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Is marijuana use associated with lower inflammation? Results from waves III and IV of the national longitudinal study of adolescent to adult health

Erin G. Ferguson, Zachary L. Mannes, Nicole Ennis*

Department of Clinical and Health Psychology, College of Public Health and Health Professions, University of Florida, P.O. Box 100165, 1225 Center Drive, Room 3146 Gainesville, FL, 32610-0165, United States

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ABSTRACT

Background: Some research suggests that marijuana use facilitates an anti-inflammatory response, yet the relationship between marijuana use and inflammation, as measured by C-reactive protein (CRP), remains poorly understood. The present study examined the association between recency of marijuana use and serum C-reactive protein levels in a nationally representative sample of adults.

Methods: Data from Waves III and IV (N = 13,166) of the National Longitudinal Study of Adolescent to Adult Health was utilized. Past 30 day marijuana use was assessed in Waves III and IV, and past year marijuana use was also assessed at Wave IV. CRP was dichotomized with a cutpoint of 3 mg/L. Logistic regression analyses examined the association between marijuana use and CRP levels at Wave IV.

Results: Past 30 day marijuana use was reported by 23.5% and 17.7% of participants at Wave III and Wave IV respectively, and 23.6% of participants reported past year marijuana use during Wave IV. Marijuana use was associated with lower CRP levels in bivariate analyses. However, these associations attenuated after adjusting for sociodemographic and health-related covariates.

Conclusions: Though marijuana and lower CRP levels were initially associated, the effect of marijuana use on CRP was later explained by gender, BMI, and anti-inflammatory medication use. This suggests that marijuana use does not confer an anti-inflammatory effect and recency of use is not relevant. Given expanding marijuana use legislation and discourse surrounding the consequences of marijuana for health, continued research is needed to elucidate the effect of marijuana on inflammation and subsequent risk of chronic disease.

1. Introduction

Marijuana is the most widely used illicit substance in the United States, with the National Survey on Drug Use and Health estimating 22 million past month users age 18 and older in 2016 (Statistics and Quality, 2016). As of November 2018, thirty three states and Washington DC have legalized marijuana use for medical and/or recreational purposes, and such policy shifts are expected to continue (National Organization for the Reform of Marijuana Laws, State Info, 2018). Although some research demonstrates an association between heavy marijuana use and adverse health effects (Volkow et al., 2014), other studies have suggested that marijuana may have medicinal benefits, such as reduced inflammation (Hill, 2015; National Academies of Sciences, E., Medicine, 2017; Whiting et al., 2015).

Cannabinoids, the active compounds within marijuana, have long been implicated in inflammatory processes (Richardson et al., 1998), and recent studies suggest that activation of the cannabinoid-2 receptor mediates anti-inflammatory processes. The acute phase reactant C-reactive protein (CRP) is a marker of systemic inflammation that is associated with the progression of several chronic diseases, including cardiovascular disease (CVD), metabolic disease, and diabetes, as well as mortality, and it has been used to examine the relationship between marijuana use and inflammation (Buckley et al., 2009; Calle and Fernandez, 2012; Collaboration, 2010; Devaraj et al., 2009; Dregan et al., 2014; Parrinello et al., 2015; Pradhan et al., 2001; Zacho et al., 2010). Acute phase reactants are generated in response to the release of cytokines into the bloodstream, resulting in secretion of acute phase proteins, such as CRP. In healthy individuals, CRP can be found in trace amounts, however CRP levels can increase up to 1000 fold in response to infection and other pathological states (Gabay and Kushner, 1999). CRP has demonstrated clinical utility in screening for disease, monitoring the body's response to inflammation and infection, and predicting cardiovascular events (Collaboration, 2012; Pearson et al., 2003). To this point, CRP levels > 3 mg/L may indicate high risk for

* Corresponding author.
E-mail address: nennis@phhp.ufl.edu (N. Ennis).

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CVD according to American Heart Association and Centers for Disease Control and Prevention guidelines (Pearson et al., 2003).

To date, the literature examining the association between marijuana use and CRP is mixed. While some studies have found no robust predictive relationship between marijuana use and CRP levels (Meier et al., 2016; Ngueta et al., 2015), Costello et al. (2013) utilized bivariate analyses and found support for a pro-inflammatory effect of marijuana on CRP in adolescents. In contrast, a study utilizing data from the National Health and Nutrition Examination Survey (NHANES) indicated that lower CRP levels (< 0.5 mg/dL) were found in past marijuana users compared to current and never-users (Rajavashisth et al., 2012). Seeking to clarify these results with more recent NHANES data, Alshaarawy and Anthony (2015) found that current marijuana users demonstrated lower CRP levels as compared to never-users over a 1 year period, failing to fully replicate the previous study's results but nevertheless suggesting an anti-inflammatory effect of marijuana. Of the five studies investigating the relationship between marijuana use and CRP, all were epidemiological, with three studies using a cross-sectional design (Ngueta et al., 2015; Alshaarawy and Anthony, 2015; Rajavashisth et al., 2012) and two studies using a longitudinal design (Meier et al., 2016; Costello et al., 2013). Given findings demonstrating that recent marijuana use (i.e. past 30 days) may confer a more robust anti-inflammatory effect compared to more remote use (i.e. past 12-months), assessing the influence of the timing of marijuana use on CRP may be particularly important to inform our understanding of the length of time in which marijuana use affects CRP levels (Alshaarawy and Anthony, 2015; Ngueta et al., 2015). Thus, the purpose of the present study was to examine the association between marijuana use and systemic inflammation, as measured by CRP, both cross-sectionally and over time (i.e. Wave III and Wave IV marijuana use predicting Wave IV CRP levels) in order to understand how recency of marijuana use impacts this association. We hypothesized that marijuana users would demonstrate significantly lower CRP levels compared to non-users at each of the time points. Furthermore, in line with recent NHANES findings, we hypothesized that the most recent time point, Wave IV current marijuana use (i.e. past 30 days), would have the strongest association with CRP levels given the temporal alignment of the both data measurements.

2. Methods

2.1. Sample and Design

Data for this study came from Waves III and IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health). Given that CRP data was collected in Wave IV, these waves were most appropriate to test our marijuana-CRP hypotheses both cross-sectionally and longitudinally. Add Health is an ongoing, school-based, nationally representative study of adolescent health and behavior, in which researchers utilized a clustered sampling design (Harris, 2013). The first wave of data (Wave I) was collected in 1994-5 and selected adolescents in grades 7–12 for in-depth in-home interviews. Respondents were interviewed again in 1996 (Wave II), 2001–2002 (Wave III), 2008 (Wave IV), and between 2016-18 (Wave V). Of the 17,670 participants who completed Wave I interviews, 15,197 and 15,701 respondents completed Waves III and IV interviews respectively. This analysis included participants who were seen at Wave III and Wave IV with a valid, non-missing CRP measurement (N = 13,166). Approximately 0.6% (n = 94) of the sample had high sensitivity-CRP (hs-CRP) levels below the limit of detection and were thus excluded from the analysis.

2.2. Measures

2.2.1. C-Reactive Protein

Detailed documentation of high sensitivity C-reactive protein (hs-CRP) collection and quality control is available online (Whitsel et al., 2012). Briefly, blood samples were collected at the end of each Wave IV interview as documented, and capillary blood spots were dried, frozen, and assayed using an adapted sandwich ELISA method. Cross-validation using paired plasma samples and CRP concentrations of a sample of 87 participants indicated strong correlation and linear association (Pearson R = .98; Plasma CRP = DBS CRP/0.4285). Sensitivity of the CRP assay was 0.035 mg/L, the within-assay coefficient of variation was 8.1%, and the between-assay coefficient of variation was 11.0%. In line with the American Heart Association and the Center for Disease Control and Prevention's guidelines for hs-CRP classification as well as cardiovascular disease risk in adults, hs-CRP was analyzed as a categorical variable, using ≤ 3 mg/L (low-average risk) as the reference value, and > 3 mg/L (elevated risk) as the main outcome value (Pearson et al., 2003). While some research suggests that CRP values > 10 mg/L can be indicative of acute infection or trauma (Pearson et al., 2003), other research suggests that CRP values > 10 mg/L may indicate increased risk for chronic disease (Shanahan et al., 2014). Given this, we included CRP values greater than 10 in all analyses, but later performed sensitivity analyses to assess the impact on our results.

2.2.2. Marijuana Use

Marijuana use was assessed at Wave III and IV, and recency of marijuana use was defined based on use versus no use when measured over the past 30 days and past year in Wave IV, as well as over the past 30 days in Wave III. In Wave IV, participants reported the number of days they had used in the past 30 days. We dichotomized this to define current marijuana use as use on 1 day or more (users) versus no use (non-users) in the past 30 days. Participants also reported the number of days they had used marijuana in the past 12 months, and we dichotomized this past year use variable (use on ≥1 day/no use). At Wave III, respondents reported the number of times they used marijuana in the past 30 days. Similar to Wave IV, we categorized respondents as users (use on ≥1 day) or non-users (no use).

2.2.3. Covariates

Covariates included variables from Wave IV associated with fluctuation in CRP levels. These included sex, race, education, income, BMI, tobacco use, and anti-inflammatory medication use. Sex was categorized as male and female. We categorized race/ethnicity as Hispanic, White, Black, American Indian, and Asian. Education was categorized as high school/vocational school or less, some college, college, and more than college. Total household income in the past year was categorized as less than $50,000, $50,000–99,999, and more than $100,000. Body mass index (BMI) was measured, and we classified participants as underweight (< 18.5), normal (18.5- < 25), overweight (25- < 30), and obese (30+). Tobacco exposure assessed any exposure to tobacco over the past 30 days, including cigarette, cigar, pipe, or chewing tobacco use versus no use. Anti-inflammatory medication use was also considered as a potential confounding variable. As detailed in Add Health documentation (Whitsel et al., 2012), this measure assessed any anti-inflammatory medication use in the past 4 weeks (e.g. non-steroidal anti-inflammatory drugs/salicylate, Cox-2 inhibitor, inhaled corticosteroid, corticotropin/glucocorticoid, antirheumetic/anti-psoriatic, or immunosuppressive medications).

2.3. Analyses

All analyses were conducted using SPSS Version 24 (Corporation, 2016) and were weighted and adjusted for the complex survey design of Add Health. We utilized descriptive analyses to determine sample characteristics, as well as chi-square analyses to examine associations between Wave IV categorical factors and CRP. Multivariable logistic regression analyses were used to assess the associations between marijuana use at Waves III and IV and hsCRP (Models 1–3). Adjusted models included race/ethnicity, sex, education, income, BMI, tobacco use, and anti-inflammatory medication use, as these variables were

significantly associated with hsCRP in bivariate analyses ($p < 0.05$). Adjusted odds ratios and 95% confidence intervals for these associations were reported. Sensitivity analyses tested whether the pattern of findings from Models 1–3 would remain the same when excluding cases with CRP > 10 mg/L, as well as whether the pattern of findings would remain the same when systematically removing covariates from the model individually, while keeping all other covariates constant. Missing data (n = 1053) was addressed via listwise deletion.

3. Results

3.1. Sample Characteristics

In the total analytic sample (N = 13, 166), over half (52.1%) were female. The majority of participants were White (76.1%), and most of the sample reported attending at least some college (67.8%). Approximately 45.6% of participants had an income below $50,000, and roughly half (50.2%) reported having been married. Most of the sample was either overweight (29.1%) or obese (38.3%), and roughly 30% reported anti-inflammatory medication use. Regarding CRP, the majority of the sample (59.8%) had CRP levels ≤3 mg/L, while 40.2% had CRP levels > 3 mg/L. Approximately 23.5% and 17.7% of participants reported current marijuana use (use in the past 30 days) at Wave III and Wave IV respectively, while 23.6% of participants reported marijuana use in the past year during Wave IV.

3.2. Associations Between Marijuana Use and C - Reactive Protein (CRP)

Chi-square analyses revealed significant relationships between 30 day marijuana use at Wave III ($X^2 = 15.01$, $p = 0.01$) and CRP in Wave IV, as well as between 30 day and past year marijuana use at Wave IV respectively ($X^2 = 46.38$, $p < 0.001$; $X^2 = 51.34$, $p < 0.001$) and CRP. Gender ($X^2 = 515.03$, $p < 0.001$), race ($X^2 = 39.37$, $p = 0.01$), education ($X^2 = 75.52$, $p < 0.001$), income ($X^2 = 64.30$, $p < 0.001$), BMI ($X^2 = 1664.07$, $p < 0.001$), anti-inflammatory medication use ($X^2 = 48.39$, $p < 0.001$), and tobacco use ($X^2 = 25.67$, $p = 0.003$) were also associated with CRP in bivariate analyses Table 1.

3.3. Model 1

To further test the hypothesis that current marijuana use (i.e. marijuana use in the past 30 days) would be associated with lower CRP levels, a multivariable logistic regression was conducted. Marijuana use in the past 30 days at Wave IV was significantly associated with lower CRP (≤3 mg/L) as compared to non-use in unadjusted analysis (OR = 0.73, 95% CI = 0.63-0.83, $p < 0.001$). However, after adjusting for variables significantly associated with CRP in bivariate analyses (i.e. gender, education, race, income, BMI, anti-inflammatory medication use, and tobacco use), marijuana use did not significantly predict lower CRP levels, (AOR = 0.97, 95% CI = 0.80–1.17, $p = 0.740$).

3.4. Model 2

To understand if past year marijuana use was related to lower CRP levels, a second multivariable logistic regression was conducted. In the unadjusted model, marijuana use in the past year at Wave IV was significantly associated with lower CRP levels (≤ 3 mg/L) as compared to non-use (OR = 0.74, 95% CI = 0.65–0.84, $p < 0.001$). After adjusting for covariates, marijuana use in the past year was not significantly predictive of lower CRP levels, (AOR = 1.00, 95% CI = 0.85–1.18, $p = 0.960$).

3.5. Model 3

A third multivariable logistic regression analysis was conducted to evaluate whether marijuana use in the past 30 days at Wave III would predict lower CRP levels. Covariates from the other models remained. Wave III 30 day marijuana use was significantly associated with being in the lower CRP level group (≤3 mg/L), (OR = 0.84, 95%CI = 0.74–0.95, $p = 0.01$) as compared to non-use. This association did not remain significant after adjusting for covariates, (AOR = 1.03, 95% CI = 0.89–1.22, $p = 0.640$) Table 2.

3.6. Sensitivity Analyses

Sensitivity analyses were conducted to evaluate the marijuana-CRP relationship excluding cases with CRP values > 10 mg/L (n = 1693). Results of multivariable regressions did not greatly differ from original analyses. Marijuana use was not associated with lower CRP (≤ 3 mg/L) after adjusting for covariates in Model 1 (AOR = 0.95, 95% CI = 0.78–1.15, $p = 0.600$), Model 2 (AOR = .97, 95% CI = 0.82–1.15, $p = 0.74$), or Model 3 (AOR = 1.01, 95% CI = 0.86–1.20, $p = 0.880$). This pattern of results is similar to original analyses, and BMI ($p < 0.001$) and sex ($p < 0.001$) remained significant predictors of CRP status in all three models. However, anti-inflammatory medication use did not remain significant in Model 1 ($p = 0.150$), Model 2 ($p = 0.150$), or Model 3 ($p = 0.130$).

Additional sensitivity analyses were conducted to assess the marijuana use-CRP relationship while systematically removing each covariate from the model individually, with all other variables remaining constant. After removing BMI from the models, marijuana use was significant in Model 1 (AOR = 0.83, 95% CI = 0.70–0.98, $p = 0.03$) and Model 2 (AOR = 0.85, 95% CI = 0.74-0.98, $p = 0.03$), but not in Model 3 (AOR = 0.91, 95%CI = 0.79–1.04, $p = 0.17$). After systematically removing all other covariates (e.g. gender, anti-inflammatory medication use, tobacco exposure, education, income, and race) from the models, marijuana use remained nonsignificant (ps > .05).

4. Discussion

Marijuana has been previously associated with anti-inflammation benefits through the activation of CB2 receptors within the endocannabinoid system. On this basis, we predicted that marijuana use over the past 30 days, over the past year, and in the past 30 days approximately six years prior, would be associated with lower levels of CRP (≤ 3 mg/L). Findings demonstrated bivariate associations between marijuana use at all three time points and CRP, such that marijuana users were more likely to be in the lower CRP group compared to non-users. However, each of these associations attenuated with the inclusion of sociodemographic and health-related covariates. We conducted post hoc analyses utilizing CRP as a continuous measure, as well as analyses utilizing marijuana as categorical variable with frequency of use categories, to understand if our null findings were driven by the categorization of our primary predictor and outcome variables. However, results were consistent. This suggests not only that recency of marijuana use may not be relevant, but also that there is no robust evidence for the hypothesized anti-inflammatory effect of marijuana use in a nationally representative sample.

Despite the comparable methodology of this study and recent work using NHANES data (e.g. nationally representative samples, strong CRP assays), this study did not replicate findings indicative of marijuana's anti-inflammatory effects. This study was strengthened by the inclusion of anti-inflammatory medication use in our models. Of note, the previously mentioned NHANES study did not control for anti-inflammatory medication use. To the authors' knowledge, this is the first study examining the marijuana-CRP relationship to control for anti-inflammatory medication use in a nationally representative sample, a key component needed to fully clarify the marijuana-CRP relationship. One prior study controlled for medication use (Costello et al., 2013), accounting solely for psychotropic and prescribed medications. The present study accounted for any anti-inflammatory medication use, prescribed or non-prescribed (i.e. over-the-counter), thus expanding upon

Table 1
Selected Demographics of Participants in Wave III and IV of Add Health Stratified by Wave IV Current Marijuana Use (N = 13,166).

VARIABLE	ENTIRE SAMPLE		MARIJUANA USERS		NON-MARIJUANA USERS		TEST STATISTICS WITH CRP	
	N	%	*N*	%	*N*	%	χ^2	*p*-value
N	13,166		2156	18	10,999	82.3		
Gender							515.03	< .001
Male	6010	50	1265	62	4736	46.7		
Female	7156	51	891	38	6263	53.3		
Race							39.37	0.01
Hispanic	136	0.90	21	1	114	0.8		
White	7211	75.20	1192	77	6017	74.8		
African American	2298	14.70	399	13.7	1893	14.9		
American Indian	570	4.80	102	5.20	468	4.8		
Asian	840	4.40	88	3.10	752	4.7		
Education							75.52	< .001
High School/Vocational School or less	4503	37	891	44	3603	35		
Some College	4575	34	800	35	3774	34		
College	2529	18	327	15	2202	19.3		
More than college	1558	11	138	7	1419	11.8		
Income							64.301	< .001
< 50,000	5504	46	1088	56	4411	44.1		
50,000-99,999	4912	39	668	33	4242	40.6		
≥100,000	1914	14	236	11	1678	15.2		
Marital Status							4.007	0.221
Never Married	6496	50	1451	67	5037	46.1		
Ever Married	6657	50	704	33	5950	53.9		
BMI Class							1664.07	< .001
Underweight	166	1	36	2	130	1.2		
Normal	3992	31	755	38	3231	29.7		
Overweight	3883	29	637	29	3244	29.4		
Obese	4977	38	706	31	4268	39.7		
Anti-Inflammatory Medication Use							48.39	< .001
No	9720	70	1470	67	7791	70.8		
Yes	3896	30	686	33	3208	29.2		
30 Day Tobacco Use								
No	7754	56	627	26	7125	62.5	25.67	0.003
Yes	5303	44	1518	74	3780	37.5		

previous findings and allowing for an observation of the marijuana-CRP relationship while controlling for the use of anti-inflammatory medication.

One of the most compelling avenues for future research lies in the utilization of biologically measured marijuana use. Substance use research has historically relied upon self-report data to assess prevalence and frequency of marijuana use. Self-report data for substance use is characterized by advantages (i.e. practical, less intrusive, less expensive), as well as disadvantages (i.e. poor recall, inaccuracy of reporting by some populations, perceived negative consequences, and social desirability), all of which may affect validity (Johnson and Fendrich, 2005; Hjorthøj et al., 2012; Rosay et al., 2007; White et al., 2014). Similar to other substance use research, this study relied on self-report data to determine the prevalence of marijuana use. It is possible that misclassification may have occurred, such that some respondents classified as non-users may have actually been users. To the authors' knowledge, no study assessing the relationship between marijuana use and CRP levels has employed objective marijuana measures. Assessing marijuana use with biological measures, such as a urinalysis or blood draw, will be an important first step in providing relative clarity to the rather ambiguous marijuana-CRP literature, as well as reducing errors in classification.

In this study, the relationship between marijuana use and CRP levels was confounded by BMI and sex, and these covariates remained significant in all models. In particular, our findings demonstrated that women have higher CRP levels compared to men, aligning with previous research (Lakoski et al., 2006; Nazmi et al., 2008; O'Connor et al., 2009). Prior studies have hypothesized that this may be a mechanism of hormonal factors, specifically stage of menstrual cycle and use of oral contraceptives. The menstrual cycle is accompanied by fluctuations in estrogen, which can result in increased CRP depending on the stage (Gaskins et al., 2012). Oral contraceptive use may be another explanation for these sex differences, as it has also been linked to higher CRP levels (Hung et al., 2008; Shanahan et al., 2013; van Rooijen et al., 2006). Alternatively, our findings may be explained by BMI. Our sensitivity analyses examining the pattern of results when removing covariates individually from each model suggested that BMI was the only variable that altered the marijuana use-CRP relationship upon removal from Models 1 and 2. This suggests that BMI was the most important confounder of the relationship between marijuana use and CRP, particularly when considering marijuana use over the past 30 days and past year. BMI has been consistently associated with increased CRP levels (Clark et al., 2016; Endeshaw, 2011; Rawson et al., 2003; Wilson et al., 2006), and previous studies have shown that women have more body fat than men at any given BMI (Choi et al., 2013; Lear et al., 2003; Shanahan et al., 2013). Furthermore, a more robust relationship between body fat and CRP levels has been demonstrated for women compared to men (Khera et al., 2009).

Our study has several important limitations to be considered and numerous strengths. First, Add Health has no information regarding the route of administration, THC/CBD content, or reason for marijuana use (i.e. medical vs. recreational use). CRP is also only measured at one point in time. Multiple CRP measurements, as well as additional information pertaining to marijuana use, may help contextualize the effects of marijuana use on CRP levels in future work. Future research is needed to continue to clarify the relationship between marijuana use and CRP levels, as well as to understand the implications of the non-immunomodulatory effect of marijuana that our findings suggest. Furthermore, future studies may benefit from considering years of marijuana use and/or frequency of use as potential mediators in the

Table 2
Logistic Regressions Examining the Relationship Between Recency of Marijuana Use and CRP (> 3 mg/L) (N = 13,166).

	Unadjusted OR[a] (CI[b])	p^c	Adjusted OR[d] (CI[b])	p^c
Model 1: Past 30 Day Marijuana Use (W4)				
Non-users (N = 10,999)	Referent		Referent	
Users (N = 2156)	0.73 (0.63–0.83)	**	0.97 (0.80–1.17)	ns
BMI				
Normal	Referent		Referent	
Underweight	0.68 (.36–1.27)	ns	0.70 (0.37–1.35)	ns
Overweight	1.86 (1.63–2.13)	**	2.24 (1.90–2.60)	**
Obese	5.92 (5.18–6.78)	**	6.72 (5.72–7.89)	**
Gender				
Male	Referent		Referent	
Female	2.27 (2.04–2.52)	**	2.61 (2.30–2.96)	**
Anti-inflammatory medication use				
No	Referent		Referent	
Yes	1.31 (1.18–1.45)	**	1.22 (1.07–1.38)	**
Model 2: Past Year Marijuana Use (W4)				
Non-users (N = 10,203)	Referent		Referent	
Users (N = 2950)	0.74 (0.65–0.84)	**	1.00 (.85–1.18)	ns
BMI				
Normal	Referent		Referent	
Underweight	0.68 (.36–1.27)	ns	0.70 (0.37–1.34)	ns
Overweight	1.86 (1.63–2.13)	**	2.24 (1.89–2.65)	**
Obese	5.92 (5.18–6.78)	**	6.73 (5.72–7.89)	**
Gender				
Male	Referent		Referent	
Female	2.27 (2.04–2.52)	**	2.61 (2.30–2.97)	**
Anti-inflammatory medication use				
No	Referent		Referent	
Yes	1.31 (1.18–1.45)	**	1.22 (1.07–1.38)	**
Model 3: Past 30 Day Marijuana Use (W3)				
Non-users (N = 8627)	Referent		Referent	
Users (N = 2395)	0.84 (0.74–0.95)	**	1.03 (.89–1.22)	ns
BMI				
Normal	Referent		Referent	
Underweight	0.68 (.36–1.27)	ns	0.71 (0.37–1.36)	ns
Overweight	1.86 (1.63–2.13)	**	2.24 (1.90–2.65)	**
Obese	5.92 (5.18–6.78)	**	6.75 (5.75–7.93)	**
Gender				
Male	Referent		Referent	
Female	2.27 (2.04–2.52)	**	2.62 (2.30–2.98)	**
Anti-inflammatory medication use				
No	Referent		Referent	
Yes	1.31 (1.18–1.45)	**	1.22 (1.07–1.38)	**

*Non significant covariates: 30 day tobacco exposure, income, race, education.
[a] Odds ratio.
[b] 95% confidence interval.
[c] $**P \leq 0.01$; $*P \leq 0.02$; ns = not significant.
[d] Adjusted for sex, income, education, race, anti-inflammatory med use, BMI, tobacco exposure.

marijuana-CRP relationship, as the greater frequency or number of years of use may confer distinct anti-inflammatory effects. Despite these limitations, this study was strengthened by its analysis of the associations between marijuana use and CRP in a nationally representative sample of adults. Moreover, these analyses were both cross-sectional and over time. Many variables known to influence CRP levels were evaluated and utilized in analyses as covariates to adjust for potential confounding, and these covariates ultimately accounted for the marijuana-CRP relationship regardless of recency of marijuana use. Although we did not find support for a hypothesized immunomodulatory effect of marijuana on CRP, these results contribute to a broader discussion of marijuana and its consequences for health.

5. Conclusion

The legalization of marijuana use in the United States continues to expand, with thirty three states and Washington D.C. currently permitting the use of marijuana for medical or recreational purposes. Given the discourse surrounding marijuana's anti-inflammatory effect and its associated health benefits, it has become increasingly important to assess this suspected effect in an empirical context. Joining previous research, findings from this nationally representative sample do not demonstrate an anti-inflammatory effect of marijuana, creating important implications for those using marijuana to provide relief from inflammation. Given conflicting results examining the association between marijuana use and CRP, future studies are needed to further investigate the effect of marijuana use on inflammation and subsequent risk of developing chronic disease.

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Conflict of interest

No conflict declared.

Contributors

EGF conceptualized the research question, and drafted the manuscript. ZLM edited the manuscript. NE conceptualized the research question, edited the manuscript, and is the senior author. All authors have reviewed and approved the final manuscript.

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