Recent Marijuana Use and Associations With Exhaled Nitric Oxide and Pulmonary Function in Adults in the United States

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BACKGROUND: The medical and recreational use of marijuana is now legal in some parts of the United States; the health effects are unknown. We aimed to evaluate associations between recent marijuana use and exhaled nitric oxide (eNO) and pulmonary function.

METHODS: We performed a cross-sectional study of 10,327 US adults participating in the National Health and Nutrition Examination Survey in the years 2007 to 2012. We examined associations between marijuana use and eNO, FEV₁, FVC, the FEV₁/FVC ratio, and forced expiratory flow (midexpiratory phase) (FEF_{25%-75%}) by weighted linear regression.

RESULTS: In the study population, there were 4,797 never users, 4,084 past marijuana users, 555 participants who used marijuana 5 to 30 days before the examination, and 891 participants who used marijuana 0 to 4 days before the examination. Current marijuana use in the past 4 days was associated with 13% lower eNO (95% CI, -18% to 8%). FVC was higher in past users (75 mL; 95% CI, 38-112) and current users in the past 5 to 30 days (159 mL; 95% CI, 80-237) and in users within 0 to 4 days of the examination (204 mL; 95% CI, 139-270) compared with never users. All associations remained unchanged and statistically significant in sensitivity analyses excluding current and past tobacco users.

CONCLUSIONS: Current marijuana use was associated with lower levels of eNO and higher FVC. The lower eNO in marijuana smokers suggests that short-term exposure to marijuana may, like tobacco, acutely affect the pulmonary vascular endothelium and impair airflow through the small airways.

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KEY WORDS: exhaled nitric oxide; marijuana; pulmonary function tests

ABBREVIATIONS: eNO = exhaled nitric oxide; FEF_{25%-75%} = forced expiratory flow (midexpiratory phase); FENO = fraction of exhaled nitric oxide; MEC = mobile examination center; NHANES = National Health and Nutrition Examination Survey; NOS = nitric oxide synthase

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Marijuana is the most commonly used illicit drug in the United States. The 2013 National Survey on Drug Use and Health reported that approximately 7.5% of those aged 12 years or older were past-month users. Daily or almost daily use of marijuana increased from 5.1 million people in 2005 to 2007 to 8.1 million people in 2013.¹ The use of medical marijuana is now legal in 23 states, the District of Columbia, and Guam, and one survey found that 76% of medical professionals would recommend the use of marijuana for some medical purposes.² Recreational use of marijuana is also increasingly tolerated, and is legal in three states as of this writing.³ Despite increasing use and acceptance of marijuana, both medically and recreationally, gaps remain in our knowledge regarding potential health effects.

Marijuana has been associated with acute increases in caloric intake, increased average caloric intake, lower levels of fasting insulin, insulin resistance, and smaller waist circumference.⁴⁻⁸ Temporal associations between marijuana use and serious adverse events, including myocardial infarction and sudden cardiac death, have been described.⁹⁻¹³ The mechanism associating marijuana use and cardiovascular events is currently unclear. Nitric oxide levels play a significant role in vascular tone and hemodynamics, and it has long been known as the endothelium-derived relaxing factor.¹⁴

Nitrogen oxides are produced endogenously in the human lung¹⁵ and are important not only for the

lung, by defending the respiratory tract from infection and counteracting bronchoconstriction of the airways, but also for the vascular system, by counteracting vasoconstriction in the pulmonary and systemic vasculature, inhibiting platelet aggregation, and promoting smooth muscle relaxation.¹⁶⁻¹⁸ Studies have consistently found that tobacco smoke acutely decreases exhaled nitric oxide (eNO),¹⁹⁻²³ most likely by decreasing the production of nitric oxide synthase (NOS) by airway epithelial cells. If the detrimental effects of tobacco on nitric oxide production are due to the combustion products in inhaled smoke, it is possible that marijuana smoke would have effects similar to those of tobacco smoke, but to our knowledge no prior studies have examined the relationship between recent marijuana use and eNO.

The bronchoconstrictive effects of tobacco smoke on lung function are now well established, but only a few studies have examined the association between marijuana use and pulmonary function, with inconsistent results.²³⁻³⁰

In this study of 10,327 participants in the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2012, aged between 18 and 59 years, we aimed to examine the associations between recent and past marijuana use and eNO and pulmonary function test results, including FEV₁, FVC, the FEV₁/FVC ratio, and FEF_{25%-75%}, the latter being the forced expiratory flow (midexpiratory phase).

Materials and Methods

Study Population

The NHANES is a periodic survey conducted by the US Centers for Disease Control and Prevention to assess the health and nutritional status of the civilian, noninstitutionalized US population.³¹ Data are released in 2-year increments. NHANES is based on a multistage, stratified, clustered probability sampling in order to select a nationally representative sample of individuals in the US population, and includes an interview, a physical examination, and blood collection. From 2007 to 2012, 10,327 people aged 18 to 59 years completed the questionnaire on illicit drug use and underwent a physical examination at the mobile examination centers (MECs).

Assessment of Marijuana Use

An audio computer-assisted self-interview system was used to assess marijuana use. The questions asked were the following:

- “Have you ever, even once, used marijuana or hashish?” (yes, no, refused, don’t know);
- “How long has it been since you last used marijuana or hashish?” (answers were given as number of days, weeks, months, or years); and

- “During the past 30 days, on how many days did you use marijuana or hashish?”

From 2009 to 2012, participants were also asked about the frequency of marijuana use:

- “How many joints or pipes did you smoke in a day?”

Each questionnaire was administered at an MEC during the MEC interview. The responses to these questions were used to classify participants as never users (never used marijuana, n = 4,797), past users (smoked marijuana at least once but not in the past 30 days, n = 4,084), and current users. We further classified current users as having smoked marijuana at least once in the past 5 to 30 days (n = 555) and at least once in the past 0 to 4 days (n = 891). Data on the frequency of use were available for 1,820 participants.

Outcomes

eNO, FEV₁, FVC, FEV₁/FVC Ratio, and FEF_{25%-75%}: eNO and pulmonary function measurements were performed in the MECs. The fraction of exhaled nitric oxide (FENO) was measured with a portable hand-held analyzer (Aerocrine AB, Solna, Sweden). The NHANES protocol required two valid FENO measurements that

were reproducible, similar to those published by the American Thoracic Society and European Respiratory Society.³² Pulmonary function testing followed the recommendations of the American Thoracic Society.³³ All measurements were collected according to standard NHANES protocol.³⁴

Sociodemographic Characteristics and Health Habits: Demographic characteristics and health habits, including age, sex, race/ethnicity, education level, income, marital status, tobacco use, and asthma status, were self-reported during the NHANES interviews or in the questionnaires. Race/ethnicity was classified as Hispanic, non-Hispanic white, non-Hispanic black, or other. Height and weight were obtained in the MECs for each participant. We classified education level as less than high school, high school or equivalent, or at least some college. Income was categorized as less than \$20,000, \$20,000 to \$44,999, \$45,000 to \$74,999, and greater than or equal to \$75,000/y. Tobacco use was defined in pack-years, and participants were further classified as never, past, and current smokers.

Statistical Analyses: We used weighted regression models to take into account the unequal probabilities of selection, oversampling, and nonresponse, and thus estimate the geometric means (when log-transformed) or means and 95% CIs of eNO, FEV₁, FVC, FEV₁/FVC, and FEF_{25%-75%}. We used χ^2 tests accounting for the sampling design to compare baseline characteristics across never, former, and current marijuana users. Because values below the limit of detection for eNO were imputed with the value of 3.5 parts per billion, we used truncated regression to estimate the effect of marijuana use on eNO by combining the values from the tail with the rest of the distribution.

Data on income were missing for 1,130 of the participants (10.0%) in the study population, so we used Markov chain Monte Carlo multiple imputation to simulate five complete data sets. All statistical analyses were performed in each data set. The results were then averaged,

using the “mi estimate” combined with the “svy” prefix commands in STATA, which essentially assign appropriate weights to take into account the unequal probabilities of selection, oversampling, and nonresponse, and *P* values and CIs incorporating the uncertainty in the imputed estimates were reported.³⁵ We then compared the imputed and observed values to assess the reasonableness of the imputation model.

The distribution of eNO was right skewed and was log-transformed to approximate normality. All estimates were standardized to the 2000 US Census population, using age adjustment with age groups 18-30, 30-40, 40-50, and more than 50 years. We first performed age-standardized analyses. Furthermore, we performed weighted linear multivariable regressions accounting for all of the following covariates, which were specified a priori as potential confounders: age, sex, race, height, body mass index, education level, income, marital status, asthma, smoking status, and pack-years of smoking. Because pulmonary function test values may be in the causal pathway of the association between marijuana use and exhaled nitric oxide, we did not include them in our models but evaluated them as separate outcomes.

We evaluated whether there was a nonlinear association between the frequency of marijuana use and log-transformed eNO, FEV₁, FVC, FEV₁/FVC, and FEF_{25%-75%} among current users of marijuana by including the difference between median intake and reported intake and the square of this value as continuous terms in our multivariable model. Moreover, we evaluated whether there was a dose-response relationship between frequency of marijuana use and eNO in the subsample of participants who provided data on frequency of use (*n* = 1,820). We also performed sensitivity analyses excluding current and past tobacco smokers to test whether the associations between marijuana use and eNO and pulmonary function test results were dependent on tobacco use. All analyses were performed in STATA version 12 (StataCorp LP).

Results

Demographic characteristics of the study population are shown in Table 1. Of the 10,327 NHANES participants in the population, 4,797 (46.5%) were never marijuana users, 4,084 (39.5%) were past marijuana users, 555 (5.4%) used marijuana in the 5 to 30 days before the examination, and 891 (8.6%) used marijuana on the same day as, or up to 4 days before, the examination. Compared with never users, current users were more likely to be male, younger, and current tobacco users (Table 1).

In the age-standardized analysis, past and current marijuana users were associated with lower eNO compared with never users. FEV₁, FVC, and FEV₁/FVC were all higher in current and past users than in never users, while FEF_{25%-75%} was significantly lower in current compared with never users (Table 2).

In the multivariable adjusted model (Table 3), eNO was lower among participants who used marijuana in the past 0 to 4 days and those who last used marijuana 5 to 30 days before the examination compared with the never users. FEV₁ was higher among participants who used

marijuana within 0 to 4 days before the examination compared with those who never used marijuana, while FVC was higher in both past and current marijuana users compared with never users. The FEV₁/FVC ratio was significantly lower among those who used marijuana in the 0 to 4 days before the examination compared with never users. The FEF_{25%-75%} was not significantly different between the groups. Among current users, we did not find evidence of a significant relationship or a nonlinear association between frequency of marijuana use and any outcome. We did not detect a dose-response relationship between frequency of marijuana use, eNO, and pulmonary function in the 1,820 participants who provided data on frequency of marijuana use (joints per day).

In sensitivity analyses restricted to those who never used tobacco (Table 3), eNO remained significantly lower among those who used marijuana in the past 0 to 4 days before the examination compared with those who never used marijuana. FEV₁ was not significantly different between the groups, but FVC was higher in past and current users compared with never users. Consequently,

TABLE 1] Demographic Characteristics of Participants From the National Health and Nutrition Examination Survey, 2007 to 2012

Characteristic	Frequency of Cannabis Use				P Value
	Never (n = 4,797)	Past (n = 4,084)	Current Use		
			Past 5-30 d (n = 555)	Past 4 d (n = 891)	
Sex, %					< .001
Male	43.3	53.1	61.7	64.1	
Female	56.7	46.9	38.3	35.9	
Race/ethnicity, %					< .001
Hispanic	22.1	9.9	8.9	8.7	
Non-Hispanic white	55.7	75.6	65.3	72.2	
Non-Hispanic black	12.1	10.6	19.1	16.8	
Other	10.1	3.9	6.6	2.3	
Age, y					< .001
18-29	26.1	24.8	46.5	43.1	
30-39	24.8	20.9	19.4	23.1	
40-49	24.7	27.4	19.5	21.2	
≥ 50	24.4	26.9	14.5	12.6	
Educational level, %					< .001
Less than high school	18.9	12.0	23.6	18.9	
High School	21.7	20.0	23.4	26.5	
Some college	55.7	64.4	49.5	51.1	
Marital status, %					< .001
Married or cohabiting	65.2	61.0	49.9	52.9	
Not married or cohabiting	31.2	35.4	46.5	43.5	
Tobacco use, %					< .001
Never	74.5	41.2	23.1	20.8	
Past	10.8	28.8	23.8	22.5	
Current	11.2	26.4	49.5	53.1	
Income, %					< .001
< \$20,000/y	15.8	12.1	22.5	20.1	
\$20,000-\$44,999/y	24.7	21.7	29.8	30.3	
\$45,000-\$74,999/y	23.1	22.6	20.1	20.0	
> \$75,000/y	36.3	43.6	27.7	29.5	
Asthma, %					< .001
Yes	13.1	15.5	15.1	20.6	
No	86.9	84.5	84.9	79.4	

Analyses were weighted to account for the survey design and to reflect national population estimates. Data are age standardized and presented as percentages. Total No. of participants, N = 10,327.

the FEV₁/FVC ratio remained significantly lower among current users while FEF_{25%-75%} was not significantly different.

Discussion

In the present analysis of NHANES data from 2007 to 2012, we found a significant association between current marijuana use and lower levels of eNO, independent of

tobacco smoking. FVC was significantly higher in past and current users compared with never users of marijuana. FEF_{25%-75%} was not significantly different among the groups.

To our knowledge, this is the first study that examines the association between eNO and marijuana use. Prior studies have examined associations between tobacco exposure and eNO in adults, and most of these have observed a reduction in eNO with tobacco

TABLE 2] Mean Values of Exhaled Nitric Oxide, Pulmonary Function Tests, BMI and Pack-Years of Smoking According to Average Marijuana Use Among Participants in the National Health and Nutrition Examination Survey, 2007 to 2012

Quantity Measured	Participants (No.)	Frequency of Cannabis Use				P Value
		Never	Past	Current Use		
				Past 5-30 d	Past 4 d	
eNO, ppb ^a	9,472	13.8	12.6	10.5	9.5	< .001
FEV ₁ , L	6,268	3.2	3.4	3.3	3.4	< .001
FVC, L	6,268	4.0	4.4	4.3	4.5	< .001
FEF _{25%-75%} , L/s	6,268	3.2	3.2	2.9	3.0	.003
FEV ₁ /FVC	6,226	0.80	0.78	0.76	0.75	< .001
BMI, kg/m ²	10,260	29.2	28.7	27.3	27.4	< .001
Pack-years, mean	9,510	3.3	8.7	10.8	14.4	< .001

Data are age standardized and presented as percentages. eNO = exhaled nitric oxide; FEF_{25%-75%} = forced expiratory flow (midexpiratory phase); ppb = parts per billion.

^aMeans for eNO are geometric.

smoking,^{19,21,36-38} in people with asthma and/or healthy individuals. In vitro studies have found that tobacco can decrease expression of cytokine-induced inducible NOS protein and mRNA in lung epithelial cells.³⁹ Even second-hand smoke exposure has been found to decrease eNO in multiple studies, including a single-blinded, placebo-controlled cross-over study of environmental tobacco smoke exposure.^{40,41}

We found that smoking marijuana in the past 0 to 4 days and in the past 5 to 30 days were both associated with lower eNO. The effect size was twice as great (−14% vs −7%) for very recent marijuana use (0-4 days) compared with recent use (5-30 days). This, combined with our finding that past marijuana use (> 30 days) was not associated with eNO, suggests that the effect of marijuana on eNO is acute, on the order of hours to days. While mechanistic studies on marijuana and eNO are generally lacking, there is one study in the pharmacological literature, which found that NOS inhibitors and cannabinoid agonists interact acutely, which would support the notion that cannabis could acutely affect nitric oxide production.⁴²

A few studies have examined the association between marijuana use and pulmonary function test results, with apparently conflicting results.^{26,27,43-45} Results from the CARDIA (Coronary Artery Risk Development in Young Adults) study demonstrated that lifetime marijuana use was associated with higher FEV₁ and FVC at low levels of exposure (up to 7 joint-years), which is likely representative of the use pattern of the majority of marijuana smokers. The CARDIA study also found that current marijuana use was associated with a higher FVC,

while increasing levels of lifetime marijuana exposure were associated with a leveling of or even a reversal of this association, for FEV₁, while FVC remained greater than the baseline values at high lifetime marijuana exposure. Some studies have associated short-term marijuana exposure with a reduced FEV₁/FVC ratio,^{24,25,28,46,47} indicative of airways obstruction, while others have found no association.^{26,43,48} The lower ratio found in marijuana users may be attributed to higher FVC, rather than to a true obstructive pattern.^{24,25,28} The majority of the studies that evaluated FEV₁ had null findings in association with marijuana use.^{24-26,49,50} In the present study, we found a higher FVC in association with recent marijuana use and a lower FEV₁/FVC ratio. While the lower ratio could suggest an obstructive effect on the small airways, this finding appears to be a consequence of the higher average FVC among marijuana smokers.

The association between recent marijuana use and higher FVC is perplexing, but is consistent with results of multiple previous studies.^{25-28,30,44,45,47} This finding could be due to reverse causation, ie, that people with underlying lung disease, who have on average a lower FVC, may be less likely to smoke marijuana. There is evidence that intense respiratory muscle training programs can increase FVC and total lung capacity in healthy individuals,⁵¹⁻⁵⁴ and it is plausible that FVC is higher among marijuana users because of a respiratory muscle training effect. The effect sizes from these intense training programs are small and similar to the magnitude of the difference between current and never smokers of marijuana in our study. Other authors have suggested that the inhalation method used by marijuana

TABLE 3] Adjusted Mean/Percent Differences in Exhaled Nitric Oxide and Pulmonary Function Test Results According to Marijuana Use Among Participants in the National Health and Nutrition Examination Survey, 2007 to 2012

Frequency of Cannabis Use	eNO (ppb)	FEV ₁ (mL)	FVC (mL)	FEV ₁ /FVC	FEF _{25%-75%} (L/s)
Multivariable adjusted^a					
Never	...	...	...	...	...
Past use	−1.5% (−5% to −3%) (<i>P</i> = .55)	42 (10-74) (<i>P</i> = .01)	75 (38-112) (<i>P</i> < .001)	−0.003 (−0.01 to 0.002) (<i>P</i> = .24)	19 (−56 to 95) (<i>P</i> = .61)
Current use (5-30 d)	−7% (−12% to −2%) (<i>P</i> = .03)	49 (−22 to 120) (<i>P</i> = .17)	159 (80-237) (<i>P</i> < .001)	−0.01 (−0.03 to −0.01) (<i>P</i> = .03)	−197 (−274 to 80) (<i>P</i> = .27)
Current use (0-4 d)	−13% (−18% to −8%) (<i>P</i> < .001)	89 (29-150) (<i>P</i> = .005)	204 (139-270) (<i>P</i> < .001)	−0.02 (−0.03 to −0.01) (<i>P</i> = .003)	−57 (−189 to 73) (<i>P</i> = .40)
Multivariable adjusted in never smokers					
Never	...	...	...	...	...
Past use	−3% (−7% to 1%) (<i>P</i> = .12)	31 (−9 to 72) (<i>P</i> = .12)	74 (38-112) (<i>P</i> < .001)	−0.003 (−0.008 to 0.002) (<i>P</i> = .21)	−6 (−85 to 73) (<i>P</i> = .88)
Current use (5-30 d)	−7% (−16% to 2%) (<i>P</i> = .13)	−35 (−188 to 118) (<i>P</i> = .65)	108 (9-207) (<i>P</i> = .03)	−0.02 (−0.04 to −0.001) (<i>P</i> = .04)	−176 (−447 to 93) (<i>P</i> = .19)
Current use (0-4 d)	−14% (−22% to −6%) (<i>P</i> = .002)	96 (−8 to 200) (<i>P</i> = .07)	214 (105-323) (<i>P</i> < .001)	−0.02 (−0.03 to −0.01) (<i>P</i> = .002)	−75 (−221 to 71) (<i>P</i> = .30)

See Table 2 legend for expansion of abbreviations.

^aAge, sex, race/ethnicity, height, education level, income, marital status, asthma, tobacco use in pack-years, smoking category, and BMI.

smokers could cause lung stretching, and eventually larger volumes.^{24,26,29}

The strengths of this study are the large representative sample of the US population and the adjustment for potential confounders, including demographic characteristics and lifestyle and health factors that were not consistently addressed in previous studies. Our results are based on cross-sectional data, and the presence of an association is not proof of causation. We have classified marijuana use according to the timing of reported last use of marijuana at the time of eNO measurement to partially address this limitation. Marijuana use is self-reported in our data, and this can lead to bias; however, given that underreporting of drug use is more probable than overreporting, any bias in our estimates would likely be toward the null. The questions answered were about any form of marijuana use without distinguishing one use over another (eg, ingestion vs inhalation). If the effects on eNO are due to combustion products of smoke then our estimates are more likely to be biased toward no association as a

result of exposure misclassification. Moreover, our findings do not allow for the determination of dose-response relationships between active ingredients of marijuana smoke and eNO or lung function, as the proportions of tetrahydrocannabinol and cannabidiol in marijuana cigarettes smoked for recreational use or by any mode of administration for medical purposes can be very different.

Conclusions

In the present study, we found an association between current marijuana use and lower levels of eNO, and higher FVC. The use of marijuana is increasing for medical purposes, based on evidence of its clinical benefits. Given that nitric oxide plays a role in inflammatory and immune defense pathways in the respiratory system and is a mediator of vasodilation in the pulmonary and systemic vasculature, it would be useful to further explore the associations between marijuana use and vascular and pulmonary function in randomized trials.

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Author contributions: The original idea for this study was proposed by M. A. M. All four authors worked on developing the protocol. S. I. P. and H. B. conducted the analyses with the help of M. A. M. and M. B. R. All authors interpreted the results; S. I. P. wrote the article and all other authors further edited it. All authors approved the final version.

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