Title

Coffee consumption is not associated with prevalent subclinical cardiovascular disease (CVD) or the risk of CVD events, in nonalcoholic fatty liver disease: results from the multi-ethnic study of atherosclerosis

Authors

Simon, Tracey G
Trejo, Maria Esther Perez
Zeb, Irfan
et al.

Publication Date

2017-10-01

DOI

10.1016/j.metabol.2017.06.007

Peer reviewed

HHS Public Access

Author manuscript

Metabolism. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Metabolism. 2017 October ; 75: 1–5. doi:10.1016/j.metabol.2017.06.007.

Coffee consumption is not associated with prevalent subclinical cardiovascular disease (CVD) or the risk of CVD events, in nonalcoholic fatty liver disease: results from the Multi-Ethnic Study of Atherosclerosis

Tracey G. Simon, MD[1], **Maria Esther Perez Trejo, PhD**[2], **Irfan Zeb, MD**[3], **Alexis C. Frazier-Wood, PhD**[4], **Robyn L McClelland, PhD**[2], **Raymond T. Chung, MD**[1], and **Matthew J. Budoff, MD**[5]

[1]Liver Center, Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School, Boston MA

[2]Department of Biostatistics, University of Washington, Seattle WA

[3]Department of Cardiology, Mount Sinai St. Luke's Roosevelt Hospital (Bronx-Lebanon Hospital Center)

[4]Children's Nutrition Research Center, Baylor College of Medicine, Houston TX

[5]Los Angeles Biomedical Research Institute, Division of Cardiology, Harbor-UCLA Medical Center, Los Angeles, CA

Abstract

Background—Atherosclerosis and its clinical sequelae represent the leading cause of mortality among patients with nonalcoholic fatty liver disease (NAFLD). While epidemiologic data support the hepatoprotective benefits of coffee in NAFLD, whether coffee improves NAFLD-associated CVD risk is unknown.

Corresponding author: Matthew J. Budoff, MD, FACC, Los Angeles Biomedical Research Institute, Division of Cardiology, Harbor-UCLA Medical Center, 1000 West Carson Street, Box 405, Torrance, CA 90509, Telephone: (310) 222-4107, Fax: (310) 782-9652, mbudoff@labiomed.org.

Ethical Approval: The study was approved by Partners Human Research Committee (Institutional Review Board).

Author contributions:

- TGS: study design, data interpretation, drafting
- MEPT: data analysis, interpretation, critical revision
- RLM: data analysis, interpretation, critical revision
- IZ: study design, critical revision
- RTC: study design, critical revision, study oversight
- MJB: study design, critical revision, study oversight

Conflict of Interest and Disclosures: The authors report no disclosures or potential conflicts of interest.

Methods—We examined 3,710 ethnically-diverse participants from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, without history of known liver disease, and with available coffee data from a validated 120-item food frequency questionnaire. All participants underwent baseline non-contrast cardiac CT from which NAFLD was defined by liver:spleen ratio (L:S<1.0), and subclinical CVD was defined by coronary artery calcium (CAC)>0. Major CVD events were defined by the first occurrence of myocardial infarction, cardiac arrest, angina, stroke, or CVD death. We used log-binomial regression to calculate the adjusted prevalence ratio (PR) for CAC>0 by coffee intake and NAFLD status, and events were compared between groups using frequency of events within adjusted Cox proportional hazard regression models.

Results—Seventeen percent (N=637) of participants met criteria for NAFLD. NAFLD participants were more likely to have elevated BMI (mean 31.1 ± 5.5 kg/m^2 vs. 28.0 ± 5.2 kg/m^2, p<0.0001), and diabetes (22% vs. 11%, p<0.0001), but did not differ in daily coffee consumption (p=0.97). Among NAFLD participants, coffee consumption was not associated with prevalent, baseline CAC>0 (PR=1.02 [0.98-1.07]). Over 12.8 years of follow-up, 93 NAFLD and 415 non-NAFLD participants experienced a CV event. However, coffee intake was not associated with incident CVD events, in either NAFLD (HR=1.05 [0.91-1.21]) or non-NAFLD participants (HR=1.03 [0.97-1.11]).

Conclusion—In a large, population-based cohort, coffee consumption was not associated with the prevalence of subclinical CVD, nor did coffee impact the future risk of major CVD events, regardless of underlying NAFLD status.

Keywords

fatty liver disease; NAFLD; cardiovascular death; ischemic heart disease; myocardial infarction; coffee; caffeine

Introduction

Among patients with nonalcoholic fatty liver disease (NAFLD), atherosclerosis and its clinical sequelae represent the leading cause of mortality [1, 2], and NAFLD has also been linked to subclinical CVD, including coronary calcification, carotid intima-media thickness, and arterial hypertension [3]. Recent data suggest that coffee exerts unique metabolic and hepatoprotective benefits in NAFLD, improving insulin sensitivity and reducing fibrosis progression [4-6]. Although the relationship between coffee and CVD risk is well studied within the general population, with modest coffee consumption associated with a neutral to mildly decreased CVD risk [7-9], little is known about the CVD benefits of coffee in NAFLD. We explored whether coffee consumption is related to prevalent coronary artery calcification (CAC) and the risk of incident CVD events among participants with NAFLD in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

MESA is a population-based, prospective study of 6,814 adults, who were free of known CVD at enrollment. After providing written informed consent, all participants completed examination 1, including a validated, 120-item food frequency questionnaire that assesses

diet over the preceding year, including average serving size and frequency of coffee, alcohol intake and other dietary variables (grams/day), and each were adjusted for daily energy expenditure [10]. Coffee consumption was analyzed in two separate models: (1) coffee intake (yes/no) and (2) daily servings of coffee (range: 0-9 servings/day). Due to non-random missing data from one center, imputed dietary data were used for a small subset of individuals to avoid biasing parameter estimates.

The methodology for measuring coronary artery calcification and other covariates within MESA, and for defining comorbidities including hypertension, dyslipidemia and diabetes, have previously been described[11]. Inflammatory biomarkers were assessed in a subset of MESA participants using methodology that has also been reported, and biomarkers included gamma-glutamyltransferase (GGT), Creactive protein (CRP), and interleukin-6 (IL-6)[12]. Finally, each participant underwent non-contrast cardiac computed tomography (CT) for measurement of coronary artery calcium (CAC) and liver fat, with steatosis defined by the validated liver-to-spleen (L:S) attenuation ratio<1.0, as previously described by our group and others[13].

L:S measurements were available for 4,389 participants. Six hundred seventy-nine individuals were excluded: 405 had a history of heavy alcohol use (>7 drinks/week in women or >14 drinks/week in men), 59 reported alcohol consumption but did not quantify intake, 22 self-reported Hepatitis B virus, 16 self-reported Hepatitis C virus, 8 reported cirrhosis, 2 were amiodarone users and 167 had missing dietary information, leaving a final population of 3,710 individuals.

Subclinical CVD was defined by CAC>0 at examination 1. Clinical events were ascertained by follow-up telephone interviews every 9-12 months, with all events adjudicated by an independent MESA committee[14]. Incident major CVD events included the first occurrence of myocardial infarction, resuscitated cardiac arrest, angina, stroke or CVD death. Prevalence ratios were calculated for the risk of baseline CAC>0 by servings/day of coffee, and compared in participants with and without radiographic NAFLD, after adjusting for cardiometabolic risk factors. Frequency of events were compared using proportional hazard regression models to estimate the relationship between coffee consumption and risk of incident major CV events, in participants with and without radiographic NAFLD.

Results

The baseline demographic and clinical characteristics of the NAFLD (n=637) and non-NAFLD (n=3,073) participants are shown in Table S1. Compared to individuals without NAFLD, those with NAFLD were younger (mean age 61±10 vs. 63±11 years, p<0.0001), but had higher mean body mass index (BMI) (31.1±5.5 vs. 28.0±5.2 kg/m^2, p<0.0001), and were more likely to have diabetes (22% vs 11%, p<0.0001) and the metabolic syndrome (65% vs. 33%, p<0.0001; Table S1). Mean daily coffee consumption did not differ between NAFLD and non-NAFLD participants (mean 1.1±1.5 servings/day in both groups; p=0.97).

At baseline, 335 NAFLD participants (52.6%) had CAC>0, compared to 1522 (49.5%) in the non-NAFLD group (p=0.164). In fully-adjusted, multivariable log-binomial regression

analysis, coffee servings/day were not associated with prevalent CAC>0 (PR=1.00 [95% CI 0.98-1.02]). This association was unchanged when the cohort was limited just to those with NAFLD (N=637; PR=1.02 [0.98-1.07]; Table 1A), and also when the cohort was limited to those with NAFLD and CRP ≥5 mg/L (N=196) (RP=1.10 [0.98-1.23]). The relationship between coffee servings/day and prevalent CAC>0 similarly did not differ between NAFLD (PR=1.02 [95% CI 0.98-1.07]) and non-NAFLD participants (PR=0.99 [95% CI 0.97-1.01]). Coffee consumption also was not associated with differences in log-transformed values of the circulating inflammatory biomarkers, GGT, CRP or IL-6 (all p>0.05; Table 1B).

Over a median 12.8 years, 93 NAFLD and 415 non-NAFLD MESA participants experienced CVD events (Table 2). In fully-adjusted Cox proportional hazard regression models accounting for the presence of NAFLD, no association was found between coffee consumption and risk of incident CV events (HR=1.03 [95% CI 0.97-1.10]). In stratified analysis, a null association was found between servings/day of coffee and incident CV events, in both NAFLD (HR=1.05, [95% CI 0.91-1.21]) and non-NAFLD participants (HR=1.03 [95% CI 0.97-1.11) (Table 2). No significant interactions were observed between coffee and age category, sex, BMI, race, smoking, alcohol intake or diabetes.

Discussion

This represents the first published study from a large, population-based, multi-ethnic cohort to describe the impact of coffee consumption on subclinical and overt CVD risk, in participants with NAFLD, compared to the general population. We found that among participants with NAFLD, coffee consumption was not associated with prevalent coronary calcification or with risk of incident CVD events. This null association persisted in dose-response analyses that accounted for daily servings of coffee, arguing against an inflection point at which a certain daily intake of coffee might give rise to protective effects.

Published data in the general population regarding the benefits of coffee on CVD outcomes are conflicting, with most studies describing neutral to perhaps beneficial effects [7, 8]. Available reports from population-based cohorts with dose-response relationships are heterogeneous, related likely to variations in statistical analyses, inadequately-measured dietary or lifestyle factors, such as smoking, which could confound coffee intake. In addition, most studies to date have relied upon primarily Caucasian populations, limiting potential generalizability[15]. Among the few available multi-ethnic analyses, a recent report from MESA demonstrated a neutral overall association between coffee, CAC prevalence, progression and incident CVD events, to date none have included NAFLD in their analyses [10].

In contrast to the general population, little is known about the relationship between coffee and CVD in patients with NAFLD. However, there is a growing appreciation of the close ties between NAFLD and both subclinical[13, 16] and overt CVD risk[1, 2]. Given that coffee has been shown to attenuate NAFLD fibrosis progression, minimize hepatocarcinogenesis and exert anti-inflammatory effects in patients with chronic liver disease, it has been hypothesized that coffee could exert uniquely beneficial effects in NAFLD, beyond that observed in the general population. However, in the present study, we found a neutral

association between coffee intake and both prevalent coronary calcification and risk of incident CV events, among participants with NAFLD, that did not differ significantly from the non-NAFLD MESA population.

The proposed benefits of coffee in NAFLD are thought to relate to caffeine-mediated inhibition of hepatic stellate cell proliferation[17], and to anti-fibrotic and anti-inflammatory hepatoprotective effects of polyphenols[18]. In epidemiologic studies, coffee consumption has been linked to numerous beneficial metabolic effects, including reduced systemic inflammation and improved insulin sensitivity[4-6], and among patients with chronic liver disease, coffee has been associated with a reduced risk of hepatic fibrogenesis and hepatocellular carcinoma (HCC)[5, 19]. However, the precise pathophysiologic mechanisms that underpin this relationship remain incompletely characterized. In a recent prospective study by Zelber-Sagi and colleagues, coffee was associated only with reduced serum markers of fibrosis over time, but did not impact steatosis [20]. Further studies are needed to determine whether coffee affects steatogenesis, or rather if the hepatoprotective benefits of coffee relate primarily to prevention of fibrosis and hepatocarcinogenesis [20].

This study benefited from a large, population-based cohort with well-characterized dietary data and adjudicated cardiovascular outcomes. Nonetheless, several limitations must be highlighted. First, its observational nature renders this study subject to residual confounding. Second, while CT is well-validated for steatosis, it cannot reliably identify NASH or fibrosis, and without hepatic histology or liver chemistry data, we could not explore coffeerelated effects by NAFLD severity. Third, our study lacked echocardiography and future analyses will be needed to explore these relationships as they relate to cardiac structure and function. Finally, although power was a concern, we achieved 80% power to detect an association of HR=0.82 between servings/day of coffee and incident CVD in NAFLD participants. This effect size is favorable to the neutral overall effect previously reported from the general MESA population[10], and roughly equivalent to estimates from a recent meta-analysis (HR=0.85)[9], suggesting that our study was adequately powered to detect previously-reported associations.

In conclusion, within this large, well-characterized cohort, we provide the first report that coffee consumption is not associated with prevalent subclinical CVD or with future risk of CVD events, in individuals with NAFLD. Future long-term studies with well-phenotyped NAFLD populations, focused upon the dose and timing of coffee consumption with respect to NAFLD severity, will allow for more complete characterization of the relationship between coffee intake and NAFLD-associated CVD risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Information / Grant Support: NIH K24 DK078772 (RTC)

The MESA Study was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167,

N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from NCATS. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

References

1. Kim D, Kim WR, Kim HJ, et al. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013; 57:1357–65. [PubMed: 23175136]
2. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006; 44:865–73. [PubMed: 17006923]
3. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 2010; 363:1341–50. [PubMed: 20879883]
4. Bambha K, Wilson LA, Unalp A, et al. Coffee consumption in NAFLD patients with lower insulin resistance is associated with lower risk of severe fibrosis. Liver Int. 2014; 34:1250–8. [PubMed: 24267865]
5. Molloy JW, Calcagno CJ, Williams CD, et al. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. Hepatology. 2012; 55:429–36. [PubMed: 21987293]
6. Catalano D, Martines GF, Tonzuso A, et al. Protective role of coffee in non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci. 2010; 55:3200–6. [PubMed: 20165979]
7. Wu JN, Ho SC, Zhou C, et al. Coffee consumption and risk of coronary heart diseases: a metaanalysis of 21 prospective cohort studies. Int J Cardiol. 2009; 137:216–25. [PubMed: 18707777]
8. Malerba S, Turati F, Galeone C, et al. A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. Eur J Epidemiol. 2013; 28:527–39. [PubMed: 23934579]
9. Ding M, Bhupathiraju SN, Satija A, et al. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014; 129:643–59. [PubMed: 24201300]
10. Miller EPZ D, Frazier-Wood AC, Michos E, Averill M, Sandfort V, Burke GL MD, Polak JF MD, Lima J, Post WS, Blumenthal RS, Guallar E, Martin SS. Association between Coffee, Tea, and Caffeine Intake with Coronary Artery Calcification and Cardiovascular Events: Results from the Multi-Ethnic Study of Atherosclerosis (MESA). The American Journal of Medicine. 2017
11. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–81. [PubMed: 12397006]
12. Bradley R, Fitzpatrick AL, Jenny NS, et al. Associations between total serum GGT activity and metabolic risk: MESA. Biomark Med. 2013; 7:709–21. [PubMed: 24044563]
13. Zeb I, Li D, Nasir K, et al. Computed tomography scans in the evaluation of fatty liver disease in a population based study: the multi-ethnic study of atherosclerosis. Acad Radiol. 2012; 19:811–8. [PubMed: 22521729]
14. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008; 168:1333–9. [PubMed: 18574091]
15. Ding M, Satija A, Bhupathiraju SN, et al. Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts. Circulation. 2015; 132:2305–15. [PubMed: 26572796]
16. VanWagner LB, Wilcox JE, Colangelo LA, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: A population-based study. Hepatology. 2015; 62:773–83. [PubMed: 25914296]
17. Shim SG, Jun DW, Kim EK, et al. Caffeine attenuates liver fibrosis via defective adhesion of hepatic stellate cells in cirrhotic model. J Gastroenterol Hepatol. 2013; 28:1877–84. [PubMed: 23808892]

18. Vitaglione P, Morisco F, Mazzone G, et al. Coffee reduces liver damage in a rat model of steatohepatitis: the underlying mechanisms and the role of polyphenols and melanoidins. Hepatology. 2010; 52:1652–61. [PubMed: 21038411]

19. Modi AA, Feld JJ, Park Y, et al. Increased caffeine consumption is associated with reduced hepatic fibrosis. Hepatology. 2010; 51:201–9. [PubMed: 20034049]

20. Zelber-Sagi S, Salomone F, Webb M, et al. Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. Transl Res. 2015; 165:428–36. [PubMed: 25468486]

Highlights

- This study is the first to explore the CV effects of coffee in adults with NAFLD.
- In those with NAFLD, no association was found between coffee and subclinical CVD.
- In those with NAFLD, coffee was not associated with reduced risk of major CV events.
- These results suggest coffee may not have unique cardioprotective benefits in NAFLD.

Table 1a, 1b

Cross-sectional association between coffee consumption and the risk of prevalent coronary artery calcification (CAC) (Panel 1A), and mean log-transformed serum inflammatory biomarker levels (Panel 1B), among MESA participants with radiographic NAFLD (N=637)

1A. Multivariable model	**Adjusted[1] prevalence ratio [95% CI] for CAC > 0**		
	No coffee	**Any coffee**	**Servings per day**
• Model 1[†]	*Ref.*	1.24 [1.03, 1.50]	1.05 [1.01, 1.10]
• Model 2[‡]	*Ref.*	1.15 [0.97, 1.37]	1.04 [0.996, 1.08]
• Model 3[∫]	*Ref.*	1.09 [0.92, 1.30]	1.03 [0.98, 1.07]
• Model 4[¥]	*Ref.*	1.08 [0.91-1.29]	1.02 [0.98-1.07]
• Model 5[€]	*Ref.*	1.08 [0.91-1.29]	1.02 [0.98-1.07]
1B. Inflammatory marker level[2]	**Adjusted[*] β coefficient [95% CI]**		
	No coffee	**Any coffee**	**Servings per day**
• Gamma glutamyltransferase, log IU/L, (N=634) (N=633)	*Ref.*	-0.0638 [-0.0739, 0.0201]	-0.0127 [-0.0558, 0.0304]
• C-reactive protein, log mg/L, (N=634)	*Ref.*	0.0739[-0.108, 0.256]	-0.0059 [-0.0629, 0.0511]
• Interleukin-6, log pg/mL, (N=627)	*Ref.*	0.0305 [-0.0789, 0.140]	-0.0138 [-0.0480, 0.0204]

[1] Multivariable adjusted prevalence ratios are shown.

[†] Model 1: unadjusted

[‡] Model 2: age, sex and race/ethnicity

[∫] Model 3: Model 2 + body mass index (BMI, kg/m^2), total cholesterol, use of any lipid-lowering medication, high-density lipoprotein (HDL) cholesterol, diabetes, hypertension, alcohol use (servings/day) and smoking status

[¥] Model 4: Model 3 + energy-adjusted intake of regular soda (servings/day), diet soda (servings per day), red meat (servings per day) and fructose (grams)

[€] Model 5: Model 4 + Chronic Kidney Disease (CKD), defined by glomerular filtration rate (GFR) < 60

[2] All serum inflammatory markers were log-transformed

[*] Multivariable linear regression model, adjusted for age, race, gender, body mass index (BMI), waist circumference, diabetes, hypertension, CKD, use of lipid-lowering medications, smoking status, alcohol use (servings/day), and energy-adjusted intake of diet soda and regular soda, fructose and red meat.

Table 2

Unadjusted and adjusted hazard ratios (95% confidence intervals) between coffee consumption and incident cardiovascular events over 12.8 years of median follow-up, according to NAFLD status

Daily coffee intake	No NAFLD (N=3,710)			NAFLD (N=637)		
	No coffee	Any coffee	Servings / day	No coffee	Any coffee	Servings / day
No. events / no. total	105/870	310/2203	-	16/164	77/473	-
IR per 1000 p-y.	10.7	12.8	-	8.7	15.2	-
• Model 1[†]	1.00	1.19 [0.96, 1.49]	1.04 [0.98, 1.10]	1.00	1.74 [1.02, 2.98]	1.09 [0.96, 1.24]
• Model 2[‡]	1.00	1.08 [0.86, 1.36]	1.04 [0.97, 1.11]	1.00	1.51 [0.85, 2.68]	1.04 [0.91, 1.20]
• Model 3[∫]	1.00	1.09 [0.87, 1.37]	1.03 [0.97, 1.10]	1.00	1.53 [0.85, 2.74]	1.05 [0.92, 1.21]
• Model 4[¥]	1.00	1.09 [0.86-1.37]	1.03 [0.97-1.11]	1.00	1.61 [0.89-2.89]	1.05 [0.91-1.21]

Abbreviations: NAFLD, nonalcoholic fatty liver disease; IR, incidence rate; p-y, person-years; No., number

[†]Model 1: unadjusted

[‡]Model 2: adjusted for age, sex and race/ethnicity

[∫]Model 3: Model 2 + body mass index (BMI, kg/m^2), total cholesterol, use of any lipid-lowering medication, high-density lipoprotein (HDL) cholesterol, diabetes, hypertension, alcohol use (servings/day) and smoking status

[¥]Model 4: Model 3 + energy-adjusted estimated daily intake of diet soda and regular soda, fructose and red meat.