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Association between marijuana use and electrocardiographic abnormalities by middle age:

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

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Abstract

Aims: To evaluate the prevalence of electrocardiogram (ECG) abnormalities in marijuana users as an indirect measure of subclinical cardiovascular disease (CVD).

Design: Longitudinal and cross-sectional secondary data analysis from the CARDIA (Coronary Artery Risk Development in Young Adults) study.

Setting: 4 communities in the United States.

Participants: A total of 2,585 participants from the 5,115 black and white men and women recruited at age 18 to 30 years in 1985 to 1986 in CARDIA.

Measurements: ECG abnormalities coded as minor and major abnormalities with the Minnesota code of electrocardiographic findings at Year 20. Self-reported current (past 30 days) and computed cumulative lifetime marijuana use (one “marijuana-year” corresponds to 365 days of use) through assessments every 2–5 years. We fitted logistic regression models adjusting for sex, race, center, education, age, tobacco smoking, physical activity, alcohol use, and body mass index.

Findings: Among the 2,585 participants with an ECG at Year 20, mean age was 46, 57% were women, 45% were black. 83% had past exposure to marijuana and 11% were using marijuana currently. One hundred and seventy-three participants (7%) had major abnormalities and 944 (37%) had minor abnormalities. Comparing current with never use in multivariable-adjusted

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models, the OR for major ECG abnormalities was 0.60 (95% CI: 0.32 to 1.15) and for minor ECG abnormalities 1.21 (95% CI: 0.87 to 1.68). Results did not change after stratifying by sex and race. Cumulative marijuana use was not associated with ECG abnormalities.

Conclusion: In a middle-aged US population, lifetime cumulative and occasional current marijuana use were not associated with increases in electrocardiogram abnormalities. This adds to the growing body of evidence that occasional marijuana use and cardiovascular disease events and markers of subclinical atherosclerosis are not associated.

Keywords

marijuana; ECG; cohort study; epidemiology; subclinical CVD; CARDIA

Introduction

Marijuana, a mix of dried flowers of the cannabis plant, is used by between 7.5% and 9.4% of the United States population.(1, 2) With increasing legalization for recreational and medical use, concern about its possible health effects is rising. Heart health is a special concern, since case reports from the early 2010s suggest that marijuana may trigger heart attacks in healthy adults without significant coronary atherosclerosis.(3, 4) Some retrospective studies in France (N=35) and the USA (N=124) explore the possible association between marijuana use and cardiovascular incidents around the same time and found recent marijuana use raised myocardial infarction incident risk nearly five-fold for a one-hour period after use (RR 2.4 to 4.8),(5, 6), but most patients in this study were predisposed to cardiovascular disease (CVD). In contrast, larger observational studies in the USA, Sweden and Belgium published between the late 90's and the late 2010's (5,000 to 65,000 participants) found no association between marijuana use and incident CVD (stroke or transient ischemic attacks, coronary heart disease, or CVD mortality).(7–13) We know marijuana can have both pro-atherogenic effects, from activating the Cannabinoid receptor type 1 (CB1), and anti-atherogenic effects, by activating CB2.(14, 15) Previous analyses of the Coronary Artery Disease Risk of the Young (CARDIA) study, a longitudinal study with over 5,000 participants and up to 30-year follow-up in the USA, found that cumulative marijuana use was not associated with markers of subclinical atherosclerosis like coronary and abdominal calcium score, but that tobacco cigarette smoking was associated with increased risk of these outcomes.(16) Since CARDIA follows a relatively young cohort into early middle-age, participants may be too young to exhibit signs of CVD. Marijuana could also be associated with increased risk of future CVD non-atherosclerotic in origin. A potential increase in future risk of CVD could be captured by studying the association between marijuana use and electrocardiograms (ECG), as observational studies following over 1,000 participants in the USA over more than 10 years suggest.(11, 17, 18)

So far, only a few, small experimental studies (about 10 participants each), mainly from the late 1970s, examined the cellular mechanism that might connect marijuana use and abnormalities in ECGs. Some identified associations between marijuana use and these ECG abnormalities: P-wave axis abnormality; atrial flutter; atrial fibrillation; transitory 2nd grade atrioventricular block; premature ventricular contraction; elevated ST-segments; T-wave axis abnormality; and, decreased or increased R-R interval (depending on intensity of use), and

signs of Brugada pattern.(19–24) Because of the limited size of participants, findings of these studies are inconsistent, differed according to sex and race, and, in most cases, could not be reproduced between studies.(19–25) We set out to explore potential associations between current and cumulative marijuana use and ECG abnormalities in a large black and white cohort, followed over two decades.

Methods

Design and participants.

We used data from the CARDIA study. CARDIA is a cohort of 5,115 black and white women and men, aged between 18 and 30 years at baseline, from four study sites in the USA (Birmingham, AL, Chicago, IL, Minneapolis, MI, Oakland, CA) followed over 30 years. The study strove for equal distribution of race, sex, education, and age at each site. Participants were invited to participate in 9 in-person clinic examinations over the study period (1985/86 [Year 0] to 2015/2016 [Year 30]). We used data from the first seven visits, up to year 20, as ECG measures were available at baseline, visit Year 7, and 20. Each participant who attended the examination received non-monetary gifts and monetary reimbursement to cover expenses. All study protocols were approved by the institutional review boards at each site.

Measures: Marijuana exposure.

Multiple marijuana use variables are available for all visits (baseline, and follow-up Years 2, 5, 7, 10, 15 and 20). Current marijuana use was assessed by 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 by 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, with 1 year of exposure equivalent to 365 days of marijuana use. We assumed that current use at each visit (ie, the number of days of using marijuana during the month before each visit) reflected the average number of days of use during the months before and after each visit. We estimated the cumulative lifetime use by adding the total number of days using marijuana during follow-up. We adjusted our estimate upwards whenever participants self-reported higher lifetime use than we compute for each visit.(10, 26–29) Marijuana use was not legal in the cities at this time.

Measures: Electrocardiographic.

Standard 12-lead electrocardiogram (ECG) was recorded at baseline, Year 7 and Year 20 visits, as described extensively elsewhere.(30–32) All abnormalities were coded according to Minnesota Code (MC) Manual of Electrocardiographic Findings (32, 33). The MC is used for population research and clinical trials and standardizes coding of ECG abnormalities. We classified abnormalities according to MC (e.g. minor ST-T abnormality for MC 4–3, 4–4, 5–3 or 5–4; major ST-T abnormality for MC 4–1, 4–2, 5–1 or 5–2). We also built composite categories of major and minor abnormalities: If an individual’s ECG contained any abnormality on the major list (e.g., major ST-T abnormality), the ECG was classed as composite major. If it contained only abnormalities on the minor list (e.g., minor ST-T

abnormality), we classed the ECG as composite minor. (34–37) This allowed us to study both composite major and minor abnormalities and specific ECG abnormalities.(38)

Measures: Covariables.

Tobacco cigarette smoking behavior was evaluated at each in-person CARDIA examination and at yearly phone follow-up between CARDIA examinations [15]. We used these data to estimate cumulative lifetime exposure to tobacco cigarettes in terms of pack-years.(26) We estimated alcohol consumption as drink-years (365 days/year x 1drink/day, see online supplement).(26) Education (in years) was the highest educational grade reached by the participant by examination Year 20. We measured physical activity at every visit with the CARDIA physical activity history questionnaire.(39) Our cardiovascular risk factor measurements included blood pressure, blood cholesterol, body mass index (BMI), binge drinking and diagnosis of diabetes mellitus, which were collected at each CARDIA examination (see online supplement).

Analyses.

We observed *prevalent* abnormalities at visit 0, 7, and 20, but focused on Year 20 since major ECG abnormalities are expectedly more prevalent later in life and since cumulative marijuana exposure rises with time.

Based on the number of computed cumulative marijuana-years and data on current use, we divided participants into four categories: (1) never used marijuana; (2) past use and moderate cumulative lifetime marijuana use, up to or 0.5 marijuana-years; (3) past use and higher cumulative lifetime marijuana use, above 0.5 marijuana-years; and, (4) current users (any use within the last 30 days before the clinical visit), no matter the level of their cumulative use.

We first analyzed the association between marijuana use and ECG abnormalities in unadjusted logistic regression models, separately at visit 0, 7, and 20. We then adjusted for demographic variables (age, sex, race, education, study site) and then further adjusted for potential confounders such as tobacco cigarette smoking, alcohol consumption, and physical activity and BMI (further referred to as multivariable adjustment).(26, 40, 41). We decided to restrict main multivariable adjusted models to the previously mentioned variables because of low event number in specific ECG abnormalities, but still performed exploratory analyses with fully adjusted models including cardiovascular health variables (blood lipids and pressure, diabetes), presented in the online supplement. To account for deaths and informative censoring in later examinations (Years 7 and 20), we used inverse probability of attrition weights (IPAWs). We separately fit a model for loss to follow-up caused by the death, and a separate model for censoring due to reasons other than death, computed in one score.(42) We used last-value-carried-forward and backward (LVCFB) imputation for missing covariables and verified results using multiple imputation. We also conducted sensitivity analyses for different classification of marijuana use. The first considered only cumulative use and not current use; the second compared daily marijuana use to less frequent, past use, and never use. Finally, we stratified our results to see if they varied by sex and race (Black and white) because prevalence of ECG abnormalities, and distribution of

exposure and covariables differs between Black and white, and male and female participants. We restricted regression analyses to ECG abnormalities that occurred in at least 50 of each race-sex stratum. We also fitted models with marijuana-years modelled as a restricted cubic spline as covariable for state of marijuana use (current versus past use).

We further modelled *incident* abnormalities between Year 0 and Year 20. We included specific major and minor abnormalities at Year 20 that were not already identified in these categories in Year 0. For example, a specific minor abnormality detected at Year 0 that evolved into a major abnormality detected at Year 20 was coded as an incident major abnormality at Year 20. We applied a series of unadjusted and multivariable adjusted models to analyze the association between current and lifetime cumulative marijuana use on incident ECG abnormalities.

Tests of statistical significance were two-tailed; alpha level was 0.05. All statistical analyses were performed on Stata version 14.2 (StataCorp LP, College Station, TX, USA).

Hypotheses:

We hypothesized that cumulative marijuana use was not associated with ECG abnormalities, but that current use might be associated with unspecific changes in ECG. Various small experimental studies suggested immediate effects after using marijuana, with measured parameters returning to pre-exposure levels after ceasing marijuana use. (3, 4, 6, 19, 20, 23–25) The primary research question and analysis plan were submitted to the CARDIA Presentation & Publication Committee, before obtaining and analysing the data. However, they were not pre-registered on a publicly available platform and the results should thus be considered exploratory.

Role of the Funding source:

The National Heart, Lung and Blood Institute had input into design and conduct of the CARDIA study. Before submission for publication, the CARDIA P&P committees reviewed and approved the manuscript. This manuscript has been reviewed by CARDIA for scientific content.

Results

Population.

Of the 5,115 participants at baseline, 5,079 had an ECG at Year 0, 3,707 at Year 7, and 2,585 at Year 20. Table 1 shows that among the 2,585 participants with an ECG at Year 20, mean age was 46, 1,463 (57%) were women, and 1,150 (45%) were Black (Table S1.1 for baseline visit demographic description). Most had already used marijuana at least once in their life (2,148; 83%), while 437 (17%) had never used marijuana. Only 282 (11%) declared they were current users, and 37 (1.4%) were daily users. Of the past users, 1,179 (45%) had accumulated 0.5 or fewer marijuana-years; 687 (27%) had accumulated more than 0.5 marijuana-years.

Marijuana use and prevalent major and minor ECG abnormalities.

Table 2 shows that at the Year 20 examination, 173 (7%) participants had composite major abnormalities and 944 (37%) had composite minor abnormalities (Table S2 for stratification by sex and race). Composite and specific major abnormalities at Year 20 did not vary with status of marijuana use, but showed a tendency towards fewer events in current marijuana users: when we compared current marijuana use to never use, the unadjusted OR for composite major ECG abnormalities was 0.77 (95% CI: 0.43 to 1.39). After multivariable adjustment, the OR was 0.55 (95% CI: 0.28 to 1.09). Tables 2 and 3 show that in the unadjusted model, composite minor abnormalities and some specific minor abnormalities were more common among current marijuana users (composite minor OR 1.46 [95% CI: 1.07 to 1.98], incomplete LBBB OR 1.92 [95% CI: 1.23–3.00], ST segment elevation OR 2.80 [95% CI: 1.31 to 5.97]). These differences were attenuated after adjustment for demographic variables (composite minor OR 1.21 [95% CI: 0.87 to 1.68], incomplete LBBB OR 1.23 [95% CI: 0.75 to 2.01], ST segment elevation OR 1.96 [95% CI: 0.85 to 4.50]). The odds ratios stayed similar between categories of marijuana use after multivariable adjustment and use of IPAW (Table 3). Figure 1 illustrates that after multivariable adjustment, no specific ECG abnormality or composite major or minor abnormalities was significantly associated with marijuana use. Current marijuana users had a multivariable adjusted OR of 0.34 (0.13 to 0.89) for major ST-T abnormalities, with a p-value across categories of 0.17. Past users with a cumulative use of over 0.5 marijuana-years had a multivariable adjusted OR of 2.06 (1.17 to 3.64) for minor ST-T abnormalities, with a p-values across categories of 0.044. At Year 0 and Year 7, no ECG abnormality was significantly associated with marijuana use (Figures S1 and S2).

Marijuana use and incident major and minor ECG abnormalities.

Table 4 shows that there were 156 composite major and 428 composite minor incident ECG abnormalities between baseline visit and Year 20. When we compared current marijuana use to never use, incident composite major ECG abnormalities multivariable adjusted OR was 0.50 (95% CI: 0.25 to 1.02) and incident composite minor ECG abnormalities multivariable adjusted OR was 1.29 (95% CI: 0.89 to 1.85) (see Table S4 for stratified results).

Sensitivity analyses.

Further adjusting for cardiovascular risk factors did not change results (see Table S3.1). We found no association between alternative categorizations of marijuana use and prevalent major or minor ECG abnormality after multivariable adjustment. When we compared >2 marijuana-years of cumulative use to never use, the multivariable adjusted OR for composite major ECG abnormalities was 0.70 (95% CI: 0.37 to 1.30) and the multivariable adjusted OR for composite minor ECG abnormalities was 1.03 (95% CI: 0.73 to 1.46) (Table S5).

When we compared daily marijuana use to never use, the proportion of composite major abnormalities was no higher (0.08 in each group, see Table S7). Because few daily users had major abnormalities (N=3/37), we did not fit logistic regression models. For composite minor ECG abnormalities, the multivariable adjusted OR was 1.72 (95% CI: 0.83 to 3.65, N=20, Table S7). We found no association between current marijuana use and ECG

abnormalities after adjusting for cumulative marijuana use (including use of restricted cubic splines, Table S8).

In stratified analyses by sex and race, black women with 0.5 to 2 marijuana-years of cumulative exposure had a multivariable adjusted OR of minor ST-T abnormalities of 2.40 (1.05 to 5.52), with a p-value across categories of 0.10 (Table S3.2). We found no abnormality associated with cumulative marijuana use in stratified analyses by sex and race at baseline or Year 7 (results not shown). Current use at Year 20 was not associated with prevalent or incident ECG abnormalities in stratified analyses (Tables S3.2, S4 and S6). Whether we applied IPAW (N deaths at visit Year 20 = 247) or not, and used LVCBF or multiple imputation, results were virtually unchanged.

Discussion and Conclusion

We found no evidence that current or lifetime cumulative use of marijuana was associated with a higher prevalence or incidence of major or minor ECG abnormalities in this cohort including black and white participants, although major ECG abnormalities seemed to be less frequent in current marijuana users. In this population, we also observed the tendency towards more minor ECG abnormalities compared to never marijuana users. Whether participants used marijuana daily, in the last 30 days or intermittently over a lifetime, marijuana use was not associated with an increase in prevalent or incident specific ECG abnormalities by middle-age. Applying different classifications of marijuana use did not change our results. Our findings did not vary by sex and race.

Unlike some small experimental studies from the USA in the late 1970’s that, in samples of around 10 people, suggested marijuana was associated with some specific ECG abnormalities, we found these were just as frequent in current or cumulative marijuana users as in never users.(19–25) The small sample size, brief exposure of participants to THC, short follow-up, and inclusion only of young, healthy men (with one exception) makes it difficult to draw useful conclusions on the population level from these experimental studies.

We found multiple case-reports from the early 2010’s about ECG abnormalities following marijuana use.(21, 22) In our large biracial 20-year cohort of women and men participants who reported a broad variety of marijuana use habits, from never users to daily users, we found no evidence to support an association between marijuana and any ECG abnormality, incident abnormalities in new marijuana users, or abnormalities that would indicate past, ongoing, or future myocardial infarction.(5, 6) Our findings align with earlier epidemiological research on thousands of participants from Europe and the USA, including participants of the same cohort, that found no association between marijuana and CVD, mortality or other measure of subclinical atherosclerosis.(7–10)

When we stratified results by sex and race, we noticed that black participants presented with a higher proportion of ECG abnormalities than white participants, regardless of their marijuana use habits,(31, 35, 43) but black marijuana users had no more ECG abnormalities than black never users; likewise, white marijuana users had no more ECG abnormalities than white never users.

Study limitation:

The assessment of exposure to marijuana was not validated by biological markers, so we rely on participant self-reports. Marijuana use was illegal during the whole course of the study and we cannot exclude social desirability bias, but because participants were queried about marijuana and other illegal drug use at each clinical visit, we could track past exposures. With this method, 84% percent of participants reported any past marijuana, suggesting that possible social desirability bias was mitigated by the trust participants had in the study personnel to report their true exposure. The low number of daily marijuana users at Year 20 in CARDIA (N=37; 1.4%) limited our ability to fit multivariable adjusted models, and our results should be carefully interpreted in this population. Future studies with higher sample size will be better equipped to assess the association between daily marijuana use and ECG abnormalities. Also, immediate effects of marijuana might not be reflected on resting ECGs performed hours or days after its use. We rely on marijuana use information provided by participants every 2 to 5 years, and participants only reported on how many days they had used marijuana within the last 30 days. Our analyses cannot inform on the acute effects of marijuana use on ECG. Previous experiments suggested acute effects of marijuana use on ECGs, with conflicting results (19, 20, 23, 24). Further experimental studies, especially among people with underlying risk of CVD, are needed to test the effects of acute marijuana use on ECG abnormalities.

Though the cohort we studied was racially diverse and spanned 20 years, our analysis was limited mainly to a middle-aged population, where CVD is not yet common. Given the high number of analyses performed across subgroups and multiple ECG abnormalities studied, there is high risk of a statistically significant false positive finding. Minor ECG abnormalities are common in healthy black people and associated with physical activity; we might have not been able to fully adjust for that. Minor abnormalities have not been associated with future CVD in young adults.(44)

While these elements inherently limit our confidence in the measures of association, CARDIA is to our knowledge the only cohort with ECG data which assessed marijuana exposure over such a long time (20 years) and in such a large cohort. While the study of daily marijuana users is of evident interest, few participants use marijuana daily, and we still need to know if marijuana use is associated with changes in ECG, even at lower exposures or from past exposure. The strength of the CARDIA dataset lies in the possibility to study the full spectrum of marijuana use intensity typical of the exposure in the general population. No other longitudinal study assessed the association between marijuana use and ECG. In this study, we did not find an association between cumulative or past use of marijuana and ECG abnormalities. Compared to the previous studies assessing the association between marijuana use and ECG, most of them published more than 4 decades ago and including only very few participants, we can now report results from a cohort more than 100 times larger than previous studies. We were able to adjust for a rich set of covariables repeatedly measured at 7 examinations and a dozen phone follow-ups. We cannot exclude the possibility of informative censoring, which is a source of bias, but addressed that issue by using IPAW, as stated in the methods section.

Conclusion:

Current or cumulative marijuana use were not associated with increases in ECG abnormalities in a middle-aged population of self-reported black and white participants in the US. While we did not find significant increases in ECG abnormalities in current marijuana users, the number of participants reporting daily marijuana use was low. Results in this population should be interpreted with caution and future studies should more fully explore the association in larger samples of daily users. Most of the study population did occasionally use marijuana, in line with the typical frequency of use in the general population. Our finding that occasional marijuana was not associated with ECG abnormalities adds to the growing body of evidence that this level of marijuana use and CVD events and markers of subclinical atherosclerosis are not associated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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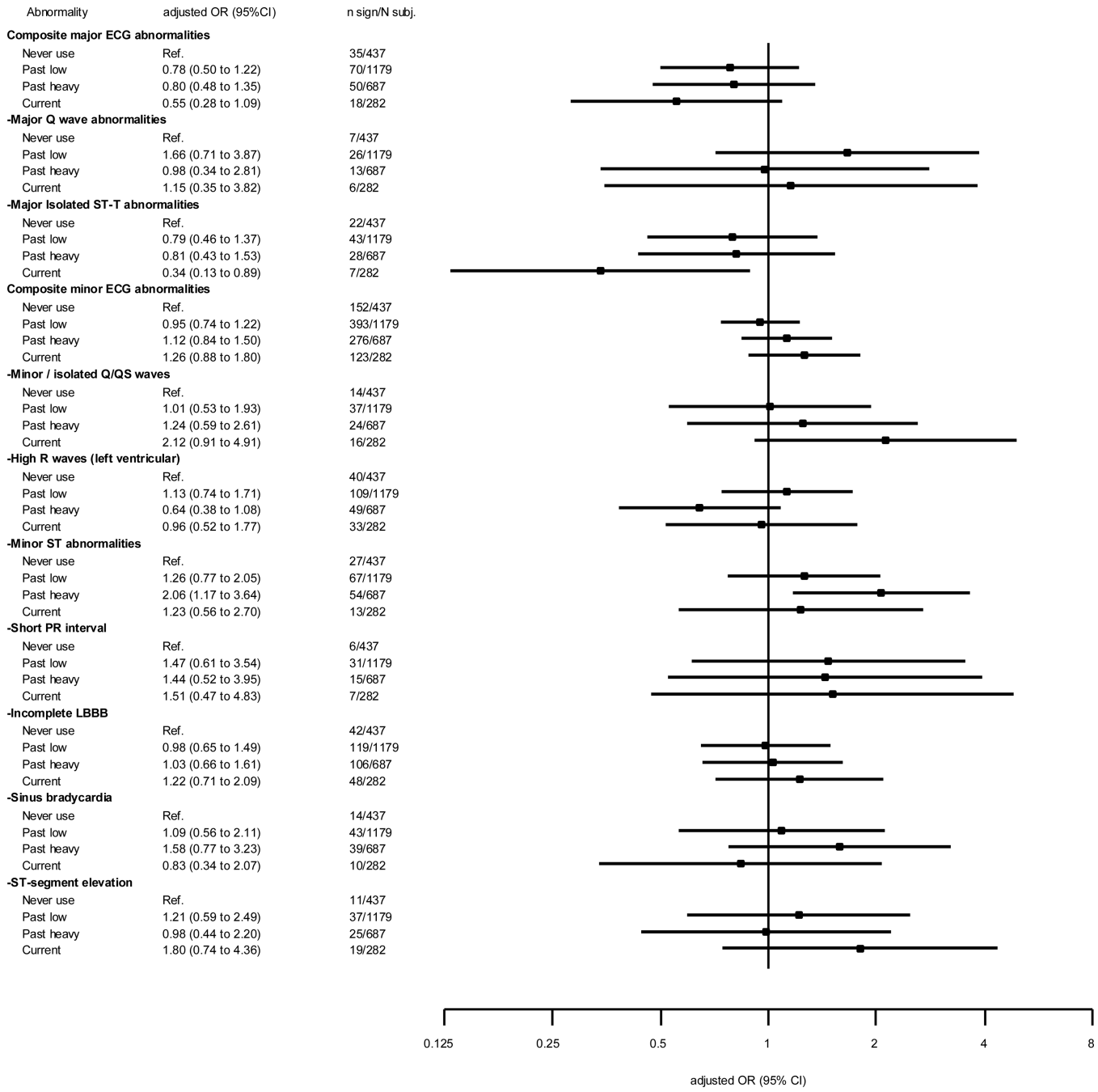

Figure 1:

Multivariable adjusted Odds Ratio of the association between ECG abnormalities and category of marijuana use at year 20 visit.[1]

Forest plot of abnormalities with **N ≥50 counts** for all marijuana use categories merged, by composite major and minor ECG abnormalities, ordered by Minnesota Code Number – visit year 20.(32)

[1] Multivariable adjustment for sex, race, age, education years, study site, current and cumulative alcohol and tobacco cigarette use, total physical activity score, BMI. Use of

inverse probability of attrition weights in the multivariable adjusted model in oder to account for deaths and potential informative censoring during follow-up

Table 1:

Characteristics of 2,585 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) with an ECG at their Year 20 visit, by category of marijuana use.

Characteristics at year 20 exam	All participants	Never used marijuana	Past ≤.5 marijuana years[1]	Past >.5 marijuana years[1]	Current marijuana use
N	2,585	437	1,179	687	282
Demographics					
Age, mean (Q1; Q3)	46 (43; 48)	45 (42; 48)	46 (43; 48)	46 (43; 48)	46 (43; 49)
Race and sex, N (col %)[2]					
- Black women	695 (27)	163 (37)	352 (30)	116 (17)	64 (23)
- Black men	455 (18)	64 (15)	162 (14)	154 (22)	75 (27)
- White women	768 (30)	116 (27)	419 (36)	179 (26)	54 (19)
- White men	667 (26)	94 (22)	246 (21)	238 (35)	89 (32)
Education years, median (Q1; Q3)	16 (14; 18)	16 (14; 18)	16 (14; 18)	15 (14; 17)	14 (12; 16)
Study site, N (col %)					
- Birmingham, AL	651 (25)	201 (46)	286 (24)	128 (19)	36 (13)
- Chicago, IL	662 (26)	115 (26)	302 (26)	192 (28)	53 (19)
- Minneapolis, MI	679 (26)	77 (18)	281 (24)	219 (32)	102 (36)
- Oakland, CA	593 (23)	44 (10)	310 (26)	148 (22)	91 (32)
Substance use exposure					
Marijuana-years[1], median (Q1; Q3)	0.2 (0.0; 1.0)	0.0 (0.0; 0.0)	0.1 (0.0; 0.2)	1.3 (0.8; 1.9)	4.6 (1.9; 8.7)
Smoking status, N (col %)					
- Never	1388 (54)	382 (87)	729 (62)	194 (28)	83 (29)
- Former	731 (28)	37 (8)	299 (25)	301 (44)	94 (33)
- Current	466 (18)	18 (4)	151 (13)	192 (28)	105 (37)
Packyears during lifetime among ever tobacco cigarette smokers, median (Q1; Q3)[3]	0 (0; 5.7)	0 (0; 0)	0 (0; 2.1)	3.2 (0; 12.7)	2.8 (0; 14.4)
Alcohol in past 24 hours, N (col %)	660 (26)	42 (10)	292 (24)	208 (31)	118 (42)
Drink-years during lifetime, median (Q1; Q3)[4]	5.9 (0.9; 17.1)	0.4 (0; 3.4)	4.7 (0.8; 13.3)	12.6 (4.0; 27.5)	17.8 (6.1; 38.1)
Cumulative binge-drinking episodes (N, col%)					
- Never	1,271 (49)	356 (81)	654 (55)	190 (28)	71 (25)
- ≤ 250 episodes	745 (29)	60 (14)	358 (30)	241 (35)	86 (30)
- > 250 episodes	569 (22)	21 (5)	167 (14)	256 (37)	125 (44)

Characteristics at year 20 exam	All participants	Never used marijuana	Past ≤.5 marijuana years[1]	Past >.5 marijuana years[1]	Current marijuana use
Physical activity					
Physical Activity score, median (Q1; Q3)[5]	277 (137; 493)	203 (93; 388)	270 (129; 493)	310 (160; 523)	358 (188; 565)
Anthropomorphic variable BMI (Q1; Q3)	27.9 (24.3; 32.6)	29.1 (25.3; 34.9)	27.4 (24.0; 32.5)	28.2 (24.3; 32.6)	27.6 (24.6; 30.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CARDIA, Coronary Artery Risk Development in Young Adults; IQR, interquartile range.

[1]Cumulative lifetime exposure to marijuana joints in marijuana-years; 1 marijuana-year of exposure is equivalent to 365 days of marijuana use (1 year × 365 days per year).(34)

[2]The CARDIA study included, by design, roughly equal numbers of self-identified white men, white women, black men, and black women.

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

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

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

Table 2:

Number and type of ECG abnormalities at year 20 by category of marijuana use.

Type of ECG abnormalities	All participants	Never used marijuana	Past ≤.5 marijuana years[1]	Past >.5 marijuana years[a][1]	Current marijuana use
Total N (%)	2,585	437 (17)	1,179 (45)	687 (27)	282 (11)
Composite major abnormalities, N (%)	**173 (7)**	**35 (8)**	**70 (6)**	**50 (7)**	**18 (6)**
- Major Q wave abnormalities [1–1, 1–2], N (%)	52 (2)	7 (2)	26 (2)	13 (2)	6 (2)
- Left ventricular hypertrophy plus ST-T abnormalities [3–1 plus 4–1, 4–2, 5–1, 5–2], N (%)	16 (1)	3 (1)	9 (1)	2 (0)	2 (1)
- Major Isolated ST or T abnormalities [4–1, 4–2, 5–1, 5–2], N (%)	100 (4)	22 (5)	43 (4)	28 (4)	7 (2)
- Complete or intermittent RBBB [7–2], N (%)	12 (0)	3 (1)	2 (0)	4 (1)	3 (1)
- Nonspecific intraventricular block [7–4], N (%)	9 (0)	3 (1)	3 (0)	1 (0)	2 (1)
- Atrial fibrillation or flutter [8–3], N (%)	3 (0)	1 (0)	0 (0)	2 (0)	0 (0)
- Supraventricular tachycardia [8-4-2 or 8-4-1 & HR>140], N (%)	7 (0)	1 (0)	2 (0)	4 (1)	0 (0)
- Major QT Prolongation [QTI≥116%], N (%)	6 (0)	2 (0)	3 (0)	0 (0)	1 (0)
Composite minor abnormalities, N (%)	**944 (37)**	**152 (35)**	**393 (34)**	**276 (41)**	**123 (44)**
- Minor Isolated Q/QS waves [1-3], N (%)	91 (4)	14 (3)	37 (3)	24 (3)	16 (6)
- Left axis deviation [2-1], N (%)	36 (1)	5 (1)	17 (1)	12 (2)	2 (1)
- Right axis deviation [2-2], N (%)	25 (1)	5 (1)	13 (1)	5 (1)	2 (1)
- High R waves (left ventricular) [3-1, 3-3, 3-4], N (%)	231 (9)	40 (9)	109 (9)	49 (7)	33 (12)
- High R waves (right ventricular) [3-2], N (%)	2 (0)	1 (0)	1 (0)	0 (0)	0 (0)
- Minor ST/T abnormalities [4-3, 4-4, 5-3, 5-4], N (%)	161 (6)	27 (6)	67 (6)	54 (8)	13 (5)
- AV-Block 1 = long PR [6-3], N (%)	34 (1)	7 (2)	14 (1)	7 (1)	6 (2)
- Short PR interval [6-5], N (%)	59 (2)	6 (1)	31 (3)	15 (2)	7 (2)

Type of ECG abnormalities	All participants	Never used marijuana	Past ≤.5 marijuana years[1]	Past >.5 marijuana years[a1]	Current marijuana use
- Incomplete right bundle branch block [7-3], N (%)	47 (2)	6 (1)	21 (2)	17 (2)	3 (1)
- Incomplete left bundle branch block [7-6, 7-7], N (%)	315 (12)	42 (10)	119 (10)	106 (15)	48 (17)
- Premature beats (supraventricular) [8-1-1], N (%)	44 (2)	8 (2)	17 (1)	10 (1)	9 (3)
- Premature beats (ventricular) [8-1-2], N (%)	26 (1)	2 (0)	13 (1)	9 (1)	2 (1)
- Premature beats (combined) [8-1-3, 8-1-5], N (%)	2 (0)	0 (0)	2 (0)	0 (0)	0 (0)
- Wandering atrial pacemaker [8-1-4], N (%)	4 (0)	0 (0)	2 (0)	1 (0)	1 (0)
- Sinus tachycardia [8-7], N (%)	3 (0)	1 (0)	1 (0)	0 (0)	1 (0)
- Sinus bradycardia [8-8], N (%)	106 (4)	14 (3)	43 (4)	39 (6)	10 (4)
- Supraventricular rhythm persistent [8-4-1], N (%)	7 (0)	1 (0)	2 (0)	4 (1)	0 (0)
- Low voltage QRS [9-1], N (%)	40 (2)	9 (2)	18 (2)	10 (1)	3 (1)
- ST-segment elevation [9-2], N (%)	92 (4)	11 (3)	37 (3)	25 (4)	19 (7)
- High amplitude P wave [9-3], N (%)	6 (0)	0 (0)	3 (0)	3 (0)	0 (0)
- Minor QT prolongation [QTI≥112%], N (%)	23 (1)	4 (1)	10 (1)	6 (1)	3 (1)

Abnormalities by major and minor classification, ordered by Minnesota Code Number – visit year 20(32). No abnormalities of the following Minnesota Code were reported: Major: AV Block 2 or 3 [6–1, 6–2], Ventricular preexcitation pattern (WPW) [6–4], Complete or intermittent LBBB [7–1], Nonspecific intraventricular block [7–4], Right bundle branch block with left anterior hemiblock [7–8], Brugada pattern [7–9], Ventricular fibrillation or asystole [8–2]; Minor: Fragmented QRS [7–10].

[1]Cumulative lifetime exposure to marijuana joints in marijuana-years; 1 marijuana-year of exposure is equivalent to 365 days of marijuana use (1 year × 365 days per year).(34)

Table 3:

Unadjusted-, minimally adjusted- (for demographics) and multivariable adjusted Odds Ratio of the association between **prevalent** ECG abnormalities and category of marijuana use at year 20 visit.[1]

Type of ECG abnormalities	Category of marijuana use	N events / N in category	Unadjusted (crude) OR (CI)	p-value[2]	Minimally Adjusted (for demographics) OR (CI)	p-value[2]	Multivariable adjusted OR (CI), IPAW	p-value[2]
Composite major abnormalities	Never marijuana use	35/437	Ref.	0.11	Ref.	0.5	Ref.	0.4
	Past ≤.5 marijuana-years	70/1179	0.72 (0.47 to 1.09)		0.79 (0.51 to 1.22)		0.78 (0.50 to 1.22)	
	Past >.5 marijuana-years	50/687	0.90 (0.57 to 1.41)		0.79 (0.48 to 1.29)		0.80 (0.48 to 1.35)	
	Current marijuana use	18/282	0.77 (0.43 to 1.39)		0.60 (0.32 to 1.15)		0.55 (0.28 to 1.09)	
Major Q wave abnormalities [1–1, 1–2]	Never marijuana use	7/437	Ref.	0.7	Ref.	0.5	Ref.	0.5
	Past ≤.5 marijuana-years	26/1179	1.39 (0.60 to 3.22)		1.38 (0.58 to 3.27)		1.66 (0.71 to 3.87)	
	Past >.5 marijuana-years	13/687	1.18 (0.47 to 2.99)		0.78 (0.28 to 2.12)		0.99 (0.34 to 2.81)	
	Current marijuana use	6/282	1.34 (0.44 to 4.02)		0.89 (0.28 to 2.78)		1.15 (0.35 to 3.82)	
Major Isolated ST or T abnormalities [4–1, 4–2, 5–1, 5–2]	Never marijuana use	22/437	Ref.	0.09	Ref.	0.4	Ref.	0.17
	Past ≤.5 marijuana-years	43/1179	0.71 (0.42 to 1.21)		0.88 (0.51 to 1.49)		0.79 (0.46 to 1.37)	
	Past >.5 marijuana-years	28/687	0.80 (0.45 to 1.42)		0.88 (0.48 to 1.61)		0.81 (0.43 to 1.53)	
	Current marijuana use	7/282	0.48 (0.20 to 1.14)		0.45 (0.18 to 1.16)		0.34 (0.13 to 0.89)	
Composite minor abnormalities	Never marijuana use	152/437	Ref.	<0.001	Ref.	0.14	Ref.	0.2
	Past ≤.5 marijuana-years	393/1179	0.93 (0.74 to 1.18)		0.91 (0.71 to 1.16)		0.95 (0.74 to 1.22)	
	Past >.5 marijuana-years	276/687	1.28 (1.00 to 1.65)		1.10 (0.84 to 1.44)		1.12 (0.84 to 1.50)	
	Current marijuana use	123/282	1.46 (1.07 to 1.98)		1.21 (0.87 to 1.68)		1.26 (0.88 to 1.80)	
Minor Isolated Q/QS waves [1–3]	Never marijuana use	14/437	Ref.	0.033	Ref.	0.11	Ref.	0.18
	Past ≤.5 marijuana-years	37/1179	0.98 (0.52 to 1.83)		1.01 (0.53 to 1.73)		1.01 (0.53 to 1.93)	
	Past >.5 marijuana-years	24/687	1.09 (0.56 to 2.14)		1.24 (0.60 to 2.53)		1.24 (0.59 to 2.61)	

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Type of ECG abnormalities	Category of marijuana use	N events / N in category	Unadjusted (crude) OR (CI)	p-value[2]	Minimally Adjusted (for demographics) OR (CI)	p-value[2]	Multivariable adjusted OR (CI), IPAW	p-value[2]
	Current marijuana use	16/282	1.82 (0.87 to 3.78)		2.19 (1.00 to 4.83)		2.12 (0.91 to 4.91)	
High R waves (left ventricular) [3–1, 3–3, 3–4]	Never marijuana use	40/437	Ref.	0.013	Ref.	0.060	Ref.	0.053
	Past ≤.5 marijuana-years	109/1179	0.99 (0.67 to 1.44)		1.15 (0.77 to 1.73)		1.13 (0.74 to 1.71)	
	Past >.5 marijuana-years	49/687	0.76 (0.49 to 1.17)		0.70 (0.43 to 1.13)		0.64 (0.38 to 1.08)	
	Current marijuana use	33/282	1.31 (0.80 to 2.13)		1.11 (0.65 to 1.90)		0.96 (0.52 to 1.77)	
Minor ST/T abnormalities [4–3, 4–4, 5–3, 5–4]	Never marijuana use	27/437	Ref.	0.02	Ref.	0.051	Ref.	0.044
	Past ≤.5 marijuana-years	67/1179	0.91 (0.58 to 1.45)		1.05 (0.65 to 1.69)		1.26 (0.77 to 2.05)	
	Past >.5 marijuana-years	54/687	1.29 (0.80 to 2.09)		1.61 (0.96 to 2.70)		2.06 (1.17 to 3.64)	
	Current marijuana use	13/282	0.73 (0.37 to 1.45)		0.78 (0.38 to 1.59)		1.23 (0.56 to 2.70)	
Short PR interval [6–5]	Never marijuana use	6/437	Ref.	0.2	Ref.	0.4	Ref.	0.9
	Past ≤.5 marijuana-years	31/1179	1.94 (0.80 to 4.68)		1.79 (0.78 to 4.13)		1.47 (0.61 to 3.54)	
	Past >.5 marijuana-years	15/687	1.60 (0.62 to 4.16)		1.91 (0.76 to 4.81)		1.44 (0.52 to 3.95)	
	Current marijuana use	7/282	1.83 (0.61 to 5.50)		2.60 (0.86 to 7.72)		1.51 (0.47 to 4.83)	
Incomplete left bundle branch block [7–6, 7–7]	Never marijuana use	42/437	Ref.	<0.001	Ref.	0.7	Ref.	0.8
	Past ≤.5 marijuana-years	119/1179	1.04 (0.72 to 1.51)		0.95 (0.64 to 1.42)		0.98 (0.65 to 1.49)	
	Past >.5 marijuana-years	106/687	1.71 (1.17 to 2.50)		1.05 (0.69 to 1.59)		1.03 (0.66 to 1.61)	
	Current marijuana use	48/282	1.92 (1.23 to 3.00)		1.23 (0.75 to 2.01)		1.22 (0.71 to 2.09)	
Sinus bradycardia [8–8]	Never marijuana use	14/437	Ref.	0.12	Ref.	0.2	Ref.	0.3
	Past ≤.5 marijuana-years	43/1179	1.14 (0.62 to 2.11)		1.03 (0.54 to 1.94)		1.09 (0.56 to 2.11)	
	Past >.5 marijuana-years	39/687	1.82 (0.97 to 3.39)		1.54 (0.80 to 2.96)		1.58 (0.77 to 3.23)	
	Current marijuana use	10/282	1.11 (0.49 to 2.54)		0.90 (0.39 to 2.08)		0.83 (0.34 to 2.07)	
ST-segment elevation [9–2]	Never marijuana use	11/437	Ref.	0.020	Ref.	0.2	Ref.	0.3

Type of ECG abnormalities	Category of marijuana use	N events / N in category	Unadjusted (crude) OR (CI)	p-value[2]	Minimally Adjusted (for demographics) OR (CI)	p-value[2]	Multivariable adjusted OR (CI), IPAW	p-value[2]
	Past ≤.5 marijuana-years	37/1179	1.25 (0.63 to 2.48)		1.35 (0.67 to 2.73)		1.05 (0.49 to 2.23)	
	Past >.5 marijuana-years	25/687	1.46 (0.71 to 3.00)		1.21 (0.59 to 2.49)		0.98 (0.44 to 2.20)	
	Current marijuana use	19/282	2.80 (1.31 to 5.97)		1.96 (0.85 to 4.50)		1.80 (0.74 to 4.36)	

Abnormalities with **N ≥50 counts**for all marijuana use categories merged, by composite major and minor ECG abnormalities, ordered by Minnesota Code Number – visit year 20(32).

[1]Crude: no adjustement. Adjusted for demographic variables: sex, race, age, education years, and study site. Multivariable adjusted: sex, race, age, education years, study site, current and cumulative alcohol and tobacco cigarette use, total physical activity score, BMI. Use of inverse probability of attrition weights in the multivariable adjusted model in oder to account for deaths and potential informative censoring during follow-up. Number of LVCFB for covariables: total physical activity score – 10; alcohol use in 24 hours prior to exam: 20; BMI - 6.

[2]P-values from a Wald test.

Table 4:

Unadjusted-, minimally adjusted- (for demographics) and multivariable adjusted Odds Ratio of the association between **incident** Major and Minor ECG abnormalities and category of marijuana use at year 20 visit.[1]

Type of ECG abnormalities	Category of marijuana use	N events / N in category	Crude OR (CI)	p-value[2]	Adjusted for demographics OR (CI)	p-value[2]	Multivariable adjusted OR (CI), IPAW	p-value[2]
Composite major abnormalities	Never marijuana use	33/437	Ref.	0.3	Ref.	0.3	Ref.	0.3
	Past ≤.5 marijuana-years	62/1179	0.67 (0.43 to 1.04)		0.75 (0.47 to 1.17)		0.73 (0.46 to 1.15)	
	Past >.5 marijuana-years	45/687	0.85 (0.53 to 1.35)		0.71 (0.43 to 1.18)		0.73 (0.42 to 1.25)	
	Current marijuana use	16/282	0.74 (0.40 to 1.37)		0.55 (0.28 to 1.07)		0.50 (0.25 to 1.00)	
Composite minor abnormalities	Never marijuana use	81/437	Ref.	0.003	Ref.	0.019	Ref.	0.2
	Past ≤.5 marijuana-years	176/1179	0.71 (0.52 to 0.98)		0.70 (0.50 to 0.97)		0.95 (0.73 to 1.23)	
	Past >.5 marijuana-years	115/687	1.03 (0.73 to 1.45)		0.92 (0.63 to 1.32)		1.13 (0.84 to 1.51)	
	Current marijuana use	56/282	1.29 (0.85 to 1.98)		1.18 (0.75 to 1.84)		1.28 (0.89 to 1.85)	

Incident abnormalities with **N ≥50 counts**for all marijuana use categories merged, by composite major and minor ECG abnormalities, according toy Minnesota Code Book – visit year 20(32). Participants with major or minor ECG abnormalities at year 0 were excluded from the analysis.

[1]Crude: no adjustement. Adjusted for demographic variables: sex, race, age, education years, and study site. Multivariable adjusted: sex, race, age, education years, study site, current and cumulative alcohol and tobacco cigarette use, total physical activity score, BMI. Use of inverse probability of attrition weights in the multivariable adjusted model in oder to account for deaths and potential informative censoring during follow-up. Number of LVCFB for covariables: total physical activity score – 10; alcohol use in 24 hours prior to exam – 20; BMI - 6.

[2]P-values from an Wald test.