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Inverse associations of total and decaffeinated coffee with liver enzyme levels in NHANES 1999–2010

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Abstract

Background—Coffee may have hepatoprotective effects and higher coffee consumption has been associated inversely with levels of liver enzymatic markers. However, it is unclear whether decaffeinated coffee is also associated with liver enzymes.

Methods—The study population included 27,793 participants, age 20 or older, in the US National Health and Nutrition Examination Survey (1999–2010). Coffee intake was evaluated by 24-hour dietary recall. Serum levels of aminotransferase (ALT), aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyl transaminase (GGT) were measured. We examined the relationship between coffee intake and enzymatic levels using weighted multiple variable logistic (abnormally elevated levels of enzymes) and linear regression (continuous enzymatic levels).

Results—Total coffee consumption was inversely associated with abnormal levels of all four liver enzymes and continuous levels of AST, ALP and GGT. Compared to those reporting no coffee consumption, participants reporting ≥3 cups per day had an odds ratio (OR) (95% confidence interval (CI)) of 0.75 (0.63, 0.89)), 0.82 (0.68, 0.98), 0.73 (0.55, 0.95) and 0.69 (0.57, 0.83) for abnormal levels of ALT, AST, ALP and GGT, respectively. Similar inverse associations were found with decaffeinated coffee intake and abnormal levels of ALT ($OR_{\geq 2 \text{ vs } 0 \text{ cup/d}}$: 0.62 (0.41, 0.94)), AST (0.74 (0.49, 1.11)), and GGT (0.70, 0.49–1.00).

Conclusion—Higher intakes of coffee, regardless of its caffeine content, were associated with lower levels of liver enzymes.

Keywords

Coffee; decaffeinated coffee; aminotransferase; aminotransferase; alkaline phosphatase; gamma glutamyl transaminase

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Author Contributions

Study concept and design: Xiao, Sinha, Graubard and Freedman. Statistical analysis: Xiao and Graubard. Interpretation of data: Xiao, Sinha, Graubard and Freedman. Drafting of the manuscript: Xiao. Critical revision of the manuscript for important intellectual content: Sinha, Graubard and Freedman. Study supervision: Freedman.

Disclosure

The authors declared no conflict of interest.

Introduction

Coffee is widely consumed around the world. The health effects of coffee have attracted considerable attention. Recent studies have linked coffee consumption with lower risks of developing multiple conditions, including mortality[1], diabetes[2], cardiovascular disease[3], and various forms of chronic liver diseases, such as non-alcoholic fatty liver disease[4], liver cirrhosis[5] and liver cancer[6]. In a prospective investigation of the first National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-Up Study, the authors reported that participants who drank more than 2 cups of coffee a day had only half the risk of developing chronic liver disease than those who drank less than 1 cup a day[7].

The potentially hepatoprotective role of coffee is further supported by studies reporting favorable levels of liver markers associated with increased coffee consumption. A growing body of literature has consistently shown an inverse relationship between coffee consumption and gamma glutamyl transaminase (GGT)[8–18], a marker of diseases of the liver or bile ducts[19]. Other studies also report that higher coffee consumption is associated with reduced serum levels of the hepatocyte damage markers, alanine aminotransferase (ALT)[5,10,17,20–22] and aspartate aminotransferase (AST)[5,10,16,17,21–23], as well as alkaline phosphatase (ALP), another commonly used marker in liver function tests[10].

However, it remains unclear whether the caffeine plays an essential role in mediating associations of coffee with liver health[24]. Some animal studies showed that caffeine itself is capable of protecting against toxin induced liver damage[25], while others suggested that coffee compounds other than caffeine may offer similar benefits[26]. Most epidemiologic studies did not distinguish between caffeinated and decaffeinated coffee, and none has directly evaluated the relationship between decaffeinated coffee intake and levels of liver enzymes.

We studied the cross-sectional association between coffee consumption and serum levels of four enzymes commonly used in liver function tests, ALT, AST, ALP and GGT in a nationally representative sample of the U.S. population, with a special emphasis on decaffeinated coffee.

Methods

Data source and study population

We used data from the 1999–2010 NHANES, a cross-sectional medical examination survey conducted by the National Center for Health Statistics of the US Centers for Disease Control and Prevention (Atlanta, Georgia)[27]. The NHANES survey is designed to evaluate health and nutritional status of a representative sample of civilian noninstitutionalized US population using a complex stratified multistage sampling design. In 1999, NHANES became a continuous program and since then has been conducted in independent, 2-year cycles. We obtained all data and detailed survey protocols from the website of the National Center for Health Statistics[27]. Of the 62,539 participants of NHANES 1999–2010, we excluded those who lacked completion of an in-person dietary recall (N=7,049), had missing

ALT, AST, ALP or GGT levels (N=17,456), and who were younger than 20 (N=10,241). The final analytic cohort included 27,793 participants. The study was approved by the Centers for Disease Control and Prevention's institutional review board.

Assessment of coffee consumption

In all cycles of NHANES 1999–2010, coffee intake was reported in 24-hour dietary recalls. Using an automated multiple-pass method[28], all food items and quantities consumed in the 24 hours preceding the interview were recorded. We used the United States Department of Agriculture Dietary Sources of Nutrients Database to identify coffee beverages[29], and we further assigned each coffee beverage into three categories of caffeine status (regular (caffeinated), decaffeinated or unspecified) (supplementary table 1). For participants in the 1999–2002 NHANES, only one in-person 24-hr dietary recall was administered. However, cycles starting from 2003 onward included two recalls, the first one in-person and the second one via telephone. Coffee consumption reported in the second recall was generally lower than that reported in the first recall. Nevertheless, the agreement between the two recalls was high (intraclass correlation coefficient: 0.67 for total and 0.60 for decaffeinated coffee). Because of the inconsistency between telephone based and in-person recalls, we used coffee intake from the first dietary recall for our main analysis for participants in the 2003 to 2010 cycles. We divided the continuous values of coffee consumption (in grams) by one cup size (10 oz or 283.5 ml) and categorized coffee consumption into five groups: none, <1, 1–<2, 2–<3, and ≥3 cup/day. In analysis of decaffeinated coffee, we combined the highest 2 categories because of smaller sample sizes.

In addition to dietary recall, a food frequency questionnaire (FFQ) was administered in NHANES 2003–2004 and 2005–2006. Participants were asked to report the number of cups of coffee they drank by choosing from 10 categories ranging from none to 6 or more cups per day. They also reported how often the coffee they drank was decaffeinated (almost never or never, 1/4, 1/2, ¾, and almost always or always). We used the FFQ data to evaluate how closely the dietary recall and the FFQ correlated with each other on coffee consumption and we found the correlation was high (Spearman correlation coefficient, 0.76).

Liver enzyme measurement

Serum specimens were refrigerated and shipped to a central laboratory for analysis. In NHANES 1999–2000, the central laboratory (Coulston Foundation, Alamogordo, NM) used a Hitachi model 704 multichannel analyzer to measure biochemistry profile, including levels of ALT, AST, ALP and GGT. Starting from 2002, NHANES changed its central laboratory to the Collaborative Laboratory Services (Ottumwa, IA) in which a Beckman Synchron LX20 analyzer was used. Despite the difference in laboratory equipment, the distribution of the liver enzyme levels were almost identical between the two time periods, therefore we used the upper reference limits recommended by NHANES 2001–2010 to define abnormal status of ALT (>47 IU/L in men or >30 IU/L in women), AST (>33 IU/L in men and women), ALP (>113 IU/L in men and women) and GGT (>65 IU/L in men or >36 IU/L in women)[30]. We also performed sensitivity analysis by using log-transformed liver enzyme levels > 2 standard deviations (SD) above the mean as the threshold for abnormal status of

liver enzymes. We calculated AST/ALT ratio, and participants with AST/ALT≥2 was considered having an abnormal ratio.

Covariates

NHANES 1999–2010 collected a wide range of sociodemographic variables including age, sex, race and ethnicity, education and marital status, and behavioral risk factors such as smoking and alcohol drinking. Additionally, NHANES participants reported medical conditions, including diabetes, cardiovascular diseases and cancer. Body mass index (body weight divided by height squared, kg/m^2) was measured by trained examiners. We also obtained data on hemoglobin A1c level and infection status of hepatitis B (infection defined as surface antigen or core antibody positive) and hepatitis C (infection defined as antibody positive) from laboratory examinations.

Statistical analysis

To evaluate the relationship between coffee consumption and abnormal liver enzyme levels, we used weighted multiple variable logistic regression, and presented the associations in odds ratios and 95% CI. We also examined the distribution of ALT, AST, ALP and GGT levels and performed log transformation to approximate a normal distribution. The associations between coffee consumption and continuous enzyme levels were assessed using weighted multiple variable linear regression models. We presented age adjusted and multivariate adjusted geometric means and 95% confidence intervals (CI) of liver enzyme levels by categories of coffee intake. In all multivariate models we adjusted for age, gender, race and ethnicity, education, smoking status, alcohol consumption, day of recall, and hepatitis B or hepatitis C positivity. BMI and diabetes were considered as potential mediators and were examined in separate models with aforementioned covariates. Because adjusting for diabetes, BMI, and year since quitting smoking did not change the results substantially (<5% of change in effect estimates), these variables were not retained in the final models. Participants who did not report drinking coffee within the previous 24 hours served as the reference group. To test for trend, we modeled categorical variables as continuous and evaluated this coefficient using a Wald test. To test for interaction between coffee consumption and BMI (<25, 25–<30, and 30+ kg/m^2), smoking (never, former and current smoker), alcohol intake (nondrinker, <2 drinks/day and 2+ drinks/day), history of diabetes (yes and no), history of HBV infection (yes and no) and history of HCV infection (yes and no), we used the likelihood ratio test comparing a model with the cross-product term to one without. In analysis of decaffeinated coffee, we excluded participants who reported drinking any regular or unspecified coffee on the previous day (N=12,457). All analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina), accounting for the complex sample design of the NHANES involving sample weighting, stratification and clustering[27]. The sample weights for analysis were calculated by using the following formula: 2/6* dietary day one 4-year sample weights for 1999–2002, and 1/6* dietary day one 2-year sample weights for 2003–2010. Results of all hypothesis tests were reported with two-sided p-values where p-values < 0.05 were considered to be statistically significant.

Results

Of all the participants, 47.1% did not report consuming coffee in the day of recall. Those who reported drinking coffee were more likely to be non-black, older, and current smokers than those who did not report drinking coffee (table 1). Overall, 32.4% of the population were obese, 13.5% reported 1 or more alcoholic drink per day, 7.6% had a history of diabetes, and 5.3% and 1.7% were positive for HBV and HCV infection, respectively. Higher coffee consumption was inversely associated with obesity and diabetes, but positively associated with alcohol drinking.

We found that higher coffee consumption was associated with lower odds of abnormal liver enzymes (table 2), and the results were largely similar before and after adjusting for confounders. Compared to those reporting no coffee consumption, those who reported three cups or more had an odds ratio of 0.75 (95% CI: 0.63, 0.89), 0.82 (0.68, 0.98), 0.73 (0.55, 0.95), and 0.69 (0.57, 0.83) for abnormal levels of ALT, ALP, AST and GGT, respectively. Similar associations were observed when we used >2 SD above the mean as the cutoff points (data not shown). Moreover, abnormal level of AST/ALT ratio was also inversely associated with coffee consumption ($OR_{3+ \text{ vs } 0 \text{ cup}}$ (95% C)): 0.55 (0.36, 0.86), *p-for-trend, 0.006*).

We observed comparable inverse associations between coffee intake and continuous levels of AST, ALP and GGT (p for trend: 0.0004, <0.0001 and 0.0007 for AST, ALP and GGT, respectively) (table 3), although such associations did not necessarily appear to be linear. Similar inverse trends were observed when we used the information on coffee intake assessed by FFQ in NHANES 2003–2006 (supplementary table 2). Observed associations also were generally consistent across subgroups defined by various risk factors of liver conditions, including BMI, smoking status, history of diabetes, and HBV and HCV infection (supplementary table 3). In subgroup analysis by alcohol intake, the inverse association between coffee consumption and liver enzyme levels appeared to be somewhat stronger among people who reported 2+drinks/day, although the p-for-interaction was not significant, probably due to small number of participants in the high alcohol intake subgroup (Table 1). We found a significant interaction between coffee intake and history of diabetes and HCV infection in relation to GGT level (p-for-interaction: <.0001 for diabetes and 0.004 for HCV infection), where the inverse associations were stronger in magnitude among people with diabetes and HCV infection.

Finally, we examined the associations between decaffeinated coffee consumption and liver enzymes (table 4). Associations with decaffeinated coffee were similar to those overall, although these associations did not always reach statistical significance, likely reflecting lower statistical power for these analyses. Higher decaf consumption was associated with lower odds of having abnormal levels of ALT ($OR_{2+ \text{ vs } 0 \text{ cup}}$ (95% C): 0.62 (0.41, 0.94)). Abnormal level of AST/ALT ratio was also inversely associated with high decaf consumption, although the confidence interval was wide due to small number of participants with an abnormal level (0.59 (0.26, 1.36)). For continuous levels of liver enzymes, we also found a generally inverse relationship with decaf intake, although the associations for ALT and AST were not statistically significant.

Discussion

In this large sample of US men and women, we found that total coffee intake reported in the dietary recall was inversely associated with lower risk of having abnormal levels of liver enzymes, ALT, AST, ALP and GGT. Inverse associations with liver enzymes largely persisted with decaffeinated coffee consumption. The inverse relationship between coffee consumption and serum levels of liver enzymes is largely consistent with findings of previous studies[8–17,20–22]. Among all commonly measured enzymes in the liver function tests, GGT has been most extensively studied[8–17], but all studies were conducted in Japan and European countries. The largest one was an investigation of the Tromsø Study, which reported a strong inverse relationship between coffee consumption and GGT level, with every additional cup of coffee associated with ~7% reduction in the mean GGT level[9]. ALT has been considered a more specific marker of liver injury[19] and several studies have examined the effect of coffee consumption on serum level of ALT[5,10,17,20–22]. Of these, two studies were conducted in the U.S. and both reported an inverse association[5,20]. Klatsky et al. found a 40% decrease in the odds of having abnormal level of ALT among participants who drank 4 or more cups a day, when compared to nondrinkers[5]. In a study or NHANES III participants, Ruhl et al. restricted their analysis to people who were at elevated risk for liver disease and reported a similarly inverse association between coffee and abnormal levels of ALT ($OR_{>\ 2\ cup\ vs\ none}$ (95% CI): 0.56 (0.31, 1.00))[20]. A few studies examined coffee consumption in relation to AST[5,10,16,17,21,22] and ALP[10] and almost all involved populations outside U.S. In general, they reported an association of heavier coffee consumption with lower levels of liver enzymes.

Caffeine is a prominent biochemical compound found in coffee drinks and a potential candidate that may be responsible for hepatoprotective associations.[24] Several studies have evaluated the relationship between caffeine and liver disease and serum levels of liver markers. Caffeine intake from coffee, tea and other caffeinated drinks was found to have a strong inverse association with chronic liver disease in the NHANES I Epidemiologic Follow-Up Study[7]. In NHANES III, Ruhl et al. also reported that higher caffeine intakes was associated with lower risk of abnormally elevated levels of serum ALT[20]. However, the caffeine and coffee intakes were highly correlated in these studies, making it difficult to determine the true associations with caffeine, independent of other coffee ingredients.

Our study is the first to examine the relationship between decaffeinated coffee and liver enzymes, and the inverse relationship between decaffeinated coffee intake and liver markers suggests that compounds other than caffeine may be associated with liver disease. Several mechanistic studies have explored possible hepatoprotective effects of candidate coffee compounds. It has been reported that coffee diterpenes, cafestol and kahweol, may offer protective effects against aflatoxin B1 induced damage in rat and in hepatocyte cultures[25,26]. Cafestol and kahweol may also induce the synthesis of glutathione, which has been suggested to have a role in detoxification and prevention of liver damage[24]. However filtered coffee, the common type consumed in the U.S. is thought to have lower levels of cafestol and kahweol, when compared with boiled coffee. Unfortunately we did not have information about filtered coffee in this study, and were not able to examine the effect of filtered coffee on liver enzymes. Other studies have suggested that polyphenols, which are

shown to have potent anti-oxidant activity, may also be partially responsible for the inverse associations with coffee[2,31].

One of the most important strengths of this study is that by combining all the available cycles of continuous NHANES, we had a large, nationally representative, sample of the U.S. population. Our large sample size has allowed us to specifically examine associations with decaffeinated coffee. Moreover, NHANES collected detailed information on other risk factors for liver disease, including smoking, alcohol drinking, diabetes, obesity, and infection of hepatitis B and C, and we were able to adjust for them in the analysis.

However, there are several limitations of this study. First of all, we used one 24 hr dietary recall to assess coffee consumption. Single dietary recall may not accurately capture usual intakes of food and beverages. Although we found relatively high agreement in coffee consumption between the two dietary recalls, and between the first dietary recall and FFQ, participants who drank coffee less then daily were likely identified as nondrinkers in our study. Therefore our reference group is a mixture of nondrinkers and sporadic coffee drinkers, which may have attenuated the magnitude of our observed findings. We were also unable to evaluate the effect of infrequent coffee consumption on liver enzymes. The misclassification could be also bidirectional, as infrequent consumers of coffee who happened to drink coffee on the day of recall could be classified as a heavier coffee drinker than they typically are. However, without further knowledge about the misclassification rates, which are not available, it is difficult to speculate about the magnitude or direction of the bias that would result from such bidirectional contamination. Second, a relatively large portion of participants did not specify whether they drank caffeinated or decaffeinated coffee. We expect that these participants most likely consumed caffeinated coffee, however some proportion of them may have also consumed decaffeinated coffee. However, the correlation across subsequent 24-hour recalls among those specifying decaffeinated drinking was relatively high (ICC=0.60), suggesting that our decaffeinated coffee exposure was specific, if not completely sensitive. Third, in stratified analysis, some subgroups, such as the high alcohol intake group, were relatively small, which may have limited our power to detect statistically significant interactions. Lastly, although we adjusted for potential confounders, residual confounding remains a possibility, as in all observational studies.

In summary, our findings suggest that coffee consumption may be associated with favorable liver health, and extend previous findings to decaffeinated coffee drinking. The similarly inverse associations for total and decaffeinated coffee with liver enzyme suggest that coffee constituents other than caffeine may be beneficial toward the liver. Future studies are needed to identify these components and the underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality. The New England journal of medicine. 2012 May 17; 366(20): 1891–1904. [PubMed: 22591295]
2. Ding M, Bhupathiraju SN, Chen M, van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes care. 2014 Feb; 37(2):569–586. [PubMed: 24459154]
3. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014 Feb 11; 129(6):643–659. [PubMed: 24201300]
4. Chen S, Teoh NC, Chitturi S, Farrell GC. Coffee and non-alcoholic fatty liver disease: brewing evidence for hepatoprotection? Journal of gastroenterology and hepatology. 2014 Mar; 29(3):435–441. [PubMed: 24199670]
5. Klatsky AL, Morton C, Udaltsova N, Friedman GD. Coffee, cirrhosis, and transaminase enzymes. Arch Intern Med. 2006 Jun 12; 166(11):1190–1195. [PubMed: 16772246]
6. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2013 Nov; 11(11):1413–1421. e1411. [PubMed: 23660416]
7. Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. Gastroenterology. 2005 Dec; 129(6):1928–1936. [PubMed: 16344061]
8. Arnesen E, Huseby NE, Brenn T, Try K. The Tromso Heart Study: distribution of, and determinants for, gamma-glutamyltransferase in a free-living population. Scand J Clin Lab Invest. 1986 Feb; 46(1):63–70. [PubMed: 2869572]
9. Nilssen O, Forde OH, Brenn T. The Tromso Study. Distribution and population determinants of gamma-glutamyltransferase. Am J Epidemiol. 1990 Aug; 132(2):318–326. [PubMed: 1973595]
10. Casiglia E, Spolaore P, Ginocchio G, Ambrosio GB. Unexpected effects of coffee consumption on liver enzymes. Eur J Epidemiol. 1993 May; 9(3):293–297. [PubMed: 8104822]
11. Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol. 1997 Dec 15; 146(12):1019–1024. [PubMed: 9420526]
12. Aubin HJ, Laureaux C, Zerah F, et al. Joint influence of alcohol, tobacco, and coffee on biological markers of heavy drinking in alcoholics. Biol Psychiatry. 1998 Oct 1; 44(7):638–643. [PubMed: 9787890]
13. Kono S, Shinchi K, Imanishi K, Todoroki I, Hatsuse K. Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan. Am J Epidemiol. 1994 Apr 1; 139(7):723–727. [PubMed: 7909403]
14. Honjo S, Kono S, Coleman MP, et al. Coffee drinking and serum gamma-glutamyltransferase: an extended study of Self-Defense Officials of Japan. Ann Epidemiol. 1999 Jul; 9(5):325–331. [PubMed: 10976859]
15. Nakanishi N, Nakamura K, Nakajima K, Suzuki K, Tatara K. Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. Eur J Epidemiol. 2000 May; 16(5):419–423. [PubMed: 10997828]
16. Tanaka K, Tokunaga S, Kono S, et al. Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. Int J Epidemiol. 1998 Jun; 27(3):438–443. [PubMed: 9698132]
17. Ikeda M, Maki T, Yin G, et al. Relation of coffee consumption and serum liver enzymes in Japanese men and women with reference to effect modification of alcohol use and body mass index. Scand J Clin Lab Invest. 2010 Apr 19; 70(3):171–179. [PubMed: 20205615]

18. Danielsson J, Kangastupa P, Laatikainen T, Aalto M, Niemela O. Dose- and gender-dependent interactions between coffee consumption and serum GGT activity in alcohol consumers. Alcohol and alcoholism. 2013 May-Jun;48(3):303–307. [PubMed: 23492307]
19. DS, P. Liver chemistry and function tests. In: Feldman, MFL.; Brandt, LJ., editors. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th ed.. Philadelphia, PA: Saunders Elsevier; 2010.
20. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology. 2005 Jan; 128(1):24–32. [PubMed: 15633120]
21. Honjo S, Kono S, Coleman MP, et al. Coffee consumption and serum aminotransferases in middle-aged Japanese men. J Clin Epidemiol. 2001 Aug; 54(8):823–829. [PubMed: 11470392]
22. Yamashita K, Yatsuya H, Muramatsu T, Toyoshima H, Murohara T, Tamakoshi K. Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: a cross-sectional study. Nutr Diabetes. 2012; 2:e33. [PubMed: 23169586]
23. Jang ES, Jeong SH, Hwang SH, et al. Effects of coffee, smoking, and alcohol on liver function tests: a comprehensive cross-sectional study. BMC gastroenterology. 2012; 12:145. [PubMed: 23075166]
24. Dranoff JA, Feld JJ, Lavoie EG, Fausther M. How does coffee prevent liver fibrosis? biological plausibility for recent epidemiological observations. Hepatology. 2014 Jan 27.
25. Shim SG, Jun DW, Kim EK, et al. Caffeine attenuates liver fibrosis via defective adhesion of hepatic stellate cells in cirrhotic model. Journal of gastroenterology and hepatology. 2013 Dec; 28(12):1877–1884. [PubMed: 23808892]
26. Arauz J, Moreno MG, Cortes-Reynosa P, Salazar EP, Muriel P. Coffee attenuates fibrosis by decreasing the expression of TGF-beta and CTGF in a murine model of liver damage. Journal of applied toxicology: JAT. 2013 Sep; 33(9):970–979. [PubMed: 22899499]
27. National Center for Health Statistics. [Accessed August 23, 2013] Hyattsville MCfDCaP. National Health and Nutrition Examination Survey 1999–2010 questionnaires, datasets, and related documentation. 2012. www.cdc.gov/nchs/nhanes.htm
28. Moshfegh AJ, Rhodes DG, Baer DJ, et al. The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. Am J Clin Nutr. 2008 Aug; 88(2): 324–332. [PubMed: 18689367]
29. Cook, A.; Friday, JE.; Subar, AF. Dietary Source Nutrient Database for USDA Survey Food Codes. Agricultural Research Service: USDA; 2004.
30. National Center for Health Statistics. Hyattsville MCfDCaP. National Health and Nutrition Examination Survey 2001–2002 lab methods. 2010
31. Torres DM, Harrison SA. Is it time to write a prescription for coffee? Coffee and liver disease. Gastroenterology. 2013 Apr; 144(4):670–672. [PubMed: 23453671]

Table 1

Selected characteristics of study sample by coffee consumption category, NHANES (1999–2010)

	coffee, cup[a] /day				
	0	**<1**	**1–<2**	**2–<3**	**3+**
N	13175	4266	5178	2618	2555
Coffee intake distribution (%)[b]					
Sex					
Male	47.8	40.6	45.5	52.5	58.7
Female	52.2	59.4	54.5	47.5	41.3
Ethnicity					
Mexican American	8.8	11.5	8.2	4.6	2.6
Other Hispanic	5.0	10.1	5.0	3.5	2.1
Non-Hispanic White	65.1	61.9	75.2	84.6	90.4
Non-Hispanic Black	15.3	9.4	7.3	3.8	2.2
Other Race	5.8	7.1	4.4	3.4	2.8
Age					
20–34	42.9	18.7	17.8	11.9	12.2
35–49	29.1	26.1	30.1	32.4	36.0
50–64	17.6	25.9	27.9	33.9	34.4
65–85	10.4	29.2	24.2	21.8	17.4
Education					
less than 9th grade	5.7	12.6	6.9	5.1	4.8
9–11th grade	13.1	14.1	12.1	10.8	12.5
High school/GED	25.2	22.8	24.3	25.8	27.4
Some college or AA degree	32.0	25.1	28.4	29.5	30.7
College and higher	23.9	25.3	28.3	28.9	24.6
BMI, kg/m2					
<18.5	2.1	1.4	1.1	1.8	1.7
18.5–24.9	31.0	32.3	31.1	27.8	30.3
25–29.9	31.2	35.5	34.8	36.9	37.5
30–34.9	18.8	18.3	19.8	19.3	18.5

	coffee, cup[a] /day				
	0	**<1**	**1–<2**	**2–<3**	**3+**
35+	15.7	10.8	11.7	12.9	11.0
Smoking					
Never	54.6	50.1	45.7	41.7	30.5
Former	18.6	25.8	27.8	29.2	29.0
Current, <1 pck/d	15.2	14.0	14.9	14.0	15.7
Current, 1+ pck/d	5.5	3.4	5.8	8.8	19.6
Alcohol					
Non-drinker	30.8	33.9	25.7	23.0	24.5
less than 1 drink/week	28.7	26.6	27.4	26.9	28.4
1–<3 drink/week	13.4	13.8	15.5	13.7	13.0
3–<7 drink/week	9.9	10.6	12.6	14.5	13.0
1–<2 drink/d	6.5	6.5	9.5	11.1	9.7
2+ drink/day	5.9	3.0	4.6	6.7	7.8
Diabetes	6.5	9.7	9.3	7.3	7.3
Hemoglobin A1c >95%	4.7	5.9	5.8	4.5	4.6
HBsAg or HBcAb positive	5.0	7.2	5.7	4.8	4.4
Hepatitis C antibody positive	1.7	1.4	1.7	1.4	2.5

[a] one cup is defined as 10 oz, or 283.5 grams of coffee

[b] Weighted percentage

Table 2

Age and multivariate[a] adjusted associations between categories of coffee intake and abnormal levels[b] of ALT, AST, ALP and GGT, NHANES (1999–2010).

	coffee, cup[c] /day					
Abnormal levels of liver enzyme[b]	**0**	**<1**	**1–<2**	**2–<3**	**3+**	**p trend**
ALT						
N (%)	1560 (11.8)	481 (11.5)	535 (10.6)	254 (10.2)	209 (8.6)	
OR (95% CI)						
age adjusted	ref	1.06 (0.92, 1.22)	0.95 (0.84, 1.08)	0.92 (0.79, 1.08)	0.75 (0.63, 0.89)	0.0003
multivariate adjusted	ref	0.97 (0.85, 1.11)	0.92 (0.81, 1.04)	0.91 (0.77, 1.06)	0.75 (0.63, 0.89)	0.0002
AST						
N (%)	1534 (10.8)	473 (11.0)	554 (10.5)	269 (10.5)	247 (9.7)	
OR (95% CI)						
age adjusted	ref	1.01 (0.90, 1.15)	0.96 (0.85, 1.08)	0.96 (0.80, 1.16)	0.88 (0.73, 1.06)	0.17
multivariate adjusted	ref	1.03 (0.90, 1.18)	0.96 (0.84, 1.10)	0.91 (0.75, 1.10)	0.82 (0.68, 0.98)	0.03
ALP						
N (%)	668 (4.5)	230 (4.4)	242 (4.2)	110 (3.4)	93 (3.7)	
OR (95% CI)						
age adjusted	ref	0.77 (0.61, 0.99)	0.76 (0.60, 0.96)	0.61 (0.47, 0.80)	0.68 (0.51, 0.90)	<0.0001
multivariate adjusted	ref	0.73 (0.58, 0.93)	0.82 (0.65, 1.03)	0.71 (0.54, 0.93)	0.73 (0.55, 0.95)	0.002
GGT						
N (%)	1484 (10.1)	516 (10.9)	571 (10.4)	295 (10.5)	218 (8.1)	
OR (95% CI)						
age adjusted	ref	0.90 (0.78, 1.04)	0.87 (0.75, 1.00)	0.87 (0.74, 1.03)	0.68 (0.57, 0.81)	<0.0001
multivariate adjusted	ref	0.86 (0.74, 1.00)	0.87 (0.75, 1.01)	0.90 (0.75, 1.06)	0.69 (0.57, 0.83)	0.0005

[a] Adjusted for age (20–34, 35–49, 50–64, 65–85 yr), gender (male, female), race and ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other), education (less than 9th grade, 9–11th grade, high school/GED, some college or AA degree, college and higher), smoking status (Never, former, current smoker with <1 pck/d, current smoker with 1+ pck/d, missing), alcohol consumption (non-drinker, <1, 1–<3, 3–<7 drink/week, 1–<2, 2+ drink/day, missing), day of recall (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday and Sunday), hepatitis B (positive serum hepatitis B surface antigen and core antibody, negative) and hepatitis C (positive serum hepatitis C antibody, negative).

[b] Defined as >47 IU/L in men or >30 IU/L in women for ALT, >33 IU/L in men and women for AST, >113 IU/L in men and women for ALP and >65 IU/L in men or >36 IU/L in women for GGT

[c] one cup is defined as 10 oz, or 283.5 grams of coffee.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transaminase; OR, odds ratio; CI, confidence interval

Table 3

Age and multivariate[a] adjusted serum levels of ALT, AST, ALP and GGT, by categories of coffee, NHANES (1999–2010).

	coffee, cup[b] /day					
	0	**<1**	**1–<2**	**2–<3**	**3+**	**p trend**
Coffee intake, gram, median (IQR)	0 (0–0)	222 (177–250)	385 (355–502)	710 (607–742)	1184 (1005–1509)	
ALT, U/L						
median (IQR)	21 (16–29)	20 (16–28)	21 (16–28)	22 (17–29)	21 (17–29)	
Geometric mean (95% CI) age adjusted	22.8 (22.6, 23.1)	22.7 (22.2, 23.1)	22.8 (22.4, 23.2)	23.8 (23.2, 24.3)	23.4 (22.8, 23.9)	0.006
multivariate adjusted	22.8 (22.6, 23.1)	22.8 (22.4, 23.2)	22.6 (22.2, 23.0)	23.0 (22.5, 23.5)	22.3 (21.9, 22.9)	0.21
AST, U/L						
median (IQR)	22 (19–27)	23 (19–27)	22 (19–27)	23 (20–27)	23 (19–26)	
Geometric mean (95% CI) age adjusted	23.6 (23.4, 23.8)	23.7 (23.4, 24.1)	23.3 (23, 23.6)	23.7 (23.3, 24.1)	23.3 (22.9, 23.7)	0.17
multivariate adjusted	23.6 (23.4, 23.8)	23.8 (23.5, 24.1)	23.2 (22.9, 23.5)	23.4 (23.0, 23.7)	22.9 (22.6, 23.3)	0.0004
ALP, U/L						
median (IQR)	67 (55–81)	67 (54–82)	65 (53–80)	65 (53–79)	64 (54–79)	
Geometric mean (95% CI) age adjusted	67.4 (66.6, 68.2)	64.6 (63.5, 65.7)	64.2 (63.3, 65.2)	63.4 (62.0, 64.7)	64.0 (62.9, 65.1)	<.0001
multivariate adjusted	67.4 (66.6, 68.2)	64.3 (63.3, 65.3)	64.8 (63.9, 65.7)	64.3 (62.9, 65.7)	63.8 (62.7, 64.9)	<.0001
GGT, U/L						
median (IQR)	19 (13–30)	19 (13–30)	20 (14–31)	21 (14–32)	20 (14–30)	
Geometric mean (95% CI) age adjusted	21.8 (21.4, 22.2)	20.5 (19.9, 21.1)	21.1 (20.5, 21.7)	21.9 (21.3, 22.7)	21.5 (20.8, 22.2)	0.63
multivariate adjusted	21.8 (21.4, 22.2)	20.8 (20.3, 21.4)	21.2 (20.6, 21.7)	21.5 (20.8, 22.2)	20.4 (19.8, 21.0)	0.0007

[a] Adjusted for age (20–34, 35–49, 50–64, 65–85 yr), gender (male, female), race and ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other), education (less than 9th grade, 9–11th grade, high school/GED, some college or AA degree, college and higher), smoking status (Never, former, current smoker with <1 pck/d, current smoker with 1+ pck/d, missing), alcohol consumption (non-drinker, <1, 1–<3, 3–<7 drink/week, 1–<2, 2+ drink/day, missing), day of recall (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday and Sunday), hepatitis B (positive serum hepatitis B surface antigen and core antibody, negative) and hepatitis C (positive serum hepatitis C antibody, negative).

[b] one cup is defined as 10 oz, or 283.5 grams of coffee.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transaminase; IQR, interquartile range; CI, confidence interval

Table 4

Multivariate[a] adjusted associations between categories of decaffeinated coffee intake and ALT, AST, ALP and GGT, NHANES (1999–2010).

	Decaffeinated coffee, cup[b] /day				
	0	**<1**	**1-<2**	**2+**	***p trend***
	Abnormal levels of liver enzymes[c]				
ALT					
N (%)[d]	1560 (11.8)	87 (9.9)	71 (8.8)	32 (7.3)	
OR (95% CI)	ref	0.82 (0.62, 1.06)	0.74 (0.52, 1.04)	0.62 (0.41, 0.94)	*0.002*
AST					
N (%)[d]	1534 (10.8)	103 (11.3)	76 (9.9)	46 (9.2)	
OR (95% CI)	ref	1.02 (0.75, 1.37)	0.84 (0.60, 1.18)	0.74 (0.49, 1.11)	*0.11*
ALP					
N (%)[d]	668 (4.5)	56 (4.7)	47 (5.8)	28 (5.5)	
OR (95% CI)	ref	0.63 (0.43, 0.94)	0.92 (0.63, 1.32)	0.93 (0.58, 1.50)	*0.34*
GGT					
N (%)[d]	1484 (10.1)	117 (10.9)	95 (12.3)	48 (9.9)	
OR (95% CI)	ref	0.71 (0.52, 0.67)	0.88 (0.67, 1.16)	0.70 (0.49, 1.00)	*0.01*
	Serum levels of liver enzymes, continuous				
N (%)[d]	13175 (88.7)	926 (4.3)	753 (3.9)	481 (3.1)	
Geometric mean (95% CI)					
ALT	22.8 (22.6, 23.0)	22.5 (21.7, 23.3)	22.4 (21.5, 23.5)	22.0 (21.2, 22.8)	*0.08*
AST	23.6 (23.4, 23.8)	23.9 (23.3, 24.5)	23.4 (22.8, 24.1)	23.0 (22.4, 23.7)	*0.09*
ALP	67.4 (66.6, 68.2)	63.8 (61.9, 65.7)	65.4 (63.2, 67.6)	65.7 (63.2, 68.3)	*0.009*
GGT	21.8 (21.4, 22.2)	19.3 (18.2, 20.5)	20.2 (19.1, 21.3)	19.5 (18.5, 20.6)	*<.0001*

[a] Adjusted for age (20–34, 35–49, 50–64, 65–85 yr), gender (male, female), race and ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other), education (less than 9th grade, 9–11th grade, high school/GED, some college or AA degree, college and higher), smoking status (Never, former, current smoker with <1 pck/d, current smoker with 1+ pck/d, missing), alcohol consumption (non-drinker, <1, 1–<3, 3–<7 drink/week, 1–<2, 2+ drink/day, missing), day of recall (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday and Sunday), hepatitis B (positive serum hepatitis B surface antigen and core antibody, negative) and hepatitis C (positive serum hepatitis C antibody, negative).

[b] one cup is defined as 10 oz, or 283.5 grams of coffee.

[c] Defined as >47 IU/L in men or >30 IU/L in women for ALT, >33 IU/L in men and women for AST, >113 IU/L in men and women for ALP and >65 IU/L in men or >36 IU/L in women for GGT

[d] People who reported drinking regular coffee or coffee with unspecified caffeine status were excluded

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transaminase; OR, odds ratio; CI, confidence interval