Associations between cannabis use and cardiometabolic risk factors: A longitudinal study of men

RUNNING TITLE: Cannabis and Cardiometabolic Risk

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Abstract

Objective: This study tested longitudinal associations between cannabis use and cardiometabolic risk factors that underlie the development of cardiovascular diseases.

Methods: Participants were men from the youngest cohort of the Pittsburgh Youth Study who were followed prospectively from approximately age 7 to 32 (n=253). Frequency of cannabis use was assessed yearly from ~ages 12-20 and again at ~ages 26, 29, and 32. The following cardiometabolic risk factors were assessed during a laboratory visit at age ~32: BMI, WHR, HDL and LDL cholesterol, triglycerides, fasting glucose, HOMA-IR, blood pressure, interleukin 6, and C-reactive protein.

Results: Greater cannabis exposure was associated with relatively lower BMI (β=-0.31, p<.001), smaller WHR (β=-0.23, p=.002), better HDL (β=0.14, p=.036) and LDL cholesterol (β=-0.15, p=.026), lower triglycerides (β=-0.17, p=.009), lower fasting glucose (β=-0.15, p<.001) and HOMA-IR (β=-0.21, p=.003), lower systolic (β=-0.22, p<.001) and diastolic blood pressure (β=-0.15, p=.028), and fewer metabolic syndrome criteria (β=-0.27, p<.001). With exception of BMI, cannabis users' mean levels on cardiometabolic risk factors were generally below clinical cutoffs for high risk. Most associations between cannabis use and cardiometabolic risk factors remained after adjusting for tobacco use, childhood SES, and childhood health. However, after adjusting for adult BMI, these associations were no longer apparent, and mediation tests suggested that cannabis users' relatively lower BMI might explain their lower levels of risk on other cardiometabolic risk factors.

Conclusions: Cannabis use is associated with lower BMI, and lower BMI is related to lower levels of risk on other cardiometabolic risk factors.

Key Words: cannabis, marijuana, cardiovascular, cardiometabolic, health

BMI=body mass index; WHR=waist-hip ratio; HDL= high density lipoprotein cholesterol; LDL= low density lipoprotein cholesterol; HOMA-IR=insulin resistance; SES=socioeconomic status

As of November 2018, recreational cannabis use has been legalized in ten U.S. states, and medical cannabis use has been legalized in 33 U.S. states. The implications of cannabis legalization for public health are largely unknown, spurring keen interest in research on the acute and longer-term effects of cannabis on health. Despite some research suggesting that cannabis acutely increases risk of myocardial infarction and stroke (1-5), the longer-term (i.e., non-acute) associations between cannabis use and cardiovascular risk are unclear (6-8). A key question is whether cannabis use, like tobacco use, is associated with cardiometabolic risk factors that underlie the development of cardiovascular diseases (9).

Most extant studies of the association between cannabis use and cardiometabolic risk factors have been cross-sectional and/or have relied on cannabis users' self-reports of health (10-32). Of the relatively few cross-sectional studies with biological markers of cardiometabolic risk, some have reported an association between cannabis use and increased cardiometabolic risk (16, 25), and others have reported an association between cannabis use and decreased cardiometabolic risk – primarily lower body mass index (BMI) (15, 17-19, 21, 24, 26). One potential explanation for mixed findings is that cross-sectional studies often rely on crude measures of cannabis use (e.g., current use, former use, never use) that do not capture important individual differences in cumulative cannabis exposure. Relatedly, cross-sectional studies rely on retrospective reports of use, which are complicated by recall problems. Thus, longitudinal studies are needed.

Only two longitudinal studies have reported on associations between cannabis use and an array of biological markers of cardiometabolic risk (29, 30). These two studies found little evidence that cannabis use for up to 15-20 years was associated with increased cardiometabolic risk. In fact, one of the two studies found that persistent cannabis use from age 18-38 was

associated with lower BMI and smaller waist circumference, and after adjusting for tobacco use, persistent cannabis use was additionally associated with slightly better HDL cholesterol, lower triglycerides, lower diastolic blood pressure, and lower glycated hemoglobin levels (30). These latter findings converge with accumulating evidence that cannabis users have lower BMI (11, 12, 14, 17-19, 21, 22, 24, 27), as well as with isolated reports from cross-sectional studies of an association between cannabis use and better lipids, blood pressure, insulin, or glucose control (10, 15, 17-19, 26).

However, additional longitudinal studies are needed for several reasons. First, given that only two previous longitudinal studies tested associations between cannabis use and an array of biological markers of cardiometabolic risk, replication in diverse samples is needed before firm conclusions can be drawn. Second, although the two previous longitudinal studies examined an array of biological markers of cardiometabolic risk, neither study examined insulin resistance, which is important given some evidence from cross-sectional studies that cannabis use is associated with lower insulin resistance and reduced risk of diabetes (17, 19). Finally, although the two previous longitudinal studies agreed that cannabis use was not associated with increased cardiometabolic risk, they differed in terms of whether cannabis use was associated with lower BMI. One study found that cannabis users had lower BMI (30) and the other study did not (29). Given accumulating evidence from cross-sectional studies of a link between cannabis use and lower BMI, reproducible findings in longitudinal studies would strengthen the evidence base.

Here we tested associations between prospectively-assessed cannabis use from ~age 12-32 and biological markers of cardiometabolic risk at ~age 32 in a longitudinal study of Black and White men. To facilitate comparisons with the two previous longitudinal studies, the present study incorporated many of the same biological markers of cardiometabolic risk. The present

study builds on the two previous longitudinal studies by incorporating, for the first time, a measure of insulin resistance. Moreover, because some cardiometabolic risks are more prevalent among Blacks (i.e., hypertension) and others are more prevalent among Whites (low HDL, high triglycerides) (33, 34), the present study tested for race differences in cannabis use-cardiometabolic risk associations.

Methods

Participants

Participants were members of the youngest cohort of the Pittsburgh Youth Study (PYS) (35), a longitudinal study of 503 boys recruited from Pittsburgh Public Schools in 1987-88 when they were in the first grade. Boys (n=849) were randomly chosen to undergo a multi-informant screening for conduct problems, with half of the sample recruited from the top 30% of the screening measure, and the rest randomly selected from the remainder for a total of 503 boys in the longitudinal sample. The boys' mean age at screening was 6.9 years, and racial composition was predominately White (40.6%) and Black (55.7%). Nearly all primary caregivers were biological mothers (92%), with 45.3% cohabitating with a partner and 16.9% completing <12 years of schooling. Over half of families (61.3%) were receiving public financial assistance (e.g., food stamps). Starting in 1987, boys were assessed every six months from ~ages 7-11 (calendar years 1987-1991) and yearly from ~ages 12-20 (calendar years 1992-2000). Follow-up assessments were conducted at ~ages 26 and 29 (calendar years 12/13/2005-02/15/2008 and 01/29/2009-03/19/2012, respectively). Retention rates at each assessment from ~age 7-29 were high and ranged from 82-95%.

When participants were ~age 32, eligible men were contacted to participate in a laboratory visit for a study examining early developmental factors associated with risk for

cardiovascular disease. During that visit, which took place from October 2012 to November 2015, biological measures of cardiometabolic risk were obtained. Exclusionary criteria were death (N=18), prior withdrawal from PYS (N=44), severe mental disability (N=4), and current incarceration (N=42). Of the 395 men remaining after exclusion, 312 (79%) agreed to participate in some or all the protocol. Among those who were eligible but did not participate, 22 declined participation, 19 failed to respond to messages or missed appointments, and 42 could not be located. Of the 312 men, some no longer lived in the Pittsburgh area, so 267 men participated in the laboratory protocol (36, 37). Analyses were restricted to the 267 men with laboratory data. An additional 14 men were missing cannabis data so the final analytic sample was 253 men. There were no differences between the 253 men and all others in terms of race ($F(1,502)=1.56$, $p=.21$), baseline childhood SES ($F(1,497)=0.84$, $p=.36$), childhood health ($F(1,501)=1.29$, $p=.26$), frequency of cannabis use at age 18 ($F(1,418)=0.01$, $p=.93$), or cigarettes smoked per day at age 18 ($F(1,418)=0.11$, $p=.74$).

Respondents and their caregivers provided written informed consent. The Pittsburgh Youth Study was approved by the Institutional Review Board at the medical school of the University of Pittsburgh.

Cannabis Joint Years

Similar to prior studies (30, 38), we created a cumulative cannabis joint-years variable indexing the number of years that participants smoked cannabis daily. Cannabis joint-years was estimated based on reported frequency of cannabis use over the past-year (0-365 days) at ~ages 12-20, 26, 29, and 32. Like in prior longitudinal studies (30), when there were gaps between assessments, estimates assumed that past-year frequency of cannabis use was representative of frequency of use in the years since the last assessment. One cannabis joint-year is equivalent to

daily cannabis use for one year. Mean joint-years for the sample was 3.20 (SD=4.21). Thus, participants used cannabis daily for an average of 3.20 years. Mean joint-years for Whites was 1.65 (2.98) and for Blacks was 4.44 (4.62) ($F(1,252)=33.99$, $p<.001$). Cannabis joint-years was positively skewed and was log-transformed prior to statistical tests.

Cardiometabolic Risk Factors

As previously described (37), when participants were age ~32, men who lived within driving distance of Pittsburgh or who planned to return for a visit were scheduled for a laboratory assessment. On arrival to the laboratory after an 8-hour fast, participants had anthropometric measurements taken and had a blood draw. Laboratory assays were conducted by the Heinz Laboratory at the University of Pittsburgh, which is a CLIA-certified laboratory and accredited by the College of American Pathologists.

Each cardiometabolic risk factor is described below and descriptive statistics are shown in **Table 1**. Because some cardiometabolic risk factors were skewed, **Supplemental Table 1** reports skew before and after log transformation, and **Supplemental Figures 1-6** show the distribution of residuals for cardiometabolic risk factors before and after log transformation. Correlations between cardiometabolic risk factors are shown in **Supplemental Table 2**.

Body mass index (BMI). Body mass index was calculated based on measurements taken by staff (weight in kg/height in m^2). The clinical cutoff for overweight and obesity is >25 and ≥ 30, respectively. BMI was skewed and was log-transformed prior to statistical tests.

Waist-hip ratio (WHR). WHR was calculated based on waist and hip measurements taken by staff.

High density lipoprotein (HDL) cholesterol. HDL cholesterol was isolated based on the method of Izawa. The intra- and inter-assay coefficients of variation were 1.8% and 2.6%,

respectively. The clinical cutoff for low HDL is <40 mg/dL (39). Participants who were not fasting at the time of blood draw (n=6) were excluded from analyses of HDL.

Low density lipoprotein (LDL) cholesterol. LDL cholesterol was calculated using the Friedewald equation. Since LDL is derived from HDL, triglycerides, and total cholesterol, we report intra- and inter-assay coefficients for HDL (above), triglycerides (below), and total cholesterol (1.8% and 3.7%, respectively). Participants who were not fasting at the time of blood draw (n=6) were excluded from analyses of LDL.

Trigylcerides. Triglyceride concentrations were determined by coupled enzymatic methods. The intra- and inter-assay coefficients of variation were 1.8% and 3.7%, respectively. The clinical cutoff for high triglycerides is ≥ 150 mg/dL (39). Participants who were not fasting at the time of blood draw (n=6) were excluded from analyses of triglycerides.

Glucose. Glucose was measured by hexokinase-coupled reaction (Boehringer Mannheim Diagnostics). The intra- and inter-assay coefficients of variation were 1.8% and 2.6%, respectively. The clinical cutoff for high fasting glucose is ≥ 100 mg/dL (39). Participants who were not fasting at the time of blood draw (n=6) were excluded from analyses of glucose. Glucose was skewed and was log-transformed prior to statistical tests.

Insulin resistance (HOMA-IR). Insulin resistance (IR) was estimated using the Homeostasis Model of Assessment equation: the product of fasting glucose and insulin divided by the constant 22.5 (40). The intra- and inter-assay coefficients of variation for glucose are reported above and for insulin were 4.8% and 10.5%, respectively. Because insulin was highly correlated with HOMA-IR, we report results for HOMA-IR and not insulin. Participants who were not fasting at the time of blood draw (n=6) were excluded from analyses of HOMA-IR. HOMA-IR was skewed and was log-transformed prior to statistical tests.

Systolic blood pressure (SBP). SBP was taken using a CARESCAPE Dinamap V100 Vital Signs Monitor (GE Medical Systems Information Technologies, Inc.) with a standard occluding cuff placed on the participant's non-dominant arm. Blood pressure measurements were taken every 2 minutes during a 10-minute rest period, and the last 3 measurements were averaged. The clinical cutoff for high SBP is ≥ 130 mm Hg (39).

Diastolic blood pressure (DBP). DBP was taken using a CARESCAPE Dinamap V100 Vital Signs Monitor (GE Medical Systems Information Technologies, Inc.) with a standard occluding cuff placed on the participant's non-dominant arm. Blood pressure measurements were taken every 2 minutes during a 10-minute rest period, and the last 3 measurements were averaged. The clinical cutoff for high DBP is ≥ 85 mm Hg (39).

Metabolic Syndrome (MetS). MetS was based on the ATP-III definition: waist circumference > 102 cm; HDL cholesterol < 40 mg/dL or use of lipid-lowering medications; triglycerides ≥ 150 mg/dL or use of lipid-lowering medications; fasting glucose of ≥ 100 mg/dL or use of anti-diabetic medications; and resting blood pressure of ≥ 130/≥ 85 mm Hg or use of antihypertensive medications (39). Due to the relative youth of participants, we used the number of risk factors above the clinical cutoffs as our primary outcome, as opposed to the conventional definition of yes/no having three or more of the five indicators.

Interleukin 6 (IL-6). IL-6 was measured in duplicate using a high sensitivity ELISA kit (R&D Systems, HS600). The intra- and inter-assay coefficients of variation were 9.1% and 10.2%, respectively. Participants (n=30) were removed from analyses of IL-6 if they reported being ill on the day of the blood draw or had CRP values of >10 mg/L, which could indicate an acute infection. IL-6 was skewed and was log-transformed prior to statistical tests.

High sensitivity C-reactive protein (CRP). High sensitivity C-reactive protein (CRP) was measured turbidimetrically. The intra- and inter-assay coefficients of variation were 5.5% and 3.0%, respectively. Participants (n=30) were removed from analyses of CRP if they reported being ill on the day of the blood draw or had CRP values of >10 mg/L, which could indicate an acute infection. The clinical cutoff for high CRP is >3 mg/L (41). CRP was skewed and was log-transformed prior to statistical tests.

Covariates

We included age, race, medication use, tobacco use, childhood socioeconomic status (SES), and childhood health as covariates.

Medication use. Medication was included as a covariate because some medications are for treatment of the cardiometabolic risk factors. In analyses of HDL cholesterol, LDL cholesterol, and triglycerides, we included a covariate indicating use of lipid medications (n=7); in analyses of fasting glucose and HOMA-IR, we included a covariate indicating use of diabetes medications (n=7); in analyses of blood pressure, we included a covariate indicating use of blood pressure medications (n=16); finally, in analyses of Il-6 and CRP, we included a covariate indicating use of anti-inflammatory medications (n=9). In analyses of the count of metabolic syndrome criteria, it was not necessary to include each of the above medications as covariates because use of each medication counts toward criteria for metabolic syndrome.

Tobacco use. We included tobacco use as a covariate because cannabis users tend to smoke tobacco, and tobacco use is associated with increased cardiometabolic risk, including worse lipids and glucose control, but is also associated with lower BMI and blood pressure (42, 43). Similar to prior studies (30), we created a cumulative tobacco pack-years variable indexing the number of years a participant smoked one pack of cigarettes (20 cigarettes) per day. Tobacco

pack-years was estimated based on reported frequency of use over the past year (0-365 days) and the number of cigarettes smoked per day at ~ages 12-20, 26, 29, and 32. Like prior studies (30), when there were gaps between assessments, estimates assumed that past-year reports of tobacco use were representative of use in the years since the last assessment. Tobacco pack-years was positively skewed and was log-transformed prior to statistical tests.

Childhood SES. We included childhood SES as a covariate because research has shown that low childhood SES is associated with substance use and adult health (44-47). Childhood SES was assessed yearly with the two-factor Hollingshead index (48), which incorporates parental educational attainment and occupational status as reported by the boy's family. As an index of average childhood SES, we took the mean Hollingshead SES across 10 occasions from ~age 7-16 and standardized scores to M=0, SD=1.

Childhood health. We included childhood health as a covariate because healthier children are at lower cardiometabolic risk as adults. Childhood health was assessed yearly from ~age 7-16 using caregiver reports of 15 health problems. Health problems were recoded as 0, 1, and 2+ health problems, and we averaged these scores and standardized them to M=0, SD=1.

Other potential covariates. We also considered other potential covariates, including childhood BMI and adult fruit and vegetable consumption, physical activity, and alcohol use. Childhood BMI was based on parent reports of the child's height and weight, averaged across ~ages 8-16. Daily fruit and vegetable consumption were assessed at ~age 32 using six items from the Behavioral Risk Factor Surveillance System fruit and vegetable module (49). Physical activity was assessed with the Paffenbarger questionnaire at ~age 32, and physical activity was computed as the average kilocalories expended in leisure activities, walking, and stair climbing

per week (50). Alcohol use was based on self-reports at ~age 32 and was computed as the average number of alcoholic drinks per week over the past year.

Statistical analyses

To determine whether cannabis use was associated with cardiometabolic risk factors, we used linear regression to test associations between cannabis joint-years (a continuous variable) from ~age 12-32 and each cardiometabolic risk factor assessed at ~age 32 (Model 1). We subsequently added tobacco pack-years as a covariate (Model 2), followed by childhood SES and health (Model 3). All analyses adjusted for age, race, and relevant medication use. Statistical analyses used robust regression with MM estimation, an approach that is robust to non-normality and outliers. (As a check, we also used ordinary least squares regression after removing the few influential outliers, and findings were similar; **Supplemental Table 3**.)

We report standardized beta coefficients from regression analyses. To aid interpretation of beta coefficients, we report age-, race-, and medication-adjusted means on each cardiometabolic risk factor as a function of cannabis joint-years, with participants grouped according to joint-years in five-year increments (never used, <5 joint-years, 5 to <10 joint-years, 10+ joint-years). To test race interactions, we added a multiplicative term (i.e., cannabis joint-years x race) to regression analyses.

Results

Characteristics of Cannabis Users

Characteristics of cannabis users are shown in **Table 2.** Twenty-two percent of the cohort had never used cannabis (n=55), and 50% (n=128), 18% (n=45), and 10% (n=25) had used cannabis for <5 joint-years, 5 to <10 joint-years, and 10+ joint-years, respectively. Black race,

low childhood SES, and tobacco pack-years were each associated with cannabis joint-years but childhood health was not.

Associations between cannabis joint-years and cardiometabolic risk factors

In initial analyses adjusting for age, race, and medication use, cannabis joint-years from ~age 12-32 was associated with reduced risk on 10 of the 12 cardiometabolic risk factors (**Table 3**, Model 1: BMI, WHR, HDL and LDL cholesterol, triglycerides, fasting glucose, HOMA-IR, systolic and diastolic blood pressure, and count of metabolic syndrome criteria). For example, a 1 SD increase in log-transformed cannabis joint-years was associated with a 0.31 SD decrease in log-transformed BMI. To help understand this association, **Table 3** shows that men who never used cannabis had a BMI of M=32.91, whereas men with 10+ joint-years had a BMI of M=26.65. Although cannabis users had lower BMI than nonusers, their BMI was still above the threshold for overweight (BMI >25). However, on other cardiometabolic risk factors, cannabis users' mean levels were generally below clinical cutoffs for high risk.

In subsequent analyses that additionally adjusted for tobacco pack-years, joint-years was associated with reduced risk on 7 of the 12 cardiometabolic risk factors **(Table 3**, Model 2: BMI, WHR, HDL cholesterol, triglycerides, fasting glucose, systolic blood pressure, and count of metabolic syndrome criteria). Estimates were generally unchanged after additionally adjusting for childhood SES and childhood health, though the association with better HDL cholesterol became statistically non-significant (**Table 3**, Model 3).

Because cannabis use was associated with reduced cardiometabolic risk, we considered several possible explanations, including whether cannabis users had lower BMI as children or healthier lifestyles as adults. Cannabis joint-years was not associated with lower childhood BMI or with a diet of fruit and vegetables, greater physical activity, or reduced alcohol use in

adulthood (**Supplemental Table 4**), which excludes these factors as explanations for associations between cannabis joint-years and reduced cardiometabolic risk. Although cannabis use was associated with reduced cardiometabolic risk, cannabis use alone accounted for <6% of the variance in each cardiometabolic risk factor (**Supplemental Table 5**).

Accounting for lower body mass index in adulthood

We tested whether associations between cannabis use and reduced cardiometabolic risk were independent of adult BMI, because research has shown that reduction in BMI is associated with improved lipids, fasting glucose, HOMA-IR, blood pressure, and inflammation (51). After adjusting for adult BMI, joint-years was no longer associated with smaller WHR, lower triglycerides, lower systolic blood pressure, and fewer metabolic syndrome criteria (**Table 3,** Model 4). However, joint-years was still associated with lower fasting glucose (**Table 3,** Model 4: β=-0.09, p=.038). **Supplemental Table 6** shows results of mediation tests, which suggested that lower BMI might explain associations between cannabis use and lower risk on cardiometabolic risk factors.

Race differences

Associations between cannabis joint-years and cardiometabolic risk factors were not statistically significantly different for Whites and Blacks with one exception: diastolic blood pressure (p=.017). Joint-years was associated with lower diastolic blood pressure for Whites (β=-0.37, 95% CIs: -0.58, -0.16, p<.001) but not Blacks (β=-0.01, 95% CIs: -0.18, 0.16, p=.93) in analyses adjusting for age and use of antihypertensive medications. This race difference was still apparent after additionally adjusting for tobacco pack-years, childhood SES, childhood health, and adult BMI (Whites: β=-0.23, 95% CIs:-0.44, -0.02, p=.039; Blacks: β=0.04, CIs -0.15, 0.22, p=.69).

Discussion

Cannabis use from ~age 12-32 was associated with lower BMI, smaller WHR, lower triglycerides, lower fasting glucose, lower systolic blood pressure, and fewer metabolic syndrome criteria at ~age 32, even after accounting for a variety of covariates, including tobacco use, childhood SES, and childhood health. Results were similar for Black and White men. Mediation analyses suggested that chronic cannabis use might lead to lower BMI, and lower BMI, in turn, might lead to reduced risk on other cardiometabolic risk factors (51). Findings are in line with accumulating evidence that cannabis users have lower BMI (11, 12, 14, 17-19, 21, 22, 24, 27).

It is currently unclear why recreational cannabis use would be associated with lower BMI, especially given evidence that cannabis acutely increases appetite (52). One possibility is that individuals with lower BMI have a tendency to become cannabis users. However, we showed that cannabis users did not have lower BMI as children, ruling out low initial BMI as an explanation. Moreover, cannabis users did not have healthier lifestyles as adults. They did not eat more fruits and vegetables; they were not more physically active; and they did not drink less alcohol, ruling out healthier lifestyle as an explanation. An alternative possibility is that the association between cannabis use and lower BMI is causal. For example, chronic cannabis use might lead to a reduction in the number and signaling efficiency of CB1 receptors (20, 53), which play a role in the regulation of food intake and energy expenditure (54). Thus, whereas short-term cannabis use might be associated with acute increases in appetite and higher BMI, long-term cannabis use might be associated with lower BMI (20). However, the observational nature of this study precludes causal inference.

This study has limitations. First, information about cannabis use was based on self-reports. Most studies of cannabis use and cardiometabolic risk have relied on self-reports of cannabis use, but the addition of biological assays could help detect underreporting of cannabis use. Notably, our prospective assessment of cannabis use and our ability to estimate cumulative cannabis exposure is an advantage over cross-sectional studies. Second, most cannabis users had used cannabis for fewer than 5 joint-years. It is possible that associations between cannabis use and increased cardiometabolic risk might only emerge with greater cannabis exposure. Third, blood markers of cardiometabolic risk were taken at only one time point in adulthood, so we could not determine if cannabis use was associated with longitudinal change in cardiometabolic risk. Future follow-ups of this cohort can address this question. Fourth, the cohort is relatively young, and it is possible that cannabis-related cardiometabolic risk might become apparent in older adulthood, when risk of cardiovascular disease increases (6). Fifth, we could not test the hypothesis that cannabis use acutely triggers serious cardiovascular events. Some evidence suggests that cannabis users are at heightened risk for cardiovascular complications in the hours after cannabis use (1-5), and the World Health Organization has called for more research on this topic (55). Sixth, findings are limited to a single cohort of men from Pittsburgh, Pennsylvania who began using cannabis in the 1990s. It is unclear if findings will generalize to women, to adults living in other areas, and to younger cohorts who will be exposed to the now higher levels of THC in cannabis (56-58).

In summary, cannabis use was associated with lower BMI and reduced risk on other cardiometabolic risk factors, but effect sizes were small in magnitude. The largest associations were observed for BMI and WHR, yet cannabis users were, on average, overweight (BMI > 25), dispelling any notion that cannabis makes a person thin. Findings of associations between

cannabis use and reduced cardiometabolic risk must be interpreted in the context of prior research showing that cannabis use acutely increases the risk of cardiovascular events (1-5), accidents and injuries (59, 60), persistent psychotic symptoms and schizophrenia (61, 62), and psychosocial problems (63-65).

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Table 1. Descriptive statistics for cardiometabolic risk factors assessed at ~age 32.

Cardiometabolic Risk Factor	Full Sample (N=253)	White (N=112)	Black (n=141)	Race Difference		
	Mean (SD)	Mean (SD)	Mean (SD)	F	df	p
Body Mass Index (kg/m^2)	29.56 (7.29)	29.37 (7.28)	29.71 (7.33)	0.09	1, 252	.77
Waist-hip Ratio	0.92 (0.07)	0.92 (0.06)	0.92 (0.07)	0.06	1, 250	.81
HDL Cholesterol (mg/dL)	46.57 (12.93)	44.03 (10.88)	48.58 (14.07)	7.74	1, 246	.006
LDL Cholesterol (mg/dL)	109.26 (34.60)	111.53 (31.49)	107.46 (36.88)	0.84	1, 246	.36
Triglycerides (mg/dL)	127.43 (95.46)	144.91 (98.03)	113.53 (91.36)	13.21	1, 245	<.001
Glucose (mg/dL)	95.05 (26.50)	97.70 (29.62)	92.96 (23.64)	2.63	1, 246	.11
Insulin Resistance	3.73 (4.45)	4.14 (4.95)	3.40 (4.00)	4.45	1, 246	.036
Systolic Blood Pressure (mm Hg)	122.28 (12.50)	120.05 (10.97)	124.07 (13.38)	6.58	1, 250	.011
Diastolic Blood Pressure (mm Hg)	72.01 (9.40)	70.24 (8.26)	73.45 (10.03)	7.45	1, 250	.007
Metabolic Syndrome	1.38 (1.39)	1.48 (1.39)	1.30 (1.39)	1.10	1, 252	.30
IL-6 (mg/L)	2.00 (1.68)	1.97 (1.61)	2.04 (1.73)	0.02	1, 222	.88
CRP (mg/L)	2.15 (2.18)	2.38 (2.29)	1.96 (2.07)	2.28	1, 222	.13

Note. BMI, triglycerides, fasting glucose, insulin resistance, IL-6, and CRP were log-transformed for statistical tests but means shown here are not log-transformed. HDL=high density lipoprotein. LDL=low density lipoprotein. IL-

Table 1. Descriptive statistics for cardiometabolic risk factors assessed at ~age 32.

Cardiometabolic Risk Factor	Full Sample (N=253)	White (N=112)	Black (n=141)	Race Difference		
	Mean (SD)	Mean (SD)	Mean (SD)	F	df	p

6=interleukin 6. CRP=C-reactive protein.

Table 2. Participant characteristics as a function of cannabis joint-years from ~age 12 to 32.

Characteristic	Cannabis Joint-Years[a] Never Used	<5 Y	5 to <10 Y	10+ Y	r[c]	95% CI	p
No.	55	128	45	25	-	-	-
Race, % Black	42	48	80	80	**0.35**	**0.23, 0.46**	**<.001**
Childhood SES,[b] M (SD)	0.12 (1.12)	0.04 (0.98)	-0.28 (0.83)	0.00 (1.07)	**-0.19**	**-0.32, -0.07**	**.002**
Childhood Health,[b] M (SD)	-0.06 (0.90)	-0.06 (0.96)	0.23 (1.17)	0.06 (1.12)	0.09	-0.03, 0.22	.14
Cannabis Joint-Years, Mean (SD)	0.00 (0.00)	1.28 (1.50)	7.43 (1.40)	12.51 (1.79)	-		-
Tobacco Pack-Years, Mean (SD)	1.43 (2.85)	5.83 (6.56)	5.39 (5.11)	5.85 (4.40)	**0.28**	**0.17, 0.40**	**<.001**

Note. a. Cannabis joint-years indicates the number of years participants used cannabis daily. b. Scores are standardized to M=0, SD=1. c. Correlations test the associations between participant characteristics and continuously-scored, log-transformed cannabis joint-years. SES=socioeconomic status. Statistically significant correlations are bolded.

Table 3. Associations between cannabis joint-years from ~age 12 to 32 and cardiometabolic risk factors at ~age 32.

	Age-, Race-, and Medication-Adjusted Means as a Function of Cannabis Use[a]				Statistical Tests[b]											
					Model 1: Adjusted for Age, Race, and Medication Use			Model 2: + Adjustment for Tobacco Pack-Years			Model 3: + Adjustment for Childhood SES and Health			Model 4: + Adjustment for BMI		
Risk Factor	Never Used	<5 Y	5 to <10 Y	10+ Y	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
BMI (kg/m^2)	32.91	29.38	27.58	26.65	**-0.31**	**-0.44, -0.19**	**<.001**	**-0.21**	**-0.34, -0.07**	**.003**	**-0.20**	**-0.34, -0.06**	**.006**	-	-	-
WHR	0.93	0.93	0.92	0.88	**-0.23**	**-0.37, -0.08**	**.002**	**-0.24**	**-0.39, -0.09**	**.002**	**-0.24**	**-0.39, -0.09**	**.002**	-0.11	-0.25, 0.03	.12
HDL[c] (mg/dL)	42.72	47.41	47.51	49.13	**0.14**	**0.01, 0.27**	**.036**	**0.14**	**0.01, 0.29**	**.047**	0.14	-0.01, 0.28	.06	0.05	-0.10, 0.19	.52
LDL (mg/dL)	113.70	100.13	100.70	109.59	**-0.15**	**-0.28, -0.02**	**.026**	-0.11	-0.25, 0.03	.11	-0.09	-0.23, 0.05	.22	-0.07	-0.22, 0.07	.30
Trig (mg/dL)	139.85	130.69	104.06	123.64	**-0.17**	**-0.30, -0.04**	**.009**	**-0.16**	**-0.30, -0.02**	**.021**	**-0.15**	**-0.29, -0.01**	**.036**	-0.09	-0.23, 0.05	.19
Glucose (mg/dL)	102.43	92.05	94.16	95.71	**-0.15**	**-0.23, -0.07**	**<.001**	**-0.13**	**-0.22, -0.04**	**.004**	**-0.13**	**-0.21, -0.04**	**.005**	**-0.09**	**-0.18, -0.01**	**.038**
HOMA-IR	5.24	3.44	3.21	2.76	**-0.21**	**-0.34, -0.07**	**.003**	-0.10	-0.24, 0.04	.18	-0.09	-0.23, 0.05	.22	0.08	-0.03, 0.18	.14
SBP (mm Hg)	125.54	122.49	118.03	121.65	**-0.22**	**-0.35, -0.10**	**<.001**	**-0.15**	**-0.28, -0.02**	**.028**	**-0.14**	**-0.27, -0.01**	**.042**	-0.06	-0.18, 0.06	.31
DBP (mm Hg)	73.82	71.93	69.08	73.76	**-0.15**	**-0.29, -0.02**	**.028**	-0.11	-0.26, 0.03	.12	-0.09	-0.24, 0.05	.21	-0.06	-0.20, 0.08	.38
MetS	2.00	1.35	0.89	1.02	**-0.27**	**-0.41, -0.14**	**<.001**	**-0.22**	**-0.36, -0.07**	**.004**	**-0.22**	**-0.37, -0.07**	**.004**	-0.07	-0.19, 0.05	.28
Il-6 (mg/L)	1.72	2.14	1.88	2.13	-0.08	-0.23, 0.07	.30	-0.11	-0.27, 0.05	.18	-0.09	-0.25, 0.07	.29	-0.02	-0.16, 0.12	.79
CRP (mg/L)	1.94	2.16	2.54	1.83	-0.03	-0.19, 0.12	.69	-0.02	-0.19, 0.15	.83	-0.02	-0.19, 0.15	.84	0.07	-0.08, 0.21	.39

Note. a. Means on cardiometabolic risk factors (adjusted for age, medication use, and race) are shown for participants grouped according to their cumulative cannabis joint-years: never used, <5 joint-years, 5 to <10 joint-years, and 10+ joint-years. BMI, triglycerides, fasting glucose, insulin resistance, IL-6, and CRP were log-transformed for statistical tests but means are

Table 3. Associations between cannabis joint-years from ~age 12 to 32 and cardiometabolic risk factors at ~age 32.

	Age-, Race-, and Medication-Adjusted Means as a Function of Cannabis Use[a]				Statistical Tests[b]											
					Model 1: Adjusted for Age, Race, and Medication Use			Model 2: + Adjustment for Tobacco Pack-Years			Model 3: + Adjustment for Childhood SES and Health			Model 4: + Adjustment for BMI		
Risk Factor	Never Used	<5 Y	5 to <10 Y	10+ Y	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p

not log-transformed. b. Statistical analyses tested associations between cannabis joint-years (a log-transformed continuous variable) and cardiometabolic risk factors, and standardized beta coefficients are presented. c. Higher values indicate better health. Statistically significant associations are bolded. BMI=body mass index. WHR=waist-hip ratio. HDL=high density lipoprotein. LDL=low density lipoprotein. Trig=triglycerides. Glucose=fasting glucose. HOMA-IR=insulin resistance. SBP=systolic blood pressure. DBP=diastolic blood pressure. MetS=count of metabolic syndrome criteria. IL-6=interleukin 6. CRP=C-reactive protein.

Supplemental Table 1. Skew for cardiometabolic risk factors before and after log transformation.

Cardiometabolic Risk Factor	Skew Before Log Transformation	Skew After Log Transformation[a]
BMI	7.29	0.57
WHR	-0.14	n/a
HDL	0.95	n/a
LDL	0.81	n/a
Trig	3.51	0.69
Glucose	4.22	1.53
HOMA-IR	5.05	0.31
SBP	1.23	n/a
DBP	0.56	n/a
MetS	0.84	n/a
Il-6	3.63	0.41
CRP	1.72	-0.37

Note. a. N/A indicates the variable was not log transformed. BMI=body mass index. WHR=waist-hip ratio. HDL=high density lipoprotein. LDL=low density lipoprotein. Trig=triglycerides. Glucose=fasting glucose. HOMA-IR=insulin resistance. SBP=systolic blood pressure. DBP=diastolic blood pressure. MetS=count of metabolic syndrome criteria. IL-6=interleukin 6. CRP=C-reactive protein.

Supplemental Table 2. Correlations between cardiometabolic risk factors.

Health Indicator	BMI	WHR	HDL	LDL	Trig	Glucose	HOMA-IR	SBP	DBP	MetS	IL-6	CRP
BMI	1.00											
WHR	**0.43**	1.00										
HDL	**-0.30**	**-0.26**	1.00									
LDL	**0.14**	**0.13**	**-0.16**	1.00								
Trig	**0.25**	**0.29**	**-0.40**	**0.27**	1.00							
Glucose	**0.27**	**0.19**	-0.11	-0.03	**0.25**	1.00						
HOMA-IR	**0.63**	**0.36**	**-0.34**	0.09	**0.43**	**0.64**	1.00					
SBP	**0.54**	**0.29**	-0.12	0.12	**0.22**	**0.32**	**0.43**	1.00				
DBP	**0.33**	**0.20**	-0.09	0.12	**0.25**	**0.20**	**0.35**	**0.75**	1.00			
MetS	**0.61**	**0.40**	**-0.50**	**0.17**	**0.62**	**0.46**	**0.66**	**0.59**	**0.48**	1.00		
IL-6	**0.28**	0.11	**-0.12**	0.03	**0.13**	0.09	**0.19**	0.13	0.08	**0.20**	1.00	
CRP	**0.45**	**0.22**	**-0.29**	**0.15**	**0.28**	**0.15**	**0.43**	**0.24**	**0.15**	**0.39**	**0.44**	1.00

Note. Statistically significant ($p<.05$) correlations are shown in bold. The following risk factors were log-transformed: BMI, fasting glucose, HOMA-IR, IL-6, and CRP. BMI=body mass index. WHR=waist-hip ratio. HDL=high density lipoprotein. LDL=low density lipoprotein. Trig=triglycerides. Glucose=fasting glucose. HOMA-IR=insulin resistance. SBP=systolic blood pressure. DBP=diastolic blood pressure. MetS=count of metabolic syndrome criteria. IL-6=interleukin 6. CRP=C-reactive protein.

Supplemental Table 3. Associations between cannabis joint-years from ~age 12 to 32 and cardiometabolic risk factors at ~age 32. Analyses were based on ordinary least squares regression after removing outliers (unlike Table 3 in the main text, which used robust regression with MM estimation and did not remove outliers).

	Statistical Tests[a]											
	Model 1: Adjusted for Age, Race, and Medication Use			Model 2: + Adjustment for Tobacco Pack-Years			Model 3: + Adjustment for Childhood SES and Health			Model 4: + Adjustment for BMI		
Risk Factor	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
BMI (kg/m^2)	**-0.32**	**-0.45, -0.19**	**<.001**	**-0.23**	**-0.37, -0.10**	**<.001**	**-0.23**	**-0.37, -0.10**	**<.001**	-	-	-
WHR	**-0.22**	**-0.35, -0.10**	**<.001**	**-0.21**	**-0.35, -0.08**	**.002**	**-0.21**	**-0.35, -0.07**	**.003**	-0.10	-0.23, 0.02	.11
HDL[a] (mg/dL)	0.13	0.00, 0.26	.059	0.12	-0.02, 0.26	.10	0.13	-0.02, 0.27	.09	0.06	-0.08, 0.20	.41
LDL (mg/dL)	**-0.14**	**-0.27, -0.01**	**.041**	-0.11	-0.25, 0.03	.14	-0.09	-0.24, 0.05	.20	-0.07	-0.22, 0.07	.33
Trig (mg/dL)	**-0.15**	**-0.28, -0.03**	**.019**	**-0.15**	**-0.29, -0.01**	**.041**	-0.14	-0.28, 0.00	.059	-0.08	-0.22, 0.06	.27
Glucose (mg/dL)	-0.11	-0.23, 0.00	0.06	-0.06	-0.18, 0.06	.37	-0.04	-0.16, 0.08	.50	0.00	-0.12, -0.12	.97
HOMA-IR	**-0.20**	**-0.33, -0.08**	**.002**	-0.12	-0.25, 0.02	.087	-0.11	-0.24, 0.03	.12	0.03	-0.09, 0.14	.64
SBP (mm Hg)	**-0.17**	**-0.28, -0.06**	**.002**	-0.11	-0.23, 0.01	.067	-0.10	-0.22, 0.02	.10	-0.02	-0.13, 0.09	.71

Supplemental Table 3. Associations between cannabis joint-years from ~age 12 to 32 and cardiometabolic risk factors at ~age 32. Analyses were based on ordinary least squares regression after removing outliers (unlike Table 3 in the main text, which used robust regression with MM estimation and did not remove outliers).

	Statistical Tests[a]											
	Model 1: Adjusted for Age, Race, and Medication Use			Model 2: + Adjustment for Tobacco Pack-Years			Model 3: + Adjustment for Childhood SES and Health			Model 4: + Adjustment for BMI		
Risk Factor	β	95% CI	p	β	95% CI	p	β	95% CI	p	β	95% CI	p
DBP (mm Hg)	**-0.14**	**-0.26, -0.02**	**.027**	-0.09	-0.22, 0.04	.17	-0.08	-0.21, 0.05	.23	-0.03	-0.16, 0.10	.65
MetS	**-0.30**	**-0.43, -0.17**	**<.001**	**-0.25**	**-0.39, -0.12**	**<.001**	**-0.25**	**-0.39, -0.11**	**<.001**	**-0.12**	**-0.23, -0.01**	**.046**
Il-6 (mg/L)	-0.03	-0.17, 0.11	.68	-0.07	-0.22, 0.09	.39	-0.05	-0.20, 0.11	.54	0.00	-0.14, 0.15	.98
CRP (mg/L)	-0.07	-0.21, 0.07	.33	-0.07	-0.22, 0.08	.35	-0.07	-0.23, 0.08	.36	0.00	-0.14, 0.14	.97

Note. BMI, triglycerides, fasting glucose, insulin resistance, IL-6, and CRP were log-transformed for statistical tests. One outlier was removed in analyses of BMI; one outlier was removed in analyses of WHR; three outliers were removed in analyses of glucose; one outlier was removed in analyses of HOMA-IR; three outliers were removed in analyses of systolic blood pressure; two outliers were removed in analyses of diastolic blood pressure; one outlier was removed in analyses of MetS. Statistical analyses tested associations between cannabis joint-years (a log-transformed continuous variable) and cardiometabolic risk factors, and standardized beta coefficients are presented. a. Higher values indicate better health. Statistically significant associations are bolded. BMI=body mass index. WHR=waist-hip ratio. HDL=high density lipoprotein. LDL=low density lipoprotein. Trig=triglycerides. Glucose=fasting glucose. HOMA-IR=insulin resistance. SBP=systolic blood pressure. DBP=diastolic blood pressure. MetS=count of metabolic syndrome criteria. IL-6=interleukin 6. CRP=C-reactive protein.

Supplemental Table 4. Correlations between cannabis joint-years and childhood BMI and fruit and vegetable intake, physical activity, and alcohol use in adulthood.

Exposure	Childhood BMI			Vegetable Intake			Fruit Intake			Physical Activity			Alcohol Use		
	r	95% CI	p	r	95% CI	p	r	95% CI	p	r	95% CI	p	r	95% CI	p
Cannabis Joint-Years	-0.04	-0.17, 0.09	.54	0.01	-0.11, 0.14	.86	0.05	-0.08, 0.17	.46	-0.04	-0.16, 0.09	.54	**0.15**	0.03, 0.27	**.020**

Note. All variables were log-transformed due to skew. Statistically significant correlations are shown in bold.

Supplemental Table 5. Estimates of the amount of variance (R^2) in each cardiometabolic risk factor accounted for by cannabis use (univariate model) and cannabis use plus additional covariates (multivariable model).

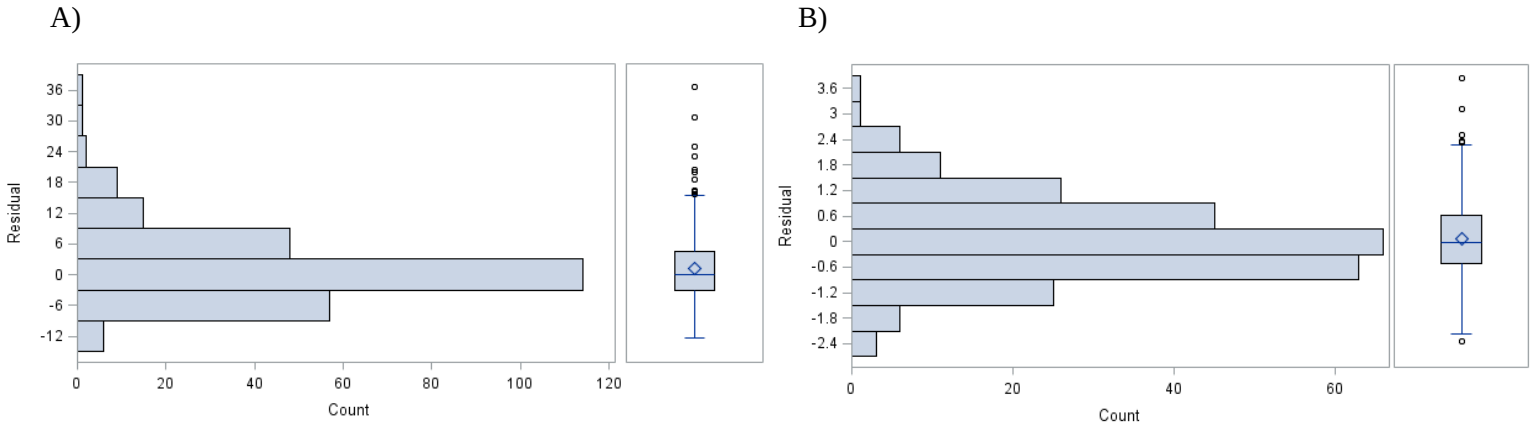
	R^2	
Cardiometabolic Risk Factors	Univariate Model	Multivariable Model
BMI[a]	5.31	10.62
WHR	2.56	24.19
HDL	2.23	8.01
LDL	2.14	5.84
Triglycerides	4.92	15.46
Glucose	3.91	13.89
HOMA-IR	4.58	37.72
SBP	2.76	28.38
DBP	0.73	16.74
MetS	5.68	30.37
Il-6	0.37	16.98
CRP	0.59	19.62

Note. The multivariable models includes covariates of age, race, medication use, childhood health, childhood SES, and adult BMI a. The multivariable model includes all covariates except adult BMI. BMI=body mass index. WHR=waist-hip ratio. HDL=high density lipoprotein. LDL=low density lipoprotein. Trig=triglycerides. Glucose=fasting glucose. HOMA-IR=insulin resistance. SBP=systolic blood pressure. DBP=diastolic blood pressure. MetS=count of metabolic syndrome criteria. IL-6=interleukin 6. CRP=C-reactive protein.

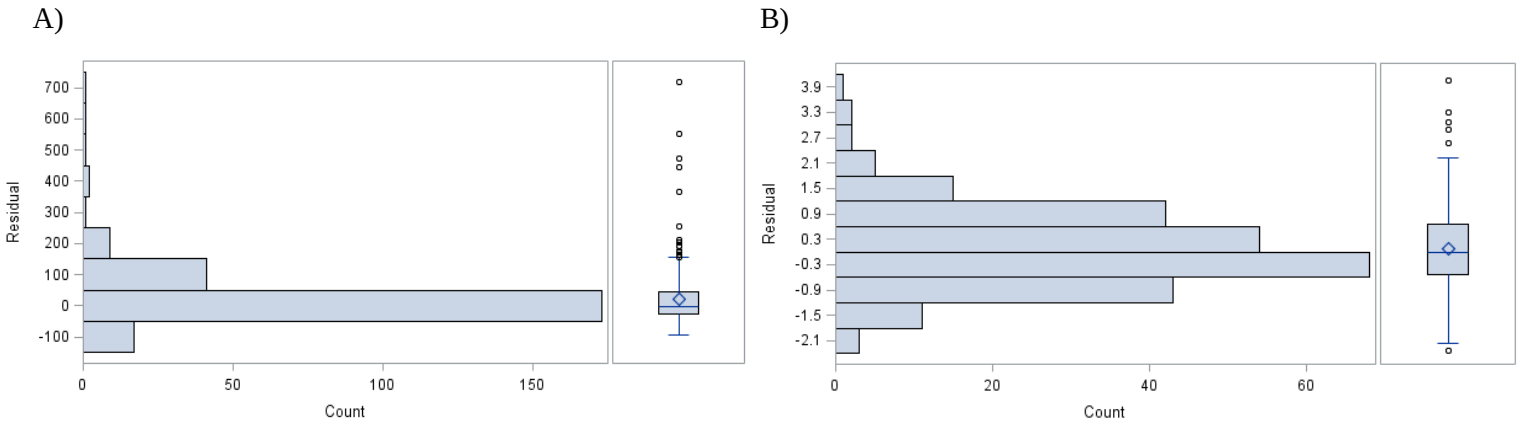
Supplemental Table 6. Results of mediation tests. Adult BMI mediates the association between cannabis use and cardiometabolic risk.

Cardiometabolic Risk Factor	Indirect Effect	95% CI	p
WHR	**-0.12**	**-0.19, -0.06**	**<.001**
HDL	**0.08**	**0.03, 0.13**	**.002**
LDL	-0.03	-0.07, 0.10	.14
Trig	**-0.07**	**-0.13, -0.03**	**.001**
Glucose	**-0.06**	**-0.11, -0.01**	**.023**
HOMA-IR	**-0.17**	**-0.25, -0.09**	**<.001**
SBP	**-0.13**	**-0.19, -0.07**	**<.001**
DBP	**-0.07**	**-0.11, -0.03**	**.002**
MetS	**-0.16**	**-0.24, -0.09**	**<.001**
Il-6	**-0.08**	**-0.13, -0.03**	**.001**
CRP	**-0.13**	**-0.20, -0.06**	**<.001**

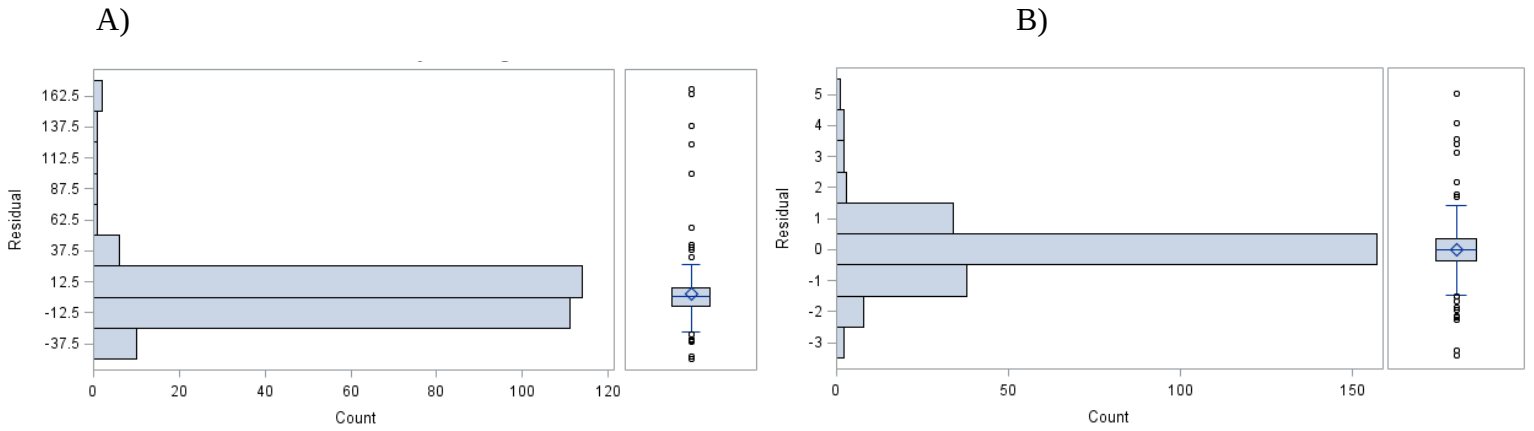
Note. Mediation tests were conducted in Mplus using maximum likelihood estimation and bootstrapped standard errors. Covariates included age, race, and medication use. Estimates represent standardized indirect effects. Mediation tests were conducted in the absence of a total effect (no evidence of an association between cannabis use and the cardiometabolic risk factor), consistent with recent recommendations (O'Rourke & MacKinnon, *J. Stud. Alcohol Drugs, 79*, 171–181, 2018). WHR=waist-hip ratio. HDL=high density lipoprotein. LDL=low density lipoprotein. Trig=triglycerides. Glucose=fasting glucose. HOMA-IR=insulin resistance. SBP=systolic blood pressure. DBP=diastolic blood pressure. MetS=count of metabolic syndrome criteria. IL-6=interleukin 6. CRP=C-reactive protein.



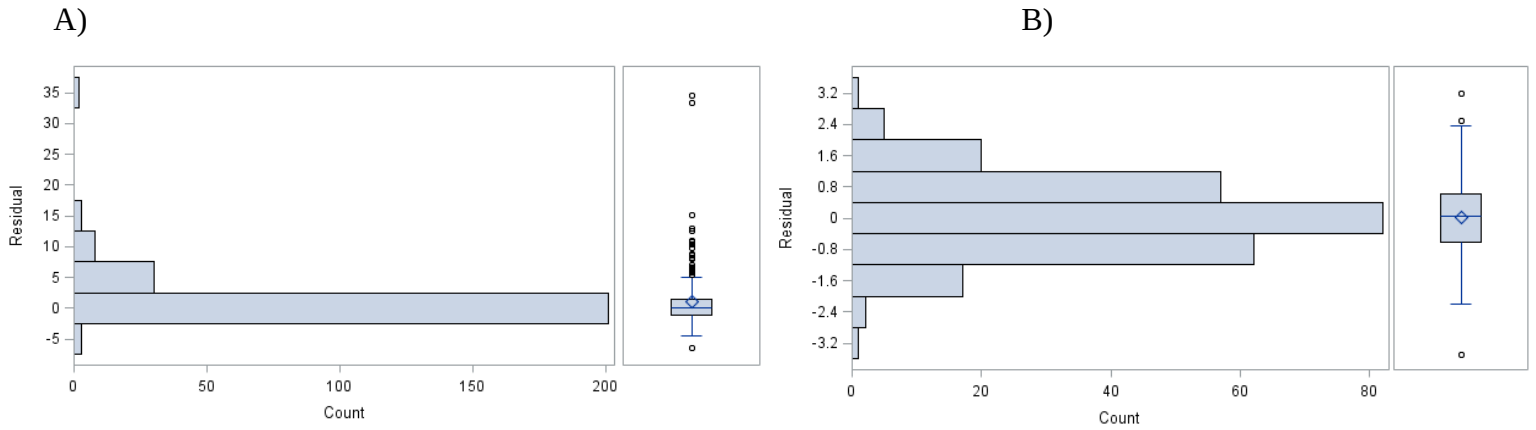
Supplemental Figure 1. The distribution of residuals for BMI (body mass index) before (A) and after (B) log transformation.



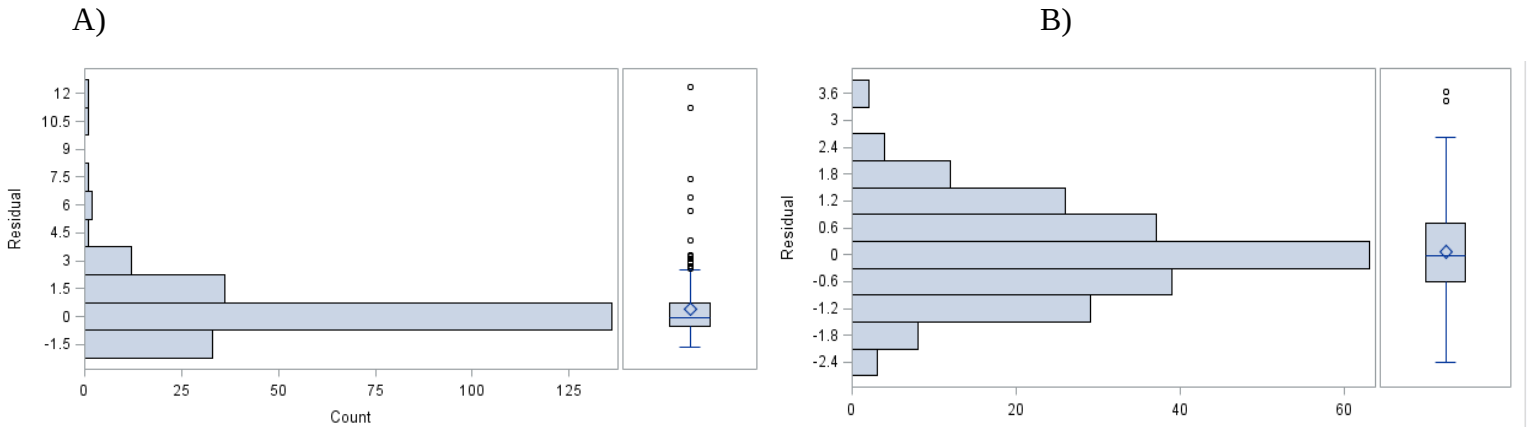
Supplemental Figure 2. The distribution of residuals for triglycerides before (A) and after (B) log transformation.



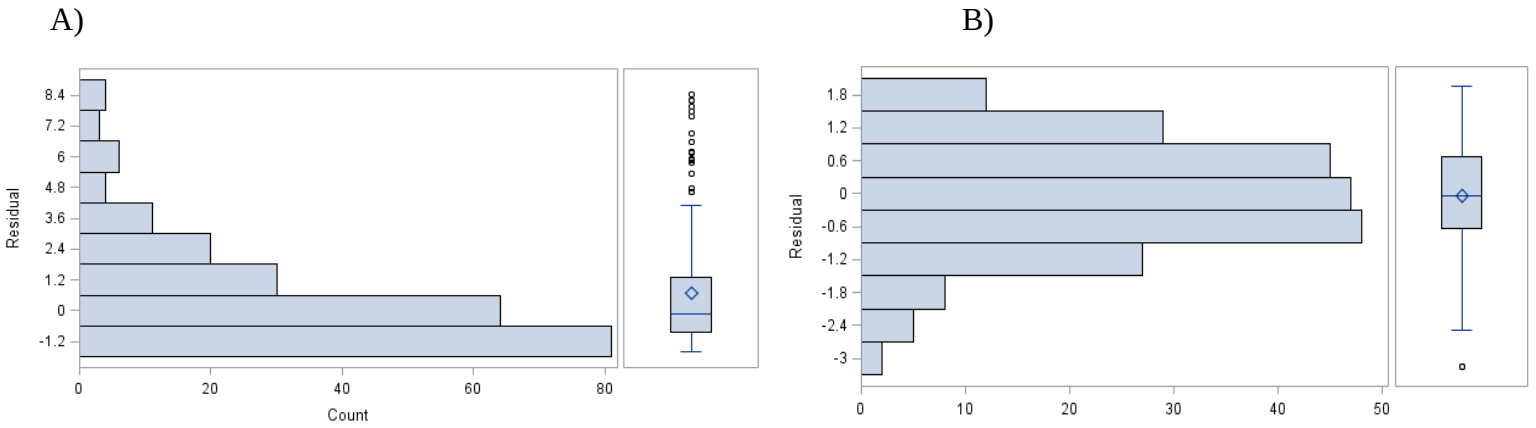
Supplemental Figure 3. The distribution of residuals for fasting glucose before (A) and after (B) log transformation.



Supplemental Figure 4. The distribution of residuals for HOMA-IR (insulin resistance) before (A) and after (B) log transformation.



Supplemental Figure 5. The distribution of residuals for II-6 (interleukin 6) before (A) and after (B) log transformation.



Supplemental Figure 6. The distribution of residuals for CRP (C-reactive protein) before (A) and after (B) log transformation.