HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Epidemiology. 2015 July ; 26(4): 597–600. doi:10.1097/EDE.0000000000000314.

Cannabis Smoking and Diabetes Mellitus: Results from Meta-Analysis with Eight Independent Replication Samples

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Abstract

Background—In preclinical animal studies, evidence links cannabis smoking (CS) with hyperphagia, obesity, and insulin resistance. Nonetheless, in humans, CS might protect against type 2 diabetes mellitus (DM). Here, we offer epidemiological estimates from eight independent replications from (1) the National Health and Nutrition Examination Surveys, and (2) the National Surveys on Drug Use and Health (2005-12).

Methods—For each national survey participant, computer-assisted self-interviews assess CS and physician-diagnosed DM; NHANES provides additional biomarker values and a composite DM diagnosis. Regression analyses produce estimates of CS-DM associations. Meta-analyses summarize the replication estimates.

Results—Recently active CS and DM are inversely associated. The meta-analytic summary odds ratio is 0.7 (95% CI = 0.6, 0.8).

Conclusions—Current evidence is too weak for causal inference, but there now is a more stable evidence base for new lines of clinical translational research on a possibly protective (or spurious) CS-DM association suggested in prior research.

Introduction

Puzzles appear in research at the intersection of cannabis smoking (CS), obesity, and type 2 diabetes mellitus (DM). Obesity-DM associations have causal mechanisms involving insulin resistance.[1] Increased appetite and obesity are plausible CS outcomes, given preclinical evidence on central activation of cannabinoid-1 (CB1) receptors that promote hyperphagia, as well as activation of CB1 receptors in liver, increased de-novo fatty acid synthesis, decreased lipolysis, and induced insulin resistance.[2,3] Against this backdrop of plausible CS harms, the puzzles involve epidemiological estimates running in an opposite direction. CS is associated with lower obesity prevalence, lower biomarker levels indicative of impaired glucose metabolism, and lower DM prevalence.[4-6]

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The authors declare no conflicts of interests.

To shed new light on these puzzles, we derive meta-analysis summary estimates from multiple recent independent nationally representative replication samples in the United States (US) – namely, National Health and Nutrition Examination Surveys (NHANES), 2005-2012, and National Drug Use and Health Surveys (NSDUH), 2005-2012. While important, these estimates cannot be judged to be conclusive. More research is needed, for reasons explained in our Discussion section.

Methods

NHANES and NSDUH draw community samples from US study populations via area probability sample survey approaches, using IRB-approved recruitment and audio computer-assisted self-interview assessment protocols (ACASI), with acceptable participation levels in 2005-2012. NHANES adds standardized clinical and lab measurements.[7,8] NHANES and NSDUH details can be found in the eAppendix, with eFigure 1 as a flow chart for each survey's sample size and eTable 1 presentation of unweighted marginal sample totals for CS and DM.

Diabetes, as the key NSDUH response variable for this study, is from standardized ACASI self-report items about physician-diagnosed health conditions. NHANES also uses DM self-report items, but adds information on current insulin and/or oral hypoglycemic medicine use, plus lab-derived glycohemoglobin (HbA1c) levels, for a composite DM indicator.[9]

CS assessment is via a separate standardized ACASI module. CS items enable distinctions between recently active CS users, past users, and never users.

Comparably measured covariates in NHANES and NSDUH assessments include age, sex, ethnic self-identification (ESI), education, and income-poverty ratio. Use of tobacco and/or alcoholic beverages also is assessed, and NHANES examinations yield body mass index values (BMI).

In our statistical approach, Tukey-style exploratory analyses were used to shed light on univariate distributions of each variable, with no exploration of the CS–DM relationships under study. In subsequent analysis/estimation steps, multiple logistic regressions (MLR) produced crude and covariate adjusted estimates for odds ratios (OR) of DM across CS categories, with Stata ‘svy’ software for complex survey data analysis, analysis weights, and Taylor series variance estimation. Via Stata ‘metan’ software, the meta-analysis step yields a summary estimate from OR estimates of the eight independent replication samples.

These primary analysis/estimation steps motivated extra analyses to probe temporal sequencing issues using NHANES standardized item data about onset-ages for DM and for CS, plus time since last CS, which were asked for a subset of NHANES participants; accordingly, statistical power and precision are constrained. Here, time to DM onset is modeled as a function of CS onset using discrete time survival analysis (DTSA).[10] Then, another DTSA model was fit, with time to CS onset modeled as a function of DM onset, in order to check whether DM diagnosis might be prompting reduced incidence of CS. Finally, time to CS cessation was modeled as a function of DM diagnosis, as a check on whether

DM diagnosis prompts CS cessation. The eAppendix provides details about these data analysis steps.

A final post-estimation exploration step probed potential subgroup variation of the CS-DM association. Subgroups considered were defined by age, sex, ESI, and BMI, as well as use of tobacco or alcohol.

Results

In general, CS preceded DM. Estimated mean age of "first diagnosis" of DM was 40 years in the aggregate NHANES samples; mean age for "first CS" was earlier, at 17 years. NSDUH did not assess DM onset-age, but its mean CS onset-age was 18 years. Appendix eFigure 2 shows a distribution of individual age differences in participants who reported both cannabis smoking and diabetes obtained via subtraction of the age of onset, indicating 93% with CS preceding DM.

The 'never CS' serve as reference subgroup for OR estimates presented in Table 1, which disclose consistent inverse CS-DM associations in each replication sample and in the covariate-adjusted meta-analytic summary estimate (OR = 0.7; 95% confidence interval, CI = 0.6, 0.8). Analyses restricted to NSDUH and NHANES self-report DM diagnosis produced a slightly wider CI (OR = 0.7; 95% CI = 0.6, 0.9). Covariate adjustment for BMI did not shift point estimates appreciably, and post-estimation exploratory steps disclosed no appreciable variations in OR estimates across covariate-specified subgroups (eTable 2).

NHANES onset-age data analyses had the above-mentioned constraints on statistical power and precision. They disclosed: (1) the DTSA hazard ratio point estimate for time to DM as a function of CS onset was inverse, but imprecise (HR = 0.9; 95% CI = 0.7, 1.1); (2) the DTSA point estimate for time to CS as a function of DM onset could not be estimated; too few NHANES participants had DM preceding CS; (3) HR point estimates for DM diagnosis age and subsequent CS cessation were inverse but imprecise (HR = 0.8; 95% CI = 0.6, 1.1).

We excluded DM-diagnosed NHANES cases, and regressed glucose metabolism biomarker levels on CS status. As shown in eTable 3, these estimates indicate possible CS-associated lower biomarker levels even when DM has not been diagnosed.

Discussion

In our judgment, these inverse CS-DM estimates are important because they have the strength of NHANES and NSDUH research approaches across multiple independent replication samples. In meta-analysis, they disclose a statistically robust inverse and possibly protective influence of cannabis smoking on diabetes mellitus. For the most part, our post-estimation analysis steps did not contradict what main analyses disclosed, and tended to be supportive. Nonetheless, due to limitations of the type listed below, we also judge that we have not yet solved the CS-DM puzzle; the CS-DM association might yet be spurious. More definitive research is needed before anyone can lay claim to this potential health benefit from cannabis smoking.

Notwithstanding important strengths in this study, we will be the first to admit that cross-sectional field survey data generally are too weak to support firm causal inferences, even when they can be very useful for motivating future studies with more probing and definitive approaches. In addition to this limitation, for the most part, we assume validity and non-differential diagnostic classification for type 2 DM. Nonetheless, in both NSDUH and NHANES, the DM assessments are based on self-report, not on carefully standardized clinical-laboratory workups by expert physicians blind to CS histories. Or, because both DM and CS were measured by self-report, there might be a bias due to 'shared methods co-variation' of a type that can be avoided in multi-wave longitudinal research. These two limitations, by themselves, are enough to prompt cautious description of this evidence as important but still too weak for firm inferences.

Moreover, there are some other limitations of note, including self-selection of cannabis smoking exposures in processes not readily controlled in observational studies, incomplete control over other sources of spurious association, such as the possibility that cannabis smoking might be more noxious for individuals with incipient DM, with CS side effects contributing to CS cessation during the DM prodrome before diagnosis. (We note that 'dry' or 'cotton' mouth is a well-known adverse CS side effect, and might exacerbate this facet of the DM prodrome.) In addition, there might be a 'healthy cannabis smoker effect' or some other process that promotes fewer physician care visits, perhaps delaying onset of physician-diagnosed DM in active CS versus never users. Or, some individuals with incipient DM might become more conscientious about health, avoiding CS among other potentially risky behaviors.

If CS truly reduces DM incidence, we have more puzzles to solve. With caution, we can speculate about underlying mechanisms. For example, chronic low grade inflammation is implicated in DM pathogenesis.[11-13] Cannabinoids (CB) inhibit release of many inflammation mediators, some of them implicated in pathological processes leading toward insulin resistance and DM, plausibly via CB-2 receptors in the immune system.[14,15] Administering cannabidiol (CB) to non-obese mice inhibits destructive insulitis and inflammatory cytokine production, which might reduce DM incidence.[16] Clinical trials also have disclosed anti-inflammatory cannabinoid effects.[17-20]

In conclusion, this epidemiological evidence from eight independently drawn replication samples tends to confirm what prior research found – namely, an inverse, possibly protective, but also possibly spurious link between active cannabis smoking and occurrence of type 2 diabetes mellitus. Even so, we have not solved the CS-DM puzzle, and we have offered reasons for caution before any firm cause-effect inference is drawn. The evidence to date is not definitive.

Any claim of 'diabetes risk-reducing benefits of cannabis smoking' is premature, but given increased prevalence of CS and DM in the US and elsewhere, there is a reason to study CS-DM linkages.[21,22] Before these CS-DM puzzles are solved, more probing experimentation of a clinical translational character is needed, including research on potential mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: This work is completed during OA's first year of postdoctoral epidemiology fellowship, supported by the National Institute on Drug Abuse (T32DA021129) and JCA's NIDA Senior Scientist Award (K05DA015799), and by Michigan State University. The content is the sole responsibility of the authors and does not necessarily represent the official views of Michigan State University, the National Institute on Drug Abuse, or the National Institutes of Health.

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Table 1

Study-specific estimates of odds ratios that quantify associations linking occurrence of diabetes mellitus among recently active cannabis smokers: Data for the United States based on eight independent replications from the National Health and Nutrition Examination Survey (NHANES) and the National Surveys on Drug Use and Health (NSDUH), 2005-2012

Independent replication sample	Unadjusted CS-DM odds ratio (95% CI)	Covariate[a] adjusted odds ratio (95% CI)	Covariate-adjusted odds ratio additionally adjusted for BMI (95% CI)[b]
NHANES 2005-06	0.3 (0.2, 0.7)	0.6 (0.3, 1.2)	0.8 (0.4, 1.5)
NSDUH 2005-06	0.3 (0.2, 0.4)	0.7 (0.5, 1.0)	----------
NHANES 2007-08	0.3 (0.2, 0.5)	0.4 (0.2, 0.7)	0.4 (0.2, 0.8)
NSDUH 2007-08	0.3 (0.2, 0.4)	0.5 (0.4, 0.7)	----------
NHANES 2009-10	0.5 (0.3, 1.1)	0.9 (0.4, 2.1)	1.0 (0.4, 2.1)
NSDUH 2009-10	0.4 (0.3, 0.6)	0.8 (0.5, 1.1)	----------
NHANES 2011-12	0.5 (0.3, 0.8)	0.7 (0.4, 1.2)	0.8 (0.4, 1.4)
NSDUH 2011-12	0.5 (0.4, 0.6)	0.9 (0.6, 1.2)	----------
Meta-analytic odds ratio summary[c]	0.4 (0.3, 0.5)	0.7 (0.6, 0.8)	0.7 (0.5, 0.97)
Heterogeneity test statistic (*p* value)	12.9 (0.08)	9.8 (0.20)	2.7 (0.43)

[a] Covariate adjustments for age (years), sex (male and female), ethnic self-identification (non-Hispanic Whites, non-Hispanic Blacks, Hispanics, and all others), education (less than high school, high school, and above high school), income-poverty ratio (<1 and ≥1), past-year alcohol drinking (never user, used before but not in the 12 months prior to the interview, and used in the 12 months prior to the interview) and tobacco cigarette smoking (never, former, non-daily, and daily smoker), using the multiple logistic regression model.

[b] Additionally adjusted for BMI (kg/m^2). The NSDUH study does not collect data on BMI.

[c] This 'random effects' meta-analysis summary estimate makes an allowance for between-replication variability in the effect estimates. The heterogeneity test statistic (degrees of freedom. = 7) suggests no appreciable variation (i.e., as gauged in relation to alpha set at 0.05); nonetheless, the 'random effects' summary estimate was retained, with resulting standard errors (and 95% CI) slightly larger than those obtained using the 'fixed effects' meta-analysis summary estimation approach.