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Association between self-reported marijuana use and incident diabetes in women and men with and at risk for HIV

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Abstract

Introduction—Marijuana use is common among persons living with HIV, but whether it's use increases the risk of type 2 diabetes in this population has not been explored.

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Contributors

CNO & SS conceived and designed the study. CNO, SS, TB, TP and MWP acquired the data and supervised the study. CNO, SS, MWP, TP & TB analyzed and interpreted the data. CNO wrote the first draft of the article and applied critical revisions to the article based on co-authors suggestions. MWP, DGM, ML, KB, HB, TP, TB & SS contributed to drafting the article. All authors contributed substantially to revise the article, read and approved the final draft of the article.

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The authors report no conflict of interest.

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Objective—To determine whether self-reported marijuana use is associated with incident type 2 diabetes in women and men living with and at risk for HIV.

Methods—We analyzed data from the Women's Interagency HIV Study (WIHS) and Multicenter AIDS Cohort Study (MACS), between 2000–2017 (WIHS) and 1999–2017 (MACS). The association between self-reported marijuana use and incident type 2 diabetes was analyzed using time-dependent Cox regression models among 3,578 and 2,682 participants in the WIHS and MACS respectively.

Results—Over the follow-up period, 452 (WIHS) and 326 (MACS) incident type 2 diabetes cases occurred. In multivariable models, the hazard ratios, collectively indicate a reduced risk of type 2 diabetes, in marijuana users compared to none users, although all associations were not statistically significant. The results were similar for HIV-positive and HIV-negative participants in both cohorts.

Conclusions—In this prospective analysis of nearly 20 years of data for women and men with and at risk for HIV in the WIHS and MACS, although we found a pattern of reduced risk of type 2 diabetes among self-reported marijuana users, the associations were not statistically significant. To better inform clinical decisions and legal policy regarding marijuana use in this population, further longitudinal investigations that biologically quantify marijuana use to assess risk for incident diabetes is warranted.

Keywords

Marijuana; Incident Diabetes; HIV; Longitudinal

1. Introduction

Marijuana is the most frequently used substance among persons living with HIV (PLWH). Among PLWH, the average self-reported marijuana use in the past six months ranges between 25% and 56% (D'Souza et al., 2012; Mimiaga et al., 2013; Okafor, Cook, et al., 2016b; Okafor, Zhou, et al., 2016; Pacek et al., 2018; Sinha et al., 2017; Vidot et al., 2017). The prevalence of daily or nearly daily marijuana use among PLWH is on the rise (D'Souza et al., 2012; Okafor, Cook, et al., 2016b). The increasing prevalence of marijuana use among PLWH corresponds with recent trends in passage of state laws governing recreational and medical marijuana across the United States. Currently, 33 states and the District of Columbia have passed legislation allowing marijuana for medical or recreational use (ProCon.org; NORML.org). PLWH report using marijuana as a self-medicating strategy to manage HIV-related symptoms such as nausea, pain, mood problems, and poor appetite (D'Souza et al., 2012). However, data on the potential benefits or adverse health effects of marijuana use in this population are limited (Volkow et al., 2014).

The endocannabinoid system is comprised of two endogenous receptors: cannabinoid receptors 1 (CBR1) and cannabinoid receptors 2 (CBR2). CBR1 are located primarily in the central nervous system including the brain (Devane et al., 1988; Pertwee, 1997), while CBR2 are on cells and tissues of the immune system (Mechoulam et al., 2007; Mechoulam and Parker, 2013; Pertwee, 1997). The primary component in marijuana, delta-9-tetrahydrocannabinol (THC) partially binds to and activates CBR1 (and, to a lesser extent,

CBR2). Stimulation of CBR1 by THC increases appetite and promotes caloric consumption (Foltin et al., 1988; Haney et al., 2005; Hart et al., 2002), suggesting that regular marijuana use may promote weight gain and concomitant higher body mass index (BMI), an established risk factor for type 2 diabetes (Ganz et al., 2014). By contrast, studies have shown that marijuana use is either not associated with BMI/waist circumference (Rodondi et al., 2006) or significantly associated with lower BMI (Alshaarawy and Anthony, 2019; Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Ngueta et al., 2015) and smaller waist circumference (Penner et al., 2013). Additionally, prior studies have found lower odds of metabolic syndrome (Vidot et al., 2016a; Yankey et al., 2016), hyperglycemia (Vidot et al., 2016a), insulin resistance (Homeostasis Model Assessment for Insulin Resistance)(Penner et al., 2013), and mean fasting glucose (Vidot et al., 2016a) among current marijuana users compared with nonusers. One recently published meta-analysis including eight cross-sectional studies reported that marijuana use was associated with reduced odds of type 2 diabetes (Alshaarawy and Anthony, 2015a). In addition to cross-sectional findings, at least two longitudinal studies have examined the association of marijuana use with incident type 2 diabetes. Bancks et al. (2015) prospectively followed up 2,758 men and women in the Study of Coronary Artery Risk Development in Young Adults (CARDIA), who contributed more than 50,000 person-years of follow-up and found no statistically significant association between marijuana use and incident type 2 diabetes, but found a higher risk of prediabetes in participants with greater lifetime marijuana use compared to never users (Bancks et al., 2015). Similarly, in their analysis of a population-based cohort of men and women in Sweden, Danielsson et al. (2016) found no statistical relationship between marijuana use and incident type 2 diabetes.

Majority of prior studies of the association between marijuana use and type 2 diabetes have been cross-sectional, (Alshaarawy and Anthony, 2015b) and existing longitudinal studies have employed few measurement occasions of cannabis use (Danielsson et al., 2016) or long follow-up measurement intervals (Bancks et al., 2015) and few follow-ups of participants. As such, prospective analysis of data with multiple, short-term spacing of marijuana measurement over a long-term period of participant follow-up, better documents changes in marijuana use in relation to incident type 2 diabetes. In addition, a prospective analysis of this type can better explore potential reverse associations between marijuana use and incident type 2 diabetes, i.e., pre–type 2 diabetes symptoms resulting in an individual potentially ceasing or reducing marijuana use during the follow-up period. In addition, prior studies have not adequately addressed the role of other confounders on the relationship between marijuana use and type 2 diabetes. For instance, marijuana use is positively associated with tobacco smoking and illicit drug use such as cocaine, heroin, methamphetamine, and other stimulants (Okafor, Cook, et al., 2016a). Tobacco smoking and stimulant use have been associated with suppression of appetite (Mineur et al., 2011) and lower body weight (Audrain-McGovern and Benowitz, 2011; Chiolero et al., 2008). Further, to our knowledge, no longitudinal analysis has addressed this question despite the high prevalence of marijuana use (D'Souza et al., 2012; Okafor, Cook, et al., 2016a, 2016b) and two-fold higher prevalence of type 2 diabetes among PLWH compared with the prevalence in the general population of adults (Hernandez-Romieu et al., 2017).

The objective of this analysis is to determine whether self-reported frequency of marijuana use is associated with incident type 2 diabetes in women and men living with and at risk for HIV. We aimed to address this question by examining the potential role of reverse causality on the relationship between self-reported marijuana use and type 2 diabetes using prospectively collected data from two large, long-term cohort studies of women and men living with and at risk for HIV with long-term follow-up. Given what is known about the mechanisms relating marijuana use to stimulation of appetite and increased caloric intake, we hypothesized that marijuana use will be associated with increased risk of type 2 diabetes.

2. Methods

2.1. Study setting

The Multicenter AIDS Cohort study (MACS) (Detels et al., 1992; Kaslow et al., 1987) and Women's Interagency HIV Study (WIHS) (Bacon et al., 2005; Barkan et al., 1998) are well-established, ongoing, prospective multicenter cohorts of men who have sex with men and women living with or at risk for HIV in the United States, respectively. Eligibility criteria and follow-up procedures for the MACS (Becker et al., 2015) and WIHS (Adimora et al., 2018) have been previously described. Participants in the MACS were recruited at four centers: Baltimore, Maryland/Washington, DC; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. Participants in the WIHS were recruited from ten sites in Brooklyn, New York; the Bronx/Manhattan, New York; Washington, DC; Chicago, Illinois; San Francisco, California; Los Angeles, California; Chapel Hill, North Carolina; Atlanta, Georgia; Birmingham, Alabama/Jackson, Mississippi; and Miami, Florida. The MACS enrolled men who have sex with men across three waves: 4,954 in 1984–1985, 668 in 1987–1991, and 1350 in 2001–2003 (Becker et al., 2015). The WIHS enrolled women across 4 waves: 2623 in 1994–1995, 1,143 in 2000–2001, 371 in 2011–2012, and 845 in 2013–2015 (Adimora et al., 2018). Data in both cohorts are collected using structured interviews and standardized physical and laboratory assessments, with study visits typically occurring every six months. HIV status was assessed by enzyme-linked immunosorbent assay with confirmatory testing at baseline for HIV-positive participants. The study questionnaires used in the MACS are available at www.aidscohortstudy.org and in the WIHS at https://statepi.jhsph.edu/wihs/wordpress/. The institutional review boards at the respective study centers approved the MACS and WIHS study protocols, and all participants provided written informed consent.

2.2. Participant selection and inclusion criteria

For both cohorts, the *index visit* was defined as the first visit at which fasting blood glucose data were available and we included HIV-positive participants with confirmatory testing at baseline and HIV-negative participants. For the WIHS, we included participants who were active beginning from October 2000 (when serum samples to measure fasting [≥ 8 hours] glucose were initially collected) to September 2017. Fasting glucose was measured at each follow-up visit beginning from October 2000 through March 2003 and then annually thereafter. Hemoglobin A1C was measured beginning from October 2000, annually through March 2006, suspended from April 2006 through October 2010 and then measured annually thereafter. Of the 4,099 active WIHS participants in October 2000, we excluded those with

prevalent type 2 diabetes at the index visit (n=352), those with less than 3 follow-up visits (n=142) and those who seroconverted (i.e. became HIV-positive) during the follow-up period (n=27), leaving a final analysis sample of 3,578. For the MACS, we included participants who were active beginning from April 1999 (when serum samples to measure fasting [≥ 8 hours] glucose were initially collected) to September 2017. Fasting glucose and Hemoglobin A1C was measured in the MACS biannually during the study follow-up period. Of the 3,570 active MACS participants in April 1999, we excluded those with prevalent type 2 diabetes at the index visit (n=115), those with less than 3 follow-up visits (n=499) and those who seroconverted during the follow-up period (n=324), leaving a final analysis sample of 2,682.

2.3. Measures

2.3.1. Outcome ascertainment: Type 2 diabetes—The primary outcome of interest in this analysis was incident type 2 diabetes. Incident diabetes was considered to have occurred if participants self-reported diabetes, and if this was confirmed by a subsequent self-report of antidiabetes medication, two fasting glucose levels of 126 mg/dL or more, or fasting glucose level of 126 mg/dL or more and concurrent hemoglobin A1C level of 6.5% or greater. This definition conforms to recommendations made by the American Diabetes Association (2014) and has been used in the MACS and WIHS (Frasco et al., 2014; Tien et al., 2012).

2.3.2. Predictor assessment: Marijuana—The primary predictor evaluated was self-reported marijuana use. In the MACS, marijuana use was assessed with the following question: “Have you used any pot, marijuana, or hash since your last visit?” Among those who responded with “yes,” frequency of use was asked with the following question: “How often did you use pot, marijuana, or hash since your last visit?” with the following response options: “daily,” “weekly,” “monthly,” and “less often.” For this analysis, we categorized participant’s marijuana use status at every visit as daily; weekly; monthly/less often, and none. In the WIHS, marijuana use was assessed with the following question: “Since your last study visit, have you used marijuana or hash?” Participants responding with a “yes” were then asked the following: “On average, how often have you used marijuana or hash since your last study visit?” with the following response options: “less than once a month,” “at least once a month, but less than once a week,” “once a week,” “2 to 3 times a week,” “4 to 6 times a week,” “once a day,” and “more than once a day.” We combined response options and categorized marijuana use like the MACS. Marijuana use was assessed biannually beginning from the index visit until when type 2 diabetes occurred or administrative censoring (i.e., last study visit for those who did not develop diabetes).

2.4. Covariates

Covariates were selected based on past studies of factors associated with marijuana use and type 2 diabetes and cardiometabolic factors (Danielsson et al., 2016; Imtiaz and Rehm, 2018; Le Strat and Le Foll, 2011; Meier et al., 2019). Sociodemographic characteristics included participant’s age (calculated from self-reported date of birth at baseline), self-reported race/ethnicity status, educational attainment (at baseline), study center, and enrollment cohort. Blood pressure was assessed at every visit and high blood pressure was defined as systolic blood pressure greater than 140 mm Hg, diastolic pressure greater than

90 mm Hg, or diagnosed with hypertension and use of medications. Family history of diabetes, alcohol use, smoking status, and illicit drug use (including cocaine, heroin, illicit opioids, and methamphetamine use) were self-reported at every visit. Antiretroviral therapy (ART) use was assessed via self-report at every visit in the WIHS and MACS and a binary (yes/no) variable was used to denote any ART use at every study visit. Plasma HIV viral load was measured using standard laboratory techniques and was classified as suppressed if the viral load was less than 200 copies/mL and unsuppressed if 200 copies/mL or greater. Other covariates included BMI (kg/m^2) and high-density lipoprotein cholesterol.

3. Statistical Analysis

We used frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables to describe characteristics of participants in the WIHS and MACS at the index visit. Next, we conducted time-dependent Cox regression models (Karim et al., 2016; Suissa, 2003) to estimate the association between self-reported frequency of marijuana use and incident type 2 diabetes separately for WIHS and MACS for the combined group (i.e., HIV positive and HIV negative) and separately by HIV status. The primary predictor variable in these models was the time-dependent self-reported frequency of marijuana use (i.e., none, monthly/less often, weekly, and daily use), with none designated as the reference group. The outcome variable was incident type 2 diabetes ascertained over the follow-up period. Time to incident type 2 diabetes was calculated as the number of years from the index visit until the visit when type 2 diabetes was ascertained or until administrative censoring (i.e., last study visit for those without type 2 diabetes). We estimated both unadjusted (with no covariates) and fully adjusted hazard ratios, with 95% CIs from the Cox regression models. Fully adjusted models included age, race/ethnicity, educational attainment (at baseline), study center, study enrollment cohort, family history of diabetes and time-dependent covariates including alcohol use, smoking status, stimulant use, high blood pressure, and BMI. The models for HIV-positive participants were additionally adjusted for time-dependent ART use and viral suppression status. We explored potential effect modification by BMI, race/ethnicity status, educational attainment, and smoking status in all models by testing multiplicative interaction terms with marijuana use variable. Prior studies have found that cannabis use is associated with lower fasting glucose, Hemoglobin A1C and BMI (Le Strat and Le Foll, 2011; Penner et al., 2013). Therefore, in secondary analysis, we used generalized estimating equations (Liang and Zeger, 1986) to assess the longitudinal associations between self-reported frequency of marijuana use and BMI, fasting blood glucose and hemoglobin A1C using the same follow-up period as the primary analysis. We accounted for the dependency between repeated measurements of the outcomes by robust estimation of error variances and specifying an unstructured correlation structure. Missing data for the primary predictor and covariates were addressed by means of multiple imputation using chained equations (van Buuren et al., 1999). Ten imputed data sets where generated for missing time-stable and time-dependent covariates; Cox regression models were conducted on each imputed data set and the hazard ratios were pooled (Toutenburg, 1990). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

4. Results

4.1. Sample characteristics at index visit

The final analysis data set included 3,578 participants in the WIHS (61% HIV positive) and 2,682 in the MACS (49% HIV positive), and their characteristics at the index visit are displayed in Table 1. The median age in the WIHS was 39 years (IQR, 33–46) and 43 years (IQR, 37–50) in the MACS. Most men in the MACS were non-Hispanic white (60%), followed by non-Hispanic black (25%). In contrast, non-Hispanic black (63%) and Hispanic (22%) women predominated in the WIHS. Eighteen percent of women in the WIHS self-reported any marijuana use in the past six months, whereas 36% self-reported any marijuana use in the MACS.

4.2. Self-reported marijuana use and incident type 2 diabetes

Women in the WIHS accumulated 30,800 person-years of follow-up (21,923 person-years of follow-up among HIV-positive participants), during which 452 incident cases of type 2 diabetes (320 cases among HIV-positive women) were ascertained, representing an unadjusted incident rate of type 2 diabetes of 1.46 per 100 person-years among all women in the WIHS. Conversely, the men in the MACS accumulated 31,281 person-years of follow-up (14,297 person-years of follow-up among HIV-positive participants), with 326 incident cases of type 2 diabetes ascertained (164 cases among HIV-positive men), and an unadjusted incident rate of type 2 diabetes of 1.04 per 100 person-years among all men in the MACS.

In the unadjusted models for the association between self-reported frequency of marijuana use and incident type 2 diabetes, among all women in the WIHS, we found a lower risk of type 2 diabetes in daily users compared with nonusers (Table 2), with the confidence intervals around the hazard ratio estimate excluding the null value. However, adjusting for BMI and other covariates, attenuated the association and increased the width of the confidence interval to include the null value (Table 2). Furthermore, in the models for all women in the WIHS and separately by HIV-status, the point estimates of the fully adjusted hazard ratios for self-reported monthly/less and weekly/less levels of marijuana use (compared to non-use), suggest a very small increased risk of type 2 diabetes compared to non-use. The point estimates for self-reported daily marijuana use indicated a reduced risk of type 2 diabetes compared to non-use. However, the confidence intervals around all the fully adjusted hazard ratios were relatively wide – spanning both the reduced, null and increased risk range (Table 2).

In the models for all men in the MACS and separately by HIV-status, the point estimates for the fully adjusted hazard ratios for most self-reported frequency levels marijuana use, collectively suggest a reduced risk of type 2 diabetes compared to non-use. Like the WIHS, the confidence intervals around the fully adjusted hazard ratios were wide, spanning both the reduced, null and increased risk range (Table 3). The fully adjusted models with covariate estimates for all models in the WIHS and MACS are included in the Supplementary Material (Tables S1 and S2, respectively)[1]. Tests of effect modification by BMI, race/ethnicity,

[1]:Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org

educational attainment, and smoking status were not statistically significant (all p's >0.10, data not shown).

In secondary analysis, in both the WIHS and MACS cohort, we found a pattern of statistically significant dose-dependent associations between increasing self-reported frequency of marijuana use and lower BMI. Specifically, as self-reported frequency of marijuana use increased, BMI decreased, with confidence intervals around all point estimates excluding the null value. Results of models evaluating the longitudinal associations between self-reported frequency of marijuana use and BMI are included in the Supplemental Material (Table S5)[2]. Additionally, there was a pattern of lower fasting blood glucose and hemoglobin A1C with increasing self-reported frequency of marijuana use in all men in the MACS cohort, as well as in most subgroup analysis (i.e. by HIV-status), with most estimates excluding the null value (supplemental table S6). However, in the WIHS cohort, although there was a consistent pattern of lower hemoglobin A1C associated with self-reported frequency of marijuana use there was a consistent pattern of higher fasting blood glucose in self-reported daily marijuana users compared to nonusers in all women in the WIHS and in HIV-positive and HIV-negative women, although the confidence intervals around the point estimates, all included the null value. Results for association of self-reported marijuana use and BMI, hemoglobin A1C and fasting glucose are included in the supplemental material (Tables S5, S6 and S7)[2].

4.3. Sensitivity analysis

We conducted sensitivity analysis to explore whether participants with imminent type 2 diabetes ceased or reduced marijuana use because of worsening health symptoms (i.e., potential reverse causality), as has been observed in studies involving alcohol use (Sarich et al., 2019; Stockwell et al., 2016). Therefore, we lagged the marijuana use variable (and time-varying covariates) by one time point (an average of six months) and re-ran all models. The pattern of results remained the same. In the MACS, although all the hazard ratios for self-reported marijuana use frequency in relation to incident type 2 diabetes indicate a reduced risk, they were not statistically significant. Further, the pattern of findings in the WIHS were similar and not statistically significant. Results for the lagged analysis of the association of self-reported frequency of marijuana use and incident type 2 diabetes are included in the Supplemental Material (Tables S3 and S4)[3]. As with BMI, high blood pressure could potentially lie on the causal pathway between marijuana use and type 2 diabetes. Thus, we re-ran analysis with and without high blood pressure, but the results remained the same.

5. Discussion

This analysis examined associations of self-reported frequency of marijuana use and incident type 2 diabetes in women and men living with and at risk for HIV in the WIHS and MACS cohorts respectively followed prospectively for nearly 20 years. Among men in the MACS, we found that self-reported frequency of marijuana use (compared to non-use) – including daily use – was associated with a reduced risk of type 2 diabetes, among all men

[2]:Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org
[3]:Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org

and in those living with and at risk for HIV, although these associations were not statistically significant. Among women in the WIHS, daily marijuana use was associated with a reduced risk of type 2 diabetes, but there was a pattern of increased type 2 diabetes risk in women with less than daily marijuana use among all women and in those living with and at risk for HIV. Albeit, these associations were not statistically significant.

To our knowledge, this is one of the largest longitudinal follow-up studies examining the relationship between marijuana use and incident type 2 diabetes in men and women living with or at risk for HIV. Data for our analysis came from two large, longitudinal cohorts with multiple observations over a long follow-up among persons living with or at-risk for HIV in midlife, when risks for incident type 2 diabetes are increased. Prior studies of the association between marijuana use and prevalence of diabetes have suggested lower odds of diabetes in subjects who use marijuana (i.e. a protective effect). One meta-analyses of eight different cross-sectional studies involving nationally representative surveys of the U.S population found an overall reduced odds of diabetes among subject who use marijuana (Alshaarawy and Anthony, 2015b). Another recent cross-sectional U.S. population-based study (not included in the above meta-analytic study) using the National Epidemiological Survey on Alcohol and Related Conditions that reported a statistically significant reduced odds of type 2 diabetes among lifetime and past 12- month marijuana use compared with never use (Imtiaz and Rehm, 2018). However, these studies utilized cross-sectional data, and thus evaluated associations between marijuana use and prevalence diabetes.

Furthermore, findings from this analysis are consistent with those from two other longitudinal studies that assessed associations between marijuana use and risk of diabetes conducted in the general population. Bancks et al (2015) followed up healthy men and women in the CARDIA Study over 18 years and reported hazard ratios indicating increased risk of diabetes in relation to greater lifetime frequency of marijuana use, but with wide confidence intervals around the hazard ratios that included the null value. Similarly, in a population-based cohort study of Swedish men and women followed up for more than 8 years, the authors found an adjusted protective odds ratio, between lifetime marijuana use (compared to never users) and diabetes risk, with wide confidence intervals around this point estimates that included the null estimates (Danielsson et al., 2016). The finding from our study and these two longitudinal studies parallel the association between marijuana use and type 2 diabetes, conducted in different populations likely underscores the power of long-term longitudinal assessments – when compared to cross-sectional studies, particularly when trying to measure incidence of a chronic disease (type 2 diabetes) linked with marijuana use over the life span.

The hazard ratios from the fully adjusted analysis for men in the MACS cohort, indicated a reduced risk of type 2 diabetes across all self-reported frequency of marijuana use (compared to non-use). Although, the confidence intervals around the adjust hazard ratios for the associations between self-reported frequency of marijuana use and incident type 2 diabetes were wide – including both the reduced, null and increase risk range – they leaned toward the reduced risk range. However, in the WIHS, the hazard ratios from the fully adjusted analysis indicated a reduced risk of type 2 diabetes only among daily users, with other user categories leaning toward an increased risk of type 2 diabetes. These findings may

point to potential sex differences in the association between marijuana use and type 2 diabetes and metabolic health. This will be consistent with other studies showing sex differences in the relationship between marijuana use and health (Cooper and Craft, 2018; Cuttler et al., 2016; Waterreus et al., 2019). As such, assessing sex differences of marijuana use on metabolic health is warranted, particularly in the context of HIV.

The mechanisms of a proposed marijuana and type 2 diabetes association, suggest that THC stimulates appetite through activation of CB1 (Riggs et al., 2012), and thus may play a role in eating behaviors among persons who use marijuana. Studies have shown significantly higher caloric intake in marijuana users compared with nonusers (Foltin et al., 1988; Ngueta et al., 2015; Rodondi et al., 2006; Smit and Crespo, 2001). Yet, the preponderance of studies documents better metabolic indicators in marijuana users compared with nonusers including higher high-density lipoprotein cholesterol levels; lower levels of fasting glucose, triglycerides, fasting insulin (Penner et al., 2013), and Homeostasis Model Assessments of Insulin Resistance (Penner et al., 2013); smaller waist circumferences (Penner et al., 2013); lower BMI (Le Strat and Le Foll, 2011); and lower odds of metabolic syndrome (Vidot et al., 2016b; Yankey et al., 2016). Indeed, in further analysis of WIHS and MACS data here, we found a statistically significant dose-dependent association between self-reported frequency of marijuana use and lower BMI. Results are included in the Supplemental Material (Table S5)[4]. Taken together, it appears that although marijuana use may stimulate appetite and increase caloric intake, it is not associated with increased BMI; on the contrary, it is dose-dependently associated with lower BMI and lower hemoglobin A1C levels.

Our study has some limitations. Information on marijuana use and other behaviors, including alcohol, smoking, and drug use, were collected via self-report and vulnerable to underreporting due to social desirability bias. Relatedly, there was no biological quantification of marijuana constituents (i.e., THC and CBD concentration) or mode of marijuana use (e.g. smoked, vaped or consumed) from participants. The imprecise measurement of marijuana use in our study could be a source of measurement error and may have contributed to the wide confidence intervals we observed. Potential confounders, such as physical activity, diet, and waist circumference, were not included in the analysis. Additionally, data from the WIHS were from predominantly black and Hispanic women, while the MACS comprises mostly non-Hispanic white men, which may signal disparities in reliable access to health care.

6. Conclusions

In this prospective analysis of nearly 20 years of data for women and men with and at risk for HIV in the WIHS and MACS cohort, respectively, we collectively found lower risk for type 2 diabetes, including among daily marijuana users compared to none users, although the associations were not statistically significant. Given that the number of state laws permitting marijuana use continues to expand in the United States, further longitudinal investigations that biologically quantify the THC/CBD concentrations of marijuana consumed by study participants to assess risk for incident diabetes is warranted.

[4]:Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org

Supplementary Material

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Aknowledgement

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Highlights

- Marijuana use is common in persons with HIV
- Prior research indicates that marijuana use is associated with prevalent diabetes
- Men and women with and at-risk for HIV were followed for nearly 20 years
- Marijuana use was not statistically associated with risk of type 2 diabetes
- Studies with biological measures of marijuana use is warranted

Table 1.

Baseline characteristics of WIHS and MACS cohorts at index visit

Characteristic	WIHS (N= 3578)				MACS (N= 2682)			
	HIV Negative (N=972)		HIV Positive (N=2171)		HIV Negative (N = 1356)		HIV Positive (N=1326)	
	N	%	N	%	N	%	N	%
Age, median (IQR), years	37 (29,45)		40 (34,46)		46 (39,53)		41 (35,47)	
Race/ethnicity								
White, non-Hispanic	112	11.5	319	12.2	962	70.9	654	49.3
Black, non-Hispanic	619	63.7	1639	62.9	252	18.6	417	31.4
Hispanic	202	20.8	567	21.8	72	5.3	116	8.7
Other	39	4.0	81	3.1	70	5.2	139	10.5
Education								
< High school	306	32.4	936	36.5	214	15.8	367	27.7
Completed high school	288	30.5	767	29.9	651	48.1	676	51.0
> High school	351	37.1	858	33.5	489	36.1	283	21.3
WIHS study center								
DC/NY	409	42.1	1031	39.6				
LA/SF	258	26.5	726	27.9				
Chicago	102	10.5	318	12.2				
NC/GA, FL, AL, MS	203	20.9	531	20.4				
MACS study center								
Baltimore					323	23.8	310	23.4
Chicago					197	14.5	301	22.7
Pittsburgh					359	26.5	302	22.8
Los Angeles					477	35.2	413	31.1
WIHS enrollment cohort								
Original cohort (pre-1994/1995)	340	35.0	1165	44.7				
Additional recruit (post-1994/1995)	632	65.0	1441	55.3				
MACS enrollment cohort								
Pre-2001					323	23.8	495	37.3
Post-2001					197	14.5	831	62.7
High blood pressure								
No	775	80.0	2012	77.2	855	69.1	877	72.6
Yes	194	20.0	593	22.8	383	30.9	331	27.4
Family history of diabetes								
No	856	88.1	2327	89.3	630	69.2	494	58.9
Yes	116	11.9	279	10.7	281	30.8	344	41.1
Alcohol use (WIHS)								
None	422	44.3	1401	54.8				

Characteristic	WIHS (N= 3578)				MACS (N= 2682)			
	HIV Negative (N=972)		HIV Positive (N=2171)		HIV Negative (N = 1356)		HIV Positive (N=1326)	
	N	%	N	%	N	%	N	%
≤8 drinks/week	375	39.3	932	36.4				
>8 drinks/week	156	16.4	224	8.8				
Alcohol use (MACS)								
None					192	14.6	236	18.4
≤13 drinks/week					1006	76.5	956	74.5
>13 drinks/week					117	8.9	92	7.2
Smoking								
Never smoker	292	30.7	889	34.7	445	33.8	413	32.0
Former smoker	152	16.0	452	17.6	474	36.0	499	38.7
Current smoker	507	53.3	1221	47.7	398	30.2	379	29.4
Stimulant drug use								
No	689	72.5	2100	82.2	1127	86.1	986	77.3
Yes	262	27.5	456	17.8	182	13.9	290	22.7
Marijuana use								
None	662	73.3	2038	84.1	888	67.2	787	61.6
Monthly/less	94	10.4	145	6.0	252	19.1	253	19.8
Weekly/less	75	8.3	119	4.9	113	8.6	122	9.5
Daily	72	8.0	120	5.0	68	5.1	116	9.1
ART use								
No			949	36.4			569	43.5
Yes			1657	63.6			738	56.5
Suppressed viral load[a]								
No			1303	52.1			626	50.9
Yes			1196	47.9			603	49.1
History of AIDS								
No			1533	58.8			1095	82.6
Yes			1073	41.2			231	17.4
BMI, median (IQR), kg/m²	29 (24,35)		27 (24, 33)		26 (23,28)		25 (23, 28)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.

[a]Suppressed viral load defined as ≤200 copies/mL.

Table 2.

Association between frequency of marijuana use and incident diabetes in the WIHS cohort

Marijuana Use	Number of events	Persons-years of follow-up	Crude HR (95% CI)	aHR (95% CI)[a]	aHR (95% CI)[b]
Overall[c]					
None	391	24,915	Reference	Reference	Reference
Monthly/less	22	1653	0.83 (0.53–1.28)	0.95 (0.60–1.51)	1.04 (0.65–1.65)
Weekly less	24	1638	1.01 (0.67–1.53)	1.13 (0.74–1.74)	1.22 (0.79–1.87)
Daily	15	2592	0.56 (0.34–0.94)	0.62 (0.37–1.04)	0.69 (0.41–1.16)
HIV Positive[d]					
None	280	18,318	Reference	Reference	Reference
Monthly/less	14	1,024	0.92 (0.53–1.62)	1.00 (0.56–1.81)	1.07 (0.59–1.93)
Weekly/less	15	910	1.13 (0.67–1.90)	1.60 (1.17–2.17)	1.34 (0.78–2.28)
Daily	11	1,670	0.73 (0.40–1.31)	0.79 (0.43–1.44)	0.90 (0.49–1.66)
HIV Negative					
None	111	6,597	Reference	Reference	Reference
Monthly/less	8	628	0.64 (0.30–1.39)	0.96 (0.42–2.18)	1.17 (0.51–2.67)
Weekly/less	9	728	0.86 (0.43–1.69)	1.15 (0.57–2.33)	1.19 (0.58–2.42)
Daily	4	921	0.37 (0.14–1.00)	0.46 (0.17–1.27)	0.48 (0.17–1.34)

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; WIHS, Women's Interagency HIV Study.

[a]Adjusted for age, race/ethnicity, education, study center, study enrollment cohort, alcohol use, smoking status, stimulant drug use, high blood pressure, and family history of diabetes.

[b]Additionally adjusted for body mass index and BMI^2

[c]Additionally adjusted for HIV status.

[d]Additionally adjusted for antiretroviral therapy use and viral suppression status.

Table 3.

Association between frequency of marijuana use and incident diabetes in the MACS cohort

Marijuana Use	Number of events	Persons-years of follow-up	Crude HR (95% CI)	aHR (95% CI)[a]	aHR (95% CI)[b]
Overall[c]					
None	250	21,896	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Monthly/less	43	4,337	0.75 (0.54–1.04)	0.89 (0.63–1.26)	0.95 (0.68–1.34)
Weekly/less	15	2,055	0.60 (0.35–1.02)	0.70 (0.41–1.20)	0.72 (0.42–1.25)
Daily	18	2,991	0.60 (0.36–1.01)	0.66 (0.39–1.14)	0.75 (0.43–1.28)
HIV Positive[d]					
None	124	9,315	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Monthly/less	20	2,176	0.63 (0.38–1.03)	0.76 (0.46–1.28)	0.80 (0.48–1.33)
Weekly/less	9	1,098	0.62 (0.31–1.25)	0.74 (0.36–1.51)	0.71 (0.35–1.45)
Daily	11	1,705	0.58 (0.30–1.12)	0.65 (0.33–1.27)	0.72 (0.37–1.42)
HIV Negative					
None	126	12,581	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Monthly/less	23	2,160	0.88 (0.56–1.38)	1.01 (0.63–1.62)	1.12 (0.70–1.81)
Weekly/less	6	956	0.54 (0.24–1.23)	0.63 (0.27–1.46)	0.74 (0.32–1.74)
Daily	7	1,285	0.64 (0.29–1.41)	0.76 (0.34–1.73)	0.86 (0.37–1.96)

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study.

[a]Adjusted for age, race/ethnicity, education, study center, study enrollment cohort, alcohol use, smoking status, stimulant drug use, high blood pressure, and family history of diabetes.

[b]Additionally adjusted for body mass index and BMI^2.

[c]Additionally adjusted for HIV status.

[d]Additionally adjusted for antiretroviral therapy use and viral suppression status