CLINICAL RESEARCH STUDY

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

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ABSTRACT

BACKGROUND: Resting heart rate can predict cardiovascular disease. Heart rate increases with tobacco smoking, but its association with cannabis use is unclear. We studied the association between current and cumulative cannabis use and heart rate.

METHODS: We used data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a large prospective cohort of 5115 Black and white women and men followed over 30 years. We explored the association between cannabis exposure and heart rate, adjusted for demographic factors, cardiovascular risk factors, alcohol and other illicit drug use, physical activity, and beta-blockers, in mixed longitudinal models censoring participants with cardiovascular disease.

RESULTS: CARDIA participants contributed to 35,654 individual examinations over 30 years. At the Year 30 examination, 471 out of 3269 (14%) currently used cannabis. In multivariable adjusted models, compared to no current use, using cannabis 5 times per month was associated with lower heart rate of −0.7 beats per minute (95% confidence interval: −1.0 to −0.3), and daily use with lower heart rate of −2.1 beats per minute (95% confidence interval: −3.0 to −1.3, overall $P < .001$). Cumulative exposure to cannabis use was not associated with heart rate.

CONCLUSION: Recent current cannabis use was associated with lower resting heart rate. The findings appeared to be transient because past cumulative exposure to cannabis was not associated with heart rate. This adds to the growing body of evidence suggesting a lack of deleterious association of cannabis use at a level typical of the general population on surrogate outcomes of cardiovascular disease.

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KEY WORDS: Cannabis; Cardiovascular disease; Heart rate

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INTRODUCTION

Cannabis is used at least once yearly by 18% of the US population, and the use by middle-aged people is rising.[1,2] For example, 12% of men between 60 and 64 years of age reported to use cannabis at least once monthly.[3] As more jurisdictions legalize its use, health care professionals, consumers, the public, and policy makers need to know if cannabis use is associated with adverse clinical or surrogate outcomes,[4] especially the association between cannabis use and cardiovascular risk factors and outcomes, as highlighted by the 2020 statement from the American Heart Association.[5,6]

CLINICAL SIGNIFICANCE

- Cannabis was not associated with higher heart rate, a surrogate marker of cardiovascular disease.
- Current cannabis use was linearly associated with lower resting heart rate.
- Cumulative exposure to cannabis was not associated with resting heart rate

The current research regarding the effects of cannabis use and cardiovascular health is mixed. In the early 2000s and 2010s, case reports and small retrospective studies suggested cannabis raised the risk of myocardial infarctions.[7-10] In vitro studies of the main psychoactive agent in cannabis, tetrahydrocannabinol (THC), tried to explain the suggested deleterious effects on smooth muscles cells and the myocardium but found ambiguous results.[11] On the other hand, large prospective cohort studies in the United States, Sweden, and Belgium published between the late 1990s and the end of the 2010s (5000 to 65,000 participants) found no association between cannabis use and incident cardiovascular disease.[4,5,12-16] These populations might have been too young, or the cannabis exposure too low to find associations with cardiovascular disease. Researchers thus studied surrogate outcomes and found no association between cannabis and subclinical atherosclerosis, carotid intima-media thickness, or electrocardiogram (ECG) abnormalities.[17-19]

Another important surrogate outcome is resting heart rate, which has been associated with incident heart failure and cardiovascular disease.[20] Prospective cohort studies suggested that risk of coronary atherosclerosis,[21] myocardial ischemia, ventricular arrhythmias, and left ventricular function continuously increase with heart rate over 60 beats per minute.[20,22,23] A 2016 review on cannabis and cardiovascular disease reported an association between acute exposure to cannabis and transient increase in heart rate,[24] but repeated exposure over a few days lowered heart rate in various studies.[25-31] These studies were small and often lacked adjustment for confounders such as physical activity, multiple cardiovascular risk factors, and medication use affecting heart rate.

We set out to determine the association between heart rate and current and cumulative cannabis use in a large cohort followed over 3 decades, with multiple assessment of cannabis, heart rate, and a rich set of confounders.

MATERIALS AND METHODS

Population

We used data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a cohort of 5115 self-identified Black and white, women and men, aged between 18 and 30 years at baseline, in 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. Participants were examined in up to 9 clinical visits over the study period (1985-1986 [Year 0] to 2015-2016 [Year 30]). All participants granted informed consent before entering the study and at every follow-up visit. All study protocols were approved by the institutional review boards at each site.

Cannabis Exposure

Multiple cannabis use variables are available for all 9 visits (baseline, and follow-up Years 2, 5, 7, 10, 15, 20, 25, and 30), but CARDIA did not assess modality (eg, smoked or ingested) of cannabis use. Current cannabis use was assessed by the following survey question: "During the last 30 days, on how many days did you use cannabis?" Direct self-reported lifetime exposure was assessed by the question: "About how many times in your lifetime have you used cannabis?" We used current use and baseline lifetime use to compute cannabis-years; 1 year of exposure was equivalent to 365 days of cannabis use. We assumed that current use at each visit (the number of days of cannabis use in the month before the visit) reflected the average number of days of use during the months before and after each visit. We estimated cumulative lifetime use by totaling the number of days using cannabis during follow-up. We adjusted our estimate upward whenever participants self-reported higher lifetime use than we computed for each visit.[15,17,32,33] Cannabis use in the 24 hours before the examination was queried at baseline and Years 2, 5, and 30: "Did you use cannabis in the last 24 hours?" (See Appendix, available online, for more information on computing cannabis exposure).

Heart Rate Measures

Before assessing heart rate at every examination, participants were sitting in a quiet room for 5 minutes. Heart rate was then measured manually by study staff before blood pressure by palpation of the radial artery, counting the number of beats in a 30-second interval. This number was multiplied by 2 to get beats per minute. At Years 0, 7, and 20,

heart rate was also measured with a single resting-ECG reading (10 seconds of recording time of sufficient quality).[34]

Covariables

We used number of daily smoked tobacco cigarettes at every visit and cumulative lifetime exposure to tobacco cigarettes in pack-years.[35] Occasional smoking was not queried in CARDIA. Education (in years) was the highest educational grade the participant reached by each examination. Physical activity was measured at every visit with questions on how much time per week the participant spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months.[36] Cardiovascular risk factor measurements included blood pressure, cholesterol levels (total, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides], body mass index (BMI), use of beta-blockers, antidepressants, antipsychotics, current and cumulative alcohol use (1 drink-year corresponding to 365 d/y × 1 drink/day, see Appendix, available online),[32] binge-drinking episodes, and current exposure to cocaine, amphetamine, and heroin. These variables were collected at each CARDIA examination.

Statistical Analyses

We used descriptive statistics to compare participants' heart rate at different levels of current and cumulative cannabis use on every visit. To account for within-subject correlation of repeated measures and to model individual departures from the trajectories determined by the fixed effects, we used linear mixed models with correlated random subject-specific intercepts and slopes.

First, we fitted unadjusted models with fixed effects for current cannabis use (days of cannabis use within the last month), and cumulative cannabis use (cannabis-years of exposure), separately. Second, we fitted minimally adjusted models including demographics, adding fixed effects for the covariables used in CARDIA to achieve balanced sampling (age, race, sex, study site, years of education). Third, we fitted fully adjusted models, adding fixed effects for alcohol, physical activity, serum lipids, BMI, systolic and diastolic blood pressure, beta-blockers, antidepressants, antipsychotics, and current cocaine, amphetamines, and heroin use. We censured participants with incident cardiovascular disease during follow-up, to eliminate potential bias of reversing the temporal order of predictor and outcome. We used inverse probability of censoring weights (IPCWs) to minimize potential bias by informative censoring for the main outcome heart rate.[15,17,35] We used last-value-carried-forward and backward imputation for missing covariables and performed sensitivity analyses using multiple imputation methods.

Our sensitivity analyses included 1) stratified analyses by sex and race; 2) using heart rate measured on ECG readings, with data available for baseline, Year 7, and Year 20; 3) analyses on participants that used cannabis in the 24 hours prior to the study visit, with data available for baseline, Years 2, 5, and 30; 4) fitting linear regressions for each clinical visit instead of pooling all the visits; 5) as positive control, models with current tobacco smoking (cigarettes per day) and cumulative tobacco use (tobacco pack-years) as main predictors; and 6) To estimate clinical significance of heart rate differences in cannabis use, exploratory models that used beta-blockers as the main exposure. Tests of statistical significance were 2-tailed; alpha level was 0.05. All analyses were conducted with Stata version 14.2 (StataCorp).

RESULTS

Population

The 5115 participants at baseline provided us with data for 35,654 participant visits over 30 years. Of the 3269 participants with available data on heart rate and current and cumulative cannabis use at the Year 30 follow-up examination, 1866 (57%) were women and 1549 (47%) were Black; 2785 (85%) participants declared they have ever used cannabis, and 471 (14%) currently used cannabis (Table 1). For participants' characteristics at baseline, see Supplementary Table 1, available online. For distribution of cannabis use over time, see Supplementary Figure 1, available online.

Main Results: Cannabis

In unadjusted models that included all participant visits, mean heart rate was 68.4 beats per minute (95% confidence interval [CI]: 68.2 to 68.6) in those not using cannabis and 66.5 beats per minute (95% CI: 65.8 to 67.1, overall $P < .001$) in daily users. Results were similar after multivariable adjustment; mean heart rate was 68.3 beats per minute (95% CI: 68.1 to 68.5) in those not using cannabis and 65.9 beats per minute (95% CI: 65.1 to 66.6, overall $P < .001$) in daily users (Table 2). In multivariable adjusted models, cumulative cannabis use was unassociated with heart rate (Table 2, Supplementary Table 2, available online). The associations between cannabis use and heart rate as continuous outcome are presented in the Figure.

Sensitivity Analyses: Sex and Race

The tests for interaction terms among sex, race, or across the four sex-race strata (Black women/Black men/white women/white men) on the association between cannabis and heart rate were not statistically significant. We found no qualitative difference in the measure of association between cannabis use and heart rate in stratified analyses (Supplementary Tables 3 and 4, available online). We observed that current cannabis use was associated with lower heart rate in analyses stratified by women and men, or Black and white participants (eg, heart rate was 68.8 beats per minute [68.5 to 69.1] in Black participants not using cannabis, and 65.5 beats per minute [64.5 to 66.5] in

Table 1 Characteristics of 3269 Participants with Heart Rate Measurement and Data of Cannabis Use at Year 30 Visit

Variable	All	Never cannabis use*	Past cannabis use*	Current cannabis use*	*P* Value†
N	3269	484	2,314	471	
Age, median (Q1; Q3), years	56 (52; 58)	55 (51; 58)	56 (53; 58)	55 (52; 58)	.007
Race/sex, n (col. %)‡					<.001
Black women	926 (28)	183 (38)	628 (27)	114 (24)	
Black men	623 (19)	75 (15)	420 (18)	128 (27)	
White women	940 (29)	116 (24)	730 (32)	94 (20)	
White men	781 (24)	110 (23)	536 (23)	135 (29)	
Years of education, median (Q1, Q3), years	16 (14; 18)	16 (14; 18)	16 (14; 18)	15 (13; 16)	<.001
Study center, n (col. %)					<.001
Birmingham, AL	719 (22)	210 (43)	457 (20)	52 (11)	
Chicago, IL	733 (22)	125 (26)	529 (23)	79 (17)	
Minneapolis, MN	829 (25)	89 (19)	588 (25)	151 (32)	
Oakland, CA	989 (30)	60 (12)	740 (32)	189 (40)	
Substance use exposure					
Cannabis					
Lifetime cannabis exposure, cannabis-years, n (col. %)§					<.001
0 cannabis-years	485 (15)	484 (100)	—	—	
0 to .5 cannabis-years	1466 (45)	—	1443 (62)	23 (5)	
.5 to 2 cannabis-years	752 (23)	—	658 (28)	94 (20)	
>2 cannabis-years	567 (17)	—	213 (9)	354 (75)	
Tobacco				114 (24)	<.001
Cigarette smoking, n (col. %)					
Never smoker	1675 (51)	418 (86)	1143 (49)		
Former smoker	1125 (34)	57 (12)	850 (37)	217 (46)	
Current smoker	470 (14)	9 (2)	321 (14)	140 (30)	
Number of cigarettes per day in current tobacco smokers, median (Q1; Q3)	10 (5; 15)	16 (6; 20)	10 (5; 12)	10 (5; 15)	.3
Lifetime tobacco exposure in ever tobacco smokers, pack-years, median (Q1, Q3)‖	12 (2; 17)	7 (0; 8)	11 (2; 17)	13 (3; 20)	<.001
Start age of smoking cigarettes, median (Q1; Q3), years	17 (15; 20)	18 (16; 25)	17 (15; 20)	17 (15; 20)	<.001
Alcohol					
Lifetime alcohol exposure among ever drinkers, drink-years, median (Q1, Q3)¶	23 (4; 31)	11 (2; 13)	22 (4; 29)	37 (11; 49)	<.001
Drink in last 24 h (col %)					<.001
0 drinks/24 h	2342 (72)	419 (87)	1651 (71)	271 (58)	
1-2 drinks/24 h	708 (22)	58 (12)	525 (23)	125 (27)	
>2 drinks /24 h	220 (7)	7(1)	138 (6)	75 (16)	
Lifetime exposure to alcohol bingeing, binge drinking days, n (col %)**					<.001
Never reported bingeing	1496 (46)	390 (80)	998 (43)	108 (23)	
≤250 bingeing days	857 (26)	59 (12)	677 (29)	121 (26)	
>250 bingeing days	917 (28)	35 (7)	639 (28)	242 (51)	
Illicit drug exposure					
Current cocaine, crack, speed or methamphetamine, n (col %)††	64 (2)	1 (0)	29 (1)	34 (7)	<.001
Current heroin, n (col %)††	12 (0)	0 (0)	6 (0)	6 (1)	.001
Physical activity					
Physical activity score, median (Q1; Q3)‡‡	260 (121; 464)	203 (83; 393)	266 (126; 464)	295 (145; 539)	<.001
Anthropomorphic variable					
BMI, mean (SD)§§	31 (±7)	32 (±7)	30 (±7)	30 (±6)	<.001
Cardiovascular risk factors					
Systolic blood pressure, mean (SD), in mm Hg	121 (±17)	121 (±17)	120 (±17)	123 (±16)	.002
Diastolic blood pressure, mean (SD), in mm Hg	74 (±11)	74 (±11)	74 (±11)	76 (±11)	<.001
LDL-cholesterol, mean (SD), in mg/dL	111 (±33)	112 (±33)	111 (±33)	106 (±32)	.007
HDL-cholesterol, mean (SD), in mg/dL	60 (±19)	58 (±17)	60 (±19)	59 (±19)	.020
Triglycerides, median (Q1; Q3), in mg/dL	108 (65; 125)	102 (63; 123)	106 (64; 124)	121 (71; 137)	.001
Diabetes, n (col %)	458 (14)	64 (15)	325 (14)	69 (15)	.8
Nonfatal cardiovascular disease, n (col %)‖‖	141 (4)	18 (4)	96 (4)	27 (6)	.2
Medication					
Currently using beta-blocker, n (col %)	268 (8)	50 (10)	185 (8)	33 (7)	.14
Currently using antidepressant drugs, n (col %)					
Currently using antipsychotic drugs, n (col. %)					

BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults study; Col. % = column percentage; LDL = low-density lipoprotein; HDL = high-density lipoprotein; n = number of participants; Q1, Q3 = 1st and 3rd quartile (percentiles 25 and 75); SD = standard deviation.

*Categories based on the answer to the questions: "Have you ever used cannabis?" and "During the last 30 days, on how many days did you use cannabis?"

†*P* values are from Kruskal-Wallis rank test for age, years of education, pack-years, number of cigarettes per day, cigarette smoking start age, drink-years, physical activity, and BMI, and from a $\chi 2$ test for race and sex, study site, current smoking status, and current alcohol use category. Values imputed for missing values.

‡By design, the CARDIA study sampled self-identified white men, white women, Black men, and Black women in roughly equal numbers for participation in the study.

§Cumulative lifetime exposure to cannabis joints in terms of cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days used cannabis (1 y × 365 d/y).

‖Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 y × 365 d/y × 1 pack/days × 20 cigarettes/pack), among ever tobacco smokers.

¶Drink-years among those reporting ever drinking alcohol. A drink-year was defined as the total amount of ethanol consumed by a person who had had 1 alcoholic drink per day for 1 year (1drink-year = 17.24 mL of ethanol/drink × 1 drink/day × 365 d/y = 6292.6 mL of ethanol).

**Binge-drinking days defined as 5 or more drinks per episode (Supporting information, Appendix, available online). If bingeing were to be constant over 25 years in 1 individual, 250 binge-drinking days would correspond to 10 episodes of bingeing per year over 25 years.

††The number of days on the illicit drug listed over the study duration was computed using current exposure (current use defined as any use within the last 30 days) at each visit and replaced by lifetime exposure when the latter was higher. Cocaine included other forms of cocaine, such as crack, powder, free base; amphetamines included speed, uppers, and methamphetamines (Methods and Supporting information, Appendix, available online).

‡‡Physical activity measured with the CARDIA physical activity history questionnaire, which queries the amount of times per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months.[3]

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

‖‖Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow up time data set to derive fatal and non-fatal outcome variables.

daily users, Supplementary Table 3, available online). When stratifying analyses by sex and race, the association between cannabis and lower heart rate was not significant anymore in white women and white men (Supplementary Table 4, available online).

Cumulative cannabis use was not associated with higher heart rate in any sex-race category (Supplementary Tables 3 and 4, available online).

ECG Measured Heart Rate

We obtained ECG measurements for a total of 11,375 participant visits. Current cannabis use was associated with lower ECG heart rate. In multivariable adjusted models, mean ECG heart rate was 64.3 beats per minute (95% CI: 64.1 to 64.6) in those not currently using cannabis and 61.9 beats per minute (95% CI: 60.9 to 62.9, overall $P < .001$) in daily users (Supplementary Table 5, available online).

Cannabis Use Within the Last 24 Hours

Results were similar to the main results. In multivariable adjusted models, mean heart rate was 68.6 beats per minute (95% CI: 67.6 to 69.6) in those not currently using cannabis and 66.4 beats per minute (95% CI: 65.4 to 67.4; overall $P = .01$) in daily users (Supplementary Table 6, available online).

Analyses Stratified by Visit

At each clinical visit, current cannabis use was associated with lower heart rate, although results were not always statistically significant. Cumulative cannabis exposure was unassociated with heart rate in analyses stratified by visit (Supplementary Table 7, available online).

Tobacco

At Year 30, 470 participants (14%) reported smoking tobacco. In multivariable adjusted models, mean heart rate was 67.8 beats per minute (95% CI: 67.6 to 68.0) in those not smoking tobacco and 70.1 beats per minute (95% CI: 69.7 to 70.5, overall $P < .001$) in those smoking 20 cigarettes per day (Supplementary Table 8, available online). Cumulative exposure to tobacco was associated with slightly higher heart rate. The associations between tobacco smoking and heart rate as continuous outcome are presented in Supplementary Figure 2.

Beta-Blockers

In a multivariable adjusted model, current use of beta-blockers was associated with lower heart rate (−4.4 beats per minute; 95% CI: −5.2 to −3.5) (Supplementary Table 9, available online).

DISCUSSION

Current cannabis use was associated with lower resting heart rate, but cumulative cannabis exposure was not. Results were similar using ECG-measured heart rate and after restricting to those who used cannabis within 24 hours of their visit. The association of cannabis and lower heart rate was similar between Black and white and men and women.

In our study, we found mean resting heart rate to be around 68 beats per minute when counted manually and around 64 beats per minute when measured by ECG. This is like resting heart rate found in other cohort studies.[37-39] Differences in heart rate in current cannabis users were low (−2.1 beats per minute in daily users) and may not be clinically relevant compared to beta-blockers, which typically

Table 2 Association Between Heart Rate and Current and Cumulative Exposure to Cannabis, Censoring Participants with CVD

Cannabis exposure	Heart rate, unadjusted (95% CI)	*P* Value*	Heart rate, adjusted for demographics (95% CI)	*P* Value*	Heart rate, fully adjusted and IPCW (95% CI)	*P* Value*
Current cannabis exposure (days of cannabis use within the last 30 days)† N= 35,298‡						
- At 0 d/mo	68.4 (68.2 to 68.6)	.001	68.3 (68.1 to 68.5)	<.001	68.3 (68.1 to 68.5)	<.001
- At 5 d/mo	68.1 (67.9 to 68.3)		68.0 (67.7 to 68.2)		67.9 (67.7 to 68.1)	
- At 15 d/mo	67.4 (67.1 to 67.8)		67.3 (66.9 to 67.6)		67.1 (66.7 to 67.5)	
- At 30 d/mo	66.5 (65.8 to 67.1)		66.2 (66.6 to 66.9)		65.9 (65.1 to 66.6)	
Cumulative exposure to **cannabis** (in cannabis-years)§ N= 35,298‡						
- At 0 cannabis-years	68.4 (68.2 to 68.6)	.005	68.1 (67.9 to 68.3)	<.001	68.2 (68.0 to 68.4)	0.9
- At 0.5 cannabis-years	68.3 (68.1 to 68.5)		68.1 (67.9 to 68.4)		68.2 (68.0 to 68.4)	
- At 1 cannabis-year	68.3 (68.1 to 68.5)		68.2 (68.0 to 68.4)		68.2 (68.0 to 68.3)	
- At 5 cannabis-years	68.0 (67.7 to 68.3)		68.7 (68.3 to 69.0)		68.2 (67.8 to 68.5)	
- At 10 cannabis-years	67.6 (67.0 to 68.1)		69.2 (68.7 to 69.8)		68.2 (67.5 to 68.8)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HDL = high-density lipoprotein; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

**P* values are from a Wald test.

†Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

‡Composite number of participant-visits used in the mixed model.

§Cumulative exposure to cannabis expressed in cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days of cannabis use. Adjusted for current cannabis use.

Main predictors (prolonged current cannabis use, cumualtive cannabis use) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow up time data set to derive fatal and non-fatal outcome variables.

First unadjusted, then adjusted for demographics (sex, race, age, education years, study center) and finally, for current and cumulative alcohol and tobacco use, total physical activity score, BMI, systolic and diastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants and antipsychotics. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

reduce heart rate by 8-15 beats per minute,[40] and around 4 beats per minute in our exploratory models.

The differences in heart rate were smaller using ECG measures. Participants' resting heart rate was lower in ECGs than in clinical measurements (overall, 64.3 beats per minute on ECGs vs 68.4 beats per minute with clinical measures), probably because participants were supine for a few minutes during the ECG preparation, shifting autonomic nervous balance toward vagal predominance.[27,28] Previous publications suggested cannabis use alters the autonomic nervous system; the direction of the shift depends on frequency of use.[28] A 2016 review on cannabis and cardiovascular disease reported an association between acute exposure to cannabis and transient increase in heart rate; its use may stimulate the sympathetic nervous system,[24] but repeated exposure may lower heart rate because it reduces sympathetic and enhanced parasympathetic activity.[30] Cannabis users may build up tolerance after a few days of use, shifting their autonomous nervous balance and reducing heart rate.[25-29,31]

Prospective cohort studies suggested that risk of cardiovascular disease continuously increases with heart rate over 60 beats per minute.[20,22,23] We did not find an increase in heart rate associated with cannabis use. Our findings align with epidemiological research on thousands of participants from Europe and the United States that found no association between cannabis and cardiovascular disease, mortality, or surrogate outcomes.[12-15]

We found no significant interaction among sex, race, or across the four sex-race strata on the association between cannabis and heart rate. Given that CARDIA included similar proportions of self-identified Black and white women and men, we explored if the measure of associations differed by race and sex. We found no qualitative differences in the measures of associations. The nonsignificance of the measures of association in the analyses stratified by race and sex should be interpreted with caution given the expected lower power to detect statistically significant findings when stratifying by subcategories in the absence of significant interaction.

Limitations

Our study has limitations. Although we could test the association between current exposure and heart rate, we could not test the association between hyperacute exposure to cannabis and heart rate; we did not know the date and time of the last exposure, or the time elapsed between exposures.

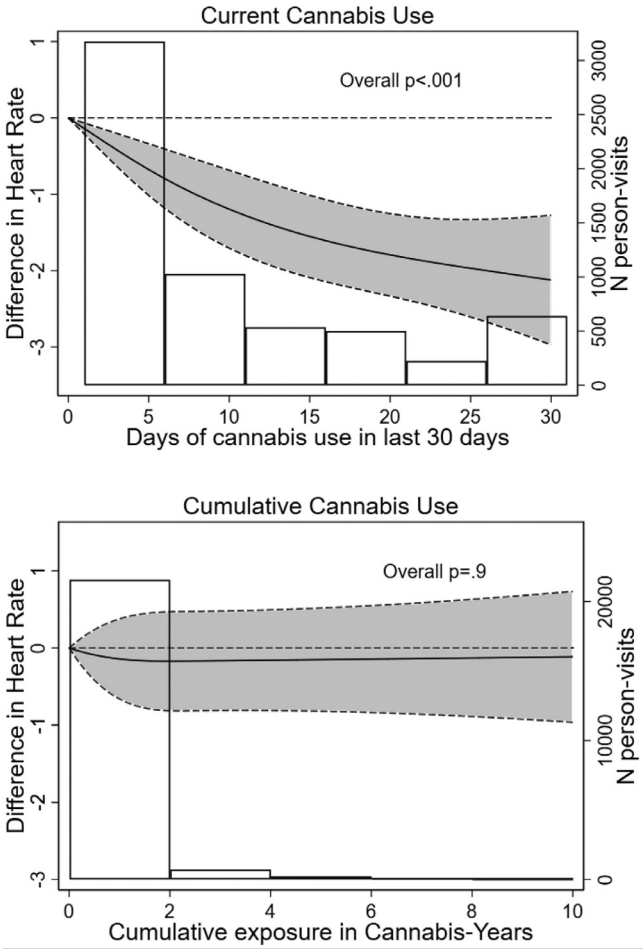

Figure 1 Association between heart rate and current and cumulative cannabis use. Results from multivariable adjusted mixed longitudinal models, using splines with 3 knots, and censoring participants with incident cardiovascular disease for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (sex, race, age, education years, study center), current and cumulative alcohol and tobacco use, total physical activity score, body mass index, systolic and diastolic blood pressure, low- and high-density lipoproteins, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights to account for potential informative censoring during follow-up. Cumulative exposure to cannabis expressed in cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days of cannabis use, adjusting for current cannabis use. N included person-visits = 35,298.

The number of daily cannabis users in CARDIA was limited but constant during the study period: 87 out of 5113 (1.7%) daily cannabis users at baseline and 82 out of 3358 (2.4%) at Year 30. Since few participants had high current exposure to cannabis, our results may not be representative of this population, but we found that daily cannabis users had even lower heart rates than users with fewer or no use of cannabis (Figure). Future studies should test the effects of acute cannabis use on heart rate and stratify analyses by occasional use or repeated exposure. As we had information on use of cannabis in days per month but not on joints per day, and as we calculated cumulative cannabis exposure on data reported every 2 to 5 years, our estimates bear some uncertainties. The CARDIA questionnaire did not inquire about the modality of use of cannabis (eg, smoked or ingested) or its type (eg, THC content). Because cannabis use was illegal during the study, social desirability bias may have affected reporting. Also, although our results suggests that cannabis use is not associated with cardiovascular risks through higher heart rate, cardiovascular disease by other mechanisms not studied in this article cannot be discounted and will require further studies. Finally, residual confounding due to different lifestyle potentially associated with cannabis use cannot be excluded.

CONCLUSION

Most participants in a middle-aged US population of self-reported Black and white participants did occasionally use cannabis in their life. Current cannabis use was associated with lower resting heart rate, which supports findings from experimental studies that observed shifts in sympathovagal balance. Past cumulative exposure to cannabis was not associated with heart rate, indicating the effects of cannabis exposure on heart rate are transient. Our findings add to the growing body of evidence suggesting a lack of deleterious association of cannabis use at a level typical of the general population on surrogate outcomes of cardiovascular disease.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.01.057.

eMethods

Measurements. See the CARDIA study.[17]

Alcohol exposure. Alcohol consumption was measured during each CARDIA 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/d, as previously reported.[33] 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/wk or >4 (>3) drinks/d].[41] 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 was 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 3 follow-up questions regarding how many drinks of wine, beer, and liquor they usually consumed per week. Assuming that 1 drink of beer, wine, or liquor contains 16.7 mL, 17.0 mL, or 19.1 mL of ethanol, respectively (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/d (365 d/y ×17.24 mL of alcohol/d = 6293 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 5 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 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 1 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, methamphetamines) and heroin.[42] 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, methamphetamines, 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) 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. For all visits, high-density lipoprotein (HDL) cholesterol was determined by dextran sulfate −magnesium precipitation on the Abbot Spectrum, and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[42] 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.

Beta-blocking medication. To evaluate the magnitude of heart rate differences associated with cannabis or tobacco use, we contrasted it to the heart rate difference with beta-blocking medication use. Use of medication was recorded at each clinical visit. All medications reported by the patients were recorded verbatim and coded through a centralized automated system and according to the Iowa Drug Information Services (IDIS; http://citeseerx.ist.psu.edu/viewdoc/download;jsessionxml:id=63F7C4551D35213274A7983C7E934392?doi=10.1.1.674.2511&rep=rep1&type=pdf). This has been done in other studies on use of antihypertensive agents.[43] We used the American Hospital Formulary Services (AHSF) and the Women's Health and Aging Study (WHAS) classifications to classify beta-blocking medications.[17] We evaluated current use of beta-blockers at every clinical visit separately and classified participants in either currently taking beta-blockers or not.

Statistical analyses. *Cannabis use.* We present an example of 2 participant included in the study illustrating the method for computing cannabis-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.[44]

According to Box 1, the participant reported having used cannabis 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

Box 1 Example of Computing Cannabis-Years for One Participant

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 cannabis during the month before the visit ("During the last 30 days, on how many days did you use cannabis?"); mj30d_imp = imputed mj30d_ variable; domj = computed cumulative days of cannabis use; life_ = self-reported lifetime use of cannabis queried at each visit ("About how many times in your lifetime have you used cannabis?"); yomj_max = computed cumulative years of cannabis use (domj/365).

examination (domj at visit 0 = 300, where domj signifies "days of cannabis").

At this baseline examination, the participant reported using cannabis 15 days per month (mj30d_). Multiplied by 12.17 months (365/30), we estimated that this participant used cannabis 182 days in the first year after the first examination (15 × 12.17). The number of days of cannabis use in the month before the baseline examination was imputed forward at year 1 (mj30d_imp). At year 2, the participant reported using cannabis 20 days per month; at year 5, they reported 4 days per month. These numbers were imputed backward and forward; when there were an uneven number of intervals (preventing us from evenly splitting the imputation based on the prior value as opposed to the postvalue), the exposure at the prior interval was favored arbitrarily. Participants then accrued lifetime days of cannabis use over follow-up. The cumulative number of cannabis-years over lifetime is presented in the last column (yomj_max). For this participant, the cumulative number of cannabis years was 8.82, corresponding to 3219 estimated days of cannabis 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 cannabis use between 2 examinations with data on this variable.

Inverse probability of censoring weights (IPCWs). To reduce the potential for informative censoring, we computed IPCWs.[44] Covariables included in the pooled logistic regression model used to estimate the IPCWs were fixed covariables: race, sex, study center and education; and 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, and visits were all modeled as 3-knot restricted cubic splines.

STROBE Statement. Filled Checklist (pages refer to the text document only, with tables situated after references)

	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	√	2-4 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	√	3-4 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	√	3-5
		(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 and eTable 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)	√	4-5
Outcome data	15*	Report numbers of outcome events or summary measures over time	√	4-5, Figure 1, Table 2, eTables 2 to 5, eFigure 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 2, eTable 2, eFigure 1
		(*b*) Report category boundaries when continuous variables were categorized	√	4-5, Figure 1, Table 2, eTable 2, eFigure 1

(*Continued*)

	Item no	Recommendation	Done	Page
		(*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 3-8, eFigure 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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√	6-7
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.

Supplementary Table 1 Characteristics of 5053 Participants with Heart Rate Measurement and Data on Cannabis Use at Baseline Visit

Variable	All	Never cannabis use*	Past cannabis use*	Current cannabis use*	*P* Value†
N	5053	1305 (26)	2321 (46)	1427 (28)	
Age, median (Q1; Q3), years	25 (22; 28)	24 (21; 28)	26 (23; 28)	25 (22; 28)	<.001
Race/sex, n (col. %)‡					<.001
Black women	1461 (29)	515 (39)	631 (27)	315 (22)	
Black men	1133 (22)	296 (23)	403 (17)	434 (30)	
White women	1299 (26)	269 (21)	749 (32)	281 (20)	
White men	1160 (23)	225 (17)	538 (23)	397 (28)	
Years of education, median (Q1, Q3), years	15 (13; 17)	15 (13; 17)	16 (14; 18)	14 (12; 16)	<.001
Study center, n (col. %)					<.001
Birmingham, AL	1173 (23)	505 (39)	433 (19)	235 (16)	
Chicago, IL	1100 (22)	323 (25)	462 (20)	315 (22)	
Minneapolis, MN	1362 (27)	320 (25)	616 (27)	426 (30)	
Oakland, CA	1418 (28)	157 (12)	810 (35)	451 (32)	
Substance use exposure					<.001
Cannabis					
Lifetime cannabis exposure, cannabis-years, n (col. %)§					
0 cannabis-years	1305 (26)	1305 (100)	0 (0)	0 (0)	
0 to 0.5 cannabis-years	2561 (51)	0 (0)	1980 (85)	581 (41)	
0.5 to 2 cannabis-years	1187 (23)	0 (0)	341 (15)	846 (59)	
>2 cannabis-years	0 (0)	0 (0)	0 (0)	0 (0)	
Tobacco					<.001
Cigarette smoking, n (col. %)					
Never smoker	2765 (55)	1028 (79)	1223 (53)	514 (36)	
Former smoker	736 (15)	77(6)	417 (18)	242 (17)	
Current smoker	1552 (31)	200 (15)	681 (29)	671 (47)	
Number of cigarettes per day in current tobacco smokers, median (Q1; Q3)	13 (6; 20)	12 (5; 20)	13 (6; 20)	13 (6; 20)	.3
Pack-years over lifetime in ever tobacco smokers, median (Q1, Q3)‖	5 (1; 7)	4 (1; 6)	5 (1; 7)	5 (1; 7)	.19
Start age of smoking cigarettes, median (Q1; Q3), years	16 (15; 18)	16 (15; 19)	16 (15; 19)	16 (14; 18)	.090
Alcohol					
Lifetime alcohol exposure among ever drinkers, drink-years, median (Q1, Q3)¶	1 (0; 1)	1 (0; 1)	1 (0; 1)	1 (0; 2)	<.001
Drink in last 24 h (row %)					
0 drinks/24 h	3786 (75)	1136 (87)	1777 (77)	873 (61)	<.001
1-2 drinks/24 h	908 (18)	130 (10)	414 (18)	364 (26)	
>2 drinks/24 h	359 (7)	39 (3)	130 (6)	190 (13)	
Lifetime exposure to alcohol bingeing, binge drinking days, n (col %)**					<.001
Never reported bingeing	3511 (69)	1124 (86)	1680 (72)	707 (50)	
≤250 bingeing days	1,542 (31)	181 (14)	641 (28)	720 (50)	
>250 bingeing days	0 (0)	0 (0)	0 (0)	0 (0)	
Physical activity					
Physical activity score, median (Q1; Q3)††	421 (198; 579)	369 (156; 515)	415 (196; 569)	477 (239; 648)	<.001
Anthropomorphic variable	24 (±5)	25 (±5)	24 (±5)	24 (±5)	0.053
BMI, mean (SD)‡‡					
Cardiovascular risk factors					
Systolic blood pressure, mean (SD), in mm Hg	110 (±11)	110 (±11)	110 (±11)	112 (±11)	<.001
Diastolic blood pressure, mean (SD), in mm Hg	69 (±10)	69 (±10)	69 (±9)	68 (±10)	.6
LDL-cholesterol, mean (SD), in mg/dL	109 (±31)	109 (±32)	110 (±31)	107 (±31)	.030
HDL-cholesterol, mean (SD), in mg/dL	53 (±13)	52 (±13)	54 (±13)	53 (±14)	.013
Triglycerides, median (Q1; Q3), in mg/dL	73 (45; 84)	70 (44; 83)	72 (45; 83)	76 (48; 87)	<.001
Diabetes, n (col %)	43 (1)	12 (1)	23 (1)	8 (1)	.4
Medication					
Currently using betablocker, n (col %)	44 (1)	16 (1)	22 (1)	6 (0)	.067
Currently using antidepressant drugs, n (col %)	24 (0)	4 (0)	14 (1)	6 (0)	.4
Currently using antipsychotic drugs, n (col. %)	10 (0)	3 (0)	5 (0)	2 (0)	.8

BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults study; Col. % = column percentage; LDL = low-density lipoprotein (LDL); HDL = high-density lipoprotein; n = number of participants; Q1, Q3 = 1st and 3rd quartile (percentiles 25 and 75); SD = standard deviation.

*Categories based on the answer to the questions: "Have you ever used cannabis?" and "During the last 30 days, on how many days did you use cannabis?"

†*P* values are from Kruskal-Wallis rank test for age, years of education, pack-years, number of cigarettes per day, cigarette smoking start age, drink-years, physical activity, and BMI, and from a $\chi 2$ test for race and sex, study site, current smoking status, and current alcohol use category. Values imputed for missing values.

‡By design, the CARDIA study sampled self-identified white men, white women, Black men and Black women in roughly equal numbers for participation in the study.[45]

§Cumulative lifetime exposure to cannabis joints in terms of cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days used cannabis (1 y $\times$ 365 d/y).[33]

‖Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 $\times$ 365 d/y $\times$ 1 pack/d $\times$ 20 cigarettes/pack).

¶Drink-years among those reporting ever drinking alcohol. A drink-year was defined as the total amount of ethanol consumed by a person who had had 1 alcoholic drink per day for 1 year (1drink-year = 17.24 mL of ethanol/drink $\times$ 1 drink/day $\times$ 365 d/y = 6292.6 mL of ethanol).

**Binge-drinking days defined as 5 or more drinks per episode (eMethods, Supporting information, Appendix, available online). If bingeing were to be constant over 25 years in 1 individual, 250 binge-drinking days would correspond to 10 episodes of bingeing per year over 25 years.

††Physical activity measured with the CARDIA physical activity history questionnaire, which queries the amount of time per week spent in 13 categories of leisure, occupational and household physical activities over the past 12 months.[46]

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

Supplementary Table 2 Association Between Heart Rate Differences and Current and Prolonged Exposure to Cannabis or Tobacco, Censoring Participants with Cardiovascular Disease

	Absolute difference in heart rate, unadjusted (95% CI)	*P* Value*	Absolute difference in heart rate, adjusted for demographics (95% CI)	*P* Value*	Absolute difference in heart rate, fully adjusted an IPCW (95% CI)	*P* Value*
Current cannabis exposure (days of cannabis use within the last 30 days)† N= 35,298						
- At 0 d/mo	Reference	<.001	Reference	<0.01	Reference	<.001
- At 5 d/mo	−0.4 (-0.7 to -0.0)		−0.6 (-0.9 to -0.3)		−0.7 (-1.0 to -0.3)	
- At 15 d/mo	−1.0 (-1.5 to - 0.5)		−1.4 (-1.9 to 0.9)		−1.6 (-2.1 to -1.0)	
- At 30 d/mo	−1.9 (-2.7 to -1.2)		−1.8 (-2.5 to -1.0)		−2.1 (-3.0 to -1.3)	
Cumulative exposure to **cannabis** (in cannabis-years)‡ N= 35,298						
- At 0 cannabis-years	Reference	<.001	Reference	<.001	Reference	.9
- At 0.5 cannabis-years	−0.5 (-0.7 to -0.3)		0.2 (-0.1 to 0.4)		−0.1 (-0.7 to 0.2)	
- At 1 cannabis-year	−0.8 (-1.2 to -0.4)		0.3 (-0.1 to 0.7)		−0.1 (-0.7 to 0.4)	
- At 5 cannabis-years	−1.1 (-1.6 to -0.7)		0.7 (0.3 to 1.2)		−0.1 (-0.8 to 0.5)	
- At 10 cannabis-years	−1.2 (-1.9 to -0.6)		1.3 (0.6 to 1.9)		−0.1 (-1.0 to 0.7)	
Current tobacco smoking (cigarettes per day) N= 35,298						
- At 0 cigarettes/day	Reference	<.001	Reference	<.001	Reference	<.001
- At 5 cigarettes/day	1.4 (1.1 to 1.6)		1.0 (0.8 to 1.2)		0.5 (0.6 to 1.1)	
- At 20 cigarettes/day	3.5 (3.1 to 4.0)		2.9 (2.5 to 3.3)		2.5 (2.0 to 3.0)	
- At 40 cigarettes/day	4.7 (3.8 to 5.7)		4.3 (3.5 to 5.2)		3.9 (2.7 to 5.0)	
Cumulative exposure to **tobacco** (in pack-years)§ N= 35,298						
- At 0 pack-years	Reference	<.001	Reference	<.001	Reference	<.001
- At 5 pack-years	1.4 (1.1 to 1.7)		1.5 (1.2 to 1.8)		0.8 (0.4 to 1.2)	
- At 10 pack-years	2.1 (1.6 to 2.5)		2.4 (2.0 to 2.9)		1.3 (0.6 to 1.9)	
- At 20 pack-years	2.1 (1.6 to 2.6)		3.2 (2.7 to 3.8)		1.4 (0.8 to 2.1)	
- At 40 pack-years	1.5 (0.6 to 2.4)		4.2 (3.3 to 5.2)		1.4 (0.2 to 2.6)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HDL = high-density lipoprotein; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

**P* values are from a Wald test.

†Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

‡Cumulative exposure to cannabis expressed in cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days of cannabis use. Adjusted for current cannabis use in full model.

§Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 y × 365 d/y × 1 pack/d × 20 cigarettes/pack), among ever tobacco smokers. Adjusted for current tobacco smoking in full model.

Main predictors (prolonged current cannabis use, cumualtive cannabis use, current smoking and cumulative exposure to smoking) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (sex, race, age, education years, study center) and finally, for current and cumulative alcohol use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

Supplementary Table 3 Association Between Heart Rate and Current and Cumulative Exposure to Cannabis, Stratified by Race or Sex, Fully Adjusted and IPCW, Censoring Participants with Cardiovascular Disease

	Black HR (95% CI)	*P* Value*	White HR (95% CI)	*P* Value*	Women HR (95% CI)	*P* Value*	Men HR (95% CI)	*P* Value*
Current cannabis exposure (days of cannabis use within the last 30 days)† N= 35,654								
- At 0 d/mo	68.8 (68.5 to 69.1)	<.001	67.8 (67.5 to 68.1)	.017	69.7 (69.4 to 69.9)	<.001	66.6 (66.3 to 66.9)	<0.001
- At 5 d/mo	68.2 (68.0 to 68.5)		67.6 (67.3 to 67.9)		69.3 (69.1 to 69.6)		66.2 (65.9 to 66.5)	
- At 15 d/mo	67.1 (66.6 to 67.7)		67.2 (66.7 to 67.7)		68.6 (68.1 to 69.2)		65.4 (64.9 to 65.9)	
- At 30 d/mo	65.5 (64.5 to 66.5)		66.6 (65.6 to 67.6)		67.6 (66.5 to 68.7)		64.2 (63.3 to 65.2)	
Cumulative exposure to **cannabis** (in cannabis-years)‡ N= 35,654								
- At 0 cannabis-years	68.7 (68.4 to 69.0)	0.15	67.7 (67.4 to 68.0)	0.6	69.6 (69.3 to 69.9)	0.5	66.5 (66.2 to 66.8)	0.04
- At 0.5 cannabis-years	68.6 (68.3 to 68.9)		67.7 (67.4 to 68.0)		69.6 (69.4 to 69.9)		66.5 (66.2 to 66.8)	
- At 1 cannabis-year	68.6 (68.3 to 68.9)		67.7 (67.5 to 68.0)		69.6 (69.4 to 69.9)		66.4 (66.1 to 66.7)	
- At 5 cannabis-years	68.3 (67.7 to 68.8)		67.8 (67.4 to 68.3)		69.8 (69.2 to 70.4)		66.1 (65.7 to 66.5)	
- At 10 cannabis-years	67.9 (66.8 to 68.9)		67.9 (67.1 to 68.8)		70.0 (68.8 to 71.3)		65.6 (64.9 to 66.4)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular death; HDL = high-density lipoprotein; HR = heart rate; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

**P* values are from a Wald test.

†Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

‡Cumulative exposure to cannabis expressed in cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days of cannabis use. Adjusted for current cannabis use in full model.

Main predictors (prolonged current cannabis use, cumualtive cannabis use) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (age, education years, study center) and for current and cumulative alcohol and tobacco use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

Supplementary Table 4 Association Between Heart Rate and Current and Cumulative Exposure to Cannabis, Stratified by Race and Sex, Fully adjusted and IPCW, Censoring Participants with Cardiovascular Disease.

	Black women HR (95% CI)	*P* Value*	Black men HR (95% CI)	*P* Value*	White women HR (95% CI)	*P* Value*	White men HR (95% CI)	*P* Value*
Current cannabis exposure (days of cannabis use within the last 30 days) † N= 35,654								
- At 0 d/mo	70.2 (69.9 to 70.6)	<.001	66.9 (66.5 to 67.4)	<.001	69.2 (68.8 to 69.5)	.15	66.3 (65.9 to 66.7)	0.065
- At 5 d/mo	69.8 (69.4 to 70.1)		66.4 (65.9 to 66.8)		68.9 (68.5 to 69.4)		66.1 (65.7 to 66.5)	
- At 15 d/mo	68.9 (68.1 to 69.6)		65.3 (64.6 to 66.0)		68.5 (67.7 to 69.4)		65.7 (65.1 to 66.4)	
- At 30 d/mo	67.6 (66.1 to 69.9)		63.7 (62.4 to 65.1)		67.9 (66.2 to 69.6)		65.2 (64.0 to 66.3)	
Cumulative exposure to **cannabis** (in cannabis-years) ‡ N= 35,654								
- At 0 cannabis-years	70.1 (69.7 to 70.5)	.8	66.9 (66.4 to 67.4)	.005	69.1 (68.7 to 69.5)	.3	66.2 (65.8 to 66.6)	0.6
- At 0.5 cannabis-years	70.1 (69.8 to 70.4)		66.8 (66.4 to 67.3)		69.1 (68.7 to 69.5)		66.2 (65.8 to 66.6)	
- At 1 cannabis-year	70.1 (69.7 to 70.4)		66.7 (66.3 to 67.1)		69.2 (68.8 to 69.5)		66.2 (65.8 to 66.6)	
- At 5 cannabis-years	70.0 (69.1 to 70.9)		65.9 (65.3 to 66.6)		69.5 (68.6 to 70.4)		66.1 (65.5 to 66.6)	
- At 10 cannabis-years	70.0 (68.1 to 71.8)		64.9 (63.7 to 66.2)		69.9 (68.2 to 71.7)		65.9 (65.0 to 66.9)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular death; HDL = high-density lipoprotein; HR = heart rate; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

*P-values are from a Wald test.

†Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

‡Cumulative exposure to cannabis expressed in cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days of cannabis use. Adjusted for current cannabis use in full model.

Main predictors (prolonged current cannabis use, cumualtive cannabis use) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (age, education years, study center) and for current and cumulative alcohol and tobacco use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

Supplementary Table 5 Association Between Heart Rate Measured on ECG and Current Exposure to Cannabis, Censoring Participants with Cardiovascular Disease

	Heart rate, unadjusted (95% CI)	*P* Value*	Heart rate, adjusted for demographics (95% CI)	*P* Value*	Heart rate, fully adjusted and IPCW (95% CI)	*P* Value*
Current cannabis exposure (days of cannabis use within the last 30 days)† N= 11,180						
- At 0 d/mo	64.3 (64.1 to 64.6)	<.001	64.3 (64.0 to 64.5)	<.001	64.3 (64.1 to 64.6)	<.001
- At 5 d/mo	63.4 (63.1 to 63.7)		63.8 (63.5 to 64.0)		63.9 (63.7 to 64.2)	
- At 15 d/mo	61.6 (61.1 to 62.1)		62.8 (62.3 to 63.3)		63.1 (62.6 to 64.6)	
- At 30 d/mo	58.8 (57.8 to 59.8)		61.3 (60.3 to 62.3)		61.9 (60.9 to 62.9)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular death; ECG = electrocardiogram; HDL = high-density lipoprotein; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

**P* values are from a Wald test.

†Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

ECG data available on visit years 0, 7, and 20. Main predictors (prolonged current cannabis use, cumualtive cannabis use, current smoking and cumulative exposure to smoking) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. First unadjusted, then adjusted for demographics (sex, race, age, education years, study center) and finally, for current and cumulative alcohol and tobacco use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

Supplementary Table 6 Association Between Heart Rate and Current Exposure to Cannabis, Among Participants with Use in Past 24 Hours, Censoring Participants with Cardiovascular Disease

	Heart rate, unadjusted (95% CI)	*P* Value*	Heart rate, adjusted for demographics (95% CI)	*P* Value*	Heart rate, fully adjusted and IPCW (95% CI)	*P* Value*
Current cannabis exposure (days of cannabis use within the last 30 days)† N= 1328						
- At 0 d/mo	68.8 (67.8 to 69.9)	<.001	68.5 (67.4 to 69.5)	.019	68.6 (67.6 to 69.6)	.01
- At 5 d/mo	68.4 (67.5 to 69.2)		68.1 (67.3 to 69.0)		68.2 (67.4 to 69.0)	
- At 15 d/mo	67.5 (66.8 to 68.1)		67.5 (66.9 to 68.1)		67.5 (66.9 to 68.1)	
- At 30 d/mo	66.1 (65.1 to 67.2)		66.4 (65.4 to 67.5)		66.4 (65.4 to 67.4)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular death; HDL = high-density lipoprotein; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

**P* values are from a Wald test.

†Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

Analyses restricted to baseline and visit Year 2, 5, and 30, as use of cannabis in past 24 hours was assessed in these visits. Only participant visits with use in past 24 hours included. Main predictors (prolonged current cannabis use, cumualtive cannabis use, current smoking and cumulative exposure to smoking) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. First unadjusted, then adjusted for demographics (sex, race, age, education years, study center) and finally, for current and cumulative alcohol and tobacco use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

Supplementary Table 7 Association Between Heart Rate Differences and Current and Cumulative Exposure to Cannabis or Tobacco, by Visit, Censoring Participants with Cardiovascular Disease

Cannabis or tobacco exposure	Absolute difference in heart rate, fully adjusted (95% CI)
Current cannabis exposure (days of cannabis use within the last 30 days)*	
- At 0 d/mo	Reference
- At 15 d/mo	
- Baseline	−1.3 (-2.2 to -0.5)
- Year 2	−1.3 (-2.3 to -0.3)
- Year 5	−0.1 (-1.5 to 1.3)
- Year 7	−0.5 (-1.7 to 0.6)
- Year 10	−1.2 (-2.4 to -0.1)
- Year 15	−0.4 (-1.7 to 0.8)
- Year 20	−1.4 (-3.0 to 0.3)
- Year 25	−1.5 (-3.2 to 0.3)
- Year 30	−0.6 (-2.4 to 1.2)
Cumulative exposure to cannabis in past cannabis users (in cannabis-years)†	
- At 0 cannabis-years	Reference
- At 1 cannabis-year	
- Baseline	−1.4 (-7.5 to 4.7)
- Year 2	−0.4 (-2.6 to 1.7)
- Year 5	−1.7 (-3.1 to -0.2)
- Year 7	−0.2 (-1.5 to 1.3)
- Year 10	0.1 (-1.1 to 1.2)
- Year 15	0.1 (-1.0 to 1.2)
- Year 20	−0.1 (-0.8 to 0.8)
- Year 25	−0.1 (-0.9 to 0.6)
- Year 30	−0.2 (-0.8 to 0.5)
Current tobacco smoking (in cigarettes per day)	
- At 0 cigarettes/d	Reference
- At 20 cigarettes/d	
- Baseline	2.0 (1.2 to 2.8)
- Year 2	2.5 (1.7 to 3.4)
- Year 5	3.4 (2.6 to 4.2)
- Year 7	3.9 (3.0 to 4.9)
- Year 10	4.4 (3.2 to 5.6)
- Year 15	4.8 (3.3 to 6.2)
- Year 20	3.2 (1.6 to 4.7)
- Year 25	2.6 (0.9 to 4.2)
- Year 30	0.6 (-1.3 to 2.5)
Cumulative exposure to tobacco smoking in past smokers (in pack-years)‡	
- At 0 pack-years	Reference
- At 20 pack-years	
- Baseline	1.4 (-1.2 to 4.1)
- Year 2	1.3 (-1.2 to 3.9)
- Year 5	2.1 (-0.1 to 4.4)
- Year 7	2.6 (0.4 to 4.7)
- Year 10	1.7 (-0.3 to 3.8)
- Year 15	1.3 (-0.4 to 3.0)
- Year 20	0.3 (-1.3 to 1.8)
- Year 25	1.0 (-0.4 to 2.5)
- Year 30	−0.1 (-1.3 to 1.2)

BMI = body mass index; CI = confidence interval;CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein;.

*Current exposure to cannabis assessed through the question, "During the last 30 days, on how many days did you use cannabis?"

†Cumulative exposure to cannabis expressed in cannabis-years, with 1 cannabis-year of exposure equivalent to 365 days of cannabis use. Adjusted for current cannabis use.

‡Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 y × 365 d/y × 1 pack/days × 20 cigarettes/pack), among ever tobacco smokers. Adjusted for current tobacco smoking.

Main predictors (prolonged current cannabis use, cumualtive cannabis use, current smoking and cumulative exposure to smoking) modeled flexibly. Results from multivariable adjusted logisitc regression models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (sex, race, age, education years, study center), for current and cumulative alcohol use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights to account for potential informative censoring during follow-up.

Supplementary Table 8 Association Between Heart Rate and Current and Cumulative Exposure to Tobacco, Censoring Participants with Cardiovascular Disease

	Heart rate, unadjusted (95% CI)	*P* Value*	Heart rate, adjusted for demographics (95% CI)	*P* Value*	Heart rate, fully adjusted and IPCW (95% CI)	*P* Value*
Current tobacco smoking (cigarettes per day) N= 35,298†						
- At 0 cigarettes/day	67.8 (67.6 to 68.0)	<.001	67.8 (67.6 to 68.0)	<.001	67.8 (67.6 to 68.0)	<.001
- At 5 cigarettes/day	68.6 (68.4 to 68.8)		68.4 (68.2 to 68.6)		68.4 (68.2 to 68.6)	
- At 20 cigarettes/day	70.9 (70.5 to 71.3)		70.4 (70.0 to 70.8)		70.1 (69.7 to 70.5	
- At 40 cigarettes/day	74.1 (73.4 to 74.8)		73.0 (72.3 to 73.8)		72.3 (71.5 to 73.2)	
Cumulative exposure to **tobacco** smoking (in pack-years)[b] N= 35,298‡						
- At 0 pack-years	68.1 (67.9 to 68.3)	<.001	67.7 (67.5 to 68.0)	<.001	68.0 (67.8 to 68.2)	.014
- At 5 pack-years	68.4 (68.2 to 68.6)		68.3 (68.1 to 68.5)		68.2 (68.0 to 68.4)	
- At 10 pack-years	68.7 (68.4 to 68.9)		68.9 (68.7 to 69.2)		68.4 (68.1 to 68.6)	
- At 20 pack-years	69.2 (68.9 to 69.7)		70.2 (69.7 to 70.6)		68.8 (68.2 to 69.3)	
- At 40 pack-years	70.4 (69.6 to 71.2)		72.6 (71.7 to 73.4)		69.5 (68.4 to 70.6)	

BMI = body mass index; CI = confidence interval; CVD = cardiovascular death; HDL = high-density lipoprotein; IPCW = inverse probability of censoring weighting; LDL = low-density lipoprotein.

**P* values are from a Wald test.

†Composite number of participant-visits used in the mixed model.

‡Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 y × 365 d/y × 1 pack/days × 20 cigarettes/pack), among ever tobacco smokers. Adjusted for current tobacco smoking in full model

Main predictors (current smoking and cumulative exposure to smoking) modeled flexibly. Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables.

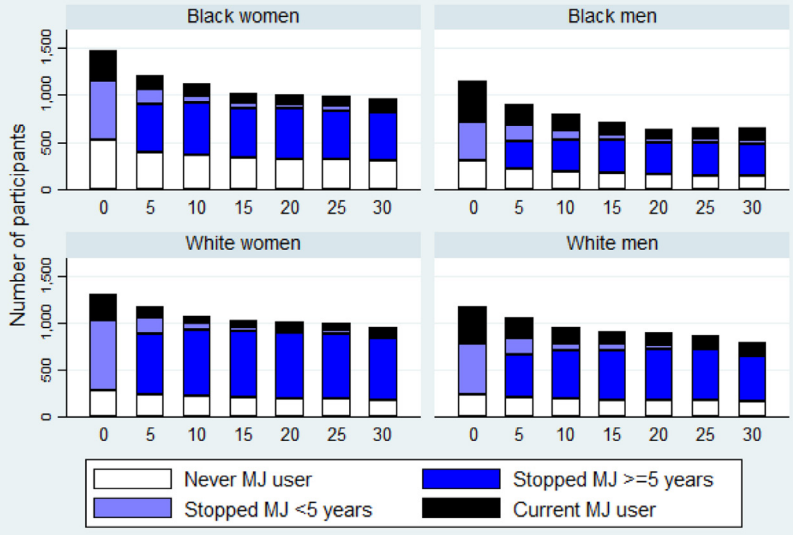
First unadjusted, then adjusted for demographics (sex, race, age, education years, study center) and finally, for current and cumulative alcohol and cannabis use, total physical activity score, BMI, systolic and diastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants and antipsychotics. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.

Supplementary Table 9 Association Between Heart Rate Differences and Current Use of Beta-Blocking Agents, Censoring Participants with Cardiovascular Disease

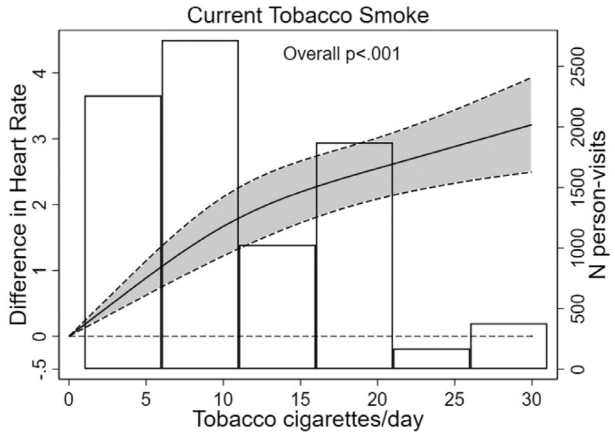
	Absolute difference in heart rate, unadjusted (95% CI)	*P* Value*	Absolute difference in heart rate, adjusted for demographics (95% CI)	*P* Value*	Absolute difference in heart rate, fully adjusted an IPCW (95% CI)	*P* Value*
Current use of beta block agent (N = 1,030)	−2.9 (−3.7 to −2.2)	<.001	−2.4 (−3.1 to −1.7)	<.001	−4.4 (−5.2 to −3.5)	<.001

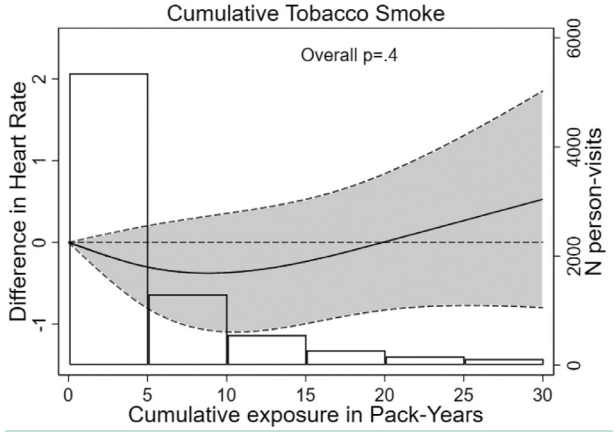
BMI = body mass index; CI = confidence interval; CVD = cardiovascular death; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

**P* values are from a Wald test.Results from multivariable adjusted mixed longitudinal models, censoring participants with incident CVD for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (sex, race, age, education years, study center) and finally, for current and cumulative alcohol use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, and triglycerides. Use of inverse probability of censoring weights in the multivariable adjusted model to account for potential informative censoring during follow-up.



Supplementary Figure 1 Cannabis status by sex-race strata and by exam year.





Supplementary Figure 2 Association between heart rate and current and cumulative tobacco smoking. Results from multivariable adjusted mixed longitudinal models, using splines with three knots, and censoring participants with incident cardiovascular disease for current and future visits. Nonfatal first event and corresponding date is captured from adjudicated morbidity data set and then linked to adjudicated death and follow-up time data set to derive fatal and nonfatal outcome variables. Adjusted for demographics (sex, race, age, education years, study center), current and cumulative alcohol and cannabis use, total physical activity score, BMI, systolic and dastolic blood pressure, LDL, HDL, triglycerides, and exposure to beta-blockers, antidepressants, and antipsychotics. Use of inverse probability of censoring weights to account for potential informative censoring during follow-up. Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 y × 365 d/y × 1 pack/days × 20 cigarettes/pack), analyses adjusted for current smoking. N included person-visits = 35,298. BMI = body mass index; CVD = cardiovascular death; HDL = high-density lipoprotein; LDL = low-density lipoprotein.