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Coffee and Caffeine Are Associated With Decreased Risk of Advanced Hepatic Fibrosis Among Patients With Hepatitis C

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BACKGROUND & AIMS: **Coffee or caffeine has been proposed to protect against hepatic fibrosis, but few data are available on their effects in patients with chronic hepatitis C virus (HCV) infection.**

METHODS: **We conducted a cross-sectional study of veterans with chronic HCV infection to evaluate the association between daily intake of caffeinated and decaffeinated coffee, tea, and soda, and level of hepatic fibrosis, based on the FibroSURE test (BioPredictive, Paris, France) (F0–F3, mild [controls] vs F3/F4–F4, advanced). Models were adjusted for multiple potential confounders including age, alcohol abuse, and obesity.**

RESULTS: **Among 910 patients with chronic HCV infection, 98% were male and 38% had advanced hepatic fibrosis. Daily intake of caffeinated coffee was higher among controls than patients with advanced fibrosis (1.37 vs 1.05 cups/d; $P = .038$). In contrast, daily intake of caffeinated tea (0.61 vs 0.56 cups/d; $P = .651$) or soda (1.14 vs 0.95 cans/d; $P = .106$) did not differ between the groups. A higher percentage of controls (66.0%) than patients with advanced fibrosis (57.9%) consumed 100 mg or more of caffeine daily from all sources ($P = .014$); controls also received a larger proportion of their caffeine from coffee (50.2% vs 43.0%; $P = .035$). Hepatoprotective effects of an average daily intake of 100 mg or more of caffeine (adjusted odds ratio, 0.71; 95% confidence interval, 0.53–0.95; $P = .020$) and 1 cup or more of caffeinated tea by non–coffee drinkers (adjusted odds ratio, 0.56; 95% confidence interval, 0.34–0.94; $P = .028$) persisted after adjustment for confounders, including insulin resistance.**

CONCLUSIONS: **A modest daily caffeine intake (as little as 100 mg) may protect against advanced hepatic fibrosis in men with chronic HCV infection. Additional research is needed to confirm these findings in women and in people with other chronic liver diseases.**

Keywords: Epidemiology; Viruses; Digestive System; Endocrinology.

Podcast interview: www.gastro.org/cghpodcast. Also available on iTunes.

Coffee is one of the most popular beverages worldwide, and there is growing evidence that it may provide helpful health benefits in a variety of conditions. Recently, a large, prospective study of more than 50,000 participants reported an inverse, dose-dependent association between coffee drinking and overall mortality.[1] Other studies have suggested that coffee drinkers are at decreased risk of developing heart disease[2] and metabolic syndrome[3] compared with non–coffee drinkers.

For the past 2 decades, studies have supported that coffee may be protective against the development of liver injury, as manifested by abnormal liver function tests and/or cirrhosis from a variety of hepatic parenchymal disorders.[4–11] Several studies including meta-analyses of case–control and cohort studies reported an inverse association between coffee consumption and hepatocellular carcinoma (HCC) in both the presence and absence of chronic hepatitis C virus (HCV) infection.[12–15]

Coffee has several ingredients that could account for its reported health benefits. Previous studies have suggested that caffeine may account for the hepatoprotective effects of coffee in HCV-related chronic

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; HALT-C, Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOMA-IR, homeostasis model assessment–estimated insulin resistance; IDU, injection drug use; MEDVAMC, Michael E. DeBakey Veterans Affairs Medical Center; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

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liver disease.[11,16,17] Other studies have shown that insulin resistance worsens hepatic inflammation in HCV patients,[18] and that the protective effect of coffee, at least in part, may be a consequence of coffee intake–associated reduction in insulin resistance and type 2 diabetes mellitus.[19] Few studies have examined the effect of coffee, as well as caffeine intake from noncoffee beverages, on the severity of liver fibrosis in patients with untreated chronic HCV infection after adjustment for insulin resistance and diabetes status.[16,17]

By using data from a large cross-sectional study among US veterans with chronic HCV infection, we investigated the association between caffeinated and decaffeinated coffee, tea, and soda on the development of HCV-related advanced liver fibrosis. We also examined the extent to which insulin resistance mediated the association between caffeine intake and the severity of liver fibrosis.

Methods

Study Population and Design

We performed a cross-sectional study at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, Texas. Study participants were chronically HCV-infected veterans, prospectively recruited from a dedicated HCV clinic at the MEDVAMC between January 5, 2009, and November 30, 2013.

Details about study design have been described previously.[20,21] Veterans ages 18 to 70 years with confirmed HCV viremia and who were not receiving antiviral therapy at the time of recruitment were eligible for inclusion. Exclusion criteria included the following: (1) hepatitis B virus (serum hepatitis B surface antigen positivity) or human immunodeficiency virus co-infection; (2) self-reported or medical record–reported history of liver transplant, decompensated liver disease, or HCC; and (3) a diagnosis of dementia or psychosis that would preclude providing consent. The study was approved by the Institutional Review Boards of the MEDVAMC and Baylor College of Medicine.

Data Collection and Study Measures

All study participants completed a detailed computerized questionnaire administered by a research assistant, had fasting venipuncture for performance of clinical laboratory tests, and had anthropometric measurements taken. The questionnaire surveyed lifetime history of alcohol, tobacco, injection drug use (IDU), marijuana use, other recreational drug use, and the presence of comorbid conditions, including diabetes mellitus. Alcohol use was classified as never, current, former, and cumulative years of use, with chronic alcohol abuse defined as 10 or more years of drinking an average of 3 or more drinks per day for men and 2 or more drinks per day for women. Participants who smoked fewer than 100 cigarettes over their entire life were classified as nonsmokers. Participants who self-reported IDU or marijuana use in the study questionnaire were classified as users. All participants with missing information on marijuana use responded to a question about recreational drug use. For those participants who self-reported "yes" to recreational drug use, their VA electronic medical record was searched for the following: *International Classification of Diseases, 9th revision*, codes for cannabis or marijuana abuse; or documented former or current marijuana use in the progress notes by using the search terms "marijuana" or "cannabis." We assessed participant levels of physical activity using the validated International Physical Activity Questionnaire.[22] We classified participants as diabetic if they self-reported ever having received a physician's diagnosis of type 2 diabetes mellitus, were excluded from fasting testing as a result of medical record documentation of a diagnosis of diabetes mellitus type 2, had a fasting blood sugar level higher than 126 mg/dL, or a nonfasting blood sugar level higher than 200 mg/dL based on serologic testing performed at enrollment. In nondiabetic patients, we calculated a homeostasis model assessment–estimated insulin resistance (HOMA-IR) score. A HOMA-IR score of 3 or higher was used as a surrogate marker of insulin resistance in nondiabetic participants. The definition of metabolic syndrome was adopted from the National Cholesterol Education Panel-Third Adult Treatment Panel as the presence of 3 or more of the following: (1) waist circumference greater than 40 inches in men or greater than 35 inches in women; (2) increased serum triglyceride level of 150 mg/dL or higher; (3) reduced high-density lipoprotein–cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women; (4) use of antihypertensive medications; and (5) increased fasting serum glucose level of 110 mg/dL or higher and/or use of insulin or hypoglycemic medication.[23] Information regarding prior antiviral treatments was collected. All participants also had their serologically determined Model for End-Stage Liver Disease (MELD) and body mass index (BMI) scores calculated.

Information on intake of caffeinated and decaffeinated coffee, tea, and carbonated soda, including use of creamers and sweeteners, also was collected. We calculated the average daily intake of coffee, tea, and soda using standard measures of consumption (eg, 8 oz cups for coffee and tea and 12 oz cans for sodas) in the year preceding study recruitment. Cumulative lifetime exposure to coffee also was gathered by asking about daily intake in each decade of life starting in the 20s. Total caffeine intake was calculated from the sum of reported daily intake from all sources, and further stratified as caffeine from coffee and noncoffee sources. Average caffeine content was estimated as follows: 137 mg for each 8-oz cup of coffee,[24] 30 mg for

each 8-oz cup of tea,[25] 46 mg for each 12-oz can of caffeinated soda,[24] and 0 mg for each cup or can of a decaffeinated beverage.

We determined the degree of hepatic fibrosis and inflammation using the FibroSURE test (BioPredictive, Paris, France). The FibroSURE test estimates the level of hepatic fibrosis and inflammation by using a proprietary algorithm incorporating serum levels of α2-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, γ-glutamyl-transpeptidase, and alanine aminotransferase; this test has been validated in HCV patients.[26–32] FibroSURE test scores are categorized into METAVIR biopsy-based equivalent degrees of hepatic fibrosis with ranges from F0 (no fibrosis) to F4 (cirrhosis), and hepatic inflammation with ranges from A0 (no inflammatory activity) to A3 (severe inflammatory activity). We classified all study participants by FibroSURE results as either advanced fibrosis cases (F3/F4–F3) or mild/absent fibrosis controls (F0–F3), and as advanced inflammatory activity cases (A2/A3–A3) or mild/no inflammatory activity controls (A0–A2).

Statistical Analyses

The main exposure variables were intake of caffeinated and decaffeinated coffee (cups per day, any use, $\geq$1, 2, or 3 cups daily), tea and sodas (cups or cans per day, any use, $\geq$1 cup or can daily), and estimated amount of caffeine ($\geq$100 mg or 200 mg/d) overall and from each beverage. The main outcome variable was advanced hepatic fibrosis (F3/F4–F4) as determined by FibroSURE test scoring. We compared exposure variables between cases and controls using *t* tests and analysis of variance for means and the chi-square and Fisher exact test for categoric variables.

We constructed unconditional logistic-regression models to examine the individual associations between coffee, tea, soda, and caffeine intake and risk of advanced hepatic fibrosis. The first multivariable model adjusted for the following potential confounders: age, chronic alcohol use, and BMI category. Because it is possible that patients with more severe liver disease would avoid drinking coffee, in the second model we further adjusted for MELD scores. In the third model, we also examined the degree of insulin resistance status categorized as diagnosed diabetic, insulin resistant (HOMA-IR $\geq$3 in nondiabetic participants), and non–insulin resistant (HOMA-IR $<$3 in nondiabetic participants) as a possible mediating variable. In the fourth model, we adjusted for the presence of the metabolic syndrome. We calculated odds ratios (ORs) and associated 95% confidence intervals (95% CIs) for each model.

All tests were 2-sided, with statistical significance determined at an α value of .05. Statistical analyses were conducted using IBM SPSS version 21 (SPSS Inc, Chicago, IL).

Results

Study Population

A total of 910 veterans with chronic HCV infection met our inclusion criteria. Based on FibroSURE scoring, 342 of those patients (37.6%) had advanced fibrosis (F3/F4–F4), and 568 (62.4%) had mild fibrosis (controls: F0–F3) (Table 1). Most participants were male (97.6%), African American (54.2%), and chronic alcohol users (54.2%), with no significant differences between cases and controls. Compared with mild fibrosis controls, advanced fibrosis cases were significantly older (average, 1.8 y), had higher BMIs, and were more likely to have type 2 diabetes mellitus and metabolic syndrome. Among nondiabetic participants, advanced fibrosis cases were more likely than controls to be insulin-resistant based on a baseline fasting HOMA-IR score of 3 or higher. Cases also were more likely to have higher MELD scores ($>$9) and to have received prior HCV antiviral therapy than controls; however, all patients had detectable HCV RNA levels at the time of the study and none were actively receiving treatment. Marijuana use, IDU, level of physical activity, and smoking history were not significantly different between the 2 groups (Table 1).

Relationship Between Coffee, Tea, and Soda Consumption and Hepatic Fibrosis in the Year Preceding Study Enrollment

Coffee. Most participants (54.6%) reported drinking some caffeinated coffee within the year preceding study enrollment, with 47.2% drinking on average 1 or more cups per day (Table 2). In contrast, few participants ($<$8%) reported decaffeinated coffee use, with less than 5% reporting an average intake of 1 or more cups per day. Mild fibrosis controls had a higher average daily intake of caffeinated coffee compared with advanced fibrosis cases (mean, 1.37 vs 1.05 cups/d; $P = .038$), and were more likely to drink an average of 1 or more cups of caffeinated coffee daily (49.8% vs 43.0%; $P = .045$). However, although the proportions of patients consuming 2 or more or 3 or more cups of caffeinated coffee a day were higher in mild fibrosis controls than advanced fibrosis cases, these differences were not statistically different. Decaffeinated coffee intake was not different between the groups (Table 2).

Tea. Approximately 70% of participants reported drinking caffeinated tea (hot or iced) within the prior year, with 22.7% consuming on average 1 or more cups per day (Table 2). Overall, caffeinated and decaffeinated tea intake was not notably different between advanced fibrosis cases and mild fibrosis controls. However, among the subset of non–coffee drinkers (n = 413), caffeinated tea use was more common among controls (26.2% vs 17.0%; $P = .030$) (Table 2).

Table 1. Demographic Characteristics of Advanced Fibrosis HCV Cases Compared With Mild Fibrosis HCV Controls

	Controls (F0–F3) N = 568 (%)	Cases (F3/F4–F4) N = 342 (%)	*P* value
Mean age, *y* (SD)	55.89 (5.60)	57.74 (4.83)	<.001
Sex			
Male	551 (97.0)	337 (98.5)	.145
Female	17 (3.0)	5 (1.5)	
Race			
White	233 (41.0)	148 (43.3)	.769
Black	313 (55.1)	180 (52.6)	
Other	22 (3.9)	14 (4.1)	
HCV genotype			
1a	327 (57.6)	199 (58.2)	.434
1b	119 (21.0)	81 (23.7)	
1 NOS	25 (4.4)	12 (3.5)	
2	54 (9.5)	22 (6.4)	
3	28 (4.9)	19 (5.6)	
Other	5 (0.9)	1 (0.3)	
Missing	10 (1.7)	8 (2.3)	
MELD score			
Mean (SD)	7.87 (2.42)	8.74 (2.62)	<.001
<9	495 (87.2)	258 (75.4)	<.001
10–19	65 (11.4)	80 (23.4)	
≥20	7 (1.2)	4 (1.2)	
Missing	1 (0.2)	0 (0.0)	
Prior HCV treatment			
Yes	50 (8.8)	47 (13.7)	.020
No	515 (90.7)	294 (86.0)	
Missing	3 (0.5)	1 (0.3)	
Years of alcohol abuse, mean (SD)	14.49 (14.56)	14.29 (14.45)	.838
Chronic alcohol abuse[a]			
Yes	308 (54.2)	185 (54.1)	.924
No	258 (45.4)	157 (45.9)	
Missing	2 (0.4)	0 (0.0)	
Marijuana use[b]			
Yes	234 (41.2)	128 (37.4)	.351
No	312 (54.9)	195 (57.0)	
Missing	22 (3.9)	19 (5.6)	
IDU use			
Yes	326 (57.4)	205 (59.9)	.450
No	242 (42.6)	137 (40.1)	
BMI categories			
<25	181 (31.9)	75 (21.9)	.005
Overweight (25–29)	211 (37.1)	145 (42.4)	
Obese (≥30)	170 (29.9)	119 (34.8)	
Missing	6 (1.1)	3 (0.9)	
DM/HOMA-IR status			
Diabetic[c]	118 (20.8)	99 (28.9)	<.001
HOMA-IR ≥3 in nondiabetic participants	149 (26.2)	129 (37.8)	
HOMA-IR <3 in nondiabetic participants	270 (47.5)	102 (29.8)	
Missing	31 (5.5)	12 (3.5)	
Metabolic syndrome[d]			
Yes	134 (23.6)	142 (41.5)	<.001
No	426 (75.0)	198 (57.9)	
Missing	8 (1.4)	2 (0.6)	
Smoking			
Nonsmoker	180 (31.7)	121 (35.4)	.404
<30 pack-years	190 (33.4)	115 (33.6)	
≥30 pack-years	196 (34.5)	105 (30.7)	
Missing	2 (0.4)	1 (0.3)	
Physical activity[e]			
Low activity	171 (30.1)	117 (34.2)	.374
Moderate activity	175 (30.8)	94 (27.5)	
High activity	222 (39.1)	131 (38.3)	

DM, diabetes mellitus; NOS, not otherwise specified.
[a]Ten or more consecutive years of drinking an average of 3 or more drinks per day for men and 2 or more drinks per day for women.
[b]Self-reported use or documented ever use of marijuana in the electronic medical record (International Classification of Diseases, 9th revision, code for cannabis or marijuana abuse; or documented former or current marijuana use in the electronic medical record when searched for the following key words: MJ, marijuana, and cannabis).
[c]Self-reported physician's diagnosis, medical record documentation, or presence of a fasting blood sugar level of greater than 126 mg/dL, or a nonfasting blood sugar level of greater than 200 mg/dL at enrollment.
[d]Metabolic syndrome was defined as the presence of 3 or more of the following: (1) waist circumference greater than 40 inches in men or greater than 35 inches in women; (2) increased serum triglyceride level of 150 mg/dL or higher; (3) reduced high-density lipoprotein cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women; (4) use of antihypertensive medications; and (5) increased fasting serum glucose level of 110 mg/dL or greater, and/or use of insulin or hypoglycemic medication.
[e]Based on participant response to the International Physical Activity Questionnaire.

Soda. An average caffeinated soda intake of 1 or more cans daily was reported more frequently in mild fibrosis controls vs advanced fibrosis cases (40.5% vs 32.5%; $P = .015$); however, among the subset of non–coffee drinkers (n = 413), intake of 1 or more cans daily of caffeinated soda use was not significant (37.9% vs 33.9%; $P = .412$). On multivariate analysis, more than 1 can of caffeinated soda daily remained significantly associated with a decreased risk of hepatic fibrosis, with some attenuation (adjusted OR, 0.74; 95% CI, 0.55–1.00; $P = .047$) after adjustment for age, BMI, and alcohol use, with similar findings when also adjusted for MELD score and the presence of metabolic syndrome. When adjusted for self-reported diabetes and HOMA-IR scores, there was further attenuation of the soda–fibrosis association (adjusted OR, 0.75; 95% CI, 0.55–1.02; $P = .063$) (Table 3). There was no notable difference in decaffeinated soda intake between cases and controls (Table 2).

Overall caffeine intake. Although quite variable, daily caffeine consumption from all beverages (coffee, tea, and soda) was, on average, higher in mild fibrosis controls than in advanced fibrosis cases (273.8 vs 218.2 mg; $P = .013$) (Table 4). The majority of caffeine consumption in both groups came from coffee (67.7% of total, with an average of 1.2 cups consumed per day), followed by soda (19.5%, with an average of 0.8 cans consumed per day), and then tea (12.8%, with an

Table 2. Comparison of Beverage Intake Between Advanced Fibrosis HCV Cases and Mild Fibrosis HCV Controls in One Year Preceding Study Enrollment

	Controls (F0–F3)	Cases (F3/F4–F4)	*P* value
Coffee intake, n (%)	568	342	
Caffeinated coffee			
Cups per day, mean (SD)	1.37 (2.39)	1.05 (1.92)	.038
Any use			
Yes	320 (56.3)	177 (51.8)	.179
No	248 (43.7)	165 (48.2)	
≥1 cup daily			
Yes	283 (49.8)	147 (43.0)	.045
No	285 (50.2)	195 (57.0)	
≥2 cups daily			
Yes	163 (28.7)	85 (24.9)	.208
No	405 (71.3)	257 (75.1)	
≥3 cups daily			
Yes	91 (16.0)	42 (12.3)	.123
No	477 (84.0)	300 (87.7)	
Decaffeinated coffee			
Cups per day, mean (SD)	0.08 (0.37)	0.07 (0.39)	.923
Any use			
Yes	42 (7.4)	26 (7.6)	.908
No	526 (92.6)	316 (92.4)	
≥1 cup daily			
Yes	26 (4.6)	14 (4.1)	.730
No	542 (95.4)	328 (95.9)	
Tea intake			
Caffeinated tea			
Cups per day, mean (SD)	0.61 (1.25)	0.56 (1.36)	.651
Any use			
Yes	401 (70.6)	235 (68.7)	.592
No	167 (29.4)	106 (31.0)	
Missing	0 (0.0)	1 (0.3)	
≥1 cup daily			
Yes	135 (23.8)	72 (21.1)	.356
No	433 (76.2)	269 (78.6)	
Missing	0 (0.0)	1 (0.3)	
Decaffeinated tea			
Any use			.423
Yes	22 (3.9)	17 (5.0)	
No	546 (96.1)	324 (94.7)	
Missing	0 (0.0)	1 (0.3)	
≥1 cup per day			
Yes	562 (98.9)	336 (98.2)	.755
No	6 (1.1)	5 (1.5)	
Missing	0 (0.0)	1 (0.3)	
Soda intake			
Caffeinated soda			
Cans per day, mean (SD)	1.14 (1.82)	0.95 (1.60)	.106
Any use			
Yes	445 (78.3)	254 (74.3)	.158
No	123 (21.7)	88 (25.7)	
≥1 can per day			
Yes	230 (40.5)	111 (32.5)	.015
No	338 (59.5)	231 (67.5)	
Decaffeinated soda			
Cans per day, mean (SD)	0.17 (0.62)	0.18 (0.65)	.753
Any use			
Yes	138 (24.3)	88 (25.7)	
No	430 (75.7)	254 (74.3)	
≥1 can per day			.963
Yes	52 (9.2)	31 (9.1)	
No	516 (90.8)	311 (90.9)	
Intake in non–coffee drinkers, n (%)	248	165	
Caffeinated tea in non–coffee drinkers			
Any use			
Yes	169 (68.1)	97 (58.8)	.062
No	79 (31.9)	67 (40.6)	
Missing	0 (0.0)	1 (0.6)	
≥1 cup daily			
Yes	65 (26.2)	28 (17.0)	.030
No	183 (73.8)	136 (82.4)	
Missing	0 (0.0)	1 (0.6)	
Decaffeinated tea in non–coffee drinkers			
Any use			
Yes	14 (5.6)	11 (6.7)	.658
No	234 (94.4)	153 (92.7)	
Missing	0 (0.0)	1 (0.6)	
≥1 cup daily			
Yes	4 (1.6)	4 (2.4)	.553
No	244 (98.4)	160 (97.0)	
Missing	0 (0.0)	1 (0.6)	
Caffeinated soda in non–coffee drinkers			
Any use			
Yes	183 (73.8)	114 (69.1)	.298
No	65 (26.2)	51 (30.9)	
≥1 can per day			
Yes	94 (37.9)	56 (33.9)	.412
No	154 (62.1)	109 (66.1)	
Decaffeinated soda in non-coffee drinkers			
Any use			
Yes	65 (26.2)	46 (27.9)	.708
No	183 (73.8)	119 (72.1)	
≥1 can per day			
Yes	26 (10.5)	17 (10.3)	.953
No	222 (89.5)	148 (89.7)	
Cream/sugar intake, n (%)	568	342	
Creamer or whitener use			
Any use	214 (37.7)	123 (35.9)	.595
No use[a]	350 (61.6)	217 (63.5)	
Missing	4 (0.7)	2 (0.6)	
Artificial sweetener use			
Any use	125 (22.0)	92 (26.9)	.173
No use[a]	430 (75.7)	246 (71.9)	
Missing	13 (2.3)	4 (1.2)	

[a]No use includes noncoffee/tea/soda drinkers.

average of 0.6 cups consumed per day; data not shown); however, controls had a higher percentage of their daily caffeine consumption derived from coffee sources. When further stratified by dose, a daily average intake of 100 mg or more and 200 mg or more of caffeine from all sources was associated with a significantly reduced risk of advanced fibrosis ($P = .014$ and $P = .045$, respectively). After excluding coffee drinkers, an intake of 100 mg or more and 200 mg or more of caffeine daily from noncoffee sources (tea and soda) was slightly higher in mild fibrosis controls than

Table 3. Association of Caffeinated and Decaffeinated Beverage Intake With Advanced Fibrosis HCV Results of Logistic Regression

	Fibrosis (F3/F4–F4 vs F0–F3)			
	N[a]	OR	95% CI	*P* value
≥100 mg of caffeine daily +from all sources				
Unadjusted	910	0.708	0.537–0.933	.014
Adjusted[b]	899	0.712	0.534–0.949	.020
Adjusted[c]	898	0.728	0.544–0.975	.033
Adjusted[d]	858	0.747	0.555–1.005	.054
Adjusted[e]	890	0.694	0.519–0.930	.014
≥100 mg of caffeine daily from coffee only				
Unadjusted	910	0.749	0.571–0.981	.036
Adjusted[b]	899	0.767	0.580–1.014	.062
Adjusted[c]	898	0.788	0.594–1.047	.100
Adjusted[d]	858	0.831	0.623–1.108	.207
Adjusted[e]	890	0.747	0.562–0.993	.044
≥200 mg of caffeine daily from all sources				
Unadjusted	910	0.754	0.571–0.995	.046
Adjusted[b]	899	0.773	0.580–1.030	.079
Adjusted[c]	898	0.817	0.610–1.094	.175
Adjusted[d]	858	0.815	0.606–1.096	.175
Adjusted[e]	890	0.746	0.557–1.001	.051
≥1 cup of caffeinated coffee daily				
Unadjusted	910	0.759	0.580–0.994	.045
Adjusted[b]	899	0.780	0.590–1.031	.081
Adjusted[c]	898	0.800	0.602–1.062	.123
Adjusted[d]	858	0.845	0.634–1.127	.252
Adjusted[e]	890	0.759	0.571–1.008	.057
≥1 cup of caffeinated tea daily in non–coffee drinkers				
Unadjusted	412	0.580	0.353–0.951	.031
Adjusted[b]	403	0.561	0.335–0.939	.028
Adjusted[c]	403	0.541	0.320–0.915	.022
Adjusted[d]	383	0.483	0.279–0.835	.009
Adjusted[e]	395	0.544	0.317–0.933	.027
≥1 can of caffeinated soda daily				
Unadjusted	910	0.706	0.533–0.936	.015
Adjusted[b]	899	0.739	0.550–0.991	.043
Adjusted[c]	898	0.737	0.548–0.992	.044
Adjusted[d]	858	0.750	0.554–1.016	.063
Adjusted[e]	890	0.737	0.546–0.995	.047

[a]Discrepancy in the number between unadjusted and adjusted models reflects the loss of individuals with missing required data on an adjustment factor.
[b]Adjustment 1 included age, alcohol use (never, former, or current), and BMI category (<25, 25–29, or ≥30).
[c]Adjustment 2 included MELD score range in addition to the variables in adjustment 1 models.
[d]Adjustment 3 included self-reported diabetes status and HOMA-IR less than 3 and HOMA-IR of 3 or greater categories in addition to the variables in adjustment 1 models.
[e]Adjustment 4 included the presence of the metabolic syndrome in addition to the variables in adjustment 1 models.

in advanced fibrosis cases, but the difference was not significant (Table 4).

Creamers/whiteners. Use of creamers/whiteners and added sweeteners was reported in 37.0% and 23.8% of participants, respectively, with no significant differences between cases and controls in the proportions of participants who reported use of these additives (Table 2).

Table 4. Comparison of Average Caffeine Intake Between Advanced Fibrosis HCV Cases and Mild Fibrosis HCV Controls in Year Preceding Study Enrollment

	Controls (F0–F3)	Cases (F3/F4–F4)	*P* value
Caffeine intake, n (%)	568	342	
Total caffeine from any beverage per day, mean (SD), *mg*	273.8 (346.7)	218.2 (291.1)	.013
Total caffeine from coffee per day, mean (SD), *mg*	187.2 (327.7)	143.8 (263.0)	.028
≥100 mg of caffeine daily from all sources			
Yes	375 (66.0)	198 (57.9)	.014
No	193 (34.0)	144 (42.1)	
≥100 mg of caffeine daily from coffee only			
Yes	285 (50.2)	147 (43.0)	.035
No	283 (49.8)	195 (57.0)	
≥100 mg of caffeine daily from noncoffee sources only			
Yes	164 (28.9)	92 (26.9)	.522
No	404 (71.1)	250 (73.1)	
≥200 mg of caffeine daily from all sources			
Yes	239 (42.1)	121 (35.4)	.045
No	329 (57.9)	221 (64.6)	
≥200 mg of caffeine daily from coffee only			
Yes	164 (28.9)	85 (24.9)	.188
No	404 (71.1)	257 (75.1)	
Intake in non–coffee drinkers, n (%)	248	165	
≥100 mg of caffeine daily from noncoffee sources only in non–coffee drinkers			
Yes	70 (28.2)	40 (24.2)	.370
No	178 (71.8)	125 (75.8)	
≥200 mg of caffeine daily from noncoffee sources only in non–coffee drinkers			
Yes	25 (10.1)	11 (6.7)	.228
No	223 (89.9)	154 (93.3)	

Lifetime Exposure to Coffee in Advanced Fibrosis Hepatitis C Virus Cases and Mild Fibrosis Hepatitis C Virus Controls

The average daily intake of coffee in prior life decades was higher in mild fibrosis controls than in advanced fibrosis cases, but none of these differences reached statistical significance. We also did not find a difference between cumulative years or lifetime consumption of coffee drinking between cases and controls (Table 5).

Table 5. Comparison of Average Daily Cups of Caffeinated Coffee Across Decades of Life in Advanced Fibrosis HCV Cases and Mild Fibrosis HCV Controls

	Controls (F0–F3) N = 568 (%)		Cases (F3–F4/F4) N = 342 (%)		
	Respondents n/N (%)	Mean (SD)	Respondents n/N (%)	Mean (SD)	*P* value
Cups per day in previous decades of life, *y*[a]					
20–29	567/907 (62.5)	1.52 (2.95)	340/907 (37.5)	1.45 (3.36)	.733
30–39	566/905 (62.5)	1.82 (3.08)	339/905 (37.5)	1.66 (2.87)	.444
40–49	559/901 (62.0)	1.93 (2.90)	342/901 (38.0)	1.72 (3.15)	.313
50–59	496/822 (60.3)	1.69 (2.42)	326/822 (39.7)	1.48 (2.50)	.227
60–69	157/287 (54.7)	1.30 (1.74)	130/287 (45.3)	1.27 (2.50)	.927
Cumulative use, *y*		24.4 (16.5)		24.5 (17.8)	.945
Lifetime average daily consumption		1.99 (2.70)		1.76 (2.76)	.221
Tertiles of lifetime coffee consumption					
First, 0–4380 cups	182 (32.0)		122 (35.7)		.502
Second, 4381–23,481 cups	191 (33.6)		112 (32.7)		
Third, >23,481 cups	195 (34.3)		108 (31.6)		

[a]One-way analysis of variance was used for each time period.

Relationship Between Coffee, Tea, Soda, and Caffeine Ingestion With Homeostasis Model Assessment–Estimated Insulin Resistance in Nondiabetic Subjects

Among nondiabetic subjects (n = 650), those with a HOMA-IR of less than 3 were significantly more likely to consume more than 100 mg of caffeine daily compared with those with insulin resistance/HOMA-IR of 3 or greater (68.8% vs 59.4%; $P = .012$). This association between caffeine intake and decreased risk of insulin resistance remained significant after adjustment for age, BMI, and alcohol use (adjusted OR, 0.64; 95% CI, 0.45–0.94; $P = .022$); MELD score (adjusted OR, 0.66; 95% CI, 0.45–0.95; $P = .024$); and the presence of the metabolic syndrome (adjusted OR, 0.63; 95% CI, 0.43–0.92; $P = .017$). However, there were no significant differences in the daily intake of caffeinated coffee, tea, or soda between the 2 groups (data not shown).

Association Between Coffee, Tea, Soda and Caffeine Intake and Risk of Advanced Hepatic Fibrosis After Controlling for Confounders

In the first multivariable model adjusting for age, alcohol use, and BMI, an average daily intake of 100 mg or more of caffeine from all sources remained associated with a significantly decreased risk of advanced fibrosis (adjusted OR, 0.71; 95% CI, 0.53–0.95; $P = .020$). With additional adjustment for MELD scores in the second multivariable model, the inverse associations between a daily intake of 100 mg or more of caffeine and hepatic fibrosis remained statistically significant. Further adjustment for our insulin resistance variable (ie, diagnosed diabetes, HOMA-IR $\geq$ 3 in nondiabetic participants, HOMA-IR $<$ 3 in nondiabetic participants) in the third model minimally attenuated the associations between coffee/caffeine intake and advanced fibrosis in those who consumed an average of 100 mg or more of caffeine, although still closely approached significance ($P = .054$). However, the association between caffeine intake and decreased risk of advanced hepatic fibrosis remained significant after adjusting for the metabolic syndrome in the multivariate regression model (adjusted OR, 0.69; 95% CI, 0.52–0.93; $P = .014$) (Table 3).

In the subset of non–coffee drinkers, caffeinated tea intake of 1 or more cups per day became more significant after adjustment for age, BMI, and alcohol use (adjusted OR, 0.56; 95% CI, 0.36–0.94; $P = .028$) and remained significant with the additional adjustments of MELD score (adjusted OR, 0.54; 95% CI, 0.32–0.92; $P = .022$), insulin resistance status (adjusted OR, 0.48; 95% CI, 0.28–0.84; $P = .009$), or the presence of the metabolic syndrome (adjusted OR, 0.54; 95% CI, 0.32–0.93; $P = .027$) (Table 3).

Relationship Between Coffee, Tea, and Soda Consumption and Hepatic Inflammation

Based on FibroSURE scoring, 252 participants (27.7%) were classified as advanced inflammatory activity cases (A2/A3–A3), and 658 (72.3%) were classified as mild inflammatory activity controls (A0–A2). There was no significant association between caffeine intake from coffee, tea, or soda in the year preceding study enrollment and severity of hepatic inflammation (Supplementary Tables 1–3) There were also no significant differences between the 2 groups in terms of average daily coffee intake in prior life decades, cumulative years of coffee drinking, or lifetime coffee consumption (data not shown).

Discussion

We found that self-reported coffee drinking and caffeine consumption from beverages were associated with a lower risk of advanced hepatic fibrosis in patients with chronic HCV but had no association with degree of hepatic inflammation. An average daily intake of an estimated 100 mg of caffeine from coffee, tea, or soda was associated with an approximately one-third reduction in odds of advanced fibrosis, although higher intake did not seem to confer any additional benefit. Interestingly, tea intake in those who did not consume coffee also was found to be associated with a decreased risk of advanced fibrosis. The inverse association between 100 mg or more of caffeine intake daily and advanced hepatic fibrosis remained significant after adjustment for potential confounders (eg, age, alcohol use, BMI, MELD score, and metabolic syndrome), and was attenuated when adjusted for HOMA-IR status. The inverse association between caffeine consumption and degree of fibrosis was found using caffeine intake data from the year preceding study recruitment, however, lifetime caffeine intake did not seem to influence this relationship.

Our finding that caffeine intake is associated with a decreased risk of advanced HCV-related fibrosis is in line with several other studies that have suggested a beneficial effect of caffeine on hepatic function in various liver diseases, including nonalcoholic steatohepatitis, alcoholic liver disease, and primary sclerosing cholangitis.[4,6,10,33–38] It also is consistent with an analysis of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial, which found that daily coffee consumption was associated with slower disease progression in patients with chronic HCV-related bridging fibrosis and cirrhosis who had failed to respond to treatment with pegylated interferon and ribavirin. However, in contrast to our findings, which suggest no substantial additional benefit of caffeine intake of 100 mg/day or more, they found a dose-dependent response with coffee drinkers who reported 3 or more cups daily experiencing the greatest (~53%) reduced risk of disease progression (ie, to decompensation or HCC) compared with non–coffee drinkers.[16] We hypothesize that the primary explanation for this discrepancy is the difference in the spectrum of HCV-related liver disease among studies because the HALT-C trial was restricted to cirrhotic patients, whereas our study population included the full spectrum of HCV-related liver disease. However, other differences in study design and among populations also may have contributed to this discrepancy. Our results suggesting that a modest dose of caffeine intake (~100 mg/d) was associated with a significantly reduced risk of advanced fibrosis in veterans with chronic HCV are similar to an earlier comparable pilot study in 91 HCV-positive veterans.[39] The consistency in these results over time further supports the internal validity of our findings.

In contrast to our results, Costentin et al[17] found no significant protective association in their study of 238 French patients with treatment-naive chronic HCV. However, they did find that daily caffeine consumption of more than 408 mg (equivalent to $\geq$3 cups of coffee) was an independent predictor of lower histologic activity grade of hepatitis. Several factors may explain this discrepancy, including differences in populations such as higher average caffeine intake but lower rates of obesity and alcohol abuse overall in the French study population, differences in methods of estimating caffeine intake, and known substantial variability in caffeine found in coffee and tea based on methods of production and preparation.

Our findings suggest that a total combined caffeine intake or dose of 100 mg or more daily is associated with a significant decrease in risk of hepatic fibrosis, but without further risk reduction with higher coffee or caffeine doses. However, the optimal hepatoprotective dose of caffeine in HCV-infected patients overall is unclear. Although some studies suggested the strongest benefit from coffee consumption was at 3 or more cups daily, or approximately 400 mg of caffeine,[16,17] other studies reported a significant reduction in the risk in HCV-related hepatic fibrosis associated with an intake of 1 or 2 cups of cups of coffee daily.[11,40] Our results suggest that as little as 100 mg or more of caffeine daily may be beneficial in a general HCV-infected population with a high prevalence of other risk factors for advanced liver disease. However, our power to evaluate the benefit of higher intake likely was limited by the small number of our study participants who reported drinking higher quantities of caffeinated beverages. Nonetheless, if validated in other HCV-infected populations in the United States, our results suggest that a relatively low (and therefore potentially more tolerable dose) of caffeine, particularly from caffeinated coffee and possibly from tea, may convey a substantial reduction in fibrosis progression.

Several mechanisms have been suggested by which caffeine may act to reduce the risk of advanced fibrosis.[41] Caffeine functions as a nonselective adenosine-receptor antagonist and a phosphodiesterase inhibitor with a broad range of attendant effects including inhibition of growth factors that contribute to hepatic fibrosis.[42–44] Caffeine is metabolized in the liver primarily by CYP1A2, with reduced expression of CYP1A2 correlated with fibrosis progression in a study of HCV patients.[45] Caffeine also has been shown in animal and in vitro studies to act as an antioxidant.[46] Other studies have suggested that the primary hepatoprotective benefit of caffeine is associated with caffeinated coffee intake.[4,6,11,16,47] However, this could be the effect of generally higher daily cumulative caffeine intake in coffee drinkers compared with consumers of other caffeinated beverages overall, or with pharmacodynamic differences in effects given the substantial differences in caffeine per unit intake of caffeinated coffee in comparison with tea or soda. Finally, it also has been postulated

that other constituents of coffee, such as diterpenes, polyphenols, kahweol, and cafestrerol, which have antioxidant activity, also may be responsible for the particular hepatoprotective effect of coffee.[48–51] However, studies, including ours, have not shown that decaffeinated coffee exerts the same effect on liver disease as caffeinated coffee.[11,47]

Inflammation is another known risk factor for progression to fibrosis in chronic HCV,[52] and the role of coffee as an anti-inflammatory agent in nonliver diseases has been suggested.[2] In our study, we found no significant association between caffeine intake and the severity of hepatic inflammation, in line with findings by Freedman et al[16] that coffee intake was not associated with lower baseline hepatic inflammation. Prior work has shown that insulin resistance worsens hepatic inflammation in HCV patients,[18] and a meta-analysis suggested that part of the hepatoprotective effect of coffee in part may be related to an associated reduction in insulin resistance and type 2 diabetes mellitus.[19] In our study, caffeine intake was associated inversely with insulin resistance via the surrogate marker of the HOMA-IR score in nondiabetic participants. Therefore, one potential mechanism linking caffeine intake or the associated lifestyle with decreased risk of advanced fibrosis is the amelioration of insulin resistance. Further studies are needed to better elucidate the underlying pathophysiological mechanisms by which caffeine or its metabolites and other constituents of coffee account for the positive health benefits seen particularly with caffeinated coffee consumption in liver disease patients.

We found that an average of 100 mg or more of caffeine daily from sodas and teas does not have the same protective effect as 100 mg or more of caffeine daily from combined sources (coffee, tea, soda) or from coffee alone, suggesting that caffeine alone may not entirely explain the effect of coffee on liver disease. Although several prior studies have not shown a lower risk of liver disease progression in those who consume caffeine from noncoffee sources such as tea[4,11,16,47] or soda,[47] this could be related to differing caffeine content, other ingredients in addition to caffeine that may be partly responsible for the proposed hepatoprotective effects of coffee, or to substantial differences in study design or populations. Among the 413 noncoffee drinkers in our current study, intake of at least 1 cup of caffeinated tea daily was more common in the mild fibrosis control group, and after controlling for potential confounders, this significance was even more pronounced. This finding provides further evidence for the protective role of caffeine from any source against the progression of liver disease.

In regards to soda, an understudied source of caffeine, we found consumption of more than 1 can of caffeinated soda daily to be associated with a decreased risk of hepatic fibrosis, supporting that caffeine likely plays a major role in coffee's hepatoprotective effects. On multivariate nonstratified analysis, more than 1 can of caffeinated soda daily remained significantly associated with a decreased risk of hepatic fibrosis, with some attenuation after controlling for possible confounders (age, alcohol, BMI, MELD score, and the presence of the metabolic syndrome). When adjusted for self-reported diabetes and HOMA-IR scores, there was a nonsignificant trend toward a decreased risk of fibrosis (adjusted OR, 0.75; 95% CI, 0.55–1.02; $P = .063$). However, in analyzing soda intake in the subgroup of non–coffee drinkers ($n = 413$), there was no notable difference in the risk of hepatic fibrosis ($P = .41$). The findings may indicate that caffeine from soda has hepatoprotective effects, but we cannot exclude the possibility that increased soda consumption reflects an increased intake of caffeinated beverages overall, including coffee. As with coffee, decaffeinated tea and soda were not found to be associated with a decreased risk of liver disease.

Our study had several strengths, including being a large study that examined the association between caffeinated coffee intake and HCV-related liver disease, and adds to the limited research in US populations. It also adds to the sparse literature on the effects of caffeinated tea and soda intake. In addition, we obtained and analyzed information on the consumption of decaffeinated coffee, tea, and soda to better elucidate the mechanisms underlying the potential hepatoprotective effects of caffeine and coffee on liver disease. Finally, our novel use of a validated noninvasive marker for liver fibrosis, the validated FibroSURE test,[26–32] allowed evaluation of a large and diverse HCV patient group, many of whom would have been precluded from biopsy based on highly prevalent comorbid conditions in this population.

Our study also had some limitations. Given the observational retrospective nature of the study, a causal association cannot be made. We studied a select patient population of HCV-monoinfected, largely male veterans, and therefore the findings may not be applicable to women with HCV or co-infected patients. Beverage consumption was self-reported, and caffeine intake was estimated based on the average reported intake, and therefore may not accurately reflect the actual intake given the known variability in caffeine levels in coffee and tea of the same type owing to differences in production and preparation. However, any misclassification should be nondifferential (ie, similar among cases and controls) and therefore any possible bias should be toward the null or finding of no association. A potential for reverse causality may be present if patients with more advanced liver disease are averse to drinking caffeine-containing beverages including coffee; however, we did not enroll patients with decompensated liver disease. We also found that the decreased risk of advanced fibrosis with an average daily intake of 100 mg or more of caffeine or 1 or more cups of tea in non–coffee drinkers remained significant or nearly significant after adjusting for MELD scores and insulin resistance. In total, 40% of our participants were classified as marijuana users, and we found no significant association with the degree of hepatic fibrosis or inflammation and marijuana use.

However, we did not have information on the duration or frequency of marijuana use, a limitation of our study.[53] Prior studies also have suggested women who consume alcohol may have a less pronounced response to the hepatoprotective effects of caffeine as measured by γ-glutamyltransferase levels,[54] and in animal models, females may recover more slowly from hepatic injury than males.[55] Our study participants were largely male (n = 888), with only 22 females represented. As such, our study lacked the statistical power to find a notable gender-specific difference in the hepatoprotective effects of caffeine or coffee.

In conclusion, we found that an average daily intake of 100 mg or more of caffeine was associated with a lower risk of hepatic fibrosis in a general clinical population with chronic HCV infection. We further showed that in non–coffee drinkers, daily caffeinated tea intake also may protect against progressive liver disease in this population. Our study further suggests that caffeinated coffee overall and caffeinated tea in non–coffee drinkers likely provide the most benefit in liver disease compared with other caffeinated beverages or decaffeinated coffee. Future prospective studies are warranted to determine the optimal dose and preparation of caffeinated beverage intake that could be safely and tolerably recommended for prevention of progressive liver disease in HCV patients in routine clinical practice.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.01.030.

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Conflicts of interest
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Supplementary Table 1. Demographic Characteristics of Advanced Inflammatory Activity HCV Cases Compared With Mild Inflammatory Activity HCV Controls

Characteristics	Inflammatory activity: Controls (A0–A2) N = 658 (%)	Inflammatory activity: Cases (A2/A3–A3) N = 252 (%)	*P* value
Mean age, *y* (SD)	53.64 (5.42)	56.43 (5.36)	.604
Sex			
Male	641 (97.4)	247 (98.0)	.598
Female	17 (2.6)	5 (2.0)	
Race			
White	253 (38.4)	128 (50.8)	<.001
Black	384 (58.4)	109 (43.2)	
Other	21 (3.2)	15 (6.0)	
HCV genotype			
1a	388 (59.0)	138 (54.8)	.237
1b	146 (22.2)	54 (21.4)	
1 NOS	26 (3.9)	11 (4.4)	
2	52 (7.9)	24 (9.5)	
3	27 (4.1)	20 (7.9)	
Other	5 (0.8)	1 (0.4)	
Missing	14 (2.1)	4 (1.6)	
MELD score			
Mean (SD)	8.23 (2.73)	8.11 (1.93)	.474
<9	540 (82.0)	213 (84.5)	.334
10–19	107 (16.3)	38 (15.1)	
≥20	10 (1.5)	1 (0.4)	
Missing	1 (0.2)	0 (0.0)	
Prior HCV treatment			
Yes	68 (10.3)	29 (11.5)	.633
No	586 (89.1)	223 (88.5)	
Missing	4 (0.6)	0 (0.0)	
Years of alcohol abuse, mean (SD)	14.31 (14.60)	14.68 (14.29)	.731
Chronic alcohol abuse[a]			
Yes	352 (53.5)	141 (56.0)	.482
No	305 (46.3)	110 (43.6)	
Missing	1 (0.2)	1 (0.4)	
Marijuana use[b]			
Yes	260 (39.5)	102 (40.5)	.756
No	369 (56.1)	138 (54.8)	
Missing	29 (4.4)	12 (4.7)	
IVD use			
Yes	386 (58.7)	145 (57.5)	.758
No	272 (41.3)	107 (42.5)	
BMI categories			
<25	194 (29.5)	62 (24.6)	.011
Overweight (25–29)	267 (40.6)	89 (35.3)	
Obese (≥30)	190 (28.9)	99 (39.3)	
Missing	7 (1.0)	2 (0.8)	
DM/HOMA-IR status			
Diabetic[c]	148 (22.5)	69 (27.4)	<.001
HOMA-IR ≥3 in nondiabetic participants	298 (45.3)	74 (29.4)	
HOMA-IR <3 in nondiabetic participants	183 (27.8)	95 (37.7)	
Missing	29 (4.4)	14 (5.5)	
Metabolic syndrome[d]			
Yes	178 (27.1)	98 (38.9)	<.001
No	473 (71.9)	151 (59.9)	
Missing	7 (1.0)	3 (1.2)	
Smoking			
Nonsmoker	221 (33.6)	80 (31.8)	.489
<30 pack-years	213 (32.4)	92 (36.5)	
≥30 pack-years	222 (33.7)	79 (31.3)	
Missing	2 (0.3)	1 (0.4)	
Physical activity[e]			
Low activity	212 (32.2)	76 (30.1)	.545
Moderate activity	198 (30.1)	71 (28.2)	
High activity	248 (37.7)	105 (41.7)	

DM, diabetes mellitus; IVD, intravenous drug use; NOS, not otherwise specified.

[a]Ten or more consecutive years of drinking an average of 3 or more drinks per day for men and 2 or more drinks per day for women.

[b]Self-reported use or documented ever use of marijuana in the electronic medical record (International Classification of Diseases, 9th revision, code for cannabis or marijuana abuse; or documented former or current marijuana use in the electronic medical record when searched for the following key words: marijuana and cannabis).

[c]Self-reported physician's diagnosis, medical record documentation, or the presence of a fasting blood sugar level of greater than 126 mg/dL, or a non-fasting blood sugar level of greater than 200 mg/dL at enrollment.

[d]Metabolic syndrome was defined as the presence of 3 or more of the following: (1) waist circumference greater than 40 inches in men or greater than 35 inches in women; (2) increased serum triglyceride level of 150 mg/dL or greater; (3) reduced high-density lipoprotein cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women; (4) increased blood pressure of 130/85 mm Hg or greater and/or use of antihypertensive medications; and (5) increased fasting serum glucose level of 110 mg/dL or greater and/or use of insulin or hypoglycemic medication.

[e]Based on participant response to the International Physical Activity Questionnaire.

Supplementary Table 2. Comparison of Beverage Intake Between Advanced Inflammatory Activity HCV Cases and Mild Inflammatory Activity HCV Controls in Year Preceding Study Enrollment

	Inflammatory activity		
	Controls (A0–A2)	Cases (A2/A3–A3)	*P* value
Coffee intake, n (%)	658	252	
Caffeinated coffee			
Cups per day, mean (SD)	1.27 (2.36)	1.19 (1.85)	.609
Any use			
Yes	347 (52.7)	150 (59.5)	.066
No	311 (47.3)	102 (40.5)	
≥1 cup daily			
Yes	301 (45.7)	129 (51.2)	.141
No	357 (54.3)	123 (48.8)	
≥2 cups daily			
Yes	182 (27.7)	66 (26.4)	.656
No	476 (72.3)	186 (73.8)	
≥3 cups daily			
Yes	100 (15.2)	33 (13.1)	.422
No	558 (84.8)	219 (86.9)	
Decaffeinated coffee			
Cups per day, mean (SD)	0.08 (0.41)	0.07 (0.33)	.629
Any use			
Yes	52 (7.9)	16 (6.3)	.425
No	606 (92.1)	236 (93.7)	
≥1 cup daily			
Yes	29 (4.4)	11 (4.4)	.978
No	629 (95.6)	241 (95.6)	
Tea intake			
Caffeinated tea			
Cups per day, mean (SD)	0.62 (1.37)	0.52 (1.05)	.256
Any use			
Yes	460 (69.9)	176 (69.8)	.959
No	197 (30.0)	76 (30.2)	
Missing	1 (0.1)	0 (0.0)	
≥1 cup daily			
Yes	151 (22.9)	56 (22.2)	.807
No	506 (77.0)	196 (77.8)	
Missing	1 (0.1)	0 (0.0)	
Decaffeinated tea			
Cups per day, mean (SD)	0.03 (0.28)	0.03 (0.22)	.819
Any use			
Yes	27 (4.1)	12 (4.8)	.664
No	630 (95.8)	240 (95.2)	
Missing	1 (0.1)	0 (0.0)	
≥1 cup per day			
Yes	7 (1.0)	4 (1.6)	.509
No	650 (98.9)	248 (98.4)	
Missing	1 (0.1)	0 (0.0)	
Soda intake			
Caffeinated soda			
Cans per day, mean (SD)	1.08 (1.69)	1.07 (1.88)	.939
Any use			
Yes	504 (76.6)	195 (77.4)	.802
No	154 (23.4)	57 (22.6)	
≥1 can per day			
Yes	254 (38.6)	87 (34.5)	.255
No	404 (61.4)	165 (65.5)	
Decaffeinated soda			
Cans per day, mean (SD)	0.19 (0.64)	0.14 (0.60)	.349
Any use			
Yes	172 (26.1)	54 (21.4)	.141
No	486 (73.9)	198 (78.6)	
≥1 can per day			
Yes	68 (10.3)	15 (6.0)	.040
No	590 (89.7)	237 (94.0)	
Intake in non–coffee drinkers, n (%)	311	102	
Caffeinated tea in non–coffee drinkers			
Any use			
Yes	207 (66.8)	59 (57.8)	.102
No	103 (33.1)	43 (42.2)	
Missing	1 (0.1)	0 (0.0)	
≥1 cup daily			
Yes	73 (23.4)	20 (19.6)	.409
No	237 (76.5)	82 (80.4)	
Missing	1 (0.1)	0 (.0)	
Decaffeinated tea in non–coffee drinkers			
Any use			
Yes	21 (6.8)	4 (3.9)	.295
No	289 (93.1)	98 (96.1)	
Missing	1 (0.1)	0 (0.0)	
≥1 cup daily			
Yes	6 (1.9)	2 (2.0)	.987
No	304 (98.0)	100 (98.0)	
Missing	1 (0.1)	0 (0.0)	
Caffeinated soda in non–coffee drinkers			
Any use			
Yes	222 (71.4)	75 (73.5)	.675
No	89 (28.6)	27 (26.5)	
≥1 can per day			
Yes	115 (37.0)	35 (34.3)	.627
No	196 (63.0)	67 (65.7)	
Decaffeinated soda in non–coffee drinkers			
Any use			
Yes	87 (28.0)	24 (23.5)	.380
No	224 (72.0)	78 (76.5)	
≥1 can per day			
Yes	36 (11.6)	7 (6.9)	.176
No	275 (88.4)	95 (93.1)	
Cream/sugar intake, n (%)	658	252	
Creamer or whitener use			
Any use	235 (35.7)	102 (40.5)	.195
No use[a]	418 (63.5)	149 (59.1)	
Missing	5 (0.8)	1 (0.4)	
Artificial sweetener use			
Any use	166 (25.2)	59 (23.4)	.493
No use[a]	477 (72.5)	191 (75.8)	
Missing	15 (2.3)	2 (0.8)	

[a]No use includes non–coffee/tea/soda drinkers.

Supplementary Table 3. Comparison of Average Caffeine Intake Between Advanced Inflammatory Activity HCV Cases and Mild Inflammatory Activity HCV Controls in Year Preceding Study Enrollment

	Inflammatory activity		
	Controls (A0–A2)	Cases (A2/A3–A3)	*P* value
Caffeine intake, n (%)	658	252	
Total caffeine from any beverage per day, mean (SD), *mg*	257.6 (341.6)	240.6 (289.1)	.483
Total caffeine from coffee per day, mean (SD), *mg*	174.1 (323.5)	162.5 (253.2)	.609
≥100 mg of caffeine daily from all sources			
Yes	411 (62.5)	160 (63.5)	.774
No	247 (37.5)	92 (36.5)	
≥100 mg of caffeine daily from coffee only			
Yes	302 (45.9)	130 (51.6)	.124
No	356 (54.1)	122 (48.4)	
≥100 mg of caffeine daily from noncoffee sources only			
Yes	194 (29.5)	62 (24.6)	.143
No	464 (70.5)	190 (75.4)	
≥200 mg of caffeine daily from all sources			
Yes	263 (40.0)	97 (38.5)	.683
No	395 (60.0)	155 (61.5)	
≥200 mg of caffeine daily from coffee only			
Yes	183 (27.8)	66 (26.2)	.624
No	475 (72.2)	186 (73.8)	
Intake in non–coffee drinkers, n (%)	311	102	
≥100 mg of caffeine daily from noncoffee sources only in non–coffee drinkers			
Yes	87 (28.0)	23 (22.5)	.282
No	224 (72.0)	79 (77.5)	
≥200 mg of caffeine daily from noncoffee sources only in non–coffee drinkers			
Yes	29 (9.3)	7 (6.9)	.444
No	282 (90.7)	95 (93.1)	