickness; LDL = low-density lipoprotein; SD = standard deviation; TRG = triglycerides.

The single association between marijuana-years in ever tobacco smokers and common carotid artery intima-media thickness modeled as a continuous variable might be explained by residual confounding from tobacco smoking because tobacco smoking and marijuana use are associated.<sup>9,16</sup> It may also be a chance finding because we ran multiple analyses that used varying definitions of carotid intima-media thickness. In the CARDIA cohort, cumulative marijuana exposure was low among users—much lower than cumulative tobacco exposure among ever tobacco users. One marijuana-year is equivalent to smoking 1 or more joints per day for a year, whereas 1 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.<sup>7,38</sup> The acute effect of marijuana might explain 1 study’s finding of a surge in myocardial

infarctions just after marijuana use.<sup>7</sup> The absence of evidence of an increase in subclinical atherosclerosis in our study and the absence of significant association in previous analyses in CARDIA<sup>14,39</sup> 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 modeling to adjust for multiple cardiovascular risk factors (CVRFs) and inverse probability of censoring weights (IPCW) to address potential informative censoring. The proportion of participants followed up to the year 20 examination 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 modeled 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.<sup>9,16,30</sup> 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.<sup>40</sup> 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. Because 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 United States—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 United States, but our study confirms the strong association between tobacco smoking and increased carotid intima-media thickness. Because 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.

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## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjmed.2020.11.026>.

## APPENDIX

### Methods

#### Measurements

##### Cigarette smoking exposure

Detailed cigarette smoking behavior was evaluated during each in-person CARDIA visit by responses to an interviewer-administered questionnaire. Participants were also asked the number of cigarettes smoked daily at yearly contact over the phone between CARDIA visits.<sup>2</sup> Current smoking was defined as smoking one cigarette or more per day. At baseline, participants were asked the number of years they had smoked in total, the age at which they started smoking regularly (“How old were you when you started smoking cigarettes regularly?”) and years since cessation (“How many years ago did you stop?”), if appropriate. These data were used to estimate cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 year  $\times$  365 days/y  $\times$  1 pack/d  $\times$  20 cigarettes/pack).<sup>3</sup> Exposure to passive smoking was queried at each CARDIA exam.<sup>1</sup> Three questions: (a) “On the average, how many hours per week are you exposed to cigarette, cigar or pipe smoke in a small space other than your home?” (b) “On the average, how many hours per week are you exposed to cigarette, cigar or pipe smoke in your home because of smoking by others?” (c) “On the average, how many hours per week are you exposed to cigarette, cigar or pipe smoke in a large indoor area (such as a restaurant, hotel lobby, lecture hall, etc.) because of smoking by others?” Question 2 was asked at each CARDIA exam, but questions 1 and 3 were not asked at Visits 2 or 5. We assumed that the hours of exposure per week at each exam indicated the number of hours per week in the years before and after each assessment. We imputed the answers to each question backwards and forwards over the 20 years of follow-up. We summed the three questions to estimate total number of hours per week of exposure, and capped exposure at 168 hours per week (maximum, 24hrs per day). The total number of hours per week allowed us to estimate the number of hours per year based on the total number of hours per week. We summed these over 20 years of follow-up to obtain cumulative number of hours of exposure to passive smoking in that period. Finally, we divided this sum by the number of hours per year, which gave us cumulative years of exposure to passive smoking (number of full years of exposure to passive smoking 24h per day for 365 days).

##### Alcohol exposure

Alcohol consumption was measured during each CARDIA visits. We estimated lifetime alcohol consumption in “drink-years,” defining 1 drink-year as the amount of alcohol consumed in 1 year by a person consuming 1 drink/day, as previously reported.<sup>5</sup> Categories of alcohol consumption (abstinent, light, heavy) were based on the sex-specific weekly maximum drinking limits published by the National Institute on Alcohol Abuse and Alcoholism [for men  $>14$  (women  $>7$ ) standard drinks/week or  $>4$  ( $>3$ ) drinks/

day].<sup>4</sup> Acute heavy exposure to alcohol (bingeing) at the Year 20 visit was defined as reporting 5 or more drinks to the following question, “During the past 24 hours, how many drinks have you had?” Information on bingeing was also elicited in a separate question and allowed us to estimate the cumulative number of binge drinking days. Alcohol consumption was measured during each CARDIA visits. Participants were asked, “Did you drink any alcoholic beverages in the past year?” and three follow-up questions regarding how many drinks of wine, beer, and liquor they usually consumed per week. Assuming that one drink of beer, wine, or liquor contains 16.7 ml, 17.0 ml, or 19.1 ml of ethanol (per CARDIA protocol), we estimated total ethanol consumption per week in milliliters of ethanol and divided it by 17.24 ml of ethanol per average drink to estimate the usual number of drinks per week that each participant reported at each visit. We estimated lifetime alcohol consumption in “drink-years,” defining 1 drink-year as the amount of alcohol consumed in 1 year by a person consuming 1 drink/day (365 days/year  $\times$  17.24 ml of alcohol/day = 6,293 ml of alcohol) Binge drinking at the Year 20 visit was assessed directly by asking participants: “During the past 30 days, on how many days did you have five or more drinks on the same occasion?” For the other visits, we computed bingeing as follows: At each visit, participants were asked: “In the past month what is the largest number of drinks you had in one day?” At the baseline, participants were additionally asked: “How many days in the past month did you have about (number of drinks answered in the previous question) drinks?”. We used the number of days participants reported having 5 or more drinks for these visits. For binge drinking events at the Year 7 visit, we used the closest available information about the number of days patients reported having 5 or more drinks if they reported having such a use in one day within the last month at the Year 7 visit.

##### Other illicit drug exposure

Other illicit substances queried included cocaine (including other forms of cocaine such as crack, powder, free base), amphetamines (speed, uppers, metamphetamines) and heroin.<sup>5</sup> Participants were asked: “Have you ever used (substance)?” “During the last 30 days, on how many days did you use (substance)?” and “How many times in your lifetime have you used (substance)?” The number of days on cocaine, crack, speed, metamphetamines and heroin over the study duration was computed using current exposure at each visit and replaced by lifetime exposure when the latter was higher.

##### Cardiovascular risk factors

Blood pressure was measured on the right arm with a Hawksley random zero sphygmomanometer (WA Baum Company, Copague, NY) by trained and certified technicians using standardized methods after the participant had rested for 5 minutes at baseline and Year 7, and at Year 20, a digital blood pressure monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA) was used.

Three measurements were obtained at 1-minute intervals. The average of the second and third measurements was used in analyses. Fasting total cholesterol and triglycerides were measured enzymatically at baseline, Years 7, and 20 by the Northwest Lipid Research Laboratory at the University of Washington (Seattle, WA). For all visits, HDL cholesterol was determined by dextran sulfate-magnesium precipitation on the Abbot Spectrum, and LDL cholesterol was calculated using the Friedewald equation.<sup>5</sup> At each visit, weight and height were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

**Statistical analyses**

**Marijuana use**

We present below an example of one participant included in the study illustrating the method for computing marijuana-years more fully and how we applied linear imputation (Box 1). This is the same method of imputation used in a previous publication by our research group.<sup>3</sup>

1. Example of computing marijuana-years for one participant:

**Box 1** Example Illustrating Computation of Marijuana-Years

visit	mj30d_	mj30d_ imp	domj	life_	yomj_max
0	15	15	300	100 to 499 times	0.82
1	.	15	482	.	1.32
2	20	20	725	100 to 499 times	1.99
3	.	20	968	.	2.65
4	.	4	1017	.	2.79
5	4	4	1066	100 to 499 times	2.92
6	.	4	1115	.	3.05
7	20	20	1358	100 to 499 times	3.72
8	.	20	1601	.	4.39
9	.	20	1844	.	5.05
10	20	20	2087	500 to 1000 times	5.72
11	.	20	2330	.	6.38
12	.	20	2573	.	7.05
13	.	10	2695	.	7.38
14	.	10	2817	.	7.72
15	10	10	2939	500 to 1000 times	8.05
16	.	10	3061	.	8.39
17	.	10	3183	.	8.72
18	.	1	3195	.	8.75
19	.	1	3207	.	8.79
20	1	1	3219	100 to 499 times	8.82

Visit : visit year; mj30d\_ : Self-reported days of using marijuana during the month before the visit (“During the last 30 days, on how many days did you use marijuana?”), mj30d\_imp: imputed mj30d\_ variable; domj: computed cumulative days of marijuana use, life\_ : self-reported lifetime use of marijuana queried at each visit (“About how many times in your lifetime have you used marijuana?”), yomj\_max: computed cumulative years of marijuana use (domj/365).

According to example 1, the participant reported having used marijuana 100 to 499 times during the lifetime (categorical variable life\_) at the baseline examination (visit 0). This was used to estimate the exposure prior to the first examination (domj at visit 0=300, where domj signifies “days of marijuana”).

At this baseline examination, the participant reported using marijuana 15 days per months (mj30d\_). Multiplied by 12.17 months (365/30), we estimated that this participant used marijuana 182 days in the first year after the first exam (15 \* 12.17). The number of days of marijuana use in the month before the baseline examination was imputed forward at year 1 (mj30d\_imp). At year 2, the participant reported using marijuana 20 days per month; at year 4, he/she reported 4 days per month. These numbers were imputed backwards and forwards; when there were an uneven number of intervals (preventing us from evenly splitting the imputation based on the prior value as opposed to the post-value), the exposure at the prior interval was favoured arbitrarily. Participants then accrued lifetime days of marijuana use over follow-up. The cumulative number of marijuana-years over lifetime is presented in the last column (yomj\_max). For this participant, the cumulative number of marijuana years was 8.82, corresponding to 3,219 estimated days of marijuana use. We found no change in the estimates when using alternate methods for imputing missing values such as using the mean number of days of marijuana use between two examinations with data on this variable.

**Inverse probability of censoring weights (IPCWs)**

To reduce the potential for informative censoring, we computed IPCWs.<sup>6</sup> Covariables included in the pooled logistic regression model used to estimate the IPCWs were: fixed covariables: race, sex, study center and education; time-dependent covariables were lagged values of: age, study visits, pack-years of cigarette smoking, current smoking, drink-years of alcohol use, binge drinking events, cumulative exposure to cocaine, crack, amphetamines and heroin. Education, drink-years of alcohol exposure, visits were all modelled as 3-knot restricted cubic splines.

**Appendix Table 1** Distribution of CIMT measures by categories of cumulative marijuana use at Year 20 exam, stratified by ever smoking exposure

IMT measure	Never Tobacco Smoker N = 1718 (53%)			Ever Tobacco Smoker N= 1539 (47%)			P Value <sup>f</sup>
	No marijuana use	>0 to <1 marijuana-years	≥1 marijuana-years	No marijuana use	>0 to <1 marijuana-years	≥1 marijuana-years	
Total N	468	1,043	207	67	853	619	
Normalized composite CIMT, standardized (Q1; Q3) <sup>a</sup>	-0.076 (-0.582; 0.453)	-0.217 (-0.664; 0.256)	-0.083 (-0.531; 0.430)	-0.099 (-0.491; 0.588)	-0.089 (-0.535; 0.398)	-0.010 (-0.452; 0.569)	<0.001
Composite CIMT in mm (Q1; Q3) <sup>b</sup>	0.865 (0.776; 0.986)	0.850 (0.771; 0.941)	0.870 (0.797; 0.965)	0.860 (0.776; 0.980)	0.866 (0.790; 0.967)	0.878 (0.795; 0.989)	0.001
Mean of CC IMT in mm (Q1; Q3) <sup>c</sup>	0.780 (0.707; 0.869)	0.768 (0.697; 0.849)	0.796 (0.717; 0.867)	0.786 (0.733; 0.881)	0.781 (0.714; 0.859)	0.806 (0.732; 0.892)	<0.001
Mean of CB IMT in mm (Q1; Q3) <sup>d</sup>	0.965 (0.837; 1.169)	0.955 (0.837; 1.105)	0.991 (0.874; 1.150)	0.956 (0.829; 1.149)	0.980 (0.857; 1.133)	0.982 (0.857; 1.155)	0.07
Mean of IC IMT in mm (Q1; Q3) <sup>e</sup>	0.773 (0.679; 0.882)	0.770 (0.690; 0.864)	0.790 (0.691; 0.892)	0.741 (0.642; 0.825)	0.766 (0.681; 0.880)	0.779 (0.695; 0.893)	0.06

Abbreviations: CIMT = carotid intima-media thickness; 1 marijuana-year is equivalent to 365 days of marijuana use; CC = common carotid artery; IC = internal carotid artery; CB = carotid bulb; USC =  
<sup>a</sup>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.(7)

<sup>b</sup>Mean of averages of CC; IC, and IC CIMT

<sup>c</sup>Average of the maximal CC IMT records (1-4 measurements)

<sup>d</sup>Average of the maximal CB IMT records (1-8 measurements)

<sup>e</sup>Average of the maximal IC IMT records (1-8 measurements)

<sup>f</sup>P-values are from a  $\chi^2$  test.

**Appendix Table 2** Association between cumulative marijuana use or cumulative tobacco smoking and CIMT as continuous measure, stratified by ever smoking exposure

Continuous measures of CIMT	Mean CIMT measure (mm) for no exposure	Cumulative exposure to marijuana	Never tobacco smoker N= 1,718 (53%)				Ever tobacco smoker N= 1,539 (47%)			
			Unadjusted		Multivariable adjusted <sup>f</sup>		Unadjusted		Multivariable adjusted <sup>f</sup>	
			Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>	Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>	Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>	Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>
Normalized composite CIMT <sup>a</sup>	n/a	At 0.5 marijuana-years	0.04 (-0.01 to 0.08)	0.31	-0.02 (-0.07 to 0.03)	0.52	0.05 (0.01 to 0.09)	0.004	0.02 (-0.02 to 0.06)	0.27
		At 1 marijuana-year	0.07 (-0.02 to 0.15)		-0.04 (-0.13 to 0.05)		0.09 (0.02 to 0.16)		0.04 (-0.04 to 0.12)	
		At 5 marijuana-years	0.12 (-0.06 to 0.29)		-0.11 (-0.31 to 0.09)		0.19 (0.07 to 0.31)		0.10 (-0.04 to 0.23)	
		At 10 marijuana-years	0.09 (-0.26 to 0.44)		-0.17 (-0.52 to 0.18)		0.20 (0.07 to 0.33)		0.12 (-0.03 to 0.27)	
Composite CIMT	0.90	At 0.5 marijuana-years	0.01 (-0.00 to 0.01)	0.52	-0.01 (-0.02 to 0.00)	0.30	0.01 (-0.00 to 0.02)	0.06	0.00 (-0.01 to 0.01)	0.97
		At 1 marijuana-year	0.01 (-0.01 to 0.03)		-0.01 (-0.03 to 0.01)		0.01 (-0.00 to 0.03)		0.00 (-0.02 to 0.02)	
		At 5 marijuana-years	0.02 (-0.02 to 0.05)		-0.03 (-0.07 to 0.01)		0.03 (0.00 to 0.06)		0.00 (-0.03 to 0.03)	
		At 10 marijuana-years	0.01 (-0.05 to 0.07)		-0.04 (-0.10 to 0.02)		0.03 (0.00 to 0.06)		0.00 (-0.03 to 0.04)	
Mean of CC IMT <sup>b</sup>	0.80	At 0.5 marijuana-years	0.01 (-0.00 to 0.01)	0.14	-0.00 (-0.01 to 0.01)	0.84	0.01 (0.00 to 0.01)	<0.001	0.01 (0.00 to 0.01)	0.001
		At 1 marijuana-year	0.01 (-0.00 to 0.03)		-0.00 (-0.02 to 0.01)		0.02 (0.01 to 0.03)		0.01 (0.00 to 0.02)	
		At 5 marijuana-years	0.02 (-0.00 to 0.05)		-0.01 (-0.04 to 0.02)		0.04 (0.02 to 0.05)		0.03 (0.01 to 0.05)	
		At 10 marijuana-years	0.02 (-0.03 to 0.08)		-0.01 (-0.07 to 0.04)		0.04 (0.02 to 0.06)		0.04 (0.02 to 0.06)	
Mean of CB IMT <sup>c</sup>	1.04	At 0.5 marijuana-years	0.01 (-0.01 to 0.02)	0.76	-0.01 (-0.03 to 0.01)	0.30	0.01 (-0.00 to 0.03)	0.10	0.00 (-0.02 to 0.02)	0.92
		At 1 marijuana-year	0.01 (-0.02 to 0.04)		-0.02 (-0.05 to 0.01)		0.03 (-0.00 to 0.05)		0.00 (-0.03 to 0.03)	
		At 5 marijuana-years	0.02 (-0.03 to 0.07)		-0.04 (-0.10 to 0.01)		0.05 (0.00 to 0.09)		-0.00 (-0.06 to 0.06)	
		At 10 marijuana-years	0.02 (-0.06 to 0.10)		-0.05 (-0.13 to 0.02)		0.04 (-0.00 to 0.08)		-0.01 (-0.07 to 0.05)	
Mean of IC IMT <sup>d</sup>	0.80	At 0.5 marijuana-years	0.00 (-0.01 to 0.02)	0.49	-0.01 (-0.02 to 0.01)	0.16	0.00 (-0.01 to 0.02)	0.53	-0.01 (-0.02 to 0.01)	0.67
		At 1 marijuana-year	0.01 (-0.01 to 0.03)		-0.01 (-0.04 to 0.01)		0.01 (-0.01 to 0.03)		-0.01 (-0.03 to 0.01)	
		At 5 marijuana-years	0.00 (-0.03 to 0.04)		-0.04 (-0.09 to 0.01)		0.02 (-0.01 to 0.05)		-0.02 (-0.06 to 0.02)	
		At 10 marijuana-years	-0.02 (-0.07 to 0.04)		-0.06 (-0.13 to 0.00)		0.02 (-0.02 to 0.06)		-0.01 (-0.06 to 0.03)	
Continuous measures of CIMT		Cumulative exposure to tobacco								
Normalized composite CIMT <sup>a</sup>	-	At 5 pack-years	-	-	-	-	0.13 (0.06 to 0.19)	<0.001	0.07 (0.01 to 0.13)	<0.001
		At 10 pack-years					0.23 (0.13 to 0.34)		0.14 (0.03 to 0.24)	
		At 20 pack-years					0.37 (0.25 to 0.49)		0.23 (0.10 to 0.36)	
		At 40 pack-years					0.56 (0.40 to 0.72)		0.36 (0.19 to 0.54)	
Composite CIMT <sup>b</sup>	0.88	At 5 pack-years					0.02 (0.01 to 0.04)	<0.001	0.01 (0.00 to 0.03)	<0.001
		At 10 pack-years					0.05 (0.02 to 0.07)		0.03 (0.01 to 0.05)	
		At 20 pack-years					0.08 (0.05 to 0.10)		0.05 (0.02 to 0.08)	
		At 40 pack-years					0.13 (0.09 to 0.17)		0.09 (0.04 to 0.13)	

Appendix Table 2 (Continued)

Continuous measures of CIMT	Mean CIMT measure (mm) for no exposure	Cumulative exposure to marijuana	Never tobacco smoker N= 1,718 (53%)				Ever tobacco smoker N= 1,539 (47%)			
			Unadjusted		Multivariable adjusted <sup>f</sup>		Unadjusted		Multivariable adjusted <sup>f</sup>	
			Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>	Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>	Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>	Coefficient (CI) <sup>g</sup>	P Value <sup>h</sup>
Mean of CC IMT <sup>c</sup>	0.79	At 5 pack-years	-	-	-	-	0.01 (0.00 to 0.02)	<0.001	0.01 (-0.00 to 0.02)	0.016
		At 10 pack-years					0.03 (0.01 to 0.04)		0.01 (-0.00 to 0.03)	
		At 20 pack-years					0.04 (0.02 to 0.06)		0.02 (0.00 to 0.04)	
		At 40 pack-years					0.05 (0.03 to 0.08)		0.04 (0.01 to 0.06)	
Mean of CB IMT <sup>d</sup>	1.02	At 5 pack-years	-	-	-	-	0.04 (0.01 to 0.06)	<0.001	0.02 (0.00 to 0.05)	0.009
		At 10 pack-years					0.07 (0.03 to 0.11)		0.05 (0.00 to 0.09)	
		At 20 pack-years					0.11 (0.07 to 0.16)		0.07 (0.02 to 0.12)	
		At 40 pack-years					0.18 (0.11 to 0.25)		0.11 (0.03 to 0.19)	
Mean of IC IMT <sup>e</sup>	0.80	At 5 pack-years	-	-	-	-	0.02 (0.00 to 0.04)	<0.001	0.02 (-0.00 to 0.03)	0.002
		At 10 pack-years					0.04 (0.01 to 0.07)		0.03 (0.00 to 0.06)	
		At 20 pack-years					0.07 (0.04 to 0.10)		0.05 (0.02 to 0.09)	
		At 40 pack-years					0.12 (0.07 to 0.17)		0.09 (0.03 to 0.15)	

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 ( $\geq 75^{\text{th}}$  percentile) to define high standardized CC at  $\geq 75^{\text{th}}$  percentile. (7)

<sup>a</sup>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. (7)

<sup>b</sup>Mean of averages of CC, IC, and IC CIMT

<sup>c</sup>Average of the maximal CC IMT records (1-4 measurements)

<sup>d</sup>Average of the maximal CB IMT records (1-8 measurements)

<sup>e</sup>Average of the maximal IC IMT records (1-8 measurements)

<sup>f</sup>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.

<sup>g</sup>Coefficients correspond to the absolute change in IMT measures, measured in mm.

<sup>h</sup>P-values are from a Wald test.

**Appendix Table 3** Association between cumulative marijuana use or cumulative tobacco smoking and high normalized composite CIMT, stratified by ever smoking exposure, stratified by sex-race strata

Normalized composite CIMT at $\geq 75^{\text{th}}$ percentile <sup>a</sup>	Race-sex strata	Cumulative exposure to marijuana	Never tobacco smoker N= 1,718 (53%)				Ever tobacco smoker N= 1,539 (47%)			
			Unadjusted		Multivariable adjusted <sup>b</sup>		Unadjusted		Multivariable adjusted <sup>b</sup>	
			Odds Ratio (CI)	P Value <sup>c</sup>	Odds Ratio (CI)	P Value <sup>c</sup>	Odds Ratio (CI)	P Value <sup>c</sup>	Odds Ratio (CI)	P Value <sup>c</sup>
		N in never; ever smoker								
	Black women	At 0.5 marijuana-years	1.03 (0.68 to 1.56)	0.42	1.19 (0.69 to 2.05)	0.82	0.89 (0.67 to 1.19)	0.58	0.94 (0.64 to 1.37)	0.92
		At 1 marijuana-year	1.07 (0.52 to 2.22)		1.35 (0.53 to 3.46)		0.81 (0.49 to 1.34)		0.89 (0.46 to 1.74)	
		At 5 marijuana-years	1.63 (0.26 to 10.2)		0.43 (0.01 to 29.1)		1.30 (0.34 to 4.92)		1.50 (0.20 to 11.1)	
		At 10 marijuana-years	3.1 (0.00 to >100)		0.0 (0.00 to >100)		8.66 (0.01 to >10)		7.7 (0.00 to >100)	
	Black men	At 0.5 marijuana-years	1.02 (0.85 to 1.23)	0.97	0.87 (0.66 to 1.14)	0.20	1.13 (0.94 to 1.35)	0.40	1.16 (0.91 to 1.48)	0.34
		At 1 marijuana-year	1.05 (0.73 to 1.49)		0.76 (0.46 to 1.28)		1.26 (0.90 to 1.78)		1.33 (0.83 to 2.13)	
		At 5 marijuana-years	1.12 (0.42 to 2.98)		0.37 (0.09 to 1.64)		1.88 (0.71 to 4.99)		2.47 (0.64 to 9.50)	
		At 10 marijuana-years	1.10 (0.33 to 3.66)		0.22 (0.04 to 1.32)		1.80 (0.58 to 5.54)		3.19 (0.68 to 15.0)	
	White women	At 0.5 marijuana-years	0.73 (0.32 to 1.66)	0.75	0.41 (0.06 to 2.98)	0.55	1.33 (0.74 to 2.36)	0.16	0.74 (0.24 to 2.31)	0.49
		At 1 marijuana-year	0.56 (0.12 to 2.60)		0.20 (0.01 to 7.60)		1.70 (0.57 to 5.05)		0.59 (0.07 to 4.83)	
		At 5 marijuana-years	0.36 (0.03 to 5.08)		2.4 (0.04 to >100)		3.19 (0.52 to 19.5)		1.37 (0.07 to 28.0)	
		At 10 marijuana-years	1.49 (0.24 to 9.20)		>10 (0 to >100)		1.54 (0.34 to 6.95)		>10 (0.04 to >100)	
	White men	At 0.5 marijuana-years	0.96 (0.80 to 1.15)	0.38	0.87 (0.67 to 1.12)	0.12	0.92 (0.78 to 1.07)	0.25	0.98 (0.79 to 1.22)	0.41
		At 1 marijuana-year	0.92 (0.66 to 1.29)		0.76 (0.47 to 1.22)		0.85 (0.63 to 1.15)		0.97 (0.64 to 1.46)	
		At 5 marijuana-years	0.70 (0.31 to 1.57)		0.38 (0.12 to 1.25)		0.74 (0.35 to 1.54)		1.05 (0.37 to 2.95)	
		At 10 marijuana-years	0.53 (0.21 to 1.30)		0.24 (0.06 to 0.94)		1.04 (0.54 to 2.00)		1.41 (0.55 to 3.62)	
	Race-sex strata	Cumulative exposure to tobacco								
	N in ever smoker									
	Black women	At 5 pack-years	-	-	-	-	1.69 (1.13 to 2.53)	0.005	1.63 (1.02 to 2.60)	0.12
		At 10 pack-years					2.69 (1.28 to 5.66)		2.47 (1.04 to 5.89)	
		At 20 pack-years					5.19 (1.62 to 16.6)		4.18 (1.07 to 16.3)	
		At 40 pack-years					10.5 (2.40 to 45.9)		5.97 (1.03 to 34.5)	
	Black men	At 5 pack-years	-	-	-	-	1.17 (0.75 to 1.83)	0.10	0.96 (0.53 to 1.73)	0.08
		At 10 pack-years					1.38 (0.60 to 3.15)		0.96 (0.32 to 2.88)	
		At 20 pack-years					1.89 (0.50 to 7.15)		1.10 (0.18 to 6.78)	
		At 40 pack-years					3.56 (0.58 to 21.7)		2.03 (0.15 to 27.6)	
	White women	At 5 pack-years	-	-	-	-	1.63 (1.02 to 2.59)	0.036	1.13 (0.66 to 1.92)	0.91
		At 10 pack-years					2.43 (1.07 to 5.52)		1.23 (0.48 to 3.20)	
		At 20 pack-years					3.60 (1.25 to 10.3)		1.31 (0.35 to 4.89)	
		At 40 pack-years					3.21 (1.05 to 9.82)		1.11 (0.21 to 5.90)	

Appendix Table 3 (Continued)

		Never tobacco smoker N= 1,718 (53%)				Ever tobacco smoker N= 1,539 (47%)				
		Unadjusted		Multivariable adjusted <sup>b</sup>		Unadjusted		Multivariable adjusted <sup>b</sup>		
Normalized composite CIMT at $\geq 75^{\text{th}}$ percentile <sup>a</sup>	Race-sex strata N in never; ever smoker	Cumulative exposure to marijuana	Odds Ratio (CI)	P Value <sup>c</sup>	Odds Ratio (CI)	P Value <sup>c</sup>	Odds Ratio (CI)	P Value <sup>c</sup>	Odds Ratio (CI)	P Value <sup>c</sup>
White men N = 364	At 5 pack-years	-	-	-	-	1.19 (0.90 to 1.58)	0.06	1.17 (0.80 to 1.73)	0.18	
	At 10 pack-years					1.39 (0.84 to 2.30)		1.36 (0.69 to 2.70)		
	At 20 pack-years					1.73 (0.90 to 3.34)		1.76 (0.71 to 4.37)		
	At 40 pack-years					2.20 (1.13 to 4.28)		2.65 (0.95 to 7.41)		

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

Distribution of all CARDIA participants examined ( $\geq 75^{\text{th}}$  percentile) to define high standardized CC at  $\geq 75^{\text{th}}$  percentile. (7)

<sup>a</sup>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.(7)

<sup>b</sup>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. Cave unstable models in high cumulative use because of low N (high OR and 95% CI).

<sup>c</sup>P-values came from a Wald test.

## STROBE Statement – Filled Checklist

	Item no	Recommendation	Done	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	✓	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓,	1
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓	2
Objectives	3	State specific objectives, including any prespecified hypotheses	✓, NA	2
Methods				
Study design	4	Present key elements of study design early in the paper	✓	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	2, see also references listed in the methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓	2, see also references listed in the methods and Supplement
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	2-3 and Supplement
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	3 and Supplement
Bias	9	Describe any efforts to address potential sources of bias	✓	4 and Supplement
Study size	10	Explain how the study size was arrived at	✓	2, 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓	3-4 and Supplement
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	✓	3-4
		(b) Describe any methods used to examine subgroups and interactions	✓	3-4
		(c) Explain how missing data were addressed	✓	4 and Supplement
		(d) If applicable, explain how loss to follow-up was addressed	✓	4 and Supplement
		(e) Describe any sensitivity analyses	✓	4 and Supplement
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓	4-5
		(b) Give reasons for non-participation at each stage	✓	Supplement
		(c) Consider use of a flow diagram	-	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓	4, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	✓	4, Table 1
		(c) Summarise follow-up time (eg, average and total amount)	✓	4

(Continued)

	Item no	Recommendation	Done	Page
Outcome data	15*	Report numbers of outcome events or summary measures over time	✓	4-5, Figure 1, Table 2, eTable 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓	4-5, Figure 1, Table 3, eTable 2
		(b) Report category boundaries when continuous variables were categorized	✓	4-5, Figure 1, Table 3, eTable 2
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓	5, eTables 1 and 2
Discussion				
Key results	18	Summarise key results with reference to study objectives	✓	5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓	6-7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓	7
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓	7

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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