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Self-Reported Marijuana Use Over 25 Years and Abdominal Adiposity: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Abstract

Aims—We investigated the association between cumulative lifetime and current marijuana use with total abdominal adipose tissue (AT), visceral AT, subcutaneous AT, intermuscular AT, and mean liver attenuation (LA) at mid-life.

Design—Longitudinal and cross-sectional secondary data analysis of participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Setting—CARDIA field centers in Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA, USA.

Participants—CARDIA participants, aged 18–30 years in 1985–1986, who were present at the clinic examination in 2010–2011 (n=2,902).

Measurements—Marijuana use was assessed from responses to self-administered questionnaires at 8 CARDIA examinations over 25 years, determined as cumulative marijuana-

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Disclosure Statement

The authors report no conflicts of interest.

Author contributions

M.P.B. is the guarantor of this work, had full access to the data in this analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the data and participated in creating, editing, and reviewing this manuscript.

years and current use status. Non-contrast computed tomography imaging of the abdomen was obtained in 2010-2011.

Findings—In 2010–2011, 84% of participants reported a history of marijuana use with 11% reporting use within the past 30 days. Before adjustment, we observed greater cumulative marijuana use was associated with lower total abdominal and subcutaneous AT volume and lower LA and current marijuana use was associated with lower subcutaneous AT. However, after adjustment for age, sex, race, field center, cigarette pack-years and current use, regular alcohol consumption, cumulative drink-years, and physical activity, neither cumulative marijuana use nor current use showed an association with any abdominal adipose depot. Our estimates did not differ by age, sex, or race nor after accounting for cohort attrition.

Conclusion—Neither cumulative marijuana use nor current marijuana use is associated with total abdominal, visceral, subcutaneous, or intermuscular adipose tissue, or liver attenuation in mid-life.

Introduction

Marijuana is one of the 3 most used psychoactive substances in the United States (US), with nearly 38 million individuals 12 years of age and older using marijuana during the past year in 2016.(1) It is unclear whether the growing utilization of marijuana for medicinal use has an impact on the prevalence of recreational use and abuse/dependence.(2–4) Acute cardiovascular health effects of marijuana use include increased heart rate(5), trigger for myocardial infarction(6), and acute respiratory conditions.(7, 8) Data on the chronic health effects associated with long-term marijuana use yield mixed findings.(7, 9) It is unclear whether marijuana use is associated with the incidence of cancer(10–13) or pulmonary disease and poorer pulmonary function(14–18), but data suggest no association of marijuana use with diabetes(19) or mortality(20). Given the prevalence of marijuana use, mounting medicinal use, potential for respiratory harm, and the limited understanding of population-level health effects, greater attention is warranted to the potential chronic health outcomes associated with this modifiable behavior.

The primary active component in marijuana, delta-9 tetrahydrocannabinol (THC), is shown to activate cannabinoid receptors that are integral to regulating energy metabolism via appetite control, lipid metabolism, and energy expenditure.(21) To date, studies assessing marijuana use and various metabolic parameters yield conflicting results. Greater long-term marijuana use is associated with higher caloric intake(22) and incident prediabetes(19), but not with incident diabetes.(19) The prevalence of obesity and odds of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) are lower in cannabis users than in nonusers, though cannabis use is not consistently associated with lower body mass index (BMI), waist circumference (WC), and insulin resistance.(22–29) Heavy chronic marijuana users are shown to have greater percentage of visceral adiposity compared to matched non-users, but do not display differences in percentage of total or subcutaneous adiposity.(26) In view of the high prevalence of overweight/obesity in the US and the suggestion for cannabinoids as a possible treatment option(21), the relationship between long-term marijuana use and abdominal adiposity in a community-based population merits investigation. Furthermore, detailed assessment of health behaviors such as physical activity, alcohol consumption, and

tobacco use should be included when evaluating metabolic health effects of marijuana use, to address potential confounding.(30, 31) Our objective was to quantify differences in total abdominal adipose tissue (AT), visceral AT, subcutaneous AT, intermuscular AT, and mean liver attenuation (LA) at midlife according to cumulative use and concurrent use of marijuana.

Methods

The Coronary Artery Risk Development in Young Adults (CARDIA) study is an ongoing longitudinal observational study of individuals recruited from four US metropolitan communities. In 1985-1986, a total of 5,115 black and white adults who were 18–30 years of age and free from cardiovascular disease were enrolled. Participants have been contacted by telephone annually and invited to participate in follow-up examinations 2, 5, 7, 10, 15, 20, 25, and 30 (2015-2016) years after baseline. Participants have provided consent at each examination and Institutional Review at each study site and coordinating center have granted approval for all exams. Details regarding the study design have been published previously. (32)

Standardized protocols, harmonized over time, and structured questionnaires were used at CARDIA clinical examinations to collect information on demographics, blood pressure, anthropometry, chemistries, medical and family history, use of medications, and behavioral health characteristics. Body weight was measured using a calibrated balance beam scale to the nearest 0.2 kg and height was measured to the nearest 0.5 cm using a vertical ruler. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Educational level was determined as the educational grade attained for participants at each visit, categorized at maximum attainment (< 12 years of education, 13–16 years, or > 16 years). At each exam, individuals completed a self-administered questionnaire covering their history of tobacco use. From this data, we derived cigarette smoking status (never, former, current) and estimated lifetime exposure to cigarettes in terms of cigarette pack-years, with 1 pack of cigarettes equivalent to 20 individual cigarettes and 1 pack-year equivalent to smoking 1 pack of cigarettes per day for 1 year. Participants reported regular consumption of alcohol over the previous week, including beer, wine, and liquor and were categorized according to standard habitual alcohol consumption levels (no regular; moderate consumption: up to 1 drink daily for women, 2 drinks daily for men; or heavy consumption: greater than 1 drink daily for women, 2 drinks daily for men).(33) From this data we also estimated the cumulative alcohol consumption in drink-years for each individual at each exam, with 1 drink-year defined as consuming 1 drink per day for 1 year, summing across exams. Self-reported sports-related physical activity was assessed as the frequency of participation over the previous 12 months for 8 vigorous-intensity and 5 moderate-intensity activities using a questionnaire with high reliability.(34) CARDIA researchers derived an overall physical activity score, in “exercise units” (EU), with a score of 300 EU corresponding to 30 minutes of moderate physical activity 5 times per week.(35)

Marijuana use

Marijuana use was assessed at each exam using detailed self-administered questionnaires, similar to those used for the National Survey on Drug Use and Health.(1) We used responses from the following survey questions to estimate cumulative and current marijuana use: “Have you ever used marijuana? About how many times in your lifetime have you used marijuana? During the last 30 days, on how many days did you use marijuana?” Current use was an affirmative to using marijuana in the past 30 days. We derived a cumulative marijuana use variable between CARDIA exams, marijuana-years, as the product-term of the number of days of using marijuana in the past 30 days and the duration between midpoints of successive exams. Cumulative lifetime marijuana use was calculated as the sum of cumulative marijuana use between CARDIA exams and the baseline examination direct response to lifetime marijuana use and we used the directly self-reported lifetime estimate whenever the derived cumulative estimate was lower than the directly self-reported lifetime estimate, consistent with other CARDIA analyses.(14) Other drug use was assessed in similar fashion for crack/cocaine, amphetamines, and opiates.

Computed tomography

The computed tomography (CT) protocol has been described previously.(36) Briefly, non-contrast CT with multi-detector General Electric (GE) or Siemens scanners was used to obtain CT images at each field center at examination year 25 [Birmingham: GE 750HD 64 and Oakland: GE LightSpeed VCT 64; GE Healthcare, Waukesha, Wisconsin. Chicago and Minneapolis: Sensation 64; Siemens Medical Solutions, Erlangen, Germany]. Image analysis and quality control were performed at a central reading center (Wake Forest University Health Sciences, Winston-Salem, North Carolina). The CT scanning protocol included scout images of the abdomen, an ECG gated chest series, and a lower abdomen series. Volume of adipose tissue was measured within a 10 millimeter (mm) block of slices centered between the 4th and 5th (L4-L5) lumbar vertebrae. Medical Image Processing, Analysis, and Visualization software (<http://mipav.cit.nih.gov/index.php>) was used to segment and quantify volume, in milliliters (mL), of visceral, subcutaneous, and intermuscular AT within each compartment. Liver attenuation (LA) was measured in Hounsfield Units (HU) in the right lobe of the liver using 2.5 to 3.0 mm thick images of the chest series images in the upper abdomen. Mean LA was calculated as the average of nine measurements from three slices using 2.6 cm³ regions of interest (ROI). Readers were trained to place the liver regions of interest avoiding the large vessels and any focal liver lesions.(37) As the amount of liver fat increases, the measured LA decreases.(37) In a subsample of 156 blinded scans, the intra-class correlation for inter-reader comparisons for visceral AT, intermuscular AT of the right psoas muscle, and LA (from 3 ROI) were 0.989, 0.948, and 0.958 to 0.975, respectively. Intra- and inter-reader technical error were low, 2.4% and 6.7% for visceral AT, 8.1% and 7.6% for right psoas intermuscular AT, and 2.7% to 3.2% and 4.1% to 5.3% for LA (from 3 ROI).

Statistical analysis

Of the 3,499 participants attending the CARDIA year 25 exam, 318 individuals were excluded from CT due to reasons of current pregnancy, body weight in excess of 450 lbs or

were unable to fit within the CT gantry. An additional 24 individuals who had inadequate or missing measurement for total abdominal, visceral, subcutaneous, intermuscular AT, or LA were excluded. Of the remaining 3,157 individuals with CT data, we excluded participants with self-reported liver disease (n=88), risk factors for chronic liver disease: self-reported HIV (n=24) and previous intravenous drug use (n=51), and individuals who were missing covariate data (n=92) for an analytic sample of 2,902 for the four adipose tissue depots. For analyses of LA, we further excluded individuals with potential secondary causes of hepatic steatosis including regular alcohol consumption ≥ 20 g/day for women and ≥ 30 g/day for men (n=308) and current hormone therapy (n=116) resulting in an analytic sample of 2,478. (38) Characteristics of those excluded from analysis are presented in Supplementary Table 1.

We modeled cumulative lifetime marijuana use through exam year 25, as a 5-level categorical variable based on cumulative marijuana-years: none, less than 0.5 marijuana-years, 0.5 to < 2 marijuana-years, 2 to < 5 marijuana-years, and ≥ 5 marijuana-years, consistent with previous CARDIA analyses.(39, 40) We generated categorical current marijuana use status at year 25 as times of use in past 30 days (none, 1–9 times, 10–19 times, and ≥ 20 times). Participant characteristics measured at CARDIA examination year 25 were summarized across category of cumulative use. Our outcomes of interest were total abdominal, visceral, subcutaneous, and intermuscular AT, and mean LA measured at year 25. All volumes were determined to be normally distributed and we used multivariable linear regression to assess the mean difference (and standard deviation, SD) in tissue volumes according to cumulative marijuana use category compared to individuals who reported zero lifetime use. We assessed the association between cumulative and current marijuana use and each outcome with an unadjusted model, two sequentially adjusted models, and a fourth model accounting for cohort attrition. The first adjusted model included age, sex, race, field center, and educational attainment. The second adjusted model included adjustment for the previous characteristics in addition to cigarette pack-years, current cigarette smoking status, regular alcohol consumption, cumulative drink-years, and regular sports-related physical activity. Individuals with high marijuana use and high abdominal adiposity may have a higher risk of being lost to follow-up before year 25 and excluded from CT scan. Therefore, for the fourth model we used inverse probability of attrition weighting (IPAW) to examine the influence of selective attrition on our estimates.(41) The objective of IPAW is to create a pseudo-population representative of the original population, wherein individuals who are followed completely who have characteristics similar to those of individuals who are lost to follow-up provide greater weight to the analysis. These methods are detailed in the supplementary material. We assessed statistical interaction of each association by age, sex, and race. We assessed linear trend in estimates across marijuana use category by assigning the median marijuana-years to each individual in the respective marijuana use category and entering this variable into a separate regression model. We assessed non-linear associations modeling marijuana-years as a 2nd order quadratic polynomial continuous variable. We also assessed the sensitivity of our estimates to other drug use, including cumulative use of crack/cocaine, amphetamines, and opiates into our final model. All statistical analyses was performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Of the 2,902 individuals included in this analysis, 57% were women, 48% were black, and the mean age was 50.6 years (SD=3.6 years) at the time of CT. The proportion of individuals who reported never using marijuana was 16% (n=476), with 54% (n=1,578), 16% (n=463), 6% (n=183), and 7% (n=202) reporting less than 0.5 marijuana-years of use, 0.5 to < 2 marijuana-years of use, 2 to < 5 marijuana-years of use, and ≥ 5 marijuana-years of use, respectively (Table 1). The mean ($\pm$ SD) total marijuana-years at CARDIA exam year 25 was 1.2 marijuana-years ($\pm$ 3.0). The percentage of the sample who reported using marijuana in the past 30 days at exam year 25 was 11% and current use was positively associated with cumulative marijuana-years. Of the total sample, 5% reported marijuana use of 1–9 times in past 30 days (n=152), 2% reported marijuana use of 10–19 times in past 30 days (n=63), and 4% reported marijuana use of 20 or more times in past 30 days (n=106). At year 25, other characteristics positively associated with greater cumulative marijuana-years included male sex, current cigarette smoking, greater cigarette pack-years, physical activity, and cumulative alcohol drink-years. In contrast, educational attainment and BMI were inversely associated with greater cumulative marijuana-years.

Descriptive statistics for total abdominal, visceral, subcutaneous, intermuscular AT, and LA according to participant characteristics can be found in Supplementary Table 2. The mean ($\pm$ SD) total abdominal AT, visceral AT, subcutaneous AT, intermuscular AT, and LA was 484.6 ml ($\pm$ 216.5), 130.5 ml ($\pm$ 72.9), 335.9 ml ($\pm$ 169.9), 18.2 ml ($\pm$ 11.1), and 55.5 HU ($\pm$ 11.8). On average, women had greater volumes of total abdominal and subcutaneous AT, lower volume of visceral AT, and less liver fat. Intermuscular AT did not differ by sex. Furthermore, compared to whites, blacks had greater mean volumes of total abdominal and subcutaneous AT, lower mean volumes of visceral and intermuscular AT, and less liver fat. At year 25, greater physical activity was inversely associated with each adipose tissue depot and positively associated with mean LA. Current cigarette smoking was associated with lower total abdominal and subcutaneous AT volumes and greater intermuscular AT volume. Greater regular alcohol intake was associated with lower total abdominal and subcutaneous AT. Greater education was associated with lower total abdominal and subcutaneous AT volume.

The results from multivariable adjusted linear regression models are presented in Tables 2 and 3. Before adjustment, greater cumulative marijuana use, according to marijuana-years category, was associated with lower total abdominal and subcutaneous AT volume and lower LA (Table 2). We consistently observed individuals with the greatest marijuana-years had significantly ($p<0.05$) lower total abdominal and subcutaneous AT volume and lower LA (greater liver fat) compared with the reference category (none) and we observed significant linear trend in the volume estimates across marijuana use category. However, after adjustment for age, sex, race, field center, and education, cumulative marijuana use was not associated with any of the abdominal adipose tissue depots or liver attenuation at CARDIA exam year 25 and remained not associated after further adjustment for lifestyle characteristics. For all marijuana use and adipose depots associations, the greatest attenuation in estimates was observed after adjustment for regular alcohol consumption. We did not find evidence for a linear trend across category of cumulative marijuana-years or

when modeling marijuana-years continuously with a quadratic term ($p > 0.10$, figures in Supplement). Similarly, greater current marijuana use at exam year 25 was not significantly associated with total abdominal AT, visceral AT, intermuscular AT, or LA before or after adjustment (Table 3). Before adjustment, greater current marijuana use appeared to be associated with lower subcutaneous AT. This association was explained with adjustment for demographics and lifestyle characteristics. When current marijuana use was assessed as yes or no, current use was not associated with any adipose tissue volume or LA. We did not find evidence for an interaction in the association between cumulative marijuana use or current marijuana use and any of the outcomes by age, sex, or race (all p for interaction > 0.05). The mean $\pm$ SD of the attrition weights was 0.99 ± 0.09 (range: 0.72, 2.05). Employing IPAW in our modeling technique did not alter our primary results (Tables 2 and 3) nor did inclusion of cumulative use of crack/cocaine, amphetamines, and opiates to our final model (not shown).

Discussion

The main findings from this analysis were that cumulative lifetime marijuana use from young adulthood through 25 years later was not associated with volume of total abdominal adipose tissue, visceral adipose tissue, subcutaneous adipose tissue, intermuscular adipose tissue, or mean liver attenuation in middle adulthood. Furthermore, we did not find an association between current use of marijuana and any abdominal adipose tissue depot. We found no variation in our results by age, sex, or race. Lastly, we did not find evidence that our results were influenced by cohort attrition.

Epidemiological data on the association between marijuana use and abdominal adipose tissue accumulation are limited. One previous cross-sectional study examined differences in abdominal adipose tissue depots between 30 current heavy cannabis users and 30 matched non-users (matched by age, sex, ethnicity, and BMI).(26) While current cannabis users had lower absolute total body fat and subcutaneous fat, they also had greater percentage visceral fat (% of total abdominal fat) compared to non-users, with no differences between the two groups in percentage of total body or subcutaneous fat or absolute volume of hepatic fat.(26) However, beyond matching criteria, no modeling adjustments were made for important potential confounding factors such as alcohol and tobacco use, which may impact weight and metabolism.(30) This is particularly concerning when concomitant tobacco use exceeded 50% among the cannabis smokers compared to 7% concomitant tobacco use among non-cannabis users in this study.(26) Investigation of marijuana use and proxies of general adiposity and abdominal adiposity, BMI and WC, is limited and conflicting. Data from the Nunavik Inuit Health Study showed a cross-sectional association between current marijuana use and lower percent body fat and BMI.(27) A large cross-sectional study of US residents using inpatient data and patient discharge records observed lower prevalence of NAFLD among current cannabis users compared to non-users.(29) Long-term marijuana use was not assessed for either study. The association between current marijuana use and lower BMI and WC in adults has been observed in some cohorts(23, 25, 28) and not others(28), and even showed an opposite direction of association in adolescent girls(42). However, longitudinal investigation of substance use in adolescents found baseline marijuana use was not associated with subsequent BMI.(43) Previous prospective analysis in CARDIA has

found greater lifetime marijuana use was not associated with BMI but was associated with lower waist circumference.(22)

The principal active ingredient of cannabis is THC, which acts on cannabinoid receptors 1 (CB₁) and 2 (CB₂) in the brain and peripheral tissues.(21, 44) Habitual cannabis use is associated with down regulation of CB receptors, reversible with cessation of use.(45) Activation of these receptors and the endocannabinoid system is thought to affect appetite regulation and energy and tissue metabolism.(21) THC may accrue and be stored in adipose tissue and subsequently released from adipocytes during lipolysis.(46, 47) In rat models, administration of THC resulted in a paradoxical phenomenon of decreased food intake and reduced body weight while promoting epididymal adipocyte hypertrophy and greater macrophage infiltration of adipocytes.(48) This suggests specific action of THC in visceral adipocytes. Consistent with this, clinical trials of CB₁ receptor antagonists in obese individuals have shown significant reductions in visceral, subcutaneous, and liver fat when compared with placebo.(49) Together these clinical and animal data suggest the endocannabinoid system has a role in adipocyte tissue accumulation and inflammation.

Our findings are germane to the general public and to clinicians, particularly considering the corollaries of increased abdominal adiposity and the general lack of prospective data on marijuana use and health outcomes. Greater visceral adiposity is associated with increased incidence of type 2 diabetes and coronary artery calcium progression, both strong risk factors for major cardiovascular events.(50, 51) Greater cumulative marijuana use was not consistently associated with developing prediabetes and diabetes in CARDIA.(19) Marijuana use is shown to be an acute trigger for myocardial infarction (MI)(6). However, for individuals presenting with acute myocardial infarction (MI), marijuana use in the preceding year was not significantly associated with greater mortality in the years following MI.(52) In CARDIA, marijuana use during young adulthood was not associated with incident cardiovascular disease over 26 years of follow-up(40), though greater marijuana use was associated with unhealthy behaviors.(22) In our data, greater marijuana use is associated with greater physical activity, without adjustment for other characteristics. This is association is likely confounded by smoking status; we do not observe an association between physical activity and marijuana use for individuals who report never smoking cigarettes or who are current cigarette smokers and former cigarette smokers may have increased their level of physical activity in the time since quitting smoking cigarettes (e.g., medical recommendation, improved physical fitness, or ability to be physically active). The dearth of data on long-term marijuana use warrants more research on the long-term health effects of marijuana use, particularly considering the uncertainty surrounding the prevalence of marijuana use before and after legalization of medicinal and recreational use in the US. (2–4)

This study was in a large biracial cohort with standardized data collection and phenotyping at all 8 exams and high retention of the original cohort at year 25. CARDIA participants were asked about drug use at each examination with a self-administered questionnaire, potentially mitigating under-reporting due to social desirability concerns. While a majority of CARDIA participants reported ever using marijuana, the average cumulative lifetime quantity was low. This may prevent us from observing an association and also limits the

interpretation of this association at heavier quantities of lifetime marijuana use. Our results may generalize to US populations of similar demographic and socioeconomic makeup. Some limitations of our study merit discussion. First, abdominal CT scans were performed at year 25, precluding investigation of change in abdominal adipose tissue. Second, we excluded individuals who were lost to follow-up and were missing covariate data at year 25. We employed statistical techniques to minimize the influence of cohort attrition on our estimates, observing minimal impact on our estimates. Third, mode of marijuana use and mixing with other substances (i.e. tobacco) was not assessed. Lastly, this is an observational study where assessment of marijuana use and other health behaviors occurred every 2–5 years and is subject to unmeasured confounding.

Our findings suggest marijuana use during young adulthood is not associated with abdominal adipose tissue accumulation in middle adulthood. In our study, neither self-reported cumulative use of marijuana nor current marijuana use were associated with volume of total abdominal adipose tissue, visceral adipose tissue, subcutaneous adipose tissue, intermuscular adipose tissue, or mean liver attenuation. We caution that additional data is needed to confirm these results and individuals who use marijuana should consider the severity of known acute and chronic health effects of marijuana use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AT	adipose tissue
BMI	body mass index
CB	cannabinoid receptors
CARDIA	Coronary Artery Risk Development in Young Adults
CT	computed tomography

EU	exercise units
HU	Hounsfield Units
IPAW	inverse probability of attrition weighting
LA	liver attenuation
ml	milliliters
NAFLD	non-alcoholic fatty liver disease
ROI	regions of interest
THC	tetrahydrocannabinol
WC	waist circumference

References

1. Center for Behavioral Health Statistics and Quality. 2016 National Survey on Drug Use and Health: Detailed Tables. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2017.
2. Cerdá M, Wall M, Keyes KM, Galea S, Hasin D. Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and Alcohol Dependence*. 2012; 120:22–27. [PubMed: 22099393]
3. Wall MM, Mauro C, Hasin DS, Keyes KM, Cerdá M, Martins SS, et al. Prevalence of marijuana use does not differentially increase among youth after states pass medical marijuana laws: Commentary on and reanalysis of US National Survey on Drug Use in Households data 2002–2011. *The International journal on drug policy*. 2016; 29:9–13. [PubMed: 26895950]
4. Hasin DS, Wall M, Keyes KM, Cerdá M, Schulenberg J, O'Malley PM, et al. Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: results from annual, repeated cross-sectional surveys. *The lancet Psychiatry*. 2015; 2:601–608. [PubMed: 26303557]
5. Fant RV, Heishman SJ, Bunker EB, Pickworth WB. Acute and residual effects of marijuana in humans. *Pharmacology, biochemistry, and behavior*. 1998; 60:777–784.
6. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation*. 2001; 103:2805–2809. [PubMed: 11401936]
7. Martinasek MP, McGrogan JB, Maysonet A. A Systematic Review of the Respiratory Effects of Inhalational Marijuana. *Respiratory care*. 2016; 61:1543–1551. [PubMed: 27507173]
8. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR. The respiratory effects of cannabis dependence in young adults. *Addiction (Abingdon, England)*. 2000; 95:1669–1677.
9. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction (Abingdon, England)*. 2015; 110:19–35.
10. Sidney S, Quesenberry CP Jr, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). *Cancer causes & control : CCC*. 1997; 8:722–728. [PubMed: 9328194]
11. Berthiller J, Straif K, Boniol M, Voirin N, Benhaim-Luzon V, Ayoub WB, et al. Cannabis smoking and risk of lung cancer in men: a pooled analysis of three studies in Maghreb. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2008; 3:1398–1403.
12. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2006; 15:1829–1834.

13. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, et al. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International journal of cancer Journal international du cancer*. 2015; 136:894–903. [PubMed: 24947688]
14. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, et al. Association between marijuana exposure and pulmonary function over 20 years. *Jama*. 2012; 307:173–181. [PubMed: 22235088]
15. Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR, McLachlan CR, et al. Effects of cannabis on lung function: a population-based cohort study. *The European respiratory journal*. 2010; 35:42–47. [PubMed: 19679602]
16. Macleod J, Robertson R, Copeland L, McKenzie J, Elton R, Reid P. Cannabis, tobacco smoking, and lung function: a cross-sectional observational study in a general practice population. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2015; 65:e89–95. [PubMed: 25624312]
17. Tan WC, Lo C, Jong A, Xing L, Fitzgerald MJ, Vollmer WM, et al. Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2009; 180:814–820.
18. Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. *Journal of general internal medicine*. 2005; 20:33–37. [PubMed: 15693925]
19. Bancks M, Pletcher M, Kertesz S, Sidney S, Rana J, Schreiner P. Marijuana use and risk of prediabetes and diabetes by middle adulthood: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetologia*. 2015; 58:2736–2744. [PubMed: 26364621]
20. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *American journal of public health*. 1997; 87:585–590. [PubMed: 9146436]
21. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological reviews*. 2006; 58:389–462. [PubMed: 16968947]
22. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *The American journal of cardiology*. 2006; 98:478–484. [PubMed: 16893701]
23. Le Strat Y, Le Foll B. Obesity and cannabis use: results from 2 representative national surveys. *American journal of epidemiology*. 2011; 174:929–933. [PubMed: 21868374]
24. Hayatbakhsh MR, O'Callaghan MJ, Mamun AA, Williams GM, Clavarino A, Najman JM. Cannabis use and obesity and young adults. *The American journal of drug and alcohol abuse*. 2010; 36:350–356. [PubMed: 20936991]
25. Vidot DC, Prado G, Hlaing WM, Florez HJ, Arheart KL, Messiah SE. Metabolic Syndrome Among Marijuana Users in the United States: An Analysis of National Health and Nutrition Examination Survey Data. *The American journal of medicine*. 2016; 129:173–179. [PubMed: 26548604]
26. Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M, et al. Metabolic effects of chronic cannabis smoking. *Diabetes care*. 2013; 36:2415–2422. [PubMed: 23530011]
27. Ngueta G, Bélanger RE, Laouan-Sidi EA, Lucas M. Cannabis use in relation to obesity and insulin resistance in the inuit population. *Obesity (Silver Spring, Md)*. 2015; 23:290–295.
28. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. *The American journal of medicine*. 2013; 126:583–589. [PubMed: 23684393]
29. Adejumo AC, Alliu S, Ajayi TO, Adejumo KL, Adegbola OM, Onyeakusi NE, et al. Cannabis use is associated with reduced prevalence of non-alcoholic fatty liver disease: A cross-sectional study. *PloS one*. 2017; 12:e0176416. [PubMed: 28441459]
30. Molenaar EA, Massaro JM, Jacques PF, Pou KM, Ellison RC, Hoffmann U, et al. Association of lifestyle factors with abdominal subcutaneous and visceral adiposity: the Framingham Heart Study. *Diabetes care*. 2009; 32:505–510. [PubMed: 19074991]
31. Vidot DC, Bispo JB, Hlaing WM, Prado G, Messiah SE. Moderate and vigorous physical activity patterns among marijuana users: Results from the 2007–2014 National Health and Nutrition Examination Surveys. *Drug Alcohol Depend*. 2017; 178:43–48. [PubMed: 28641129]

32. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988; 41:1105–1116. [PubMed: 3204420]
33. US Department of Health Human Services. Dietary guidelines for Americans 2015–2020. Skyhorse Publishing Inc; 2017.
34. Jacobs DJ, Hahn L, Haskell W, Pirie P, Sidney S. Validity and reliability of a short physical activity history: CARDIA and the Minnesota Heart Health Program. *J Cardiopulm Rehabil*. 1989; 9:448–459.
35. American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. Position stand of the American College of Sports Medicine. *Schweizerische Zeitschrift fur Sportmedizin*. 1993; 41:127–137. [PubMed: 8211083]
36. VanWagner LB, Ning H, Lewis CE, Shay CM, Wilkins J, Carr JJ, et al. Associations between nonalcoholic fatty liver disease and subclinical atherosclerosis in middle-aged adults: the Coronary Artery Risk Development in Young Adults Study. *Atherosclerosis*. 2014; 235:599–605. [PubMed: 24956534]
37. Davidson LE, Kuk JL, Church TS, Ross R. Protocol for measurement of liver fat by computed tomography. *Journal of applied physiology* (Bethesda, Md : 1985). 2006; 100:864–868.
38. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* (Baltimore, Md). 2012; 55:2005–2023.
39. Auer R, Vittinghoff E, Yaffe K, Kunzi A, Kertesz SG, Levine DA, et al. Association Between Lifetime Marijuana Use and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *JAMA internal medicine*. 2016; 176:352–361. [PubMed: 26831916]
40. Reis JP, Auer R, Bancks MP, Goff DC Jr, Lewis CE, Pletcher MJ, et al. Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *American journal of public health*. 2017; 107:601–606. [PubMed: 28207342]
41. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology* (Cambridge, Mass). 2012; 23:119–128.
42. Farhat T, Iannotti RJ, Simons-Morton BG. Overweight, obesity, youth, and health-risk behaviors. *American journal of preventive medicine*. 2010; 38:258–267. [PubMed: 20171527]
43. Pasch KE, Velazquez CE, Cance JD, Moe SG, Lytle LA. Youth substance use and body composition: does risk in one area predict risk in the other? *Journal of youth and adolescence*. 2012; 41:14–26. [PubMed: 21853355]
44. Gaoni Y, Mechoulam R. Isolation and structure of DELTA.-tetrahydrocannabinol and other neutral cannabinoids from hashish. *Journal of the American Chemical Society*. 1971; 93:217–224. [PubMed: 5538858]
45. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, et al. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular psychiatry*. 2012; 17:642–649. [PubMed: 21747398]
46. Johansson E, Noren K, Sjoval J, Halldin MM. Determination of delta 1-tetrahydrocannabinol in human fat biopsies from marihuana users by gas chromatography-mass spectrometry. *Biomedical chromatography : BMC*. 1989; 3:35–38. [PubMed: 2539872]
47. Gunasekaran N, Long LE, Dawson BL, Hansen GH, Richardson DP, Li KM, et al. Reintoxication: the release of fat-stored delta(9)-tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *British journal of pharmacology*. 2009; 158:1330–1337. [PubMed: 19681888]
48. Wong A, Gunasekaran N, Hancock DP, Denyer GS, Meng L, Radford JL, et al. The major plant-derived cannabinoid Delta(9)-tetrahydrocannabinol promotes hypertrophy and macrophage

- infiltration in adipose tissue. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et métabolisme. 2012; 44:105–113. [PubMed: 22189757]
49. Despres JP, Ross R, Boka G, Almeras N, Lemieux I. Effect of rimonabant on the high-triglyceride/low-HDL-cholesterol dyslipidemia, intraabdominal adiposity, and liver fat: the ADAGIO-Lipids trial. Arteriosclerosis, thrombosis, and vascular biology. 2009; 29:416–423.
50. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. Diabetes care. 2000; 23:465–471. [PubMed: 10857936]
51. Kramer CK, von Muhlen D, Gross JL, Barrett-Connor E. A prospective study of abdominal obesity and coronary artery calcium progression in older adults. The Journal of clinical endocrinology and metabolism. 2009; 94:5039–5044. [PubMed: 19846732]
52. Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman M. A Marijuana use and long-term mortality among survivors of acute myocardial infarction. American heart journal. 2013; 165:170–175. [PubMed: 23351819]

Characteristics of 2,902 participants in the Coronary Artery Risk Development in Young Adults study (2010-2011) with computed tomography data according to cumulative lifetime marijuana use

Table 1

Characteristic	Cumulative lifetime marijuana use by 2010-2011					P-value
	None	1 day to < 0.5 marijuana-years	0.5 to < 2 marijuana-years	2 to < 5 marijuana-years	5 marijuana-years	
N (% sample)	476 (16%)	1,578 (54%)	463 (16%)	183 (6%)	202 (7%)	
Age, years	50.2 (3.8)	50.7 (3.6)	50.9 (3.5)	50.1 (3.7)	50.3 (3.7)	0.26
Women, %	60	65	43	42	37	<0.001
White, %	47	56	49	46	51	<0.001
> 16 years education, %	29	28	17	13	11	<0.001
Physical activity, EU	282 (260)	336 (274)	382 (294)	325 (268)	391 (264)	<0.001
Body Mass Index, kg/m ²	31.5 (7.3)	30.1 (7.3)	29.7 (6.6)	30.8 (7.5)	29.2 (5.2)	0.04
Regular alcohol intake						
No daily, %	68	44	34	37	25	
Moderate daily, %	28	42	46	43	42	<0.001
Cumulative alcohol, drink-years	4.2 (8.8)	12.1 (16.2)	24.5 (30.0)	27.2 (30.4)	36.8 (38.6)	<0.001
Current cigarette smoker, %	4	12	31	34	37	<0.001
Cigarette smoking, pack-years	1.0 (5.1)	4.2 (8.6)	10.0 (12.6)	9.3 (11.3)	10.0 (13.7)	<0.001
Marijuana-years	0 (0)	0.1 (0.1)	1.2 (0.4)	3.3 (0.8)	10.5 (4.9)	<0.001
Marijuana use past 30 days, %	0	2	6	42	79	<0.001

Within column mean (standard deviation) for continuous variables and percent for categorical variables. Moderate daily alcohol consumption is any up to 1 drink daily for women and any up to 2 drinks daily for men. Drink-years: consuming 1 alcoholic drink per day for 1 year. EU is exercise units, 300 EU corresponding to 30 minutes of moderate physical activity 5 times per week. Marijuana-year: 1 year of exposure is equivalent to 365 days used marijuana. Cigarette pack-year: 1 year of exposure is equivalent to smoking 1 pack of cigarettes (20 individual cigarettes) per day for 365 days. P-value is an ANOVA test for continuous characteristics and a chi-square for categorical characteristics, according to marijuana use category.

Table 2

Multivariable adjusted mean difference (and 95% confidence limits) in total abdominal, visceral, subcutaneous, and intermuscular adipose tissue volume (ml) and liver attenuation (Hounsfield Units; HU) according to cumulative lifetime marijuana use (2010-2011), the Coronary Artery Risk Development in Young Adults study

Mean difference in adipose tissue volume (ml) or liver attenuation (HU)						
None	1 day to < 0.5 marijuana-years	0.5 to < 2 marijuana-years	2 to < 5 marijuana-years	5 marijuana-years		
Abdominal tissue depot	n=476	n=1,578	n=463	n=183	n=202	P for trend
Total abdominal adipose tissue, ml						
Unadjusted	Reference	-48.3 (-70.4, -26.2)	-62.9 (-90.5, -35.4)	-28.8 (-65.6, 8.0)	-78.2 (-113.7, -42.8)	0.01
Model 1	Reference	-42.4 (-64.6, -20.2)	-52.0 (-79.9, -24.2)	-18.5 (-55.1, 18.2)	-62.9 (-98.7, -27.1)	0.10
Model 2	Reference	-26.5 (-49.1, -3.9)	-20.3 (-50.2, 9.5)	7.3 (-30.4, 45.0)	-18.9 (-56.5, 18.7)	0.57
Model 2 IPAW	Reference	-26.9 (-49.8, -3.9)	-21.4 (-51.4, 8.5)	7.6 (-30.2, 45.5)	-17.9 (-55.5, 19.8)	0.50
Visceral adipose tissue, ml						
Unadjusted	Reference	-6.6 (-14.1, 0.8)	2.9 (-6.4, 12.2)	15.2 (2.8, 27.7)	2.0 (-9.9, 14.0)	0.03
Model 1	Reference	-8.1 (-15.4, -0.9)	-8.3 (-17.5, 0.8)	4.7 (-7.3, 16.8)	-11.3 (-23.0, 0.5)	0.11
Model 2	Reference	-6.3 (-13.7, 1.2)	-4.8 (-14.7, 5.0)	5.7 (-6.8, 18.1)	-6.0 (-18.5, 6.4)	0.16
Model 2 IPAW	Reference	-6.0 (-13.6, 1.5)	-4.8 (-14.7, 5.1)	6.0 (-6.5, 18.5)	-5.4 (-17.9, 7.0)	0.16
Subcutaneous adipose tissue, ml						
Unadjusted	Reference	-41.7 (-59.0, -24.4)	-66.9 (-88.5, -45.3)	-46.0 (-74.8, -17.3)	-81.2 (-108.9, -53.4)	0.02
Model 1	Reference	-33.2 (-49.5, -16.9)	-43.0 (-63.5, -22.5)	-24.1 (-51.1, 2.9)	-51.0 (-77.3, -24.6)	0.17
Model 2	Reference	-19.0 (-35.7, -2.3)	-14.6 (-36.6, 7.5)	1.4 (-26.5, 29.2)	-11.9 (-39.7, 15.8)	0.22
Model 2 IPAW	Reference	-19.6 (-36.5, -2.7)	-15.6 (-37.7, 6.6)	1.4 (-26.5, 29.3)	-11.4 (-39.2, 16.4)	0.22
Intermuscular adipose tissue, ml						
Unadjusted	Reference	0.0 (-1.1, 1.2)	1.0 (-0.4, 2.4)	2.0 (0.1, 3.9)	0.9 (-0.9, 2.7)	0.10
Model 1	Reference	-1.1 (-2.2, 0.0)	-0.7 (-2.1, 0.7)	0.9 (-0.9, 2.8)	-0.6 (-2.4, 1.2)	0.10
Model 2	Reference	-1.2 (-2.3, 0.0)	-1.0 (-2.5, 0.6)	0.2 (-1.7, 2.2)	-1.0 (-2.9, 1.0)	0.13
Model 2 IPAW	Reference	-1.2 (-2.4, 0.0)	-1.1 (-2.6, 0.5)	0.2 (-1.7, 2.2)	-1.0 (-2.9, 0.9)	0.13
Liver attenuation, HU	n=445	n=1,359	n=381	n=151	n=142	
Unadjusted	Reference	-1.1 (-2.3, 0.2)	-2.3 (-3.9, -0.6)	-1.2 (-3.3, 1.0)	-3.1 (-5.4, -0.9)	0.005
						0.02

Mean difference in adipose tissue volume (ml) or liver attenuation (HU)						
Abdominal tissue depot	None	1 day to < 0.5 marijuana-years n=1,578	0.5 to < 2 marijuana-years n=463	2 to < 5 marijuana-years n=183	5 marijuana-years n=202	P for trend
Model 1	Reference	0.2 (-1.1, 1.4)	0.7 (-0.9, 2.3)	1.0 (-1.1, 3.2)	0.0 (-2.2, 2.2)	0.11
Model 2	Reference	0.1 (-1.2, 1.4)	0.5 (-1.3, 2.2)	1.1 (-1.1, 3.4)	-0.3 (-2.6, 2.0)	0.13
Model 2 IPAW	Reference	0.0 (-1.3, 1.3)	0.6 (-1.2, 2.3)	1.1 (-1.2, 3.3)	-0.4 (-2.7, 1.9)	0.13
						0.86
						0.90
						0.89

Model 1: age, sex, race, field center, and educational attainment

Model 2: Model 1 + cigarette pack-years, current cigarette smoking status, regular alcohol consumption, cumulative drink-years, and regular sports-related physical activity

IPAW, Inverse probability for attrition weighting

P for trend is test of linear trend in estimates across marijuana use category

Table 3

Multivariable adjusted mean difference (and 95% confidence limits) in total abdominal, visceral, subcutaneous, and intermuscular adipose tissue volume (ml) and liver attenuation (Hounsfield Units; HU) according to marijuana use in past 30 days (2010-2011), the Coronary Artery Risk Development in Young Adults study

		Mean difference in adipose tissue volume (ml) or liver attenuation (HU)			
Zero		1 to 9 times in past 30 days	10 to 19 times in past 30 days	20 times in past 30 days	
Abdominal tissue depot	n=2,581	n=152	n=63	n=106	Model R ² P for trend
Total abdominal adipose tissue, ml					
Unadjusted	Reference	-41.4 (-76.8, -6.0)	-55.4 (-109.5, -1.3)	-20.1 (-62.1, 22.0)	0.003 0.09
Model 1	Reference	-39.2 (-73.8, -4.6)	-48.4 (-101.5, 4.7)	-10.0 (-51.4, 31.3)	0.06 0.26
Model 2	Reference	-8.4 (-42.6, 25.8)	-21.2 (-72.9, 30.6)	11.2 (-29.5, 51.9)	0.12 0.80
Model 2 IPAW	Reference	-9.3 (-43.3, 24.7)	-20.3 (-71.6, 31.0)	14.2 (-26.5, 54.9)	0.12 0.68
Visceral adipose tissue, ml					
Unadjusted	Reference	-1.3 (-13.3, 10.6)	-4.6 (-22.8, 13.7)	10.5 (-3.7, 24.6)	0.001 0.24
Model 1	Reference	-5.0 (-16.4, 6.3)	-12.8 (-30.2, 4.7)	0.6 (-13.0, 14.1)	0.11 0.68
Model 2	Reference	-0.2 (-11.5, 11.1)	-8.5 (-25.6, 8.6)	2.8 (-10.7, 16.2)	0.16 0.93
Model 2 IPAW	Reference	-0.5 (-11.8, 10.7)	-8.2 (-25.1, 8.8)	4.0 (-9.4, 17.5)	0.15 0.79
Subcutaneous adipose tissue, ml					
Unadjusted	Reference	-39.8 (-67.6, -12.0)	-49.0 (-91.4, -6.6)	-31.8 (-64.7, 1.2)	0.01 0.01
Model 1	Reference	-33.4 (-58.9, -7.9)	-33.8 (-72.9, 5.4)	-12.0 (-42.4, 18.5)	0.17 0.16
Model 2	Reference	-7.4 (-32.7, 17.8)	-11.0 (-49.2, 27.3)	7.3 (-22.7, 37.4)	0.22 0.79
Model 2 IPAW	Reference	-8.0 (-33.1, 17.1)	-10.5 (-48.4, 27.3)	9.0 (-21.0, 39.0)	0.22 0.71
Intermuscular adipose tissue, ml					
Unadjusted	Reference	-0.3 (-2.1, 1.5)	-1.8 (-4.6, 0.9)	1.2 (-0.9, 3.4)	0.001 0.54
Model 1	Reference	-0.8 (-2.5, 0.9)	-1.9 (-4.5, 0.8)	1.3 (-0.7, 3.4)	0.10 0.48
Model 2	Reference	-0.7 (-2.5, 1.0)	-1.7 (-4.4, 0.9)	1.1 (-1.0, 3.2)	0.13 0.58
Model 2 IPAW	Reference	-0.7 (-2.5, 1.0)	-1.6 (-4.3, 1.0)	1.1 (-0.9, 3.2)	0.13 0.54
Liver attenuation, HU		n=114	n=46	n=70	
Unadjusted	Reference	-0.5 (-2.7, 1.7)	0.0 (-3.5, 3.4)	-2.0 (-4.8, 0.8)	0.001 0.18
Model 1	Reference	0.6 (-1.5, 2.7)	1.4 (-1.9, 4.7)	-0.9 (-3.6, 1.8)	0.11 0.76

Mean difference in adipose tissue volume (ml) or liver attenuation (HU)					
	Zero	1 to 9 times in past 30 days	10 to 19 times in past 30 days	20 times in past 30 days	
	n=2,581	n=152	n=63	n=106	
Abdominal tissue depot					P for trend
Model 2	Reference	0.1 (-2.0, 2.3)	0.9 (-2.4, 4.2)	-0.9 (-3.6, 1.8)	0.13
Model 2 IPAW	Reference	0.3 (-1.9, 2.4)	1.1 (-2.1, 4.4)	-1.0 (-3.7, 1.6)	0.63

Model 1: age, sex, race, field center, and educational attainment

Model 2: Model 1 + cigarette pack-years, current cigarette smoking status, regular alcohol consumption, cumulative drink-years, and regular sports-related physical activity

IPAW: Inverse probability for attrition weighting

P for trend is test of linear trend in estimates across marijuana use category