Decreased Prevalence of Diabetes in Marijuana Users: Cross-sectional Data from the National Health and Nutrition Examination Survey (NHANES) III

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Decreased Prevalence of Diabetes in Marijuana Users: Cross-sectional Data from the National Health and Nutrition Examination Survey (NHANES) III

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ABSTRACT

Objectives: To determine the association between diabetes mellitus (DM) and marijuana use.

Design: Cross-sectional study

Setting: Data from the National Health and Nutrition Examination Survey (NHANES III, 1988-1994) conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).

Participants: The study included participants of the NHANES III, a nationally representative sample of the United States population. The total analytic sample was 10,896 adults. The study included four groups (n = 10,896): non-marijuana-users (61.0%), past marijuana-users (30.7%), light (1-4 times/month) (5.0%) and heavy (>5 times/ month) current marijuana-users (3.3%). DM was defined based on self-report or abnormal glycemic parameters. We analyzed data related to demographics, body mass index, smoking status, alcohol use, total serum cholesterol, high density lipoprotein, triglyceride, serum 25-hydroxy vitamin D, plasma hemoglobin A1c, fasting plasma glucose level, and the serum levels of C reactive protein (CRP) and four additional inflammatory markers as related to marijuana use.

Main outcome measures: Odds ratio for diabetes mellitus associated with marijuana use adjusted for potential confounding variables (i.e., odds of diabetes mellitus in marijuana users compared with non-marijuana-users).

Results: Marijuana-users had a lower age-adjusted prevalence of DM compared to non-marijuana-users [odds ratio (OR) 0.42; 95% confidence interval (CI)= 0.33 to 0.55 (P<0.0001)]. The prevalence of elevated CRP (> 0.5 mg/dL) was significantly higher (P<0.0001) among non-marijuana-users (18.9%) than past (12.7%) or current-light (15.8%) or heavy-users (9.2%). In a robust multivariate model controlling for socio-demographic factors, laboratory values, and co-morbidity, the lower odds of DM among marijuana users was significant [adjusted OR 0.36; CI=0.24 to 0.55 (P<0.0001)].

Conclusions: Marijuana use was independently associated with a lower prevalence of DM. Further studies are needed to show a direct effect of marijuana on DM.

Article Summary

Article focus: We hypothesized that the prevalence of DM would be reduced in marijuana users due to the presence of one or more CBs because of their immunomodulatory and anti-inflammatory properties.

Key message:

- Marijuana use was associated with a decreased prevalence of DM.
- Prospective studies in rodents and humans are needed to determine a causal relationship between cannabinoid receptor activation and DM.
- Until those studies are performed, we do not advocate the use of marijuana in patients at risk for DM.

Strength and limitations:

- Strength:
  - Population based national representative sample of the United States.
- Limitations:
  - Cross-sectional data.
  - Marijuana use was based on self-report and self-report of illicit substances is often under-estimated on self-reports. Self-report is subjected to recall bias. However, we expect that recall bias would be similar in those with DM as those without DM and would be unlikely to bias our results.
- Although current marijuana-users were divided into heavy and light users based on the number of times they reported using marijuana per month, the amount of marijuana consumed, route of consumption (inhaled vs oral), duration of use, and time when they quit were not reported.

INTRODUCTION

The prevalence of type 2 DM is increasing and it is projected that in the United States alone, type 2 DM will increase to 48.3 million by 2050.[1] In addition to defects in pancreatic β-cell function and insulin sensitivity, systemic inflammation is thought to be involved in its pathogenesis.[1,2]

Marijuana is the most commonly used illicit drug in the United States and is currently used by 14.4 million Americans.[3] The Cannabis sativa (marijuana) plant contains bioactive components termed cannabinoids (CB). The major psychoactive CB is delta 9-tetrahydrocannabinol (THC) whose effect is mediated through the CB1 and the CB2 subtypes of CB receptors found in the brain and lymphoid tissues.[4] The endocannabinoids, a group of neuromodulatory lipids also bind to these receptors.[5] Cannabis, THC and other CBs have been shown to have both beneficial[6] and detrimental effects.[7] Marijuana-users have higher caloric intake while eating less nutrient-rich foods,[8] yet have similar[8] or slightly lower[9] body mass index (BMI) than non-users.

We hypothesized that the prevalence of DM would be reduced in marijuana users due to the presence of one or more CBs because of their immunomodulatory and anti-inflammatory properties.[4] We assessed the association between DM and marijuana use among adults 20-59 years old in a national sample of the general population.

METHODS

Study Population

The study included participants of the NHANES III,[10] conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES III used a highly stratified multistage probability sampling (total N=39,695) and employed over-sampling of the elderly (N=2,273), non-Hispanic blacks (N=11,061) and Mexican Americans (N=11,110). Descriptions of the

survey, sampling procedures, and details of the laboratory tests evaluated can be found on the CDC website (http://www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman).

We limited the analysis to adults 20 to 59 years of age, as those less than 20 years did not have plasma glucose testing and only participants up to 60 years old were asked about marijuana use. In addition, we excluded those with missing laboratory data. The total analytic sample was 10,896 adults. A flow diagram showing the number of subjects selected and reasons for exclusion is listed in Supplement Fig. 1.

Study Variables

Data on marijuana use were collected by self-report. Non-marijuana-users included never users (n = 6,667) and those who reported ever having used marijuana, but who had not used marijuana in the past month (i.e., past users) (n = 3,346). We classified participants who reported using marijuana in the past month by frequency of use as either light-current-users [≤ four days per month (n = 557)] or heavy-current-users [≥ five days per month (n = 326)] as previously described.[9] The definition of marijuana for purposes of this survey includes "hash," "pot" or "grass" or any other references to the Cannabis plant. The phrase "used marijuana" refers to either smoking or ingesting marijuana.

Subjects were defined as having DM if they answer “yes” to the question "Have you ever been told you have sugar/diabetes?" (n=525) or had a fasting blood glucose level ≥126 mg/dL (n=194). Of the 719 patients with DM, 418 answered the question about whether they take insulin and 116 said they do take insulin. Of those, nine said they began using insulin at age ≤ 20, the majority being likely to have type 1 DM, although a few may have had type 2 DM. Thus, we estimate that 1.5% of patients with DM (unadjusted) had type 1 DM and because of this low number, we analyzed all subjects with DM together. There was no difference in any of our analyses if the nine patients of age ≤ 20 were excluded.

Plasma glucose and whole blood hemoglobin A1c (HbA1c) were measured at the University of Missouri-Columbia School of Medicine Department of Child Health, Diabetes Reference Laboratory, Columbia, MO, David Goldstein, M.D., Director.[11]

Subjects were classified as obese/non obese according to the BMI level using a cut off of 30 kg/m^2.

We analyzed data related to DM, age, gender, race/ethnicity, education level, family history of DM, physical activity, BMI, cigarette smoking, cocaine use, alcohol use, total serum cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, serum 25-hydroxy vitamin D (Vitamin D), HbA1c, fasting plasma glucose level (FPG), C-reactive protein (CRP) level and the serum levels of less robust inflammatory markers [ferritin, fibrinogen, white blood cell (WBC) count and uric acid] that have been previously used in NHANES III analysis.[12] Physical activity was assessed using self-report to several questions (http://www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman). For the physical activity variable, subjects were classified as inactive if they did not report engaging in any of the following activities during the previous month: walking, jogging, bike riding, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, or other physical activity outside of their occupation. Physical activity was classified as moderate or vigorous intensity based on metabolic equivalent intensity levels. Individuals were considered to fulfill national recommendations for physical activity if they reported five or more episodes per week of moderate-intensity physical activity or three or more episodes per week of vigorous-intensity physical activity.

Statistical analysis

Descriptive statistics were used to characterize the subjects (mean and standard deviation for continuous variables, and percentages for categorical variables). To test the statistical difference between the groups,

we used Chi-square test for categorical variables and two-sided t-tests for continuous variables. P<0.05 was considered significant.

Univariate and multivariate logistic regression analyses (for categorical outcome – DM/no DM) were used to determine the relationship between DM and marijuana use. We used multivariate logistic regression to adjust for confounding variables and reported the odds ratio (OR) and the 95% confidence interval (CI). Variables considered as possible confounders in the multivariate analysis were age, gender, race/ethnicity, BMI, education level, cigarette smoking, alcohol use, physical activity, serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides, vitamin D, CRP, ferritin, fibrinogen, WBC and uric acid. In order to confirm that marijuana use was associated with DM and not due to confounders, we analyzed how each potential confounder changed the OR of having DM. Variables which changed the OR by ≥ 10% were considered as confounders and included in the multivariate model.

We did stratified analysis to test for effect modification. For effect modifier variable, multivariate logistic regression model was constructed for each subgroup.

Data were analyzed using SAS (Release 9.1.3, 2002; SAS, Inc., Cary, NC) and the survey module of STATA (Release 10, 1984-2007 Statistics/Data Analysis, StataCorp, College Station, Texas 77845 USA). Sample weights, provided by the NCHS, were used to correct for differential selection probabilities and to adjust for non-coverage and non-response.[13]

RESULTS

Among NHANES III participants 20-59 years old, there were 6,667 (54.5%) non-marijuana-users, 3,346 (36.7%) past marijuana-users, 557 (5.5%) light current users, and 326 (3.3%) heavy current users. As shown in Table 1, current and past marijuana-users tended to be < 40 years old, be male, had a BMI < 30 kg/m^2, smoked cigarettes, and used alcohol and cocaine more frequently compared to non-marijuana-users.

Compared to non-marijuana-users, past-users tended to be White and to have a college-education, while current users included more White and Black subjects and were more likely to have a high school education or less. Non-marijuana-users, past and current marijuana-users had a similar percentage of family history of DM ($P > 0.05$) but significantly different percentage of physical activity levels (P<0.001) with past and current marijuana users being more active than non-marijuana users.

As shown in Supplement Table 1, marijuana-users (past and current) had a lower adjusted prevalence of DM, but not hypertension, stroke, myocardial infarction or heart failure compared to non-marijuana-users.

The unadjusted prevalence of DM for non-marijuana-users, past-marijuana-users, current light-marijuana-users and current-heavy-marijuana-users was 6.3%, 2.9%, 1.9% and 3.0%, respectively and there was a statistically significant difference between the groups (P<0.0001) (Table 1). For subjects without DM (n=10,165), 46.4% were marijuana-users and 53.6% were non-marijuana-users (P<0.0001) (Supplement Table 2). For subjects with DM (n=719), 26.9% were marijuana-users and 73.1% were non-marijuana-users (P<0.0001). The difference in % of marijuana-users between those with and without DM was highly significant (P<0.0001).

As shown in Table 1, all marijuana-users had a higher prevalence of serum HDL cholesterol > 40 mg/dL, total cholesterol < 240 mg/dL and triglycerides < 200 mg/dL compared to non-users (P<0.0001). Current-marijuana-users had a higher prevalence of LDL-cholesterol < 160 mg/dL (P<0.05). All marijuana-users had a higher prevalence of CRP < 0.5 mg/dL (P<0.0001). Past users, but not current-users had a lower prevalence of vitamin D level < 70 nmol/L, compared to non-users (P<0.0001). All marijuana-users had a higher prevalence of plasma HbA1c < 6.0% (P<0.0001). Serum glucose levels and BMI were lower in all marijuana-user groups compared to non-marijuana-users (Table 1).

We then examined the variation of markers of inflammation with marijuana use (Table 1). Serum CRP and fibrinogen were significantly (P<0.001) lower in past-marijuana-users compared to current and non-marijuana-users suggesting lower inflammation in past-marijuana-users. In contrast, serum ferritin levels were higher in past and current heavy users, and lower in light users, compared to non-users. Serum uric acid levels were higher in past and lower in current users, compared to non-users. WBC count was higher among current users relative to non-users and past users.

In order to confirm that marijuana use was associated with a decreased prevalence of DM and not due to confounders, we analyzed how each potential confounder changed the OR of having DM. Variables which changed the odds ratio by ≥ 10% were considered as confounders (addition of age, BMI, alcohol use, total cholesterol, triglyceride, CRP, and hypertension changed the OR by ≥ 10% from 0.42 to 0.60, 0.49, 0.50, 0.46, 0.47, 0.46, 0.46 respectively) (Supplement Table 3). Table 2 shows the unadjusted as well as the cumulative effect of the confounders including race/ethnicity, physical activity, and those variables that showed changes of ≥ 10% in the odds ratio of having DM among all marijuana-users relative to non-users in a series of regression models. Of note, race/ethnicity and physical activity did not change the odds ratio by ≥ 10% but we included them in the model because they are known risk factors. The interaction effect of the marijuana use and age was significant in the model indicating that age is an effect modifier (i.e., the association between DM and marijuana use was modified by age and the association differed for different age groups) (OR for interaction=1.83; CI, 1.2-2.9). Stratified analysis by age group found an association between marijuana use and DM among subjects >40 years old (P<0.01) and no association among subjects ≤ 40 years old (Table 2). The association of DM and marijuana was significant in both the overall and older age group even after adjusting for social variables (race/ethnicity, physical activity, alcohol use, and BMI), laboratory variables (total cholesterol and triglyceride), inflammatory marker (CRP) and the co-morbidity variable (hypertension) to the previous model.

We examine whether DM as diagnosed by self-report as compared to laboratory evidence of hyperglycemia was correlated with different prevalence of marijuana use. As shown in the Supplement Table 2, there was no difference in marijuana use among those with DM by self-report and those with DM who were included based on an elevated fasting glucose (P = 0.73). Patients with DM by self-report who were hyperglycemic (fasting glucose $\geq$ 126 mg/dL) at the time of sampling had a statistically similar rate of marijuana use as those whose DM was well-controlled (fasting glucose < 126 mg/dL) at the time of sampling (P = 0.09), although there was a trend for patients with a history of DM by self-report who were euglycemia at the time of sampling to be associated with a lower rate of non-marijuana use. Those with DM by self-report and those with DM who were included based on an elevated fasting glucose had similar rates of the type of marijuana use (heavy current users, light current users and past users) (data not shown). Additionally, for subjects who did not have DM by self-report and did not have an elevated fasting glucose level, but had an elevated HgbA1C (>7.0%) (n=22), their prevalence of non-marijuana use (72.2%) was similar to the prevalence of non-marijuana use among subjects with DM (73.1%).

We then examined the prevalence of all marijuana-users among subjects with different fasting glucose levels. As shown in Fig. 1, the highest prevalence of marijuana-users was found in those with the lowest glucose levels. As the glucose levels increased, the prevalence of marijuana-users decreased. For subjects with DM (fasting glucose > 125 mg/dL), the prevalence of marijuana-users was 23.6%. Similarly, the highest prevalence of marijuana-users was found in those subjects with the lowest plasma HbA1c values (Fig. 2). As the HbA1c levels increased, the prevalence of marijuana-users decreased.

Furthermore, we analyzed the data using logistic regression to assess the odds of having DM, an elevated glucose value or an elevated HbA1c for the categories of marijuana use. The OR for all marijuana-users to have DM was 0.42 (CI = 0.33 to 0.55), which was statistically significant [i.e., marijuana- non-users were 2.4 times more likely to have DM relative to all marijuana-users]. Relative to non-marijuana-

users, past-marijuana-users had an OR of having DM of 0.44 (CI=0.33-0.59), current-light-marijuana-users had an OR of 0.29 (CI=0.13-0.65) and current-heavy-marijuana-users had an OR of 0.47 (CI=0.22-0.98), all were statistically significant from non-marijuana users (P<0.001) (Fig. 3). Relative to non-marijuana-users, marijuana-users had significantly lower odds of having glucose level of > 125 mg/dL (OR=0.36 [95% CI=0.24-0.52)] and HbA1c level > 7.0% [OR=0.35 (95% CI=0.22-0.54); P<0.0001].

DISCUSSION

Our analyses of adults 20-59 years of age in the NHANES III database showed that participants that used marijuana had lower prevalence of DM and had lower odds of DM relative to non-marijuana users. We did not find an association between the use of marijuana and other chronic diseases such as hypertension, stroke, myocardial infarction and heart failure. This could be due to the smaller prevalence of stroke, myocardial infarction and heart failure in the examined age group.

We noted the lowest prevalence of DM in current-light-marijuana-users, with current-heavy-marijuana-users and past-users also having a lower prevalence of DM than non- marijuana-users. The finding that past-marijuana-users had lower odds of prevalent DM than non-users suggests that early exposure to marijuana may affect the development of DM and a window of time of marijuana exposure earlier in life could be a factor to study. Similarly, our findings of a significant association between marijuana use and DM was only found in those ≥ 40 years suggests the possibility of some protection from marijuana use may require many years before they become manifested. By contrast, it could reflect the increased prevalence of DM with age and the ability to detect an association with a lesser sample size when there is a greater cohort at-risk for DM. The possible association of light marijuana use with decreased DM is similar to that of alcohol on DM and the metabolic syndrome, in which mild alcohol use was associated

with lower prevalence of DM and the metabolic syndrome,[14,15] and higher alcohol use associated with higher prevalence of DM and the metabolic syndrome.[14,16]

Smit and Crespo[9] used the NHANES III population to examine dietary factors of non-marijuana-users and marijuana-users among adults aged 20-59. Similar to our data, they found that 45% reported used marijuana in their lifetime and 8.7% used marijuana in the past month. Current marijuana-users had higher intakes of energy and nutrients and consumed more soft drinks but had slightly lower BMI than non-current-marijuana-users. Thus, it is unlikely that a healthier diet contributed to the decreased prevalence of DM among marijuana users found in our study. In our study, all marijuana-users had lower BMI than non-users, with heavy-marijuana-users having the lowest BMI. The lower BMI may be protective for DM, although when we controlled for BMI, the prevalence of DM was not significantly changed suggesting additional BMI-independent pathways. Smit and Crespo[9] did not record glycemic parameters or prevalence of DM.

Using NHANES III data, marijuana users had lower rates of obesity (BMI ≥30) and lower mean BMI, with current-heavy-marijuana-users having the lowest BMI, in agreement with a recent report using National Epidemiologic Survey on Alcohol (2001–2002) and the National Comorbidity Survey–Replication (2001–2003) databases.[17] Correcting for the effect of BMI, the association between marijuana use and DM was reduced by 17% , but remained highly significant.

We postulate that the decreased prevalence of DM and marijuana use may be due to the anti-inflammatory properties of marijuana. CBs found in marijuana favorably modify inflammation probably through the inhibitory actions on prostaglandins and COX-2.[18] Hu and colleagues reported that CRP, but not interleukin-6 and tumor necrosis factor-α receptor-2, was associated with the risk of developing DM.[2] In our study, serum level of CRP, fibrinogen ferritin, uric acid and WBC counts revealed varied associations with marijuana use. Of note, the CRP assay used in NHANES III was not a highly sensitive

assay [11] and is unlikely to pick up small changes in an inflammatory state in a single individual, however, it is still a robust measure of inflammation and is useful in population studies.[12] However, we did find a U-shaped association between the CRP levels and marijuana use groups.

Rodent studies using CBs have shown significant benefits against diabetic complications and atherosclerosis.[19,20] Additionally, lower doses of CBs appear to be anti-inflammatory in rodents.[19] CBs, including the non-psychoactive cannabidiol, have also been shown to attenuate progression of type 1 DM in animal models.[21,22] We have not identified any study in human subjects or animals examining marijuana or its active ingredients and the incidence of type 2 DM, although one study found similar glucose levels in marijuana-users as non-users.[8] We examined physical activity in patients using marijuana and found that it did not confound the association between marijuana and DM.

Although the CB1 antagonist, rimonabant has been used successfully to treat DM,[23] we are not surprised at the association between marijuana use and decreased prevalence of DM. Marijuana contains a variety of CBs, of which some, such as cannabidiol and delta9-tetrahydrocannabivarin, have antagonist properties may mediate the anti-inflammatory properties of marijuana.[24]

A limitation of our study was its cross-sectional nature. Despite the efforts of NHANES to enroll a random representative sample of the US population, persons attending the study visits may differ from those not attending in subtle ways that may affect the results of this study. We are unable to conclude that marijuana use does not lead to DM nor do we suggest marijuana should be a treatment for DM. Although we controlled for major confounders, it is possible that non-marijuana users and subjects with DM share some, as yet unknown, characteristic accounting for the relationship between DM and non-marijuana use.

An additional limitation is that the marijuana use was based on self-report and self-report of illicit substances is often under-estimated on self-reports.[25,26] Self-report is subjected to recall bias. However, we expect that recall bias would be similar in those with DM as those without DM and would be unlikely to

bias our results. Although current marijuana-users were divided into heavy and light users based on the number of times they reported using marijuana per month, the amount of marijuana consumed, route of consumption (inhaled vs oral), duration of use, and time when they quit were not reported.

A potential limitation was that most patients with DM were identified by self-report, with a smaller number of patients identified by having an elevated fasting blood glucose levels. Because some patients with DM receiving treatment are euglycemic, blood glucose levels alone cannot be used to identify those patients with DM. However, the percentage of marijuana-user was similar in those patients with DM identified by self-report as that of those with DM identified by fasting glucose testing. While we analyzed all patients with DM together, we estimated that over 98% of the patients had type 2 DM and therefore our results are likely to apply only to patients with type 2 DM. Another limitation is the possibility of a cohort effect, since those who use marijuana may have other factors that may predispose decreased prevalence of diabetes compared to non-users besides lower body mass index.

In conclusion, marijuana use was associated with a decreased prevalence of DM. Prospective studies in rodents and humans are needed to determine a causal relationship between cannabinoid receptor activation and DM. Until those studies are performed, we do not advocate the use of marijuana in patients at risk for DM.

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Contributors: T.B.R. Conceived and designed project, drafted and reviewed manuscript, M.S. Designed project, drafted and reviewed manuscript, analyzed and interpreted data, provided statistical expertise and collected data, K.C.N. drafted and reviewed manuscript, D.P. analyzed data, provided statistical expertise and collected data, S.S. drafted manuscript, J.O. drafted manuscript, T.C.F. Conceived and designed project, drafted and reviewed manuscript, provided statistical expertise, analyzed and interpreted data. M.S. and T.C.F. are guarantors.

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Competing Interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: T.B.R. is the owner of Omics Biotechnology, Inc., a company with an interest in using modifications of cannabinoids-mediated cell signaling to treat DM and other diseases of inflammation. T.B.R. was not involved in the data collection or statistical analyses. M.S., K.C.N., D.P., S.S., J.O and T.C.F. have no relationships with companies that might have an interest in the submitted work in the previous 3 years. T.B.R, M.S., K.C.N., D.P., S.S., J.O and T.C.F have no non-financial interests that may be relevant to the submitted work and their spouses, partners, or children have no financial relationships that may be relevant to the submitted work.

Ethical approval: This study was exempt from Institutional Review Board (IRB) review. This exemption complied with the policy of the CDU institutional review board related to the use of publically available data for research and publication.

Data sharing: The NHANES data are publically available. Statistical code and working dataset are available from the corresponding author at <magdashaheen@cdrewu.edu>.

Table 1. Diabetes mellitus (DM), socio-demographic characteristics, body mass index, general laboratory characteristics and select inflammatory markers of adults 20-59 years old who were self-identified as marijuana-users or non-marijuana-users (N=10,896).

	Non-marijuana-users	Past-users	Current-users	
			1-4 times/month	≥5 times/month
	$Weighted% or mean [SD]	$Weighted% or mean [SD]	$Weighted% or mean [SD]	$Weighted% or mean [SD]
		*	*	*
DM (yes)	6.3%	2.9%	1.9%	3.0%
Age (years)		*	*	*
≤40	46.2%	73.4%	86.6%	84.0%
>40	53.8%	26.6%	13.4%	16.0%
Gender		*	*	*
Male	42.9%	53.6%	64.4%	73.0%
Female	57.1%	46.5%	35.6%	27.0%
Race		*	*	*
White	70.6%	81.2%	72.6%	74.9%
Black	11.0%	11.3%	17.3%	14.6%
Hispanic	7.4%	4.1%	3.6%	4.4%
Asian/other	11.0%	3.5%	6.5%	6.2%
Education		*	*	†
≤High School	21.4%	15.3%	23.1%	25.7%
High School	34.8%	33.4%	41.2%	39.2%
College	43.8%	51.3%	35.7%	35.1%
Family History of DM				
Yes	46.2%	48.3%	52.5%	48.3%
No	53.8%	58.3%	47.5%	51.7%
BMI (kg/m^2)		*	*	*
≥30	25.0%	18.8%	16.6%	12.5%
<30	75.0%	81.2%	83.4%	87.5%
Physical Activity		*	*	*
Inactive	17.0%	10.3%	8.0%	10.9%
Insufficient activity	46.0%	47.5%	48.6%	37.3%
Recommended level of activity	37.1%	42.2%	43.4%	51.8%
Cigarette Smoke		*	*	*
Yes	22.0%	40.1%	60.3%	68.0%
No	78.0%	59.9%	39.7%	32.0%
Alcohol		*	*	*
Yes	57.3%	74.7%	90.4%	87.9%
No	42.7%	25.3%	9.6%	12.1%
Cocaine		*	*	*
Yes	0.7%	25.8%	47.2%	58.8%
No	99.3%	74.2%	52.8%	41.2%

	Non-marijuana-users [$]Weighted% or mean [SD]	Past-users [$]Weighted% or mean [SD]	Current-users	
			1-4 times/month [$]Weighted% or mean [SD]	≥5 times/month [$]Weighted% or mean [SD]
BMI (kg/m^2)	28.0 [0.2]	26.9 [0.3]*	24.8 [0.7]*	24.1 [0.4]*
Prevalence of select laboratory characteristics				
HDL (mg/dL)				
≤40	42.6%	39.5%**	29.8%**	22.5%**
>40	57.4%	60.6%	70.2%	77.5%
LDL (mg/dL)				
≥160	16.1%	13.9%	9.6%‡	3.5%‡
<160	83.9%	86.1%	90.4%	96.5%
Total Cholesterol (mg/dL)				
≥240	18.7%	12.3%**	8.1%**	8.6%**
<240	81.3%	87.7%	91.9%	91.4%
Triglyceride (mg/dL)				
≥200	17.7%	13.5%*	13.1%*	12.7%*
<200	82.3%	86.5%	86.9%	87.3%
CRP (mg/dL)				
≥0.5	18.9%	12.7%**	15.8%**	9.2%**
<0.5	81.1%	87.3%	84.2%	90.8%
25-hydroxy Vitamin D (nmol/L)				
≤70	51.9%	41.1%**	56.4%**	59.5%**
>70	48.1%	58.9%	43.6%	40.5%
HbA1c (%)				
≥6.0	8.7%	4.1%**	4.2%**	3.2%**
<6.0	91.3%	96.0%	95.8%	96.8%
Serum levels of select laboratory values				
Glucose (mg/dL)	97.8[0.6]	93.1[0.7] *	92.7[0.6] *	92.3[0.7] *
HDL (mg/dL)	50.1[0.5]	50.5[0.8]	49.8[1.8]†	50.5[1.4]
LDL (mg/dL)	126.4[1.2]	122.3[1.5]*	116.6[3.1]*	113.1[3.7]*
Total cholesterol (mg/dL)	201.6[1.4]	195.2[1.6]*	188.7[3.3]*	186.9[3.3]*
Triglycerides (mg/dL)	125.4[2.2]	112.1[2.9]*	111.7[6.9]*	116.6[7.3]*
25-hydroxy Vitamin D (nmol/L)	73.0[1.2]	80.5[1.8]*	78.0[3.5]*	85.0[4.8]*
Select Inflammatory Markers				
CRP (mg/dL)	0.43[0.01]	0.36[0.02]*	0.42[0.09]	0.44[0.11]
Ferritin (ng/mL)	138.1[2.9]	149.5[9.1]*	132.5[19.3]	157.8[24.1]‡
Fibrinogen (mg/dL)	296.1[4.1]	283.5[3.7]*	287.8[15.3]	285.2[12.4]
Uric Acid (mg/dL)	5.3[0.04]	5.5[0.08]*	5.1[0.3]*	5.1[0.2]*
White blood count (x10^3/μL)	7.2[0.06]	7.3[0.07]	7.6[0.19]*	8.0[0.21]*

[$]We used the sample weight provided by the National Center for Health Statistics to weigh the data

* P<0.001 compared with non-marijuana-users † P<0.05 compared with non-marijuana-users

**P<0.0001 compared with non-marijuana-users ‡P<0.01 compared with non-marijuana-users
†P<0.05 compared with non-marijuana users
BMI- body mass index, LDL – low density lipoproteins; CRP – C reactive protein; HDL high density lipoproteins

Table 2. Multivariate logistic model for the change in the association between marijuana use and DM (total and by age group) (N=10,896).

Outcome: DM	**Total**	**Age group 41-59 years**	**Age group 20-40 years**
Model	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Unadjusted	0.42 (0.33-0.55)^	0.51 (0.36-0.73)^	0.74 (0.48-1.14)
Model 1 - Adjusted for social variables	0.31(0.20-0.48)^	0.34 (0.20-0.59)^	0.80 (0.43-1.50)
Model 2 - Adjusted for social variables and laboratory variables	0.33(0.22-0.50)^	0.35 (0.21-0.61)^	0.87 (0.47-1.63)
Model 3 - Adjusted for social variables, laboratory variables, and inflammatory marker	0.36(0.24-0.54)^	0.37 (0.21-0.63)^	0.95 (0.50-1.78)
Model 4 - Adjusted for social variables, laboratory variables, and inflammatory marker, and co-morbidity	0.36(0.24-0.55)^	0.37 (0.22-0.62)^	0.93 (0.51-1.70)

^ P<0.0001; compared to non-marijuana-users

Odds Ratio (OR) for having DM among marijuana-users compared to non-users and 95% confidence interval (CI)

Social variables: race/ethnicity, physical activity, alcohol use, interaction of alcohol and Marijuana use, and body mass index

Laboratory variables: total cholesterol, and triglyceride

Inflammatory marker: C reactive protein

Co-morbidity: hypertension

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Figure Legends

Fig. 1: The prevalence of marijuana-users (past and current) among subjects according to fasting glucose levels (mg/dL). Percent and 95% Confidence Interval (CI) are depicted. *, P<0.05 compared to glucose level ≤ 94 mg/dL

Fig. 2: The prevalence of marijuana-users (past and current) among subjects according to plasma HbA1c levels. Percent and 95% Confidence Interval (CI) are depicted. *, P<0.05 compared to ≤ 5.8%

Fig. 3: Odds Ratio and 95% Confidence Interval (CI) of having DM among past and current marijuana- users relative to non-marijuana-users.

Fig. 1

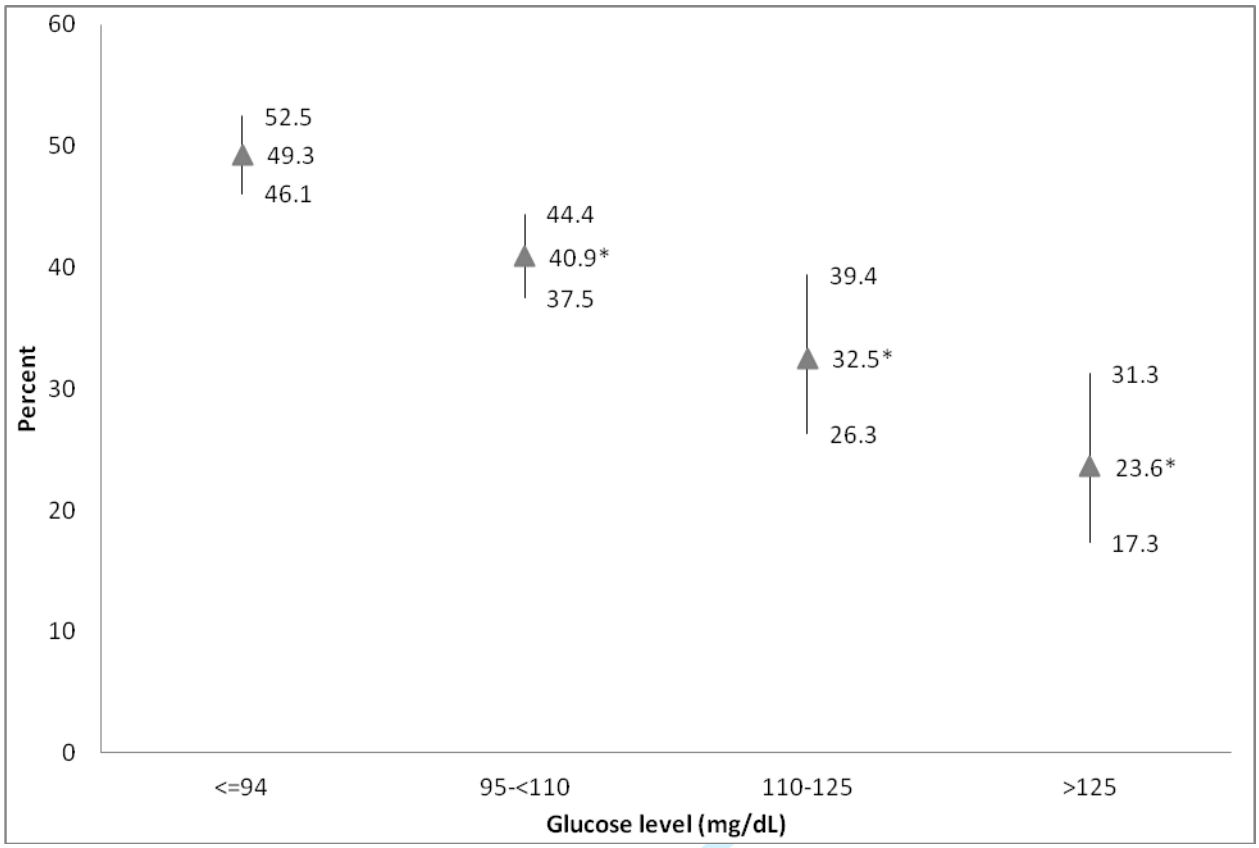


Fig. 2

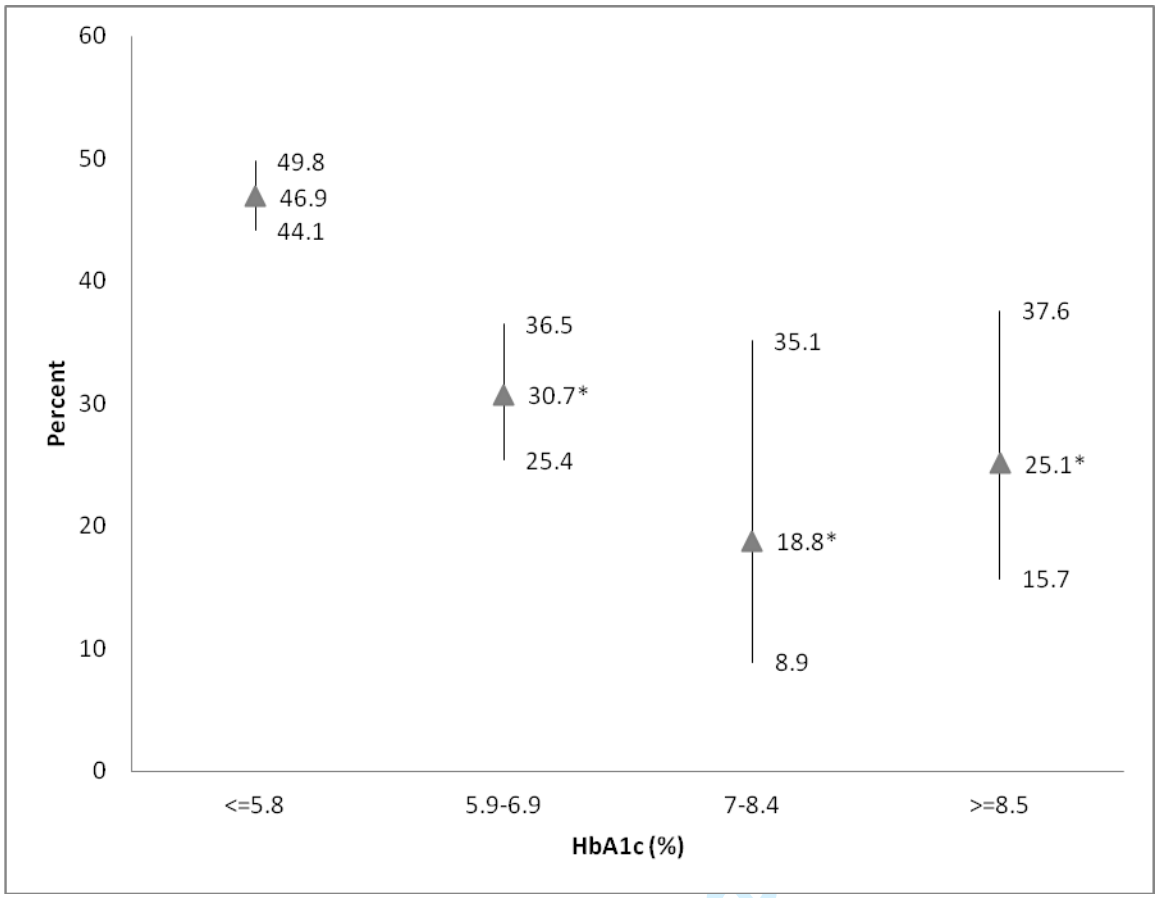
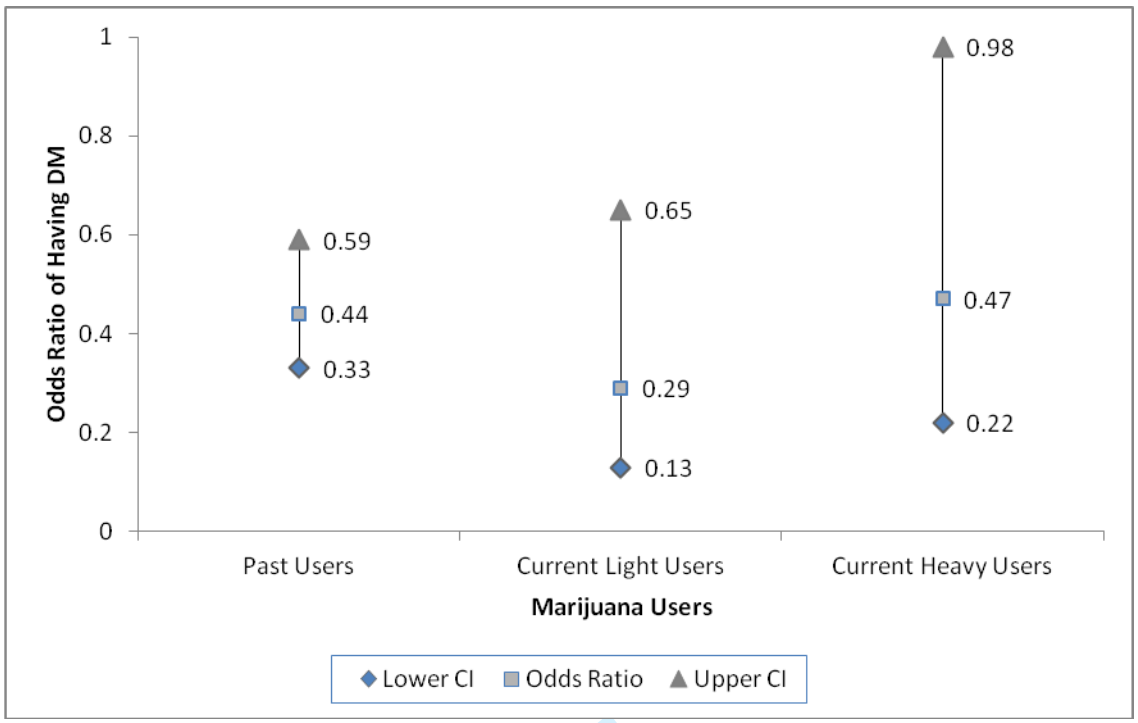


Fig. 3



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5-6
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	19-20
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	19-20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Decreased Prevalence of Diabetes in Marijuana Users: Cross-sectional Data from the National Health and Nutrition Examination Survey (NHANES) III

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Decreased Prevalence of Diabetes in Marijuana Users: Cross-sectional Data from the National Health and Nutrition Examination Survey (NHANES) III

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Key terms: Marijuana, smoking, inflammation, diabetes, metabolic syndrome

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Word Count: 3,727 ~~356~~

ABSTRACT

Objectives: To determine the association between diabetes mellitus (DM) and marijuana use.

Design: Cross-sectional study

Setting: Data from the National Health and Nutrition Examination Survey (NHANES III, 1988-1994) conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).

Participants: The study included participants of the NHANES III, a nationally representative sample of the United States population. The total analytic sample was 10,896 adults. The study included four groups (n = 10,896): non-marijuana-users (61.0%), past marijuana-users (30.7%), light (1-4 times/month) (5.0%) and heavy (>5 times/ month) current marijuana-users (3.3%). DM was defined based on self-report or abnormal glycemic parameters. We analyzed data related to demographics, body mass index, smoking status, alcohol use, total serum cholesterol, high density lipoprotein, triglyceride, serum 25-hydroxy vitamin D, plasma hemoglobin A1c, fasting plasma glucose level, and the serum levels of C reactive protein (CRP) and four additional inflammatory markers as related to marijuana use.

Main outcome measures: Odds ratio for diabetes mellitus associated with marijuana use adjusted for potential confounding variables (i.e., odds of diabetes mellitus in marijuana users compared with non-marijuana-users).

Results: Marijuana-users had a lower age-adjusted prevalence of DM compared to non-marijuana-users [odds ratio (OR) 0.42; 95% confidence interval (CI)= 0.33 to 0.55 (P<0.0001)]. The prevalence of elevated CRP (> 0.5 mg/dL) was significantly higher (P<0.0001) among non-marijuana-users (18.9%) than past (12.7%) or current-light (15.8%) or heavy-users (9.2%). In a robust multivariate model controlling for socio-demographic factors, laboratory values, and co-morbidity, the lower odds of DM among marijuana users was significant [adjusted OR 0.36; CI=0.24 to 0.55 (P<0.0001)].

Conclusions: Marijuana use was independently associated with a lower prevalence of DM. Further studies are needed to show a direct effect of marijuana on DM.

Article Summary

Article focus: We hypothesized that the prevalence of DM would be reduced in marijuana users due to the presence of one or more CBs because of their immunomodulatory and anti-inflammatory properties.

Key message:

- Marijuana use was associated with a decreased prevalence of DM.
- Prospective studies in rodents and humans are needed to determine a causal relationship between cannabinoid receptor activation and DM.
- Until those studies are performed, we do not advocate the use of marijuana in patients at risk for DM.

Strength and limitations:

- Strength:
  - Population based national representative sample of the United States.
- Limitations:
  - Cross-sectional data.
  - Marijuana use was based on self-report and self-report of illicit substances is often under-estimated on self-reports. Self-report is subjected to recall bias. However, we expect that recall bias would be similar in those with DM as those without DM and would be unlikely to bias our results.
- Although current marijuana-users were divided into heavy and light users based on the number of times they reported using marijuana per month, the amount of marijuana consumed, route of consumption (inhaled vs oral), duration of use, and time when they quit were not reported.

INTRODUCTION

The prevalence of type 2 DM is increasing and it is projected that in the United States alone, type 2 DM will increase to 48.3 million by 2050.[1] In addition to defects in pancreatic β-cell function and insulin sensitivity, systemic inflammation is thought to be involved in its pathogenesis.[1,2]

Marijuana is the most commonly used illicit drug in the United States and is currently used by 14.4 million Americans.[3] The Cannabis sativa (marijuana) plant contains bioactive components termed cannabinoids (CB). The major psychoactive CB is delta 9-tetrahydrocannabinol (THC) whose effect is mediated through the CB1 and the CB2 subtypes of CB receptors found in the brain and lymphoid tissues.[4] The endocannabinoids, a group of neuromodulatory lipids also bind to these receptors.[5] Cannabis, THC and other CBs have been shown to have both beneficial[6] and detrimental effects.[7] Marijuana-users have higher caloric intake while eating less nutrient-rich foods,[8] yet have similar[8] or slightly lower[9] body mass index (BMI) than non-users.

We hypothesized that the prevalence of DM would be reduced in marijuana users due to the presence of one or more CBs because of their immunomodulatory and anti-inflammatory properties.[4] We assessed the association between DM and marijuana use among adults 20-59 years old in a national sample of the general population.

METHODS

Study Population

The study included participants of the NHANES III,[10] conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES III used a highly stratified multistage probability sampling (total N=39,695) and employed over-sampling of the elderly (N=2,273), non-Hispanic blacks (N=11,061) and Mexican Americans (N=11,110). Descriptions of the

survey, sampling procedures, and details of the laboratory tests evaluated can be found on the CDC website (http://www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman).

We limited the analysis to adults 20 to 59 years of age, as those less than 20 years did not have plasma glucose testing and only participants up to 60 years old were asked about marijuana use. In addition, we excluded those with missing laboratory data. The total analytic sample was 10,896 adults (complete data for Marijuana use and DM). Subjects with missing data for the laboratory variables (n=2,769) were excluded and the number for the final model was 8,127 adults. A flow diagram showing the number of subjects selected and reasons for exclusion is listed in Supplement Fig. 1.

Study Variables

Data on marijuana use were collected by self-report. Non-marijuana-users included never users (n = 6,667) and those who reported ever having used marijuana, but who had not used marijuana in the past month (i.e., past users) (n = 3,346). We classified participants who reported using marijuana in the past month by frequency of use as either light-current-users [≤ four days per month (n = 557)] or heavy-current-users [≥ five days per month (n = 326)] as previously described.[9] The definition of marijuana for purposes of this survey includes "hash," "pot" or "grass" or any other references to the Cannabis plant. The phrase "used marijuana" refers to either smoking or ingesting marijuana.

Subjects were defined as having DM if they answer “yes” to the question "Have you ever been told you have sugar/diabetes?" (n=525) or had a fasting blood glucose level ≥126 mg/dL (n=194). Of the 719 patients with DM, 418 answered the question about whether they take insulin and 116 said they do take insulin. Of those, nine said they began using insulin at age ≤ 20, the majority being likely to have type 1 DM, although a few may have had type 2 DM. Thus, we estimate that 1.5% of patients with DM (unadjusted) had type 1 DM and because of this low number, we analyzed all subjects with DM together. There was no difference in any of our analyses if the nine patients of age ≤ 20 were excluded.

The study included 151 pregnant women (1.5%). Of them, 8 women had diabetes. There was no difference in the use of marijuana by DM. Because of the low number in the diabetes category, we included them in the analysis. A series of sensitivity analyses excluding the pregnant women showed no difference.

Plasma glucose and whole blood hemoglobin A1c (HbA1c) were measured at the University of Missouri-Columbia School of Medicine Department of Child Health, Diabetes Reference Laboratory, Columbia, MO, David Goldstein, M.D., Director.[11]

Subjects were classified as obese/non obese according to the BMI level using a cut off of 30 kg/m^2.

We analyzed data related to DM, age, gender, race/ethnicity, education level, family history of DM, physical activity, BMI, cigarette smoking, cocaine use, alcohol use, total serum cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, serum 25-hydroxy vitamin D (Vitamin D), HbA1c, fasting plasma glucose level (FPG), C-reactive protein (CRP) level and the serum levels of less robust inflammatory markers [ferritin, fibrinogen, white blood cell (WBC) count and uric acid] that have been previously used in NHANES III analysis.[12] Physical activity was assessed using self-report to several questions (http://www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman). For the physical activity variable, subjects were classified as inactive if they did not report engaging in any of the following activities during the previous month: walking, jogging, bike riding, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, or other physical activity outside of their occupation. Physical activity was classified as moderate or vigorous intensity based on metabolic equivalent intensity levels. Individuals were considered to fulfill national recommendations for physical activity if they reported five or more episodes per week of moderate-intensity physical activity or three or more episodes per week of vigorous-intensity physical activity.

Statistical analysis

Descriptive statistics were used to characterize the subjects (mean and standard deviation for continuous variables, and percentages for categorical variables). To test the statistical difference between the groups, we used Chi-square test for categorical variables and two-sided t-tests for continuous variables. $P<0.05$ was considered significant.

Univariate and multivariate logistic regression analyses (for categorical outcome – DM/no DM) were used to determine the relationship between DM and marijuana use. We used multivariate logistic regression to adjust for confounding variables and reported the odds ratio (OR) and the 95% confidence interval (CI). Variables considered as possible confounders in the multivariate analysis were age, gender, race/ethnicity, BMI, education level, cigarette smoking, alcohol use, physical activity, serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides, vitamin D, CRP, ferritin, fibrinogen, WBC and uric acid. In order to confirm that marijuana use was associated with DM and not due to confounders, we analyzed how each potential confounder changed the OR of having DM. Variables which changed the OR by $\geq$ 10% were considered as confounders and included in the multivariate model.

We performed ~~did~~ stratified analysis to test for effect modification. For effect modifier variable, multivariate logistic regression model was constructed for each subgroup.

In addition, *to* help adjust for selection bias, we analyzed the data using the propensity score matching and estimated the average treatment effect for the treated, bootstrap standard error, and t-statistics. We added the propensity score to the logistic regression model as inverse weight, blocks (N=8) that satisfy the balancing property, and quartiles.

Data were analyzed using SAS (Release 9.1.3, 2002; SAS, Inc., Cary, NC) and the survey module of STATA (Release 10, 1984-2007 Statistics/Data Analysis, StataCorp, College Station, Texas 77845

USA). Sample weights, provided by the NCHS, were used to correct for differential selection probabilities and to adjust for non-coverage and non-response.[13]

RESULTS

Among NHANES III participants 20-59 years old, there were 6,667 (54.5%) non-marijuana-users, 3,346 (36.7%) past marijuana-users, 557 (5.5%) light current users, and 326 (3.3%) heavy current users. As shown in Table 1, current and past marijuana-users tended to be < 40 years old, be male, had a BMI < 30 kg/m^2, smoked cigarettes, and used alcohol and cocaine more frequently compared to non-marijuana-users. Compared to non-marijuana-users, past-users tended to be White and to have a college-education, while current users included more White and Black subjects and were more likely to have a high school education or less. Non-marijuana-users, past and current marijuana-users had a similar percentage of family history of DM ($P > 0.05$) but significantly different percentage of physical activity levels (P<0.001) with past and current marijuana users being more active than non-marijuana users.

As shown in Supplement Table 1, marijuana-users (past and current) had a lower adjusted prevalence of DM, but not hypertension, stroke, myocardial infarction or heart failure compared to non-marijuana-users.

The unadjusted prevalence of DM for non-marijuana-users, past-marijuana-users, current light-marijuana-users and current-heavy-marijuana-users was 6.3%, 2.9%, 1.9% and 3.0%, respectively and there was a statistically significant difference between the groups (P<0.0001) (Table 1). For subjects without DM (n=10,165), 46.4% were marijuana-users and 53.6% were non-marijuana-users (P<0.0001) (Supplement Table 2). For subjects with DM (n=719), 26.9% were marijuana-users and 73.1% were non-marijuana-users (P<0.0001). The difference in % of marijuana-users between those with and without DM was highly significant (P<0.0001).

As shown in Table 1, all marijuana-users had a higher prevalence of serum HDL cholesterol > 40 mg/dL, total cholesterol < 240 mg/dL and triglycerides < 200 mg/dL compared to non-users (P<0.0001). Current-marijuana-users had a higher prevalence of LDL-cholesterol < 160 mg/dL (P<0.05). All marijuana-users had a higher prevalence of CRP < 0.5 mg/dL (P<0.0001). Past users, but not current-users had a lower prevalence of vitamin D level < 70 nmol/L, compared to non-users (P<0.0001). All marijuana-users had a higher prevalence of plasma HbA1c < 6.0% (P<0.0001). Serum glucose levels and BMI were lower in all marijuana-user groups compared to non-marijuana-users (Table 1).

We then examined the variation of markers of inflammation with marijuana use (Table 1). Serum CRP and fibrinogen were significantly (P<0.001) lower in past-marijuana-users compared to current and non-marijuana-users suggesting lower inflammation in past-marijuana-users. In contrast, serum ferritin levels were higher in past and current heavy users, and lower in light users, compared to non-users. Serum uric acid levels were higher in past and lower in current users, compared to non-users. WBC count was higher among current users relative to non-users and past users.

In order to confirm that marijuana use was associated with a decreased prevalence of DM and not due to confounders, we analyzed how each potential confounder changed the OR of having DM. Variables which changed the odds ratio by $\geq$ 10% were considered as confounders (addition of age, BMI, alcohol use, total cholesterol, triglyceride, CRP, and hypertension changed the OR by $\geq$ 10% from 0.42 to 0.60, 0.49, 0.50, 0.46, 0.47, 0.46, 0.46 respectively) (Supplement Table 3). Table 2 shows the unadjusted as well as the cumulative effect of the confounders including race/ethnicity, physical activity, and those variables that showed changes of $\geq$ 10% in the odds ratio of having DM among all marijuana-users relative to non-users in a series of regression models. Of note, race/ethnicity and physical activity did not change the odds ratio by $\geq$ 10% but we included them in the model because they are known risk factors. The interaction effect of the marijuana use and age was significant in the model indicating that age is an effect modifier (i.e., the

association between DM and marijuana use was modified by age and the association differed for different age groups) (OR for interaction=1.83; CI, 1.2-2.9). Stratified analysis by age group found an association between marijuana use and DM among subjects >40 years old (P<0.01) and no association among subjects ≤ 40 years old (Table 2). The association of DM and marijuana was significant in both the overall and older age group even after adjusting for social variables (race/ethnicity, physical activity, alcohol use, and BMI), laboratory variables (total cholesterol and triglyceride), inflammatory marker (CRP) and the co-morbidity variable (hypertension) to the previous model.

Using the propensity score matching, we found similar results showing a lower prevalence of DM among marijuana-users relative to non-users. The average treatment effect for the users (total sample)= -0.024, bootstrap standard error=0.005, and t=-4.46, p<0.05 (i.e., marijuana-users had lower prevalence of DM). When we added the propensity score to the logistic regression model, marijuana-users still had lower odds of DM than non-users (OR=0.54, 95% confidence level=0.40-0.73, p=0.001). Adding it as inverse weight, yielded an OR=0.52 (95% confidence level=0.39-0.71, p=0.001). We also added it as blocks (N=8) and found an OR=0.53, (95% confidence level=0.40-0.73, p=0.001). Adding it as quartiles yielded an OR=0.51 (95% confidence level=0.38-0.69, p=0.001). All still revealed a lower odds of DM with marijuana use. For age group 41-59, adding the propensity score as quartiles to the model, we found an OR=0.55, (95% confidence level=0.35-0.88, p=0.012) whereas for age group 20-40, OR=0.88 (95% confidence level=0.53-1.47, p>0.05).

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We examine whether DM as diagnosed by self-report as compared to laboratory evidence of hyperglycemia was correlated with different prevalence of marijuana use. As shown in the Supplement Table 2, there was no difference in marijuana use among those with DM by self-report and those with DM who were included based on an elevated fasting glucose (P = 0.43 ~~73~~). Patients with DM by self-report who

were hyperglycemic (fasting glucose ≥ 126 mg/dL) at the time of sampling had a statistically similar rate of marijuana use as those whose DM was well-controlled (fasting glucose < 126 mg/dL) at the time of sampling (P = 0.06 ~~9~~), although there was a trend for patients with a history of DM by self-report who were euglycemia at the time of sampling to be associated with a lower rate of non-marijuana use. Those with DM by self-report and those with DM who were included based on an elevated fasting glucose had similar rates of the type of marijuana use (heavy current users, light current users and past users) ~~(data not shown)~~. Additionally, for subjects who did not have DM by self-report and did not have an elevated fasting glucose level, but had an elevated HgbA1C (>7.0%) (n=22), their prevalence of non-marijuana use (72.2%) was similar to the prevalence of non-marijuana use among subjects with DM (73.1%).

We then examined the prevalence of all marijuana-users among subjects with different fasting glucose levels. As shown in Fig. 1, the highest prevalence of marijuana-users was found in those with the lowest glucose levels. As the glucose levels increased, the prevalence of marijuana-users decreased. For subjects with DM (fasting glucose > 125 mg/dL), the prevalence of marijuana-users was 23.6%. Similarly, the highest prevalence of marijuana-users was found in those subjects with the lowest plasma HbA1c values (Fig. 2). As the HbA1c levels increased, the prevalence of marijuana-users decreased.

Furthermore, we analyzed the data using logistic regression to assess the odds of having DM, an elevated glucose value or an elevated HbA1c for the categories of marijuana use. The OR for all marijuana-users to have DM was 0.42 (CI = 0.33 to 0.55), which was statistically significant [i.e., marijuana- non-users were 2.4 times more likely to have DM relative to all marijuana-users]. Relative to non-marijuana-users, past-marijuana-users had an OR of having DM of 0.44 (CI=0.33-0.59), current-light-marijuana-users had an OR of 0.29 (CI=0.13-0.65) and current-heavy-marijuana-users had an OR of 0.47 (CI=0.22-0.98), all were statistically significant from non-marijuana users (P<0.001) (Fig. 3). Relative to non-marijuana-

users, marijuana-users had significantly lower odds of having glucose level of > 125 mg/dL (OR=0.36 [95% CI=0.24-0.52)] and HbA1c level > 7.0% [OR=0.35 (95% CI=0.22-0.54); P<0.0001].

DISCUSSION

Our analyses of adults 20-59 years of age in the NHANES III database showed that participants that used marijuana had lower prevalence of DM and had lower odds of DM relative to non-marijuana users. We did not find an association between the use of marijuana and other chronic diseases such as hypertension, stroke, myocardial infarction and heart failure. This could be due to the smaller prevalence of stroke, myocardial infarction and heart failure in the examined age group.

We noted the lowest prevalence of DM in current-light-marijuana-users, with current-heavy-marijuana-users and past-users also having a lower prevalence of DM than non- marijuana-users. The finding that past-marijuana-users had lower odds of prevalent DM than non-users suggests that early exposure to marijuana may affect the development of DM and a window of time of marijuana exposure earlier in life could be a factor to study. Similarly, our findings of a significant association between marijuana use and DM was only found in those $\geq$ 40 years suggests the possibility of some protection from marijuana use may require many years before they become manifested. By contrast, it could reflect the increased prevalence of DM with age and the ability to detect an association with a lesser sample size when there is a greater cohort at-risk for DM. The possible association of light marijuana use with decreased DM is similar to that of alcohol on DM and the metabolic syndrome, in which mild alcohol use was associated with lower prevalence of DM and the metabolic syndrome,[14,15] and higher alcohol use associated with higher prevalence of DM and the metabolic syndrome.[14,16]

Smit and Crespo[9] used the NHANES III population to examine dietary factors of non-marijuana-users and marijuana-users among adults aged 20-59. Similar to our data, they found that 45% reported used

marijuana in their lifetime and 8.7% used marijuana in the past month. Current marijuana-users had higher intakes of energy and nutrients and consumed more soft drinks but had slightly lower BMI than non-current-marijuana-users. Thus, it is unlikely that a healthier diet contributed to the decreased prevalence of DM among marijuana users found in our study. In our study, all marijuana-users had lower BMI than non-users, with heavy-marijuana-users having the lowest BMI. The lower BMI may be protective for DM, although when we controlled for BMI, the prevalence of DM was not significantly changed suggesting additional BMI-independent pathways. Smit and Crespo[9] did not record glycemic parameters or prevalence of DM.

Using NHANES III data, marijuana users had lower rates of obesity (BMI ≥30) and lower mean BMI, with current-heavy-marijuana-users having the lowest BMI, in agreement with a recent report using National Epidemiologic Survey on Alcohol (2001–2002) and the National Comorbidity Survey–Replication (2001–2003) databases.[17] Correcting for the effect of BMI, the association between marijuana use and DM was reduced by 17% , but remained highly significant.

We postulate that the decreased prevalence of DM and marijuana use may be due to the anti-inflammatory properties of marijuana. CBs found in marijuana favorably modify inflammation probably through the inhibitory actions on prostaglandins and COX-2.[18] Hu and colleagues reported that CRP, but not interleukin-6 and tumor necrosis factor-α receptor-2, was associated with the risk of developing DM.[2] In our study, serum level of CRP, fibrinogen ferritin, uric acid and WBC counts revealed varied associations with marijuana use. Of note, the CRP assay used in NHANES III was not a highly sensitive assay [11] and is unlikely to pick up small changes in an inflammatory state in a single individual, however, it is still a robust measure of inflammation and is useful in population studies.[12] However, we did find a U-shaped association between the CRP levels and marijuana use groups.

Rodent studies using CBs have shown significant benefits against diabetic complications and atherosclerosis.[19,20] Additionally, lower doses of CBs appear to be anti-inflammatory in rodents.[19] CBs, including the non-psychoactive cannabidiol, have also been shown to attenuate progression of type 1 DM in animal models.[21,22] We have not identified any study in human subjects or animals examining marijuana or its active ingredients and the incidence of type 2 DM, although one study found similar glucose levels in marijuana-users as non-users.[8] In a prospective study using a cannabis-based medicinal extract compared to placebo to treat diabetic neuropathy, glycemic indices were not mentioned.[23] We examined physical activity in patients using marijuana and found that it did not confound the association between marijuana and DM.

Although the CB1 antagonist, rimonabant has been used successfully to treat DM,[24,3] we are not surprised at the association between marijuana use and decreased prevalence of DM. Marijuana contains a variety of CBs, of which some, such as cannabidiol and delta9-tetrahydrocannabivarin, have antagonist properties may mediate the anti-inflammatory properties of marijuana.[25,4]

A limitation of our study was its cross-sectional nature. Despite the efforts of NHANES to enroll a random representative sample of the US population, persons attending the study visits may differ from those not attending in subtle ways that may affect the results of this study. We are unable to conclude that marijuana use does not lead to DM nor do we suggest marijuana should be a treatment for DM. Although we controlled for major confounders, it is possible that non-marijuana users and subjects with DM share some, as yet unknown, characteristic accounting for the relationship between DM and non-marijuana use.

An additional limitation is that the marijuana use was based on self-report and self-report of illicit substances is often under-estimated on self-reports.[26,27] Self-report is subjected to recall bias. However, we expect that recall bias would be similar in those with DM as those without DM and would be unlikely to bias our results. Although current marijuana-users were divided into heavy and light users based on the

number of times they reported using marijuana per month, the amount of marijuana consumed, route of consumption (inhaled vs oral), duration of use, and time when they quit were not reported.

A potential limitation was that most patients with DM were identified by self-report, with a smaller number of patients identified by having an elevated fasting blood glucose levels. Because some patients with DM receiving treatment are euglycemic, blood glucose levels alone cannot be used to identify those patients with DM. However, the percentage of marijuana-user was similar in those patients with DM identified by self-report as that of those with DM identified by fasting glucose testing. While we analyzed all patients with DM together, we estimated that over 98% of the patients had type 2 DM and therefore our results are likely to apply only to patients with type 2 DM. Another limitation is the possibility of a cohort effect, since those who use marijuana may have other factors that may predispose decreased prevalence of diabetes compared to non-users besides lower body mass index.

In conclusion, marijuana use was associated with a decreased prevalence of DM. Prospective studies in rodents and humans are needed to determine a potential causal relationship between cannabinoid receptor activation and DM. Until those studies are performed, we do not advocate the use of marijuana in patients at risk for DM.

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Competing Interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: T.B.R. is the owner of Omics Biotechnology, Inc., a company with an interest in using modifications of cannabinoids-mediated cell signaling to treat DM and other diseases of inflammation. T.B.R. was not involved in the data collection or statistical analyses. M.S., K.C.N., D.P., S.S., J.O and T.C.F. have no relationships with companies that might have an interest in the submitted work in the previous 3 years. T.B.R, M.S., K.C.N., D.P., S.S., J.O and T.C.F have no non-financial interests that may be relevant to the submitted work and their spouses, partners, or children have no financial relationships that may be relevant to the submitted work.

Ethical approval: This study was exempt from Institutional Review Board (IRB) review. This exemption complied with the policy of the CDU institutional review board related to the use of publically available data for research and publication.

Data sharing: The NHANES data are publically available. Statistical code and working dataset are available from the corresponding author at <magdashaheen@cdrewu.edu>.

Table 1. Diabetes mellitus (DM), socio-demographic characteristics, body mass index, general laboratory characteristics and select inflammatory markers of adults 20-59 years old who were self-identified as marijuana-users or non-marijuana-users (N=10,896).

	Non-marijuana-users	Past-users	Current-users	
			1-4 times/month	≥5 times/month
	[$]Weighted% or mean [SD]	[$]Weighted% or mean [SD]	[$]Weighted% or mean [SD]	[$]Weighted% or mean [SD]
		*	*	*
DM (yes)	6.3%	2.9%	1.9%	3.0%
Age (years)		*	*	*
≤40	46.2%	73.4%	86.6%	84.0%
>40	53.8%	26.6%	13.4%	16.0%
Gender		*	*	*
Male	42.9%	53.6%	64.4%	73.0%
Female	57.1%	46.5%	35.6%	27.0%
Race		*	*	*
White	70.6%	81.2%	72.6%	74.9%
Black	11.0%	11.3%	17.3%	14.6%
Hispanic	7.4%	4.1%	3.6%	4.4%
Asian/other	11.0%	3.5%	6.5%	6.2%
Education		*	*	†
≤High School	21.4%	15.3%	23.1%	25.7%
High School	34.8%	33.4%	41.2%	39.2%
College	43.8%	51.3%	35.7%	35.1%
Family History of DM				
Yes	46.2%	48.3%	52.5%	48.3%
No	53.8%	58.3%	47.5%	51.7%
BMI (kg/m^2)		*	*	*
≥30	25.0%	18.8%	16.6%	12.5%
<30	75.0%	81.2%	83.4%	87.5%
Physical Activity		*	*	*
Inactive	17.0%	10.3%	8.0%	10.9%
Insufficient activity	46.0%	47.5%	48.6%	37.3%
Recommended level of activity	37.1%	42.2%	43.4%	51.8%
Cigarette Smoke		*	*	*
Yes	22.0%	40.1%	60.3%	68.0%
No	78.0%	59.9%	39.7%	32.0%
Alcohol		*	*	*
Yes	57.3%	74.7%	90.4%	87.9%
No	42.7%	25.3%	9.6%	12.1%
Cocaine		*	*	*
Yes	0.7%	25.8%	47.2%	58.8%
No	99.3%	74.2%	52.8%	41.2%

	Non-marijuana-users [$]Weighted% or mean [SD]	Past-users [$]Weighted% or mean [SD]	Current-users 1-4 times/month [$]Weighted% or mean [SD]	Current-users ≥5 times/month [$]Weighted% or mean [SD]
BMI (kg/m^2)	28.0 [0.2]	26.9 [0.3]*	24.8 [0.7]*	24.1 [0.4]*
Prevalence of select laboratory characteristics				
HDL (mg/dL)				
≤40	42.6%	39.5%**	29.8%**	22.5%**
>40	57.4%	60.6%	70.2%	77.5%
LDL (mg/dL)				
≥160	16.1%	13.9%	9.6%‡	3.5%‡
<160	83.9%	86.1%	90.4%	96.5%
Total Cholesterol (mg/dL)				
≥240	18.7%	12.3%**	8.1%**	8.6%**
<240	81.3%	87.7%	91.9%	91.4%
Triglyceride (mg/dL)				
≥200	17.7%	13.5%*	13.1%*	12.7%*
<200	82.3%	86.5%	86.9%	87.3%
CRP (mg/dL)				
≥0.5	18.9%	12.7%**	15.8%**	9.2%**
<0.5	81.1%	87.3%	84.2%	90.8%
25-hydroxy Vitamin D (nmol/L)				
≤70	51.9%	41.1%**	56.4%**	59.5%**
>70	48.1%	58.9%	43.6%	40.5%
HbA1c (%)				
≥6.0	8.7%	4.1%**	4.2%**	3.2%**
<6.0	91.3%	96.0%	95.8%	96.8%
Serum levels of select laboratory values				
Glucose (mg/dL)	97.8[0.6]	93.1[0.7] *	92.7[0.6] *	92.3[0.7] *
HDL (mg/dL)	50.1[0.5]	50.5[0.8]	49.8[1.8]†	50.5[1.4]
LDL (mg/dL)	126.4[1.2]	122.3[1.5]*	116.6[3.1]*	113.1[3.7]*
Total cholesterol (mg/dL)	201.6[1.4]	195.2[1.6]*	188.7[3.3]*	186.9[3.3]*
Triglycerides (mg/dL)	125.4[2.2]	112.1[2.9]*	111.7[6.9]*	116.6[7.3]*
25-hydroxy Vitamin D (nmol/L)	73.0[1.2]	80.5[1.8]*	78.0[3.5]*	85.0[4.8]*
Select Inflammatory Markers				
CRP (mg/dL)	0.43[0.01]	0.36[0.02]*	0.42[0.09]	0.44[0.11]
Ferritin (ng/mL)	138.1[2.9]	149.5[9.1]*	132.5[19.3]	157.8[24.1]‡
Fibrinogen (mg/dL)	296.1[4.1]	283.5[3.7]*	287.8[15.3]	285.2[12.4]
Uric Acid (mg/dL)	5.3[0.04]	5.5[0.08]*	5.1[0.3]*	5.1[0.2]*
White blood count (x10^3/μL)	7.2[0.06]	7.3[0.07]	7.6[0.19]*	8.0[0.21]*

[$]We used the sample weight provided by the National Center for Health Statistics to weigh the data

* P<0.001 compared with non-marijuana-users † P<0.05 compared with non-marijuana-users

**P<0.0001 compared with non-marijuana-users ‡P<0.01 compared with non-marijuana-users
†P<0.05 compared with non-marijuana users
BMI- body mass index, LDL – low density lipoproteins; CRP – C reactive protein; HDL high density lipoproteins

Table 2. Multivariate logistic model for the change in the association between marijuana use and DM (total and by age group) (N= 8,127). ~~10,896).~~

Outcome: DM	**Total**	**Age group 41-59 years**	**Age group 20-40 years**
Model	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Unadjusted	0.42 (0.33-0.55)^	0.51 (0.36-0.73)^	0.74 (0.48-1.14)
Model 1 - Adjusted for social variables	0.31(0.20-0.48)^	0.34 (0.20-0.59)^	0.80 (0.43-1.50)
Model 2 - Adjusted for social variables and laboratory variables	0.33(0.22-0.50)^	0.35 (0.21-0.61)^	0.87 (0.47-1.63)
Model 3 - Adjusted for social variables, laboratory variables, and inflammatory marker	0.36(0.24-0.54)^	0.37 (0.21-0.63)^	0.95 (0.50-1.78)
Model 4 - Adjusted for social variables, laboratory variables, and inflammatory marker, and co-morbidity	0.36(0.24-0.55)^	0.37 (0.22-0.62)^	0.93 (0.51-1.70)

^ P<0.0001; compared to non-marijuana-users

Odds Ratio (OR) for having DM among marijuana-users compared to non-users and 95% confidence interval (CI)

Social variables: race/ethnicity, physical activity, alcohol use, interaction of alcohol and Marijuana use, and body mass index

Laboratory variables: total cholesterol, and triglyceride

Inflammatory marker: C reactive protein

Co-morbidity: hypertension

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Figure Legends

Fig. 1: The prevalence of marijuana-users (past and current) among subjects according to fasting glucose levels (mg/dL). Percent and 95% Confidence Interval (CI) are depicted. *, P<0.05 compared to glucose level ≤ 94 mg/dL

Fig. 2: The prevalence of marijuana-users (past and current) among subjects according to plasma HbA1c levels. Percent and 95% Confidence Interval (CI) are depicted. *, P<0.05 compared to ≤ 5.8%

Fig. 3: Odds Ratio and 95% Confidence Interval (CI) of having DM among past and current marijuana- users relative to non-marijuana-users.

Fig. 1

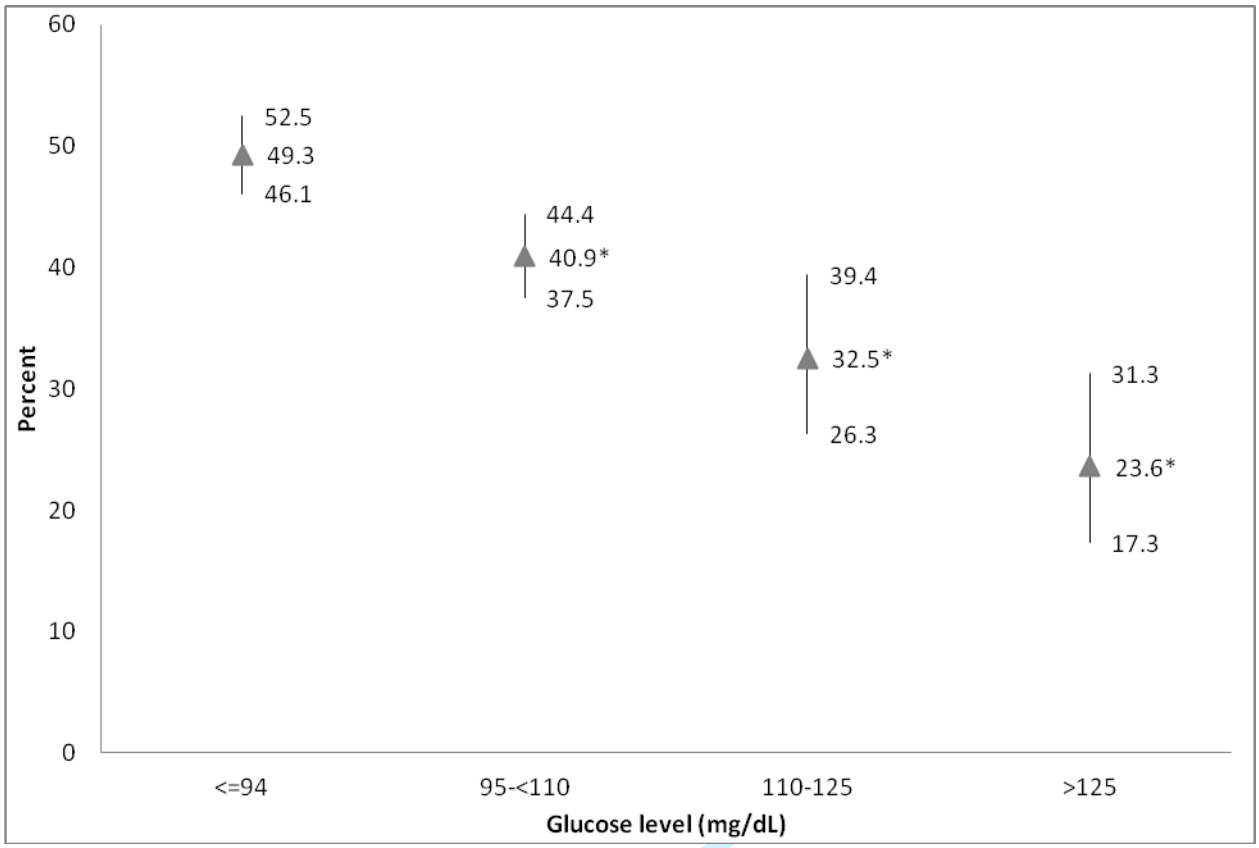


Fig. 2

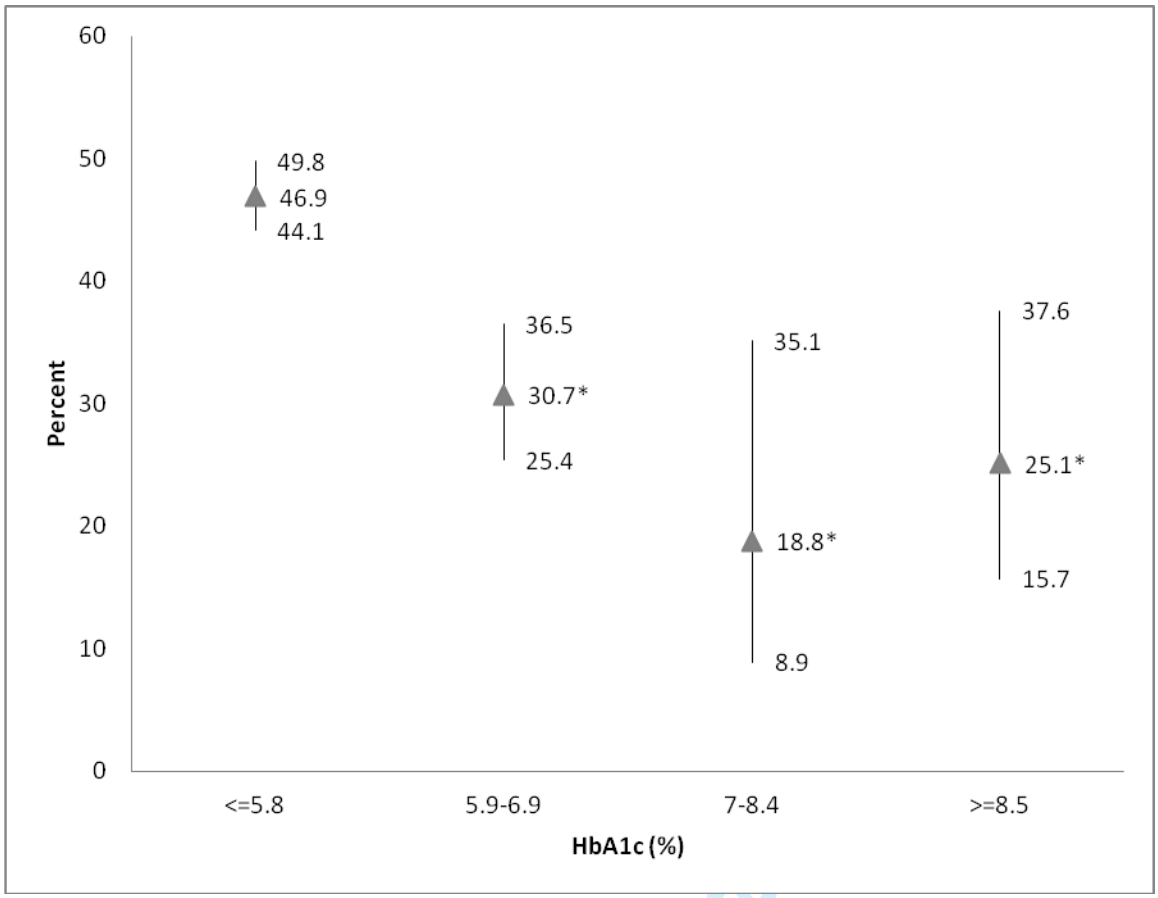
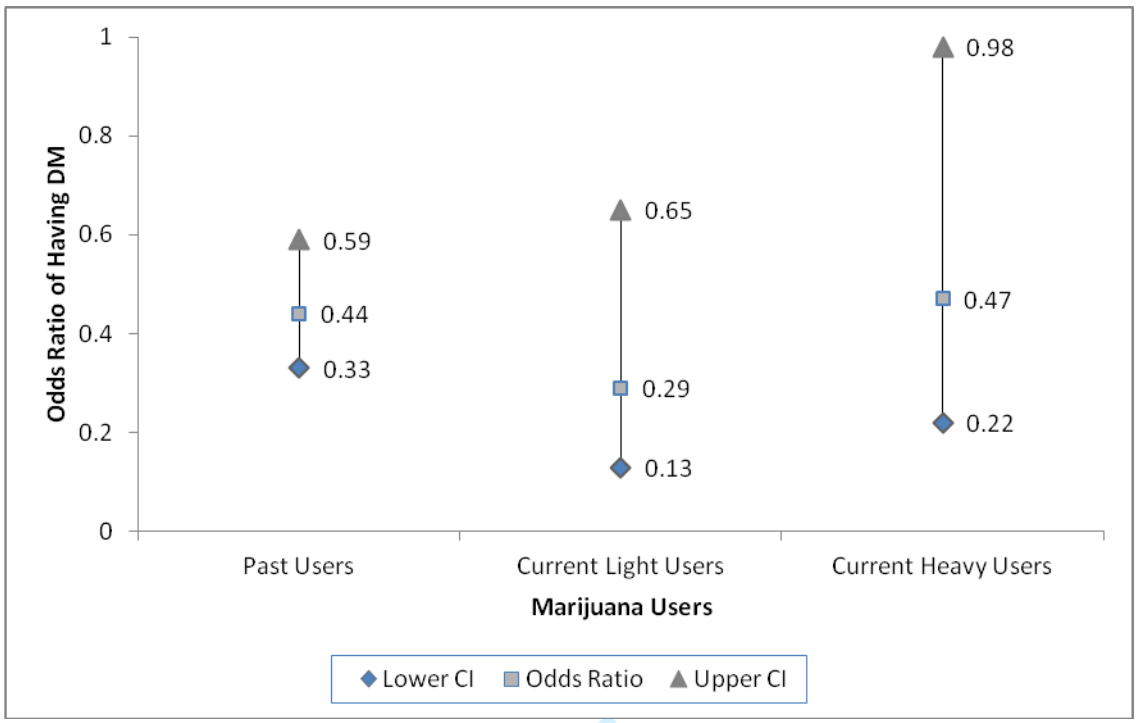


Fig. 3



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5-6
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	19-20
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	19-20
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplement Table 1. Age adjusted prevalence of chronic diseases of adults 20-59 years old who were self-identified as marijuana-users or non-marijuana-users (N=10,896).

	Non-marijuana-users Weighted %	Marijuana-users (Weighted %)
Diabetes Mellitus	4.3	2.9*
Hypertension	17.8	18.9
Stroke	0.69	0.32
Myocardial infarction	1.1	1.2
Heart failure	0.66	0.82

* P<0.001

Supplement Table 2. Prevalence of marijuana use by DM as diagnosed by self-report and compared to laboratory evidence of hyperglycemia

	Total population		**Population with DM**			
Diagnosis	**Without DM**	***With DM**	**DM diagnosed by yes to self-report**	**DM diagnosed by FBG ≥ 126**	**DM diagnosed by yes to self-report and FBG ≥ 126**	**DM diagnosed by yes to self-report and FBG <126**
n	**10,165**	**719**	**525**	**194**	**275**	**235**
Marijuana-Non-users (%)	53.6	73.1	73.7	71.8	79.8	65.3
Past users	37.4	22.5	22.5	22.6	19.1	27.5
Current users						
1-4 times/month	5.7	2.2	1.4	4.4	0.9	2.1
≥5 times/month	3.3	2.2	2.4	1.5	0.2	5.1
P-value	#0.00001		0.43		0.06	

*With DM by self report or fasting glucose level ≥126 mg/dL

# $P < 0.0001$; compared to non-marijuana-users

Supplement Table 3. Variables affected the association between marijuana use and DM among adults 20-59 years old (Odds Ratios for DM) (N=8,127).

	OR (95% Confidence Interval)	%Change in the odds ratio[$]
Marijuana use (yes)	**0.42 (0.33-0.55)***	
Marijuana use+age	0.60 (0.46-0.78)*	**43%**
Marijuana use+gender	0.42 (0.33-0.55)*	0%
Marijuana use+race	0.43 (0.33-0.55)*	2%
Marijuana use+education	0.44 (0.34-0.57)*	5%
Marijuana use+BMI	0.49 (0.38-0.65)*	**17%**
Marijuana use+current cigarette smoking	0.42 (0.32-0.55)*	0%
Marijuana use+alcohol use	0.50 (0.38-0.66)*	**19%**
Marijuana use+cocaine use	0.42 (0.33-0.54)*	0%
Marijuana use+HDL	0.44 (0.33-0.57)*	5%
Marijuana use+LDL	0.33 (0.21-0.54)*	**-21%**
Marijuana use+total cholesterol	0.46 (0.35-0.59)*	**10%**
Marijuana use+triglyceride	0.47 (0.36-0.6)*	**12%**
Marijuana use+CRP	0.46 (0.35-0.59)*	**10%**
Marijuana use+White Blood Count	0.42 (0.32-0.54)*	**0%**
Marijuana use + hypertension	0.46 (0.35-0.60)*	**10%**
Marijuana use + stroke	0.43 (0.33-0.56)*	2%
Marijuana use + myocardial infarction	0.44 (0.34-0.57)*	5%
Marijuana use + heart failure	0.43 (0.33-0.56)*	2%

*p<.0001 on the associate of marijuana with DM.
[$]A change of ≥10% of the odds ratio indicates a confounding effect of that variable.

Supplement Fig. 1: Flow diagram for the sample selection and reasons for exclusion.