Marijuana Use and Estimated Glomerular Filtration Rate in Young Adults

Julie H. Ishida,† Reto Auer,‡§ Eric Vittinghoff,‖ Mark J. Pletcher,*‖ Jared P. Reis,¶ Stephen Sidney,** Kirsten L. Johansen,*†‖ Kirsten Bibbins-Domingo,*‖ Carmen A. Peralta,*†† and Michael G. Shlipak*††*

Abstract

Background and objectives Marijuana use has become more widely accepted in the United States and has been legalized in many areas. Although it is biologically plausible that marijuana could affect kidney function, epidemiologic data are lacking.

Design, setting, participants, & measurements We conducted a cohort study among young adults with preserved eGFR (*i.e.*, eGFR≥60 ml/min per 1.73 m^2) using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study. At scheduled examinations occurring every 5 years and starting at study year 10 (calendar years, 1995–1996), cystatin C was collected over a 10-year period, and urine albumin-to-creatinine ratio was collected over a 15-year period. We investigated the cross-sectional association between current and cumulative marijuana use (in marijuana-years; one marijuana-year equals 365 days of marijuana use) and eGFR by cystatin C ($eGFR_{cys}$) at year 10. In longitudinal analyses, we investigated the association between cumulative marijuana use and $eGFR_{cys}$ change and rapid (≥3%/year) $eGFR_{cys}$ decline over two 5-year intervals and prevalent albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g) over a 15-year period.

Results Past or current marijuana use was reported by 83% (3131 of 3765) of the cohort, and the mean $eGFR_{cys}$ was 111 ml/min per 1.73 m^2 at year 10. Over the following 10 years, 504 had rapid $eGFR_{cys}$ decline, and over the following 15 years, 426 had prevalent albuminuria. Compared with no use, daily current use and ≥5 marijuana-years of cumulative use were associated with lower $eGFR_{cys}$ at year 10: −4.5% (95% confidence interval, −8.1 to −0.7%; P=0.02) and −3.0% (95% confidence interval, −5.6 to −0.4%; P=0.03), respectively. Marijuana use was not significantly associated with $eGFR_{cys}$ change, rapid $eGFR_{cys}$ decline, or prevalent albuminuria.

Conclusions Although we identified a modest cross-sectional association between higher marijuana exposure and lower $eGFR_{cys}$ among young adults with preserved eGFR, our findings were largely null and did not demonstrate a longitudinal association between marijuana use and $eGFR_{cys}$ change, rapid $eGFR_{cys}$ decline, or prevalent albuminuria.

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Departments of *Medicine and ‖Epidemiology and Biostatistics, University of California, San Francisco, California; †Division of Nephrology, San Francisco Veterans Affairs Medical Center, San Francisco, California; ‡Institute of Primary Health Care, University of Bern, Bern, Switzerland; §Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland; ¶Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland; **Division of Research, Kaiser Permanente, Oakland, California; and ††Kidney Health Research Collaborative, San Francisco Veterans Affairs Medical Center and University of California, San Francisco, California

Correspondence: Dr. Julie H. Ishida, Division of Nephrology, Department of Medicine, University of California, San Francisco and San Francisco Veterans Affairs Medical Center, 4150 Clement Street, Box 111J, San Francisco, CA 94121. Email: julie.ishida@ucsf.edu

Introduction

In the United States, legalization of marijuana for medical and recreational purposes has become more common, and marijuana use has increased over the last decade according to some reports (1–6). Associations between marijuana use and adverse psychosocial, cognitive, and respiratory outcomes have been demonstrated (7–11), but the effect of marijuana use on kidney disease has been largely unexplored. CKD affects >20 million Americans (12), and the identification of potentially modifiable risk factors for adverse kidney outcomes is of public health importance.

Marijuana is derived from the hemp plant (*Cannabis sativa*) (13), which contains >60 cannabinoid molecules, including Δ^9-tetrahydrocannabinol, which is primarily responsible for its psychoactive properties (14,15). The initial discovery of Δ^9-tetrahydrocannabinol prompted the identification of the endogenous cannabinoid system, consisting of the cannabinoid receptors CB_1 and CB_2 and their endogenous ligands, and its recognition as an important physiologic regulator (14,16). In the kidney, the endogenous cannabinoid system plays a role in regulating kidney hemodynamics and sodium transport (14), and animal models suggest that CB_1 activity may contribute to the pathogenesis of diabetic and obesity-related nephropathy and kidney fibrosis (17–21), whereas CB_2 activity may be reno-protective (22–24).

Although it is biologically plausible that marijuana may play a role in the pathogenesis of kidney disease, data in humans are limited to case reports of AKI in the setting of synthetic cannabinoid use (25–27) and single-center studies of small sample size and relatively short duration (28–30). The Coronary Artery Risk Development in Young Adults (CARDIA) study provides an opportunity to investigate whether marijuana use has implications for kidney disease in a large cohort of young adults with preserved eGFR and

marijuana exposure documented over the course of 25 years. Our primary aim was to investigate the association between marijuana exposure and eGFR. We hypothesized that marijuana exposure would be associated with lower eGFR.

Materials and Methods

Study Design and Population

We conducted a cohort study using data from the CARDIA study, which was designed to investigate the development and determinants of cardiovascular disease in young adults (31). Briefly, 5115 healthy black and white women and men aged 18–30 years were enrolled between 1985 and 1986 from four centers in the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Follow-up examinations were completed at study years 2, 5, 7, 10, 15, 20, and 25. Marijuana measures were collected at each study visit; cystatin C was collected at years 10, 15, and 20; and urine albumin-to-creatinine ratio was collected at years 10, 15, 20, and 25. All participants provided written informed consent, and the institutional review boards at each center approved the study protocol.

Our study cohort consisted of 3765 persons with a cystatin C measurement at year 10 and preserved eGFR (*i.e.*, eGFR≥60 ml/min per 1.73 m^2 on the basis of the available serum creatinine at year 0). We restricted the cohort to persons with preserved eGFR in order to have a homogeneous and generalizable study population. In a cross-sectional analysis, we investigated the association between marijuana use and eGFR by cystatin C ($eGFR_{cys}$) at year 10. In longitudinal analyses, we investigated the association between marijuana use and change in $eGFR_{cys}$ and rapid (≥3%/year) $eGFR_{cys}$ decline over two 5-year intervals (*i.e.*, years 10–15 and 15–20) among persons with cystatin C measures at two consecutive study visits (n=3118). In a longitudinal analysis, we also examined the association between marijuana use and prevalent albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g) over a 15-year period (from years 10 to 25) among persons with a urine albumin-to-creatinine ratio measurement at year 10 (n=3732).

Exposure Measures

Marijuana use was assessed at each study visit (years 0, 2, 5, 7, 10, 15, 20, and 25) with a self-administered questionnaire. Current use was reported as the number of days of marijuana use within the 30 days preceding each study visit, and lifetime use was reported as the number of times marijuana had been used in one's lifetime. Until year 10, the quantity of marijuana used on a typical day (in joints or filled pipe bowls smoked) was assessed.

Using data on lifetime marijuana use reported at year 0, the current frequency of marijuana use, and the quantity of marijuana smoked per day, we calculated cumulative marijuana exposure in marijuana-years (one marijuana-year is equivalent to 365 days of marijuana use) and joint-years (one joint-year is equivalent to 365 joints or filled pipe bowls smoked) at each study visit as previously described (Supplemental Appendix 1) (10,32).

The primary exposures were cumulative and current marijuana use. We considered marijuana-years as the primary means of assessing cumulative exposure because these data were available for the entire duration of follow-up. We also performed an exploratory analysis with cumulative use expressed in joint-years, with use beyond year 10 estimated as detailed in Supplemental Appendix 1, in order to capture associations with quantity of use. As previously defined by our research group (10,32), marijuana use was categorized as follows: cumulative use in marijuana-years (never, >0–<0.5, 0.5–<2, 2–<5, and ≥5), cumulative use in joint-years (never, >0–5, >5–10, and >10), and current use (none, 1–10, 11–29, and 30 days).

Outcome Measures

Using stored sera collected at years 10, 15, and 20 as part of an ancillary study, cystatin C measurements were performed simultaneously at the University of Minnesota by nephelometry with the N Latex cystatin C kit (Dade Behring, now Siemens, Munich, Germany) and calibrated for drift as previously described (33). Kidney function was estimated using the 2012 CKD Epidemiology Collaboration cystatin C equation and expressed as $eGFR_{cys}$ (ml/min per 1.73 m^2) (34). As in prior CARDIA analyses, we estimated kidney function using cystatin C rather than creatinine because cystatin C–based methods have been demonstrated to have superior accuracy among those with preserved kidney function (35,36) and allow for earlier detection of decrements in kidney function (37). Additionally, simultaneous measurements of cystatin C performed in a single laboratory optimized precision and our ability to interpret changes in kidney function. Albumin-to-creatinine ratio was measured from untimed (spot) urine samples collected at years 10, 15, 20, and 25 and expressed in milligrams of albumin per gram of creatinine. Urine albumin was measured using nephelometry, and urine creatinine was assessed using the Jaffé method (38).

Our primary outcomes were: (*1*) log-transformed $eGFR_{cys}$ at year 10; (*2*) annualized changes in $eGFR_{cys}$ between years 10–15 and 15–20, as percentages of the value at the beginning of the interval; and (*3*) rapid $eGFR_{cys}$ decline (≥3%/year) between years 10–15 and 15–20 (n=518 events). Prevalent albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g) at year 10, 15, 20, or 25 (n=640 events) was a secondary outcome. Cystatin C was available in 3765, 3118, and 2995 participants in years 10, 15, and 20, respectively, but was not available at year 25.

Covariates

Age, race, sex, income, employment, education, and substance use were obtained with a self-administered questionnaire. Substance use was expressed in cumulative years of tobacco smoking; heavy and binge alcohol use; and cocaine, amphetamine, and heroin use as previously described (10). At each study visit, three seated systolic and diastolic BPs were obtained with a sphygmomanometer in years 0–15 and automated oscillometric BP monitor in years 20 and 25, and the mean of the second and third readings was calculated. Diabetes was defined as a fasting blood glucose ≥126 mg/dl or use of insulin and/or oral hypoglycemic medications. Hyperlipidemia was defined as an LDL cholesterol >130 mg/dl or use of lipid-lowering medications. Body mass index was calculated from weight measured with light clothing and height without shoes (39). Physical activity score was obtained by a

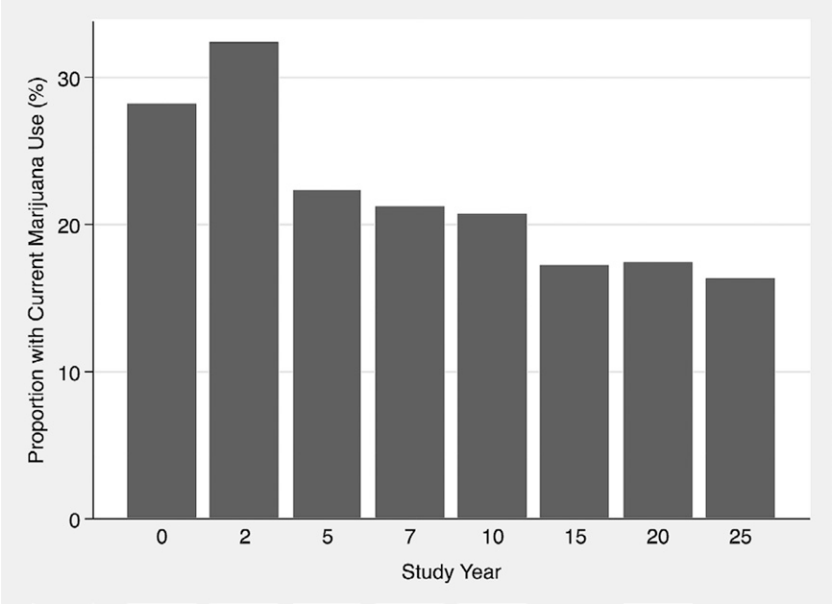

Figure 1. | Proportion of cohort with current marijuana use from CARDIA (Coronary Artery Risk Development in Young Adults) study year 0 (calendar years, 1985–1986) through study year 25 (calendar years, 2010–2011). The proportion of current marijuana use was highest at years 0 and 2 but remained greater than 15% throughout the entire follow-up period. Study year 10 (calendar years, 1995–1996) was used as the baseline timepoint for this study. The mean age of the cohort at study year 0 was 35 years (range, 26–45 years).

validated interviewer-administered questionnaire and log-transformed (10,39).

Statistical Analyses

We compared baseline characteristics at year 10 by category of marijuana use using chi-squared and Kruskal–Wallis testing as appropriate. At year 10, we used linear regression to estimate the associations of cumulative and current marijuana use, modeled as separate exposures, with log-transformed $eGFR_{cys}$. The back-transformed estimates for each category of marijuana use can be interpreted as the percent difference in $eGFR_{cys}$ compared with the referent category. We chose year 10 as the baseline timepoint because this was the first visit at which cystatin C was available.

Models for the longitudinal outcomes focused only on cumulative marijuana use because this was thought to be the relevant exposure for outcomes that may reflect cumulative toxicity rather than acute effects. We used linear mixed models to estimate the association of cumulative marijuana use, treated as a time-dependent exposure, with repeated annualized changes in $eGFR_{cys}$ over the year 10–15 and 15–20 intervals, as percentages of the year 10 and 15 values, respectively. We modeled $eGFR_{cys}$ changes in 5-year intervals in order to account for nonlinearity in rates of decline. Within-participant correlation was modeled using an unstructured correlation matrix for the residuals. We then used generalized estimating equation Poisson models with robust SEMs to evaluate the association between cumulative marijuana use, treated as a time-dependent exposure, and the following repeated binary outcomes: (*1*) rapid decline in $eGFR_{cys}$ in the year 10–15 and 15–20 intervals and (*2*) prevalent albuminuria at year 10, 15, 20, or 25. In the model for prevalent albuminuria, participants contributed to the analysis at all years in which they experienced the outcome.

For each outcome, we performed an unadjusted and multivariable-adjusted analysis controlling for age, race, sex, study site, income, education, employment, systolic and diastolic BP, diabetes, hyperlipidemia, body mass index, physical activity, and cumulative years of tobacco smoking, heavy and binge alcohol use, and cocaine, amphetamine, and heroin use. Adjustment variables were evaluated at year 10 in the analysis for $eGFR_{cys}$ and treated as time-varying (if subject to change) in the analyses for the longitudinal outcomes. We performed tests for trend across categories of marijuana use and tested for interaction by race, sex, and tobacco smoking status categorized as never, former, or current. In order to account for the possibility of informative censoring due to loss to follow-up, we performed sensitivity analyses with inverse probability of censoring weighting. The tests for statistical significance were two-tailed, and $P<0.05$ was considered significant. Analyses were performed with STATA version 14 (StataCorp LP, College Station, TX).

Results

At year 10, the majority of the study cohort (3131 out of 3765 [83%]) reported past or current marijuana use; the mean age was 35 years, and the mean $eGFR_{cys}$ was 111 ml/min per 1.73 m^2. The proportion of current marijuana use was highest at years 0 and 2 but remained persistently >15% throughout the entire follow-up period (Figure 1). Characteristics associated with cumulative marijuana use included age, sex, race, study site, income, employment, education, BP, body mass index, and physical activity (Table 1). Current marijuana use and use of other substances were also higher among those with higher cumulative marijuana use.

Table 1. Characteristics of 3765 participants by cumulative marijuana use category at Coronary Artery Risk Development in Young Adults Study year 10 (calendar years, 1995–1996)

Characteristic	Cumulative Marijuana Use at Yr 10 (Marijuana-Yr)				
	Never Used (*n*=634)	>0–<0.5 (*n*=1744)	0.5–<2 (*n*=930)	2–<5 (*n*=330)	≥5 (*n*=127)
Mean age (SD), yr	34 (4)	35 (4)	35 (3)	35 (4)	35 (3)
Race and sex, *n* (%)					
Black women	237 (37)	560 (32)	165 (18)	74 (22)	15 (12)
Black men	113 (18)	253 (15)	251 (27)	120 (36)	34 (27)
White women	153 (24)	572 (33)	241 (26)	41 (12)	16 (13)
White men	131 (21)	359 (21)	273 (29)	95 (29)	62 (49)
Study site, *n* (%)					
Birmingham, AL	271 (43)	402 (23)	144 (15)	55 (17)	21 (17)
Chicago, IL	157 (25)	379 (22)	213 (23)	52 (16)	17 (13)
Minneapolis, MN	129 (20)	428 (25)	310 (33)	125 (38)	42 (33)
Oakland, CA	77 (12)	535 (31)	263 (28)	98 (30)	47 (37)
Annual income, *n* (%)					
<$25,000	132 (21)	294 (17)	212 (23)	114 (35)	31 (24)
$25,000–<$50,000	248 (39)	596 (34)	333 (36)	114 (35)	49 (39)
≥$50,000	254 (40)	850 (49)	385 (41)	102 (31)	47 (37)
Employment, *n* (%)					
Working	536 (86)	1474 (86)	781 (85)	266 (82)	108 (87)
Unemployed	61 (10)	148 (9)	110 (12)	52 (16)	14 (11)
Homemaker	29 (4)	89 (5)	28 (3)	7 (2)	2 (2)
Highest level of education, *n* (%)					
Less than high school	21 (3)	53 (3)	67 (7)	27 (8)	11 (9)
High school completed	124 (20)	279 (16)	224 (24)	108 (33)	36 (28)
College or more	489 (77)	1408 (81)	639 (69)	195 (59)	80 (63)
Mean systolic BP (SD), mmHg	110 (12)	109 (13)	111 (13)	113 (13)	113 (11)
Mean diastolic BP (SD), mmHg	73 (10)	72 (10)	72 (11)	74 (10)	72 (10)
Diabetes, *n* (%)	50 (8)	119 (7)	55 (6)	17 (5)	5 (4)
Hyperlipidemia, *n* (%)	151 (24)	390 (22)	222 (24)	67 (20)	34 (27)
Mean body mass index (SD), kg/m^2	28.4 (6.7)	27.4 (6.9)	27.2 (5.8)	27.9 (6.6)	26.4 (4.4)
Mean physical activity score (SD)	239 (229)	280 (245)	310 (259)	335 (282)	342 (272)
Current marijuana use, days per month, *n* (%)					
None	634 (100)	1703 (98)	748 (80)	119 (36)	17 (13)
1–10 d	0 (0)	41 (2)	179 (19)	144 (44)	24 (19)
11–29 d	0 (0)	0 (0)	3 (0.3)	55 (17)	51 (40)
30 d (daily)	0 (0)	0 (0)	0 (0)	12 (4)	35 (28)
Tobacco smoking, *n* (%)					
Never	550 (87)	1055 (60)	264 (28)	86 (26)	32 (25)
Former	45 (7)	361 (21)	285 (31)	87 (26)	32 (25)
Current	39 (6)	328 (19)	381 (41)	157 (48)	63 (50)
Cumulative yr of tobacco use until yr 10 among ever tobacco smokers, mean (SD)	1.4 (4.5)	4.5 (7.3)	9.2 (8.4)	9.9 (8.8)	10.2 (8.7)
Cumulative yr of heavy and binge drinking until yr 10 among ever drinkers, mean (SD)	3.2 (4.3)	4.0 (4.8)	6.2 (5.3)	7.5 (5.8)	9.4 (5.9)
Cumulative yr of cocaine, amphetamine, and heroin use until yr 10 among ever users, mean (SD)	0.1 (0.2)	0.2 (0.4)	0.4 (0.7)	0.7 (1.0)	0.7 (0.9)

We did not observe a dose-response relationship between cumulative marijuana use and $eGFR_{cys}$ at year 10. However, there was an association with lower $eGFR_{cys}$ at year 10 among those with at least 5 marijuana-years of use (Table 2). There was a statistically significant interaction with race (*P* value for interaction=0.03) (Table 2), but the findings appeared similar for men and women (*P* value for interaction=0.56). There was a statistically significant interaction by tobacco smoking status ($P<0.001$). Among those with at least 5 marijuana-years of use, the point estimates for the marijuana associations with $eGFR_{cys}$ were in the direction of harm in multivariable-adjusted models for never (percent difference $eGFR_{cys}$, −1.4%; 95% CI, −5.9 to 3.4%; $P=0.56$) and former (percent difference $eGFR_{cys}$, −6.4%; 95% CI, −11.8 to −0.7%; $P=0.03$), but not current (percent difference $eGFR_{cys}$, 6.7%; 95% CI, 1.2 to 12.6%; $P=0.02$), tobacco smokers. Higher levels of current marijuana use were associated with lower $eGFR_{cys}$ at year 10 in multivariable-adjusted models, and the interaction with race was statistically significant (*P* value for interaction=0.04) (Supplemental Table 1). Findings appeared similar for men and women (*P* value for interaction=0.82).

Table 2. Percent difference in $eGFR_{cys}$ at Coronary Artery Risk Development in Young Adults Study year 10 (calendar years, 1995–1996) among participants with cumulative marijuana use (in marijuana-years) compared with never-users

Cumulative Marijuana Use at Yr 10 (Marijuana-Yr)	Participants (*n*)	$eGFR_{cys}$, mean (SD)	Unadjusted		Multivariable-Adjusted	
			% Difference $eGFR_{cys}$ (95% CI)	*P* Value[a]	% Difference $eGFR_{cys}$ (95% CI)	*P* Value[a]
Overall cohort						
Never used	634	111 (13)	Referent		Referent	
>0–<0.5	1744	111 (13)	0.0 (−1.2 to 1.3)	0.97	0.2 (−1.1 to 1.4)	0.79
0.5–<2	930	111 (13)	−0.2 (−1.6 to 1.2)	0.74	1.0 (−0.5 to 2.5)	0.18
2–<5	330	110 (14)	−0.8 (−2.6 to 1.1)	0.42	0.3 (−1.6 to 2.2)	0.77
≥5	127	108 (15)	−3.2 (−5.7 to −0.6)	0.02[b]	−3.0 (−5.6 to −0.4)	0.03[b]
P value trend[c]				<0.01[b]		0.04[b]
Race[d]						
White						
Never used	284	110 (12)	Referent		Referent	
>0–<0.5	931	110 (12)	−0.5 (−2.3 to 1.3)	0.56	−0.9 (−2.7 to 0.8)	0.30
0.5–<2	514	109 (12)	−1.3 (−3.2 to 0.7)	0.20	−0.5 (−2.5 to 1.5)	0.61
2–<5	136	108 (13)	−2.5 (−5.2 to 0.3)	0.08	−1.9 (−4.5 to 0.9)	0.19
≥5	78	104 (15)	−6.1 (−9.3 to −2.8)	<0.001[b]	−6.0 (−9.2 to −2.7)	<0.001[b]
P value trend[c]				<0.001[b]		<0.001[b]
Black						
Never used	350	112 (14)	Referent		Referent	
>0–<0.5	813	113 (14)	0.9 (−0.8 to 2.7)	0.30	1.0 (−0.6 to 2.7)	0.22
0.5–<2	416	113 (14)	1.2 (−0.8 to 3.2)	0.25	2.5 (0.5 to 4.6)	0.02[b]
2–<5	194	112 (15)	0.2 (−2.2 to 2.7)	0.85	2.1 (−0.4 to 4.6)	0.10
≥5	49	113 (12)	1.5 (−2.6 to 5.8)	0.48	1.0 (−3.1 to 5.2)	0.64
P value trend[c]				0.60		0.51

Multivariable model adjusted for age, race, sex, study site, income, education, employment, systolic BP, diastolic BP, diabetes, hyperlipidemia, body mass index, physical activity, and cumulative years of tobacco smoking, heavy and binge alcohol use, and cocaine, amphetamine, and heroin use. The results can be interpreted as the percent difference in $eGFR_{cys}$ at year 10 compared with the referent category. For example, in the multivariable-adjusted model, compared with participants who never used marijuana, those with ≥5 marijuana-years of use had a 3.0% lower $eGFR_{cys}$, and this difference was statistically significant (*P*=0.03). $eGFR_{cys}$, eGFR as calculated with the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation (ml/min per 1.73 m^2); 95% CI, 95% confidence interval.

[a]*P* values for percent difference in $eGFR_{cys}$ compared with the referent (never use).

[b]*P* values <0.05.

[c]*P* values for test for trend across categories of marijuana use.

[d]*P* value for test for interaction by race=0.03.

Table 3. Percent difference in $eGFR_{cys}$ change per year during Coronary Artery Risk Development in Young Adults Study years 10–15 (calendar years, 1995–1996 to 2000–2001) and 15–20 (calendar years, 2000–2001 to 2005–2006) among participants with cumulative marijuana use (in marijuana-years) compared with never-users

Cumulative Marijuana Use (Marijuana-Yr)[a]	5-Yr Person-Intervals (*n*)	$eGFR_{cys}$ Change per Yr, Mean (SD)	Unadjusted		Multivariable-Adjusted	
			% Difference $eGFR_{cys}$ (95% CI)	*P* Value[b]	% Difference $eGFR_{cys}$ (95% CI)	*P* Value[b]
Never used	995	−0.7 (4.3)	Referent		Referent	
>0–<0.5	2709	−0.6 (6.8)	−0.1 (−0.4 to 0.1)	0.33	−0.2 (−0.5 to 0.1)	0.16
0.5–<2	1411	−0.8 (2.1)	−0.1 (−0.4 to 0.2)	0.57	−0.2 (−0.5 to 0.1)	0.25
2–<5	462	−0.6 (2.3)	−0.1 (−0.4 to 0.3)	0.79	−0.1 (−0.6 to 0.3)	0.58
≥5	238	−0.9 (2.2)	−0.2 (−0.7 to 0.4)	0.52	−0.1 (−0.7 to 0.5)	0.72
P value trend[c]				0.63		0.82

Multivariable model adjusted for age, race, sex, study site, income, education, employment, systolic BP, diastolic BP, diabetes, hyperlipidemia, body mass index, physical activity, and cumulative years of tobacco smoking, heavy and binge alcohol use, and cocaine, amphetamine, and heroin use. The results can be interpreted as the percent difference in change in $eGFR_{cys}$ per year during years 10–15 and 15–20 compared with the referent category. For example, in the multivariable-adjusted model, compared with participants who never used marijuana, the annualized change in $eGFR_{cys}$ relative to the value at the beginning of each 5-yr interval was smaller by 0.1% per year among those with ≥5 marijuana-years of use, but this difference was not statistically significant (*P*=0.72). CARDIA, Coronary Artery Risk Development in Young Adults; $eGFR_{cys}$, estimated glomerular filtration rate as calculated with the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation (ml/min per 1.73 m^2); 95% CI, 95% confidence interval.

[a]Cumulative marijuana use was evaluated at CARDIA years 10 (calendar years, 1995–1996) and 15 (calendar years, 2000–2001).

[b]*P* values for percent difference in $eGFR_{cys}$ change per year compared with the referent (never use).

[c]*P* values for test for trend across categories of marijuana use.

There were no statistically significant associations of cumulative marijuana use with changes per year in $eGFR_{cys}$ between years 10–15 and 15–20 (Table 3). Among the study cohort, 504 had experienced rapid decline in $eGFR_{cys}$ in at least one interval between visits and 426 had prevalent albuminuria. There were no statistically significant associations between the higher categories of cumulative marijuana use and rapid $eGFR_{cys}$ decline or prevalent albuminuria in multivariable-adjusted models (Table 4).

The results were similar in exploratory analyses evaluating cumulative marijuana use in joint-years. Higher exposure in joint-years was associated with lower $eGFR_{cys}$ at year 10, and the interaction with race was statistically significant (*P* value for interaction <0.01) (Supplemental Table 2). Findings appeared similar for men and women (*P* value for interaction=0.76). There was a statistically significant interaction by tobacco smoking status (*P* value <0.001), and among those with at least 10 joint-years of use, we observed similar results for the analysis stratified by tobacco smoking status as we did for marijuana-years. There were no statistically significant associations between the higher categories of joint-years and change in $eGFR_{cys}$, rapid $eGFR_{cys}$ decline, or prevalent albuminuria in the multivariable-adjusted models (Supplemental Tables 3 and 4). In a sensitivity analysis using inverse probability of censoring weighting, the associations of both marijuana-years and joint-years with log-transformed $eGFR_{cys}$ at year 10 were similar in magnitude to those of the original analyses (Supplemental Tables 5 and 6).

Discussion

In a large cohort of young adults with preserved eGFR followed for up to 15 years, we found that greater marijuana exposure was associated with worse $eGFR_{cys}$ at year 10, but we did not detect an association between marijuana use and subsequent change in $eGFR_{cys}$, rapid $eGFR_{cys}$ decline, or prevalent albuminuria. The magnitude of the association with $eGFR_{cys}$ at year 10 was more pronounced among whites than blacks and among never or former smokers relative to current smokers.

To our knowledge, our study is the first to examine the association between marijuana use and kidney function in the general population. Previous literature is limited to case reports of AKI associated with synthetic cannabinoid use (25–27) and studies of small sample size and relatively shorter duration. In a single-center study investigating the effect of illicit drug use and kidney function among hypertensive men (*n*=647), marijuana users did not have a significantly higher risk of kidney function decline (defined as an increase in serum creatinine of ≥0.6 mg/dl) over a median follow-up of 7 years compared with nonusers (28). In a prospective cohort study designed to assess the safety of marijuana use for chronic noncancer pain, cannabis use for 1 year did not significantly change serum creatinine among 78 users (29). Finally, among kidney transplant recipients (*n*=1225), marijuana use was not associated with death, graft failure, or worse graft function at 1 year post-transplant (30). Differences in study populations and methodology preclude direct comparison of our results with those of previous studies.

The mechanisms underlying marijuana's potential influence on kidney function are uncertain, but it is possible that marijuana use could either acutely lower kidney function or result in cumulative toxicity. The cannabinoid receptor CB_1 is expressed in various regions and cell types within the kidneys of animals and humans; data regarding the expression of CB_2 receptors in the kidney are less

Table 4. Kidney outcomes measured during Coronary Artery Risk Development in Young Adults Study year 10 (calendar years, 1995–1996) through year 20 (calendar years, 2005–2006) or year 25 (calendar years, 2010–2011) among participants with cumulative marijuana use (in marijuana-years) compared with never-users

Cumulative Marijuana Use (Marijuana-Yr)[a]	Events (*n*)	5-Yr Person-Intervals or Visits (*n*)[b]	Urine ACR, median (IQR)	Unadjusted		Multivariable-Adjusted	
				PRR (95% CI)	*P* Value[c]	PRR (95% CI)	*P* Value[c]
Rapid $eGFR_{cys}$ decline[d]							
Never used	95	995		1.00 (Referent)		1.00 (Referent)	
>0–<0.5	233	2709		0.90 (0.72 to 1.13)	0.35	1.02 (0.80 to 1.30)	0.87
0.5–<2	121	1411		0.90 (0.70 to 1.15)	0.40	0.98 (0.73 to 1.30)	0.87
2–<5	39	462		0.90 (0.64 to 1.27)	0.55	0.98 (0.66 to 1.45)	0.92
≥5	30	238		1.18 (0.81 to 1.74)	0.39	1.14 (0.73 to 1.78)	0.56
P value trend[e]					0.42		0.66
Prevalent albuminuria[f]							
Never used	134	1995	4 (3–7)	1.00 (Referent)		1.00 (Referent)	
>0–<0.5	269	5604	4 (3–6)	0.71 (0.54 to 0.93)	0.01[g]	0.80 (0.61 to 1.05)	0.11
0.5–<2	140	2938	4 (3–6)	0.76 (0.57 to 1.02)	0.07	0.73 (0.54 to 1.00)	0.05
2–<5	55	980	4 (3–7)	0.86 (0.59 to 1.25)	0.42	0.80 (0.55 to 1.17)	0.26
≥5	42	740	4 (3–6)	0.82 (0.53 to 1.27)	0.38	0.79 (0.47 to 1.32)	0.37
P value trend[e]					0.68		0.41

Definitions: rapid $eGFR_{cys}$ decline =≥3%/year; albuminuria = ACR≥30 mg/g. Multivariable model adjusted for age, race, sex, study site, income, education, employment, systolic BP, diastolic BP, diabetes, hyperlipidemia, body mass index, physical activity, and cumulative years of tobacco smoking, heavy and binge alcohol use, and cocaine, amphetamine, and heroin use. CARDIA, Coronary Artery Risk Development in Young Adults; ACR, urine albumin-to-creatinine ratio (mg/g); IQR, interquartile range; PRR, prevalence rate ratio; 95% CI, 95% confidence interval; $eGFR_{cys}$, eGFR as calculated with the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation.

[a]Cumulative marijuana use was evaluated at CARDIA years 10 (calendar years, 1995–1996) and 15 (calendar years, 2000–2001) for rapid $eGFR_{cys}$ decline and years 10 (calendar years, 1995–1996), 15 (calendar years, 2000–2001), 20 (calendar years, 2005–2006), and 25 (calendar years, 2010–2011) for prevalent albuminuria.

[b]5-yr person-intervals for rapid $eGFR_{cys}$ decline and visits for prevalent albuminuria.

[c]*P* values for prevalence rate of outcome compared with the referent (never use).

[d]Measured between CARDIA years 10–15 and 15–20.

[e]*P* values for test for trend across categories of marijuana use.

[f]Measured at CARDIA years 10, 15, 20, and 25.

[g]*P* values <0.05.

consistent (14). In normal rat kidneys, the endogenous ligand anandamide, acting *via* CB_1 receptors expressed in afferent and efferent arterioles, decreased eGFR by preferential vasodilation of the efferent arteriole, an effect that was blocked by CB_1 antagonists (40). Animal models suggest that CB_1 activity may be pathogenic, whereas CB_2 activity may be reno-protective. In mouse and rat models of diabetic and obesity-related nephropathy and kidney fibrosis, CB_1 antagonism and CB_2 activation were associated with improved kidney parameters (*e.g.*, reduced albuminuria, proteinuria, and kidney fibrosis, and increased creatinine clearance) (17–23), and CB_2 antagonism was associated with worsened kidney parameters (*e.g.*, increased albuminuria, reduced creatinine clearance) (23,24).

Our study has several limitations. We only observed an association cross-sectionally but not longitudinally, which may reflect greater susceptibility of cross-sectional analyses to confounding due to unmeasured interindividual differences. Although we adjusted for a comprehensive list of variables, it is possible that the associations we observed at year 10 could be explained by confounding, such as by smoking; tobacco use is common among marijuana users (41) and has been associated with worse kidney function in several reports (42–45). Additionally, our cohort consisted of young adults with preserved eGFR, so rapid decline and albuminuria were rare. Thus, our power to detect longitudinal associations was limited, and we cannot exclude benefit or harm for these outcomes.

Marijuana exposure was determined on the basis of self-report, although misclassification should have been mitigated by use of a self-administered questionnaire and is unlikely to be differential according to outcome status. We lacked the information to account for changes in marijuana exposure (*e.g.*, quality, composition) and self-reporting that may have changed over time and may vary by geographic location. Active marijuana use was more common during the earlier years of follow-up before kidney measures were available, so we were unable to evaluate the influence of marijuana when its use was maximal. We are also unable to discern whether current or cumulative use was responsible for the association we observed at year 10, and we cannot distinguish whether this represents a transient or enduring effect. The spectrum of marijuana use may also be biased toward the moderate side because heavy users in the general population may be less likely to participate in the ongoing evaluations required of CARDIA participants. Our results are not generalizable to older adults among whom marijuana use has been increasing (1) and who are at higher risk for adverse kidney outcomes (46). Finally, we were unable to determine whether the larger associations of marijuana with lower $eGFR_{cys}$ among whites than blacks reflect a true biologic difference or a chance finding. However, investigation of whether marijuana has different associations with $eGFR_{cys}$ across racial groups merits further study.

Strengths of our study are the large sample size, long duration of follow-up, and repeated assessments of marijuana use and kidney outcomes. We have reason to be confident in the quality of our exposure measures given that previous CARDIA papers have demonstrated robust associations with other health outcomes (10,32) using the same methods of assessing marijuana use.

Because marijuana use is becoming increasingly accepted in the United States (1), there is a critical need for epidemiologic data to assess the risk-to-benefit ratio of a substance that may be poised for more widespread use. Although our findings were largely negative, we observed that higher marijuana use was associated with modestly lower $eGFR_{cys}$ among adults with preserved eGFR. This result may not translate into a clinically meaningful difference and may be insufficient to inform decision-making concerning marijuana use. However, it is possible that the association could be stronger among patients with established kidney disease, and additional research to define the effect of marijuana use on kidney outcomes in other study populations is warranted.

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Disclosures

None.

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