CLINICAL RESEARCH STUDY

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The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults

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ABSTRACT

BACKGROUND: There are limited data regarding the relationship between cannabinoids and metabolic processes. Epidemiologic studies have found lower prevalence rates of obesity and diabetes mellitus in marijuana users compared with people who have never used marijuana, suggesting a relationship between cannabinoids and peripheral metabolic processes. To date, no study has investigated the relationship between marijuana use and fasting insulin, glucose, and insulin resistance.

METHODS: We included 4657 adult men and women from the National Health and Nutrition Examination Survey from 2005 to 2010. Marijuana use was assessed by self-report in a private room. Fasting insulin and glucose were measured via blood samples after a 9-hour fast, and homeostasis model assessment of insulin resistance (HOMA-IR) was calculated to evaluate insulin resistance. Associations were estimated using multiple linear regression, accounting for survey design and adjusting for potential confounders.

RESULTS: Of the participants in our study sample, 579 were current marijuana users and 1975 were past users. In multivariable adjusted models, current marijuana use was associated with 16% lower fasting insulin levels (95% confidence interval [CI], −26, −6) and 17% lower HOMA-IR (95% CI, −27, −6). We found significant associations between marijuana use and smaller waist circumferences. Among current users, we found no significant dose-response.

CONCLUSIONS: We found that marijuana use was associated with lower levels of fasting insulin and HOMA-IR, and smaller waist circumference.

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KEYWORDS: Glucose; Insulin; Insulin resistance; Marijuana use

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Marijuana is the most commonly used illicit drug in the United States, and use is increasing. The 2010 National Survey on Drug Use and Health reported that between 2007 and 2010, the prevalence of marijuana use among persons aged 12 years and older increased from 5.8% to 6.9%, meaning there are an estimated 17.4 million current users of marijuana. Approximately 4.6 million of these users smoked marijuana daily or almost daily.[1] With the recent legalization of recreational marijuana in 2 states and the legalization of medical marijuana in 19 states and the District of Columbia, physicians will increasingly encounter marijuana use among their patient populations.[2] Marijuana use is associated with an acute increase in caloric intake,[3] and people who smoke marijuana have higher average caloric intake levels than nonusers.[4,5]

Despite these associations with increased caloric intake, marijuana use has been associated with lower body mass index (BMI)[4] and a lower prevalence of obesity[6] and diabetes mellitus.[7] The mechanisms underlying this paradox have not been determined, and the impact of regular marijuana use on insulin resistance and cardiometabolic risk factors remains unknown. In this study of 4657 participants in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2010, we examined the associations between habitual marijuana use and measures of fasting glucose and insulin levels, insulin resistance, and components of the metabolic syndrome.

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MATERIALS AND METHODS

Study Population

The NHANES is a cross-sectional, continuous survey administered annually by the National Center for Health Statistics;[8] data are released in 2-year increments. The survey uses a complex, multistage probability sampling design to select a nationally representative sample of individuals in the US population, and uses interview, physical examination, and laboratory components to assess health and nutritional status. From 2005 to 2010, 11,335 persons aged 20 to 59 years completed the questionnaire on illicit drug use, including 4657 participants who also were asked to provide a fasting blood sample.

CLINICAL SIGNIFICANCE

- Marijuana use is increasingly common, and use of medical marijuana is now legal in 19 states and the District of Colombia.
- Despite its associations with increased appetite and caloric intake, marijuana use also is associated with lower body mass index and prevalence of diabetes.
- In a nationally representative survey population, we found current use of marijuana to be associated with lower levels of fasting insulin, lower insulin resistance (homeostasis model assessment of insulin resistance), and smaller waist circumference.

Assessment of Marijuana Use

Participants completed the drug use questionnaire in a private room, using the Audio Computer Assisted Self Interview system. They were asked:

- "Have you ever, even once, smoked marijuana or hashish?" (yes, no, refused, don't know);
- "How long has it been since you last used marijuana or hashish?" (answers were given as number of days, weeks, months, or years); and
- "During the past 30 days, on how many days did you use marijuana or hashish?"

Responses to these questions were used to classify participants as never users (never smoked marijuana, n = 2103); past users (smoked marijuana at least once but not in the past 30 days, n = 1975); and current users (smoked marijuana at least once in the prior 30 days, n = 579).

Outcomes

Insulin, Glucose, Homeostatic Model Assessment Insulin Resistance Score, High-Density Lipoprotein Cholesterol, Hemoglobin A1c, and Triglycerides. Participants provided blood samples in the morning after a 9-hour fast. The homeostasis model assessment of insulin resistance (HOMA-IR), a measure of insulin resistance, was calculated as fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405.

From 2005 to 2006, high-density lipoprotein cholesterol (HDL-C) testing was performed at Johns Hopkins University, using the Hitachi 717 and Hitachi 912 (Roche Diagnostics, Indianapolis, Ind). In this cycle, values were corrected because of bias from quality controls (Solomon Park Research Laboratories, Kirkland, Wash), using the following formula: corrected HDL-C = [(Solomon Park assigned HDL-C value) × (participant HDL-C)]/(quality control HDL-C value associated with participant sample)]. From 2007 to 2010, HDL-C testing was performed at the University of Minnesota, using the Roche Modular P chemistry analyzer (Roche Diagnostics).

From 2005 to 2006, hemoglobin A1c measurements were performed on the A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc, South San Francisco, Calif). From 2007 to 2010, measurements were performed on the A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc). The hemoglobin A1c data from 2007 to 2010 exhibited higher values compared with the 1999 to 2006 data. No relationship to laboratory method, survey design, or population changes could be determined for this shift; therefore, no adjustments were made to these values.

Blood Pressure, Body Mass Index, and Waist Circumference. All measurements were collected during the physical examination in mobile examination centers, according to standard NHANES protocol.[9] Blood pressure estimates were calculated by averaging 3 blood pressure readings. BMI was calculated as weight in kilograms divided by the square of height in meters.

Characterization of Sociodemographics and Health Habits

Participants reported age, sex, race/ethnicity, education level, income, marital status, tobacco use, physical activity level, and alcohol use. Race/ethnicity was classified as Hispanic, non-Hispanic white, non-Hispanic black, or other. We classified education level as less than high school, high school or equivalent, or some college. Income was categorized as less than $20,000, $20,000 to $44,999, $45,000 to $74,999, and greater than or equal to $75,000. Participants were classified into 3 groups of tobacco cigarette exposure: current user of tobacco cigarettes, past user of tobacco cigarettes, and lifetime nonsmoker (defined as <100 cigarettes in lifetime). Physical activity was classified as active, defined as report of any regular moderate or vigorous physical activity, or inactive, defined as report of no regular moderate or vigorous physical activity. Alcohol use was classified as nondrinkers, less than or equal to 1 drink per week, 1 to 14 drinks per week, or more than 14 drinks per week.

Table 1 Characteristics (%) of Participants from the National Health and Nutrition Examination Survey (n = 4657), 2005 to 2010*

		Frequency of Cannabis Use			
	No. of Persons	Never	Past Use	Current Use	*P* Value
Sex					<.0001
Male	2279	43.6	51.8	66.2	
Female	2378	56.4	48.3	33.9	
Race/ethnicity					<.0001
Hispanic	1410	22.8	9.1	8.3	
Non-Hispanic white	2087	55.8	77.6	70.6	
Non-Hispanic black	955	11.4	10.2	17.6	
Other	205	10.0	3.2	3.6	
Age, y					<.0001
20-29	1229	22.3	22.8	45.0	
30-44	1732	38.8	34.2	32.7	
45-59	1696	38.9	42.9	22.3	
Educational Level					<.0001
Less than high school	1142	18.4	12.3	22.7	
High school	1109	21.8	22.6	29.5	
Some college	2401	59.7	65.1	47.8	
Marital Status					.0001
Married or cohabiting	2899	70.0	65.3	51.1	
Not married or cohabiting	1756	30.0	34.6	48.9	
Tobacco Use					<.0001
Never	2568	77.7	41.6	26.2	
Past	846	10.4	30.0	14.3	
Current	1242	11.9	28.3	59.5	
Alcohol Use					<.0001
Nondrinkers	1528	43.0	19.30	10.7	
<1 drink/wk	1247	29.3	28.8	19.3	
1-14 drinks/wk	1565	25.8	43.8	50.2	
>14 drinks/wk	307	1.9	8.1	19.7	
Income					<.0001
<$20,000/y	828	13.2	9.0	21.1	
$20,000-$44,999/y	1324	25.8	21.9	26.1	
$45,000-$74,999/y	1018	26.6	26.7	23.4	
>$75,000/y	1171	34.3	42.3	29.4	
Physical Activity					.07
Inactive	2100	41.1	36.2	36.3	
Active	2557	58.9	63.8	63.7	

Analyses were weighted to reflect national population estimates.

Statistical Analyses

All analyses were weighted to adjust for the complex sampling design of the NHANES. We used chi-square tests to compare baseline characteristics across never, former, and current marijuana users.

Because data on income were missing in 306 participants (7%) in the study population, we used Markov chain Monte Carlo multiple imputation to simulate 5 complete datasets. All statistical analyses were performed in each dataset. The results were then averaged using the *mi estimate* command in STATA, and *P* values and confidence intervals (CIs) incorporating the uncertainty in the imputed estimates were reported.[10] We then compared the imputed and observed values to assess the reasonableness of the imputation model.

Insulin, HOMA-IR, and triglycerides were skewed and log-transformed to approximate normality. We fit separate multiple linear regression models with BMI, logarithmic fasting insulin levels, fasting glucose levels, logarithmic HOMA-IR, hemoglobin A1c, logarithmic triglyceride levels, HDL-C levels, systolic blood pressure, diastolic blood pressure, and waist circumference as continuous outcomes. We first examined models adjusted for age and sex, and then performed multivariable regressions accounting for all of the following covariates, which were specified a priori as potential confounders: age, sex, race/ethnicity, education level, income, marital status, tobacco use, physical activity level, and alcohol use. Because BMI may mediate the association between marijuana use and our study outcomes, we examined the impact of further adjusting for BMI in multivariable models.

We examined whether there was a nonlinear association between frequency of marijuana use and logarithmic fasting

Table 2 Mean Values (Standard Errors) of Fasting Insulin and Glucose According to Average Marijuana Use Among Participants from the National Health and Nutrition Examination Survey, 2005 to 2010

		Frequency of Cannabis Use			
	No. of Persons	Never	Past Use	Current Use	*P* Value
Insulin (μU/mL)*	4606	10.1 (0.2)	8.8 (0.2)	7.5 (0.3)	<.0001
Glucose (mg/dL)	4657	103.5 (0.7)	100.6 (0.7)	99.7 (1.1)	.007
HOMA-IR*	4606	2.5 (0.05)	2.2 (0.06)	1.8 (0.07)	<.0001
HbA1c (%)	3076	5.5 (0.03)	5.4 (0.03)	5.4 (0.05)	.03
Triglycerides* (mg/dL)	4627	108.5 (2.0)	111.1 (2.0)	110.8 (2.9)	.37
HDL-C (mg/dL)	4635	53.4 (0.4)	53.9 (0.6)	53.9 (0.7)	.78
BMI (kg/m^2)	4633	29.1 (0.2)	28.5 (0.2)	27.2 (0.3)	<.0001
Waist circumference (cm)	4602	97.4 (0.5)	97.6 (0.5)	93.6 (0.8)	.0002
SBP (mm Hg)	4347	117.4 (0.6)	117.0 (0.4)	118.8 (0.7)	.08
DBP (mm Hg)	4330	70.4 (0.4)	70.5 (0.4)	69.3 (0.6)	.17

BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; SBP = systolic blood pressure.

*Means for insulin, HOMA-IR, and triglycerides are geometric.

insulin and HOMA-IR among current users of marijuana by including the difference between median intake and reported intake and the square of this value as continuous terms in our multivariable regression model. Because people with diabetes mellitus may alter their marijuana use habits, we also performed a sensitivity analysis excluding participants with diabetes mellitus. All analyses were conducted using STATA 12 (StataCorp LP, College Station, Tex).

RESULTS

Of the 4657 NHANES participants in our study sample, 579 (representing 12.2%) were current users of marijuana and 1975 (representing 47.7%) had used marijuana at least once in their lifetime, but not in the past 30 days. Compared with lifetime nonusers, participants who reported marijuana use in the past month tended to be male, younger, and current users of tobacco (**Table 1**).

In unadjusted analyses, past and current marijuana use were associated with lower levels of fasting insulin, glucose, HOMA-IR, BMI, and hemoglobin A1c (**Table 2**). Current marijuana use also was found to be inversely associated with waist circumference. Models adjusted for age and sex demonstrated statistically significant associations between past and current use of marijuana with lower levels of fasting insulin, glucose, HOMA-IR, and BMI. Also, current use was associated with higher HDL-C levels and lower waist circumference (**Table 3**). In multivariable-adjusted models, the associations of current marijuana use with lower levels of fasting insulin and HOMA-IR, as well as with higher HDL-C levels and lower waist circumference, remained statistically significant (**Table 3**). Compared with participants reporting never having used marijuana in their lifetimes, current use was associated with 16% lower fasting insulin levels (95% CI, −26 to −6), 17% lower HOMA-IR (95% CI, −27 to −6), and 1.63 mg/dL higher HDL-C levels (95% CI, 0.23-3.04) in multivariable adjusted models. Among current users, we found no significant dose-response relationship and no evidence for a U- or J-shaped curve. We did not find any significant associations between marijuana use and triglyceride levels, systolic blood pressure, or diastolic blood pressure.

In an analysis adjusting for BMI, a potential mediator of the associations between marijuana use and the cardiometabolic outcomes, the associations between current marijuana use and fasting levels of insulin, HOMA-IR, and waist circumference were attenuated, but remained statistically significant (**Table 3**). In addition, the results were not materially different in analyses that excluded participants with diabetes mellitus (**Table 3**).

DISCUSSION

In this large, cross-sectional study, we found that subjects who reported using marijuana in the past month had lower levels of fasting insulin and HOMA-IR, as well as smaller waist circumference and higher levels of HDL-C. These associations were attenuated among those who reported using marijuana at least once, but not in the past 30 days, suggesting that the impact of marijuana use on insulin and insulin resistance exists during periods of recent use.

There have been discrepant findings on the relationship between marijuana use and BMI. A study of young adults examining associations between marijuana use and cardiovascular risk factors reported no significant trend between marijuana use and BMI,[5] whereas analyses of 2 large nationally representative surveys found lower BMI and decreased prevalence of obesity.[4,6] Few studies have explored possible underlying explanations for these associations. However, a recent analysis using NHANES III data showed that marijuana users had a lower prevalence of diabetes mellitus compared with nonusers;[7] similar results have been found with administration of cannabidiol in a mouse model.[11] In the present study, we demonstrate a significant association between current marijuana use and lower levels of fasting insulin and insulin resistance in

Table 3 Adjusted Mean/Percent Differences in Measures of Carbohydrate Metabolism and Body Mass Index According to Marijuana Use Among Participants From the National Health and Nutrition Examination Survey, 2005 to 2010

Frequency of Marijuana Use	Insulin*	HOMA-IR*	Glucose	Hemoglobin A1c
Age, sex adjusted				
Never				
Past use	−14.0% (−19.0%, −8.7%)	−16.3% (−21.8%, −10.3%)	−3.69 (−5.85, −1.53)	−0.13 (−0.20, −0.06)
Current use	−27.6% (−33.7%, −21.0%)	−28.8% (−35.0%, −22.0%)	−2.34 (−4.64, −0.03)	−0.08 (−0.18, −0.01)
Multivariable adjusted†				
Never				
Past use	−5.5% (−11.5%, 1.0%)	−7.0% (−13.5%, 0.1%)	−2.10 (−4.24, 0.03)	−0.07 (−0.16, 0.03)
Current use	−14.9% (−23.1%, −5.7%)	−15.4% (−23.9%, −5.9%)	−0.94 (−3.10, 1.21)	−0.01 (−0.14, 0.12)
Multivariable adjusted, with BMI				
Never				
Past use	−5.3% (−11.2%, 0.9%)	−6.9% (−13.1%, −0.2%)	−2.16 (−4.22, −0.11)	−0.07 (−0.17, 0.02)
Current use	−11.8% (−19.0%, −3.9%)	−12.0% (−19.4%, −4.0%)	−0.47 (−2.51, −1.57)	0.02 (−0.11, 0.15)
Multivariable adjusted, excluding diabetic persons				
Never				
Past use	−7.1% (−13.1%, −0.6%)	−7.7% (−14.1%, −0.8%)	−0.62 (−1.42, 0.19)	−0.01 (−0.05, 0.02)
Current use	−17.6% (−27.4%, −6.6%)	−18.2% (−27.9%, −7.0%)	−0.64 (−1.74, 0.47)	−0.04 (−0.09, 0.02)

Frequency of Marijuana Use	Triglycerides*	HDL	BMI	Waist Circumference	SBP	DBP
Age, sex adjusted						
Never						
Past use	0.36% (−4.8%, 5.5%)	1.37 (−0.01, 2.74)	−0.65 (−1.13, −0.18)	−0.49 (−1.68, 0.70)	−1.08 (−2.39, 0.24)	−0.36 (−1.28, 0.56)
Current use	2.0% (−3.7%, 7.6%)	3.46 (2.00, 4.92)	−1.54 (−2.24, −0.83)	−3.50 (−5.31, −1.69)	2.00 (0.40, 3.60)	−0.16 (−1.46, 1.13)
Multivariable adjusted†						
Never						
Past use	0.29% (−5.1%, 6.0%)	0.15 (−1.19, 1.49)	−0.08 (−0.63, 0.47)	0.22 (−1.11, 1.55)	−1.04 (−2.55, 0.47)	−0.01 (−1.06, 1.04)
Current use	1.2% (−6.9%, 8.8%)	1.63 (0.23, 3.04)	−0.61 (−1.31, 0.09)	−1.89 (−3.73, −0.04)	0.64 (−1.11, 2.39)	0.49 (−0.98, 1.96)
Multivariable adjusted, with BMI						
Never						
Past use	0.5% (−4.8%, 6.0%)	0.14 (−1.10, 1.38)		0.09 (−0.40, 0.58)	−1.03 (−2.46, 0.40)	0.00 (−1.05, 1.05)
Current use	−2.8% (−4.6%, 10.7%)	1.22 (−0.25, 2.70)		−0.79 (−1.4, −0.18)	0.86 (−0.86, 2.58)	0.66 (−0.85, 2.16)
Multivariable adjusted, excluding diabetic persons						
Never						
Past use	0.1% (−5.4%, 6.1%)	0.49 (−0.87, 1.84)	−0.15 (−0.71, 0.41)	−0.07 (−1.32, 1.17)	−0.87 (−2.39, 0.65)	0.08 (−1.10, 1.27)
Current use	−0.0% (−8.1%, 8.8%)	3.19 (1.48, 4.80)	−0.89 (−1.83, 0.06)	−2.83 (−5.15, −0.51)	0.97 (−0.90, 2.85)	0.45 (−1.24, 2.13)

BMI = body mass index; HOMA-IR = homeostasis model assessment of insulin resistance.

*Insulin, HOMA-IR, and triglycerides were log-transformed.

†Adjusted for age, sex, race/ethnicity, education level, income, marital status, tobacco use, alcohol use, and physical activity.

multivariable adjusted analyses even after excluding participants with prevalent diabetes mellitus.

Particular focus has been given to the plant cannabinoid (-)-trans-Δ^9-tetrahydrocannabinol, which acts as a partial agonist at both the cannabinoid type 1 and 2 receptors, and cannabidiol, which has lower affinity for the cannabinoid receptors but appears to antagonize both cannabinoid type 1 and 2.[12,13] In addition, it has been found that repeated administration of cannabinoids reduces cannabinoid type 1 receptor density, producing a tolerance to its physiologic effects.[12,14] Thus, a dose-response relationship may be expected; however, we did not find any evidence of this in the present study.

Although not completely elucidated, the mechanisms by which cannabinoids affect peripheral metabolism via these receptors have been studied extensively; the cannabinoid type 1 receptor antagonist, rimonabant, was found to improve insulin sensitivity in wild-type mice, but not in adiponectin knockout mice, suggesting that adiponectin at least partially mediates the improvement in insulin sensitivity;[15] adiponectin has been reported to improve insulin sensitivity.[16] This rimonabant-induced improvement in insulin resistance has been confirmed in human studies.[17] Furthermore, in a randomized clinical trial, rimonabant was significantly associated with an increase in plasma adiponectin levels, as well as weight loss and a reduction in waist circumference.[18] Cannabis itself, when administered to obese rats, was associated with weight reduction and an increase in the weight of pancreata, implying beta-cell protection.[19] In addition, cannabinoid type 1 knockout mice are resistant to diet-induced obesity, suggesting that the role of this receptor is central in the metabolic processes leading to obesity.[20] Given that 2 of the main active phytocannabinoids in marijuana, (-)-trans-Δ^9-tetrahydrocannabinol and cannabidiol, are classified as partial agonists and antagonists, respectively, and are thus capable of producing antagonistic effects at the cannabinoid receptors, it is possible that the associations observed in the aforementioned studies, as well as in the present study, are due at least in part to this adiponectin-mediated mechanism.

In our analyses, we presented alternative models, controlling for BMI as a potential confounder of the relationship between marijuana use and the remainder of the cardiometabolic parameters. We generated this model because of the potential for BMI to affect marijuana use and independently affect the cardiometabolic parameters. On the other hand, BMI may be a mediator of the association between marijuana use and the cardiometabolic outcomes, and thus was excluded from our primary multivariable model.

Study Limitations

This was a cross-sectional study with all of the inherent limitations of that study design. In addition, data on marijuana use were self-reported and may be subject to underestimation or denial of illicit drug use.[21] However, underestimation of drug use would likely yield results biased toward observing no association.

It is possible that the inverse association in fasting insulin levels and insulin resistance seen among current marijuana users could be in part due to changes in use patterns among those with a diagnosis of diabetes (ie, those with diabetes may have been told to cease smoking). However, in the sensitivity analysis excluding those subjects with a diagnosis of diabetes mellitus, associations between marijuana use and insulin levels, HOMA-IR, waist circumference, and HDL-C were similar and remained statistically significant.

CONCLUSIONS

With the recent trends in legalization of marijuana in the United States, it is likely that physicians will increasingly encounter patients who use marijuana and should therefore be aware of the effects it can have on common disease processes, such as diabetes mellitus. We found that current marijuana use is associated with lower levels of fasting insulin, lower HOMA-IR, and smaller waist circumference.

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