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Dietary history and physical activity and risk of advanced liver disease in veterans with chronic hepatitis C infection

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Abstract

Background—The role of customary diet and physical activity in development of advanced HCV-related liver disease is not well-established.

Methods—We conducted a retrospective association study in 91 male veterans with PCR-confirmed chronic HCV and biopsy-determined hepatic pathology. Respondents completed the Block Food Frequency and the International Physical Activity questionnaires. We conducted three independent assessments based on hepatic pathology: fibrosis (advanced=F3-F4 vs. mild=F1-F2), inflammation (advanced=A2-A3 vs. mild=A1) and steatosis (advanced=S2-S3 vs. mild=S1). Each assessment compared estimated dietary intake and physical activity in veterans with advanced disease to that in analogous veterans with mild disease. Multivariate models adjusted for total calories, age, race/ethnicity, biopsy-to-survey lag-time, BMI, pack-years smoking, and current alcohol use.

Results—Average veteran age was 52, with 48% African-American. Advanced fibrosis was more prevalent than advanced inflammation or steatosis (52.7% vs. 29.7% vs. 26.4% respectively). The strongest multivariate association was the suggestive 14-fold significantly decreased advanced fibrosis risk with lowest dietary copper intake (OR=0.07, 95% CI 0.01–0.60). Other suggestive associations included the 6.5-fold significantly increased advanced inflammation risk with lower vitamin E intake and 6.2-fold significantly increased advanced steatosis risk with lower riboflavin intake. The only physical activity associated with degree of hepatic pathology was a 2-fold greater weekly MET-minutes walking in veterans with mild compared to advanced steatosis (p=0.02).

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Conclusions—Several dietary factors and walking may be associated with risk of advanced HCV-related liver disease in male veterans. However, given our modest sample size, our findings must be considered as provisional pending verification in larger prospective studies.

Keywords

Nutrition Assessment; Exercise; Infectious Diseases; Military Personnel; Epidemiology; Gastroenterology

Background

An estimated 4.1 million persons in the U.S. are infected with the hepatitis C virus (HCV), 3.2 million with chronic infection.[1] From 5–25% of those with chronic infection ultimately develop cirrhosis after a period of 25–30 years.[2] HCV-related cirrhosis is now the leading cause of liver transplant[3] and conveys the greatest excess risk of hepatocellular carcinoma (HCC)[4] in the U.S.

A number of factors are known to increase risk of hepatic disease progression in the context of chronic HCV infection: increasing age, male gender, longer duration of infection, African-American ethnicity and chronic alcohol abuse. Recent research suggests type 2 diabetes[5–9] and higher body mass index (BMI)[5;7;9;10] also increase risk of HCV-related hepatic disease.

Several epidemiologic studies have evaluated diet as a risk factor for advanced liver disease. [11–17] Most employed either an ecological design that correlated population-level consumption of specific foods with population-level levels of liver disease mortality,[14;15] or a case-control design that compared cases with varied etiologies for liver disease (e.g., hepatitis B, HCV) to controls without liver disease.[11–13;16;17] Most studies evaluated only a single or a few selected macro- or micro-nutrients. Further, none of the ecological studies had confirmatory liver biopsies to stage pathology. A single case-control study had liver biopsy data for both the case and control group.[17] This study, conducted in an Italian population, reported multivariate associations between increased intake of four dietary components (total calories, carbohydrate, lipids and polyunsaturated fats) above government-recommended daily allowance guidelines and risk of biopsy-confirmed advanced liver disease in HCV-infected patients.[17] It is unclear if these results would generalize to U.S. populations given marked differences in customary diet and prevalence of obesity.

One group in the U.S. that has been particularly affected by HCV is the 8.1 million veterans enrolled in the U.S. Department of Veterans Affairs (VA) healthcare system.[18] A national seroprevalence study demonstrated a markedly higher rate of HCV among veterans using the VA compared to that in the general U.S. population (5.4%[19] vs. 1.8%[20] respectively).

We performed a retrospective nutritional epidemiology association study in a multiethnic sample of HCV-infected male veterans who access the VA medical system. Our primary goals were: 1) to evaluate whether dietary factors associated with risk of advanced HCV-related liver disease in an Italian population[17] were similarly associated with disease risk in a U.S. population, 2) to evaluate multiple additional potential dietary risk factors, and 3) to perform a novel evaluation of the association between physical activity and advanced HCV-related liver disease.

Methods

Design and Study Population Recruitment

We performed a retrospective association study among chronically HCV-infected male patients seen at the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, Texas. For purposes of our study, our sampling frame consisted of all consecutive male veterans aged 18–70 years who met the following eligibility criteria: 1) had received a liver biopsy within three years of study enrollment; 2) had positive ELISA and PCR tests indicating chronic HCV, 3) were not on HCV treatment either at the time of biopsy or at study recruitment, 4) were serologically-confirmed as negative for both HIV and chronic hepatitis B viral infections (HBV surface antigen), 5) never had either confirmed or suspected decompensated liver disease or liver cancer, and 6) were residents of the greater Houston Metropolitan Statistical Area or lived within 1.5 hours driving time of MEDVAMC given participation necessitated a clinic visit.

We contacted by phone the first 150 consecutive study eligible veterans from among the over 300 HCV-infected veterans who had biopsies performed at MEDVAMC during the 3 years prior to study initiation. Total time to complete all study activities including an extensive research survey and having anthropometric measures taken was 1.5 hours. Participants received \$30 remuneration.

This research study was approved by the Institutional Review Boards for MEDVAMC and Baylor College of Medicine.

Data Collection and Study Measures

Electronic Medical Record Review—A physician performed a structured electronic medical record review of all potentially study eligible HCV+ veterans listed in our biopsy-based sampling frame prior to study recruitment to: 1) confirm the veteran in fact still met clinical eligibility criteria for recruitment, and 2) to record relevant clinical data including viral load and genotype.

Questionnaires—Trained interviewers administered a structured survey to all study participants during a research visit at MEDVAMC. We collected history of lifetime alcohol and tobacco use employing validated questions previously created for U.S. population-based cohort research.[21]

Block Food Frequency Questionnaire (FFQ)—We assessed dietary intake using the validated Block FFQ which interrogates quantity and frequency of consumption of customary as well as of seasonal or irregularly-eaten individual foods and beverages during the year prior to survey administration.[22;23] Estimation of customary serving size is aided by use of a pictorial guide. Each participant's dietary item responses were aggregated and interrogated using the BFFQ's validated proprietary algorithm. It then generated estimated average daily dietary intake of all major macronutrients (e.g., protein and saturated fats) and micronutrients (e.g., vitamin E and copper) for all individual participants during this one-year time period. Participants in our study were further advised that if their customary diet had changed due to their HCV infection diagnosis or any associated symptoms, that they should answer the dietary questions for the year prior to making any dietary modifications.

Recommended Daily Allowance (RDA)—We obtained U.S. government recommended daily allowance (RDA) for micro- and macro-nutrient intake to maintain basic health for 97%-99% of adult males ages 18 and 70 from published Reference Daily Intake tables.[24]

International Physical Activity Questionnaire—We evaluated study participant's physical activity with the International Physical Activity Questionnaire, short-form (IPAQ-sf).[25] The IPAQ-sf quantifies total physical activity during the last seven days across four domains: leisure-, domestic-, work- and transportation-related activity. A total physical activity score is computed for sedentary, walking, moderate- and vigorous-intensity activities using type, frequency, duration and metabolic equivalent of task (MET) for activities within each domain and is reported as MET-minutes per week. The IPAQ-sf also classifies total combined weekly physical activity scores as representing high, moderate or low activity based on published guidelines and research.

Anthropometric Measurements—We used a single dedicated physician beam scale with height rod to measure weight in pounds and standing height in inches without shoes. All anthropometric measurements were taken twice and the average measurement was used to calculate BMI ([weight in pounds/height in inches²]*703).

Hepatic Pathology Assessment—All pathology slides were re-evaluated for this study by a single study pathologist who was blinded as to participant's medical history. Hepatic fibrosis was assessed using the METAVIR system[26] five-point scale (F0-F4); F0, fibrosis is absent; F1, portal/perivenular fibrosis without septa; F2, fibrosis with a few septa; F3, numerous septa but cirrhosis is absent; and F4, cirrhosis present. We also assessed necroinflammatory activity using the METAVIR system (A0-A3); A0, no histologic evidence of activity; A1, mild inflammatory activity present; A2 moderate activity present; and A3, severe activity present. Finally, we assessed degree of steatosis (S0-S3); S0, 2% affected hepatocytes; S1, 3–29% affected; S2, 30–59% affected, and S3, 60% affected hepatocytes.[27]

Statistical Analyses

We conducted three comparisons based on hepatic fibrosis (F3-F4 vs. F1-F2), inflammation (A2-A3 vs. A1) or steatosis (S2-S3 vs. S1). We compared estimated daily dietary intake and daily physical activity in cases within each category of advanced liver disease to that in analogous controls with mild liver disease using the Brown-Mood test for medians computed from continuous variables and the χ^2 for categorical variables.

We employed unconditional binary logistic regression to evaluate the association between an individual dietary factor and risk of advanced fibrosis, inflammation or steatosis. In order to evaluate for a potential dose-response relationship, estimated daily intake in all models was by convention divided into tertiles defined as lowest, moderate and high daily consumption. We used the observed dietary factor distribution in the controls to define tertile cutpoints.

All multivariate models compared risk of each sub-type of advanced liver disease in those with lowest and moderate dietary intake compared to those with highest, or upper 1/3, daily dietary intake based on the distribution in the mild liver disease control group. Every model was adjusted for total daily calories consumed so that reported dietary effect estimates are energy-adjusted or isocaloric.[28] We also adjusted each model for potential confounding by age, race/ethnicity, BMI, lag-time between biopsy and survey, current alcohol use and pack-years of smoking. We evaluated for potential interaction or effect modification between all main effects; interaction terms were included in final reported models only if significant at $p < 0.15$. Model-based parameter estimates are reported as odds ratios with associated 95% confidence intervals. Results were considered significant if the p-value was less than 0.05, and approaching significance if the p-value was between 0.05 and 0.10.

All analyses were conducted using SAS 9.2 (SAS Institute, Cary, N.C.)

Results

We successfully contacted 111 male veterans by phone (78% phone contact rate) during our study recruitment period (January 2007-August 2007). Most (N=99) veterans contacted consented to participate (89% consent rate). Our analyses are restricted to the 91 participants with complete data for all key risk factors, outcomes and confounders. Of the nine participants not included in our analyses, four were excluded because they provided highly inconsistent answers to the dietary questionnaire, two because they failed to complete a sufficient number of the over 100-item dietary questionnaire to validly calculate nutrient intake, and three because they had liver biopsies with less than the minimum required 11 portal tracts. Overall, our study participant sample represents approximately 10% of all HCV+ veterans seen at MEDVAMC during the study period.

The average age at biopsy was 52 years, and most participants were African-American (48%) or White non-Hispanic (41%). (Table 1) Approximately half (47%) had completed at least some college education and most (88%) were infected with HCV genotype 1.

Twenty-seven (29.7%) participants were classified as cases of advanced inflammation (scores A2-A3), 48 (52.7%) were classified as cases of advanced fibrosis (scores F3-F4), and twenty-four (26.4%) were classified as cases with advanced steatosis (scores S2-S3). (Table 1)

The prevalence of health behaviors that increase risk of advanced liver disease was high. More than 91% of these HCV+ veterans reported a positive lifetime history of ever regularly consuming alcohol, with almost 42% reporting they currently consumed alcohol. (Table 1) Prevalence of a positive lifetime history of smoking was almost as high (87%), with over 36% reporting that they currently smoke. Further, more than three-fourths of these veterans were either overweight (42%) or obese (35%).

Dietary History as Risk Factor for Advanced Liver Disease

Few crude comparisons in median daily dietary intake between cases with advanced liver disease and controls with mild liver disease reached or approached statistical significance. Only four dietary factors (carbohydrates, reduced glutathione, percentage of calories from carbohydrates and glycemic index) were significantly different in cases with advanced steatosis compared to controls with mild steatosis. Only one dietary factor, median daily dietary intake of the carotenoid antioxidant lutein, was significantly lower in cases with advanced inflammation compared to controls with mild inflammation (1707 $\mu\text{g/day}$ vs. 2767 $\mu\text{g/day}$ respectively, $p=0.01$). Intake of the carotenoid antioxidant lycopene was also lower in advanced inflammation cases, with this effect approaching significance. Only one dietary factor, percentage of calories from sweets, was significantly higher in advanced fibrosis cases compared to mild fibrosis controls ($p=0.048$). The lower median intake of the carotenoid anti-oxidant alpha-carotene in advanced fibrosis cases approached significance. (Table 2)

Fibrosis—In multivariate analysis, lower dietary intake of copper and of fiber were both associated with strong decreased risk of advanced fibrosis, with approximately 14.3-fold and 7.1-fold statistically significant decreased fibrosis risk in those with lowest and moderate daily copper intake, and a 7.7-fold and 5.9-fold statistically significant decreased fibrosis risk with lowest and moderate daily fiber intake compared to those with highest daily intake. (Table 3) Lowest daily intake of both protein and of total glutathione also conveyed decreased fibrosis risk that approached significance.

In contrast, lower dietary intake of daily fat servings was positively associated with advanced fibrosis, with moderate intake conveying a significant 4-fold increased risk. Similarly, those with the lowest percentage of daily calories from sweets also had over 4-fold increased risk compared to those with high daily intake. However, moderate intake conveyed no increased risk ($OR_{adjusted}=1.03$, 95% CI 0.32–3.28).

The strongest risk factor for advanced fibrosis was African-American ethnicity, which consistently conveyed significant 80–100% increased risk in all multivariate dietary models. (data not shown) Other factors associated with significant increased risk included current alcohol drinking and smoking which consistently conveyed from 2.8–3.2% excess fibrosis risk per pack-year smoked. No significant interactions were detected among any covariates in these fibrosis risk models.

Inflammation grade—No dietary factor assessed was significantly associated with reduced risk of advanced inflammation. However, lower dietary intake of several factors was associated with significantly increased inflammation risk.

Lower daily intake of vitamin E intake conveyed strong increased risk of advanced inflammation, though this effect was significant only for moderate intake ($OR_{adjusted}=6.24$, $p=0.03$ and $OR_{adjusted}=4.16$, $p=0.12$ moderate and lowest intake compared to highest intake respectively). (Table 3) Lower number of daily servings of grains (refined + unrefined) also increased risk, though this effect was significant only for those with lowest daily intake ($OR_{adjusted}=6.58$, $p=0.04$ and $OR_{adjusted}=3.45$, $p=0.11$ for lowest and moderate intake respectively). Both lowest daily intake of lutein and lowest number of daily fat servings as well as moderate calorie intake were associated with increased inflammation risk that closely approached significance ($OR_{adjusted}=3.46$, $p=0.08$, $OR_{adjusted}=4.61$, $p=0.06$, and $OR=3.57$ (1.00–12.61), $p=0.05$ for lutein, daily fat servings, and total calories respectively). In marked contrast to advanced fibrosis, neither African-American ethnicity nor smoking conveyed either strong or significant excess risk of advanced inflammation in any multivariate dietary model. (data not shown) However, similar to advanced fibrosis, no interactions were detected.

Steatosis—No dietary factor assessed was associated with significantly decreased risk of advanced steatosis in multivariate analysis. The single dietary factor associated with significantly increased steatosis risk was lower daily intake of riboflavin where moderate intake was associated with a 6.5-fold increased risk compared to those with highest daily intake. (Table 3) Although lowest daily riboflavin intake also conveyed over 4-fold increased risk, the association was no longer significant ($p=0.20$). Those with the lowest percentage of caloric intake from carbohydrates also had increased steatosis risk that closely approached significance ($OR_{adjusted}=4.14$, $p=0.06$). (Table 3) Among other sociodemographic and behavioral risk factors we adjusted for, only BMI conveyed significant excess risk in all multivariate models, with an associated 11.1%–14.5% increase in risk of advanced steatosis per unit increase in BMI. (data not shown) No interactions were detected in any steatosis risk models.

Coffee drinking—Lower daily intake of coffee was the only dietary factor that was associated with increased risk of advanced liver disease risk (range $OR_{lowest\ coffee\ intake}=2.54$ – 3.04 and $ORs_{moderate\ coffee\ intake}=1.66$ – 3.19) across all sub-types of advanced liver disease (steatosis, fibrosis and inflammation). However, none of the effects reached significance. (Table 3)

Physical Activity

Median MET-minutes per week of walking were very similar while moderate physical activity was modestly lower among controls with mild disease compared to cases with advanced disease for both fibrosis and inflammation. (Table 3) In contrast, median MET-minutes per week of walking and of moderate physical activity were both much higher in controls with mild steatosis compared to cases with advanced steatosis, with these effects significant for walking and closely approaching significance for moderate physical activity ($p=0.02$ and $p=0.05$ respectively).

Overall, more than half of these veterans were IPAQ-sf classified as having high cumulative weekly levels of physical activity. (Table 3) However, the relative percentage of veterans classified as having high activity varied according to the severity and sub-type of liver disease. For both fibrosis and inflammation, the percentage of veterans with high activity was greater with advanced disease cases compared to mild disease controls (71.9% vs. 51.99% and 72.9% vs. 58.1% for advanced vs. mild inflammation and fibrosis respectively). In contrast, the percentage of veterans with high physical activity was lower in cases with advanced steatosis compared to controls with mild disease (50.0% vs. 71.6% for advanced vs. mild steatosis).

Discussion

Our current study in male veterans who use the VA healthcare system is the first study to evaluate the association of both multiple potential dietary risk factors and physical activity with advanced liver disease in a HCV-infected population in the U.S. We examined and reported risk estimates for a broad number of macronutrients, micronutrients and food-groups, including our novel evaluation of dietary factors of particular interest like the essential mineral copper.

The dietary risk factors we identified as potentially associated with advanced HCV-related liver disease risk varied according to sub-type of hepatic pathology evaluated. For example, although our multivariate analyses suggest lower daily dietary intake of fiber may be associated with strong decreased risk of advanced liver fibrosis, it was not similarly associated with decreased risk of steatosis.

The largest association we observed was the suggestive 7–14 fold reduced risk of advanced fibrosis with lower daily dietary copper intake; both effect sizes were highly significant and followed a dose-response relationship. Some evidence supportive of the biological plausibility of this finding is the well-known increased risk of advanced liver disease in persons with excessive hepatic copper accumulation (e.g., Wilson's disease, Indian Childhood Cirrhosis).

A single large hospital-based case-control study performed in Italy similarly examined the association between dietary intake and risk of advanced HCV-related liver disease. Some important consistencies in findings include concordance in direction of effect (i.e., risk promoting, no effect, or risk reducing) for 8 of 12 possible individual dietary intake comparisons between studies. Additionally, each study identified several unique dietary factors significantly associated with advanced HCV-related liver disease risk. However, caution must be used when comparing these studies particularly given some key differences in design, including in the underlying target population and the methodology employed to assess dietary intake (i.e., food frequency questionnaire vs. 7-day dietary diary).

Our findings suggesting lower coffee intake may increase risk of advanced fibrosis, steatosis and inflammation are in agreement with other recent research that demonstrated increased

coffee and caffeine intake were associated with significantly decreased HCV-related liver disease progression.[29;30] If replicated in a larger and therefore more adequately powered study, our results suggest that potentially important hepatoprotective benefits may be obtained with even a comparatively modest, and therefore potentially more widely acceptable, increased intake of coffee.

Our physical activity assessments suggest an increased risk of advanced steatosis with lower weekly MET-minutes per week of customary physical activity, with effects statistically significant for walking and approaching significance for moderate physical activity. The few studies that have evaluated modest exercise interventions in HCV-infected populations indicate that they are well-tolerated and convey benefits in terms of improved liver function and health-related quality of life.[31;32] Taken together, our results in conjunction with those from these exercise intervention studies suggest physicians who treat HCV-infected patients may wish to incorporate a specific recommendation on the importance of increased walking.

Our study has multiple strengths. Our utilization of a well-validated food-frequency questionnaire, as opposed to a 3- or 7-day food diary, allowed us to obtain a more stable estimate of daily nutritional intake over a much longer time period while also accounting for any potential effect of seasonal or irregularly eaten foods on disease risk. Isocaloric or energy-adjusted analyses allowed a more valid evaluation of the role individual nutrients may play in disease risk, as did our measurement and adjustment for multiple important confounders for advanced liver disease risk including smoking, alcohol use and BMI. Additionally, our study provides important novel information on estimated effect sizes and variances for multiple potential dietary risk factors within a defined HCV-infected population the U.S., including several that have not been reported on within any other defined HCV-infected population as well. This information is necessary to design adequately powered future nutritional epidemiology studies.

Our study also has several limitations that are important to acknowledge. First, we are unable to make conclusive temporal assessments necessary to infer causality. Although we instructed participants to provide information on their customary diet for the last year if it was indicative of their long-term dietary habits, or else for the year prior to disease diagnosis and any related symptom-onset, we cannot be sure that our single time-point assessment completely accurately reflected actual dietary intake for the salient time period. Also, other than BMI and dietary history, we did not have other measures of nutritional status including a parallel assessment of calorimetry to determine basal metabolic rate or of nutritional biomarkers. Nutritional biomarkers can be particularly useful for purposes of validating self-reported dietary intake and for augmenting information on dietary intake with potentially metabolically effective intake.[33] However, they also have important limitations including the limited number of valid and reliable dietary biomarkers, substantial associated costs and interpretative complexity. Additionally, our study included only male veterans who use the VA. Although they represent an important and very large sub-group of HCV cases in the U.S., it is unclear if our findings in this veteran population will generalize to HCV-infected female veterans and mixed gender civilian populations in the U.S. A final limitation was our modest total sample size. We consequently had low study power that limited our ability to: reliably estimate precise confidence intervals, perform traditional statistical criteria-based adjustment for multiple comparisons, or evaluate for potential interaction among multiple dietary factors. Therefore, even our strongest findings of from 7- to 14- fold significantly decreased risk of advanced fibrosis with reduced daily dietary copper intake must be qualified as provisional pending verification in larger prospective studies.

Our study in an HCV-infected male veteran population suggests several components of diet and physical activity may be associated with risk of advanced liver. Additional research examining the role potentially modifiable factors like diet and physical activity may play in risk for advanced liver disease is particularly important in this population as so many HCV-infected individuals are either not treatment candidates, or cannot tolerate or respond to treatment.

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Abbreviations

FFQ	Food Frequency Questionnaire
HCV	Hepatitis C virus
IPAQ-sf	International Physical Activity Questionnaire, short form
MEDVAMC	Michael E. DeBakey VA Medical Center
MET	metabolic equivalent of task
RDA	recommended daily allowance
VA	Department of Veteran Affairs

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* May; 2006 144(10):705–714. [PubMed: 16702586]
2. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet.* 1997; 349:825–832. [PubMed: 9121257]
3. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl.* Nov; 2003 9(11):S1–S9. [PubMed: 14586888]
4. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology.* Nov; 2004 127(5 Suppl 1):S35–S50. [PubMed: 15508101]
5. Kallwitz ER, Layden-Almer J, Dhamija M, Berkes J, Guzman G, Lepe R, Cotler SJ, Layden TJ. Ethnicity and Body Mass Index Are Associated With Hepatitis C Presentation and Progression. *Clin Gastroenterol Hepatol.* Aug.2009
6. Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, Bonkovsky HL, Ghany MG. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. *Gastroenterology.* Aug; 2009 137(2):549–557. [PubMed: 19445938]
7. Hu SX, Kyulo NL, Xia VW, Hillebrand DJ, Hu KQ. Factors associated with hepatic fibrosis in patients with chronic hepatitis C: a retrospective study of a large cohort of U.S. patients. *J Clin Gastroenterol.* Sep; 2009 43(8):758–764. [PubMed: 19238091]
8. Alsatie M, Kwo PY, Gingerich JR, Qi R, Eckert G, Cummings OW, Imperiale TF. A multivariable model of clinical variables predicts advanced fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* Apr; 2007 41(4):416–421. [PubMed: 17413613]
9. Leandro G, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G, Adinolfi LE, Asselah T, Jonsson JR, Smedile A, Terrault N, Pazienza V, Giordani MT, Giostra E, Sonzogni A, Ruggiero G,

- Marcellin P, Powell EE, George J, Negro F. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology*. May; 2006 130(6):1636–1642. [PubMed: 16697727]
10. FriedenberG F, Pungpapong S, Zaeri N, Braitman LE. The impact of diabetes and obesity on liver histology in patients with hepatitis C. *Diabetes Obes Metab*. May; 2003 5(3):150–155. [PubMed: 12681021]
 11. Corrao G, Lepore AR, Torchio P, Galatola G, Arico S, di OF. Interaction between dietary pattern and alcohol intake on the risk of liver cirrhosis. The Provincial Group for the Study of Chronic Liver Disease. *Rev Epidemiol Sante Publique*. 1995; 43(1):7–17. [PubMed: 7892519]
 12. Corrao G, Torchio P, Zambon A, D'Amicis A, Lepore AR, di OF. Alcohol consumption and micronutrient intake as risk factors for liver cirrhosis: a case-control study. The Provincial Group for the study of Chronic Liver Disease. *Ann Epidemiol*. Apr; 1998 8(3):154–159. [PubMed: 9549000]
 13. Corrao G, Zambon A, Bagnardi V, Arico S, Loguercio C, D'Amicis A. Nutrient intakes, nutritional patterns and the risk of liver cirrhosis: an explorative case-control study. *Eur J Epidemiol*. 2004; 19(9):861–869. [PubMed: 15499896]
 14. Bridges FS. Relationship between dietary beef, fat, and pork and alcoholic cirrhosis. *Int J Environ Res Public Health*. Sep; 2009 6(9):2417–2425. [PubMed: 19826553]
 15. Nanji AA, French SW. Relationship between pork consumption and cirrhosis. *Lancet*. Mar; 1985 1(8430):681–683. [PubMed: 2858627]
 16. Rotily M, Durbec JP, Berthezene P, Sarles H. Diet and alcohol in liver cirrhosis: a case-control study. *Eur J Clin Nutr*. Aug; 1990 44(8):595–603. [PubMed: 2209515]
 17. Loguercio C, Federico A, Masarone M, Torella R, Blanco C, Persico VM. The impact of diet on liver fibrosis and on response to interferon therapy in patients with HCV-related chronic hepatitis. *Am J Gastroenterol*. Dec; 2008 103(12):3159–3166. [PubMed: 18786125]
 18. National Center for Veterans Analysis and Statistics. VA Stats at a Glance. Aug. 2009 http://www1.va.gov/vetdata/docs/4X6_summer09_sharepoint.pdf
 19. Dominitz JA, Boyko EJ, Koepsell TD, Heagerty PJ, Maynard C, Sporleder JL, Stenhouse A, Kling MA, Hrushesky W, Zeilman C, Sontag S, Shah N, Ona F, Anand B, Subik M, Imperiale TF, Nakhle S, Ho SB, Bini EJ, Lockhart B, Ahmad J, Sasaki A, van der LB, Toro D, Martinez-Souss J, Huilgol V, Eisen S, Young KA. Elevated prevalence of hepatitis C infection in users of United States veterans medical centers. *Hepatology*. Jan; 2005 41(1):88–96. [PubMed: 15619249]
 20. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, Kaslow RA, Margolis HS. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med*. Aug; 1999 341(8):556–562. [PubMed: 10451460]
 21. Satia-Abouta J, Galanko JA, Potter JD, Ammerman A, Martin CF, Sandler RS. North Carolina Colon Cancer Study. Associations of total energy and macronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina colon cancer study. *Am J Epidemiol*. Nov; 2003 158(10):951–962. [PubMed: 14607803]
 22. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol*. 1990; 43(12):1327–1335. [PubMed: 2254769]
 23. Boucher B, Cotterchio M, Kreiger N, Nadalin V, Block T, Block G. Validity and reliability of the Block98 food-frequency questionnaire in a sample of Canadian women. *Public Health Nutr*. Feb; 2006 9(1):84–93. [PubMed: 16480538]
 24. National Academy of Sciences. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC: National Academies Press; 2006.
 25. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. Aug; 2003 35(8):1381–1395. [PubMed: 12900694]
 26. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology*. Jul; 1994 20(1 Pt 1): 15–20. [PubMed: 8020885]

27. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol.* Sep; 1999 94(9):2467–2474. [PubMed: 10484010]
28. Willett, W. *Nutritional Epidemiology*. 2. New York: Oxford University Press; 1998.
29. Freedman ND, Everhart JE, Lindsay KL, Ghany MG, Curto TM, Shiffman ML, Lee WM, Lok AS, Di Bisceglie AM, Bonkovsky HL, Hoefs JC, Dienstag JL, Morishima C, Abnet CC, Sinha R, HALT C. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. *Hepatology.* Nov; 2009 50(5):1360–1369. [PubMed: 19676128]
30. Modi AA, Feld JJ, Park Y, Kleiner DE, Everhart JE, Liang TJ, Hoofnagle JH. Increased caffeine consumption is associated with reduced hepatic fibrosis. *Hepatology.* Jan; 2010 51(1):201–209. [PubMed: 20034049]
31. Vazquez-Vandyck M, Roman S, Vazquez JL, Huacuja L, Khalsa G, Troyo-Sanroman R, Panduro A. Effect of Breathwalk on body composition, metabolic and mood state in chronic hepatitis C patients with insulin resistance syndrome. *World J Gastroenterol.* Dec; 2007 13(46):6213–6218. [PubMed: 18069762]
32. Payen JL, Pillard F, Mascarell V, Riviere D, Couzigou P, Kharlov N. Is physical activity possible and beneficial for patients with hepatitis C receiving pegylated interferon and ribavirin therapy? *Gastroenterol Clin Biol.* Jan; 2009 33(1 Pt 1):8–14. [PubMed: 19070444]
33. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. *Hum Genet.* Jun; 2009 125(5–6):507–525. [PubMed: 19357868]

Table 1

Sociodemographic and clinical characteristics of chronically HCV-infected male veterans seen at a VA Hepatitis C clinic (N=91).

<u>Characteristic</u>	<u>Mean (SD)</u>
Mean age in years	55.7 (6.94)
	<u># (%)</u>
Race/Ethnicity	
African-American	44 (48.3%)
Caucasian Non-Hispanic	37 (40.7%)
Hispanic and Native American Indian [#]	10 (11.0%)
Education	
<High school	13 (14.2%)
High school graduate or GED	35 (28.5%)
Some College	33 (36.3%)
College graduate	10 (11.0%)
Smoking History	
Never	12 (13.2%)
Previous Smoker	46 (50.5%)
Current Smoker	33 (36.3%)
Pack-years smoking (current + previous smokers only)	
<5 years	9 (11.4%)
5–9 years	10 (12.6%)
10–19 years	12 (15.2%)
20–29 years	15 (19.0%)
30 years+	33 (41.8%)
Alcohol Use History	
Never	8 (8.8%)
Previous Drinker	45 (49.4%)
Current Drinker	38 (41.8%)
Maximum drinks/week (current + previous drinkers only)	
<7 drinks/week	12 (14.5%)
7–14 drinks/week	13 (15.7%)
15–28 drinks/week	16 (19.3%)
29–42 drinks/week	11 (13.2%)
43+ drinks/week	31 (37.3%)
HCV Genotype	
1	80 (87.9%)
2	7 (7.7%)
3	4 (4.4%)
	<u>Mean (SD)</u>
HCV Viral Load _{log 10}	5.91 (0.70)

Characteristic	
BMI	28.61 (5.06)
	# (%)
BMI Classification ^{##}	
Mildly Thin (BMI 17.0–18.49)	3 (3.3%)
Normal (BMI 18.5–24.99)	18 (19.8%)
Overweight (BMI 25.0–29.99)	38 (41.8%)
Obese (BMI 30.0+)	32 (35.1%)

[#] Nine Hispanic and 1 Native American Indian/Hispanic.

^{##} Adapted from World Health Organization guidelines (1995, 2000, 2004).

Table 2

Median daily intake of dietary factors according to degree of hepatic pathology in chronically HCV-infected male veterans (N=91).

BIOPSY-ASSESSED DEGREE OF LIVER DISEASE										
Dietary Factor	Fibrosis			Steatosis			Inflammation			
	Median Daily Intake			Median Daily Intake			Median Daily Intake			
	Mild	Advanced	p-value	Mild	Advanced	p-value	Mild	Advanced	p-value	
Calories	2128	2144	0.91	2164	1964	0.38	2128	2145	0.87	
Carbohydrate	256.7	254.1	0.76	264.4	218.5	0.02 *	265.7	254.1	0.77	
Protein	76.8	79.3	0.60	80.3	72.6	0.17	78.2	72.8	0.45	
Fat	89.4	99.3	0.91	97.3	99.55	0.95	100.0	95.7	0.77	
Saturated fat	27.1	30.1	0.34	28.9	28.6	0.94	27.1	29.17	0.87	
Omega-3 fats	1.9	2.0	0.91	2.0	1.8	0.68	2.0	1.9	0.77	
Transfat	4.7	5.1	0.60	5.5	4.2	0.17	5.2	4.8	0.97	
Polyunsaturated fat (PUFA)	20.5	23.4	0.34	20.4	23.4	0.59	21.1	22.5	0.87	
Monounsaturated fat (MUFA)	36.4	38.7	0.35	36.9	38.6	0.58	36.9	38.5	0.54	
Dairy servings	1.1	0.9	0.25	0.9	1.0	0.95	1.0	0.9	0.45	
Meat/Protein servings	2.8	2.9	0.91	2.9	2.6	0.68	3.0	2.6	0.23	
Fruit servings	0.8	1.2	0.34	0.9	0.7	0.38	0.9	1.1	0.54	
Vegetable servings	2.9	3.5	0.60	2.1	2.1	0.95	3.4	3.1	0.45	
Fat servings	4.6	4.1	0.47	4.5	3.6	0.17	4.5	4.3	0.46	
Grain servings	5.9	6.0	0.91	5.3	4.5	0.38	6.3	5.8	0.78	
% calories carbohydrates	45.6	46.2	0.91	47.3	43.7	0.006**	44.1	46.6	0.28	
% calories protein	14.2	14.1	0.92	14.2	15.0	0.13	14.6	14.2	0.22	
% calories fat	40.4	40.2	0.76	39.4	41.8	0.14	39.7	39.3	0.78	
% calories sweets	20.4	16.8	0.048 *	17.4	13.2	0.17	17.1	19.1	0.77	
Glycemic Index	53.9	53.7	0.47	54.1	52.7	0.02 *	53.4	54.0	0.54	
Cholesterol	306.7	311.0	0.91	316.2	303.8	0.38	348.8	306.6	0.45	
Fiber	14.6	19.4	0.34	16.5	16.7	0.95	16.8	16.5	0.77	
Folate	283.4	309.6	0.60	310.4	294.0	0.38	321.7	295.1	0.45	

BIOPSY-ASSESSED DEGREE OF LIVER DISEASE

	Fibrosis			Steatosis			Inflammation		
	Median Daily Intake			Median Daily Intake			Median Daily Intake		
	Mild	Advanced	p-value	Mild	Advanced	p-value	Mild	Advanced	p-value
Retinol	429.7	446.8	0.60	433.6	429.6	0.95	430.9	439.0	0.86
Vitamin B1 (thiamin)	1.5	1.8	0.17	1.6	1.5	0.17	1.5	1.6	0.54
Vitamin B2 (riboflavin)	1.9	2.0	0.80	2.0	1.9	0.37	1.9	1.8	0.53
Vitamin B3 (niacin)	21.4	23.8	0.17	23.0	21.2	0.38	22.6	22.7	0.87
Vitamin B6 (pyridoxine)	1.8	2.2	0.34	2.0	1.7	0.17	1.9	2.0	0.87
Vitamin B12 (cobalamin)	5.0	5.4	0.34	5.2	5.2	0.95	5.2	5.3	0.87
Vitamin C	85.2	102.7	0.34	94.9	74	0.37	97.0	81.6	0.44
Vitamin D	1.5	1.3	0.47	1.4	1.4	0.95	1.4	1.3	0.77
Vitamin E	8.64	9.45	0.60	9.4	8.54	0.68	9.40	8.62	0.77
Glutathione-total	44.0	41.4	0.45	46.8	34.7	0.07 [^]	46.1	40.5	0.17
Glutathione-reduced	26.2	28.9	0.17	28.9	23	0.02 [*]	28.3	26.3	0.18
Alpha-carotene	263.9	378.5	0.07 [^]	295.3	383	0.59	295.3	300.1	0.87
Beta-carotene	2508.1	2497.5	0.91	2458.1	2886.0	0.58	3156.9	2332.8	0.23
Cryptoxanthin	88.8	95.4	0.34	92.0	90.4	0.68	95.8	95.2	0.77
Lycopene	4140.9	3598.5	0.25	3844.5	4094.9	0.31	4322.4	3835.5	0.10 [^]
Lutein	1943.6	1793.2	0.47	1943.6	1637.1	0.38	2766.9	1707.4	0.01
Calcium	757.6	751.6	0.91	757.6	792.8	0.95	793.5	713.0	0.77
Copper	1330	1440	0.59	1330	1440	0.70	1400	1370	0.99
Iron	14.2	16.5	0.34	15.9	13.5	0.17	14.9	15.3	0.87
Selenium	103.9	109.2	0.60	106.5	98.2	0.68	109.5	104.5	0.45
Sodium	3.2	3.4	0.17	3.3	2.9	0.38	3.2	3.3	0.28
Zinc	13.1	12.8	0.76	12.9	12.6	0.68	13.5	12.7	0.45
Coffee	0.7	0.4	0.47	0.7	0.4	0.18	0.6	0.4	0.77

^{*} Significant at p<0.05,

^{**} p<0.01;

[^] Approach significance at p 0.10.

Table 3A

Dietary Factor ###	Lowest Daily Intake ##			Moderate Daily Intake ##		
	OR	95% CI	p-value	OR	95% CI	p-value
calories	0.89	(0.22 – 3.59)	0.88	3.57	(1.00 – 12.61)	0.05 [^]
carbohydrate	0.83	(0.08 – 8.40)	0.87	0.40	(0.06 – 2.53)	0.33
protein	0.84	(0.09 – 7.94)	0.88	0.50	(0.09 – 2.77)	0.43
fat	3.73	(0.38 – 37.00)	0.26	1.39	(0.25 – 7.66)	0.71
saturated fat	2.06	(0.21 – 20.39)	0.54	1.28	(0.21 – 7.85)	0.79
omega 3	2.12	(0.27 – 16.73)	0.48	1.44	(0.25 – 8.42)	0.69
transfat	0.61	(0.14 – 2.64)	0.51	3.01	(0.71 – 12.69)	0.13
MUFA	0.45	(0.05 – 4.08)	0.48	0.77	(0.14 – 4.35)	0.77
PUFA	0.29	(0.04 – 1.95)	0.20	0.21	(0.04 – 1.14)	0.07 [^]
dairy (daily servings)	1.37	(0.32 – 5.87)	0.67	0.62	(0.16 – 2.30)	0.47
meat (daily servings)	0.98	(0.16 – 5.87)	0.98	0.34	(0.08 – 1.51)	0.16
fruit (daily servings)	0.87	(0.23 – 3.26)	0.83	0.15	(0.32 – 4.14)	0.83
vegetables (daily servings)	2.20	(0.58 – 8.38)	0.25	3.16	(0.77 – 13.01)	0.11
fat (daily servings)	4.61	(0.92 – 23.12)	0.06 [^]	2.37	(0.57 – 9.78)	0.23
grains (daily servings)	6.58	(1.07 – 40.50)	0.04 [*]	3.45	(0.77 – 15.55)	0.11
% calories carbohydrate	0.45	(0.13 – 1.58)	0.21	1.35	(0.35 – 5.19)	0.66
% calories protein	0.92	(0.26 – 3.33)	0.90	0.39	(0.11 – 1.37)	0.14
% calories fat	1.47	(0.42 – 5.21)	0.55	2.28	(0.63 – 8.34)	0.21
% calories sweets	1.41	(0.39 – 5.15)	0.60	0.64	(0.19 – 2.19)	0.48
glycemic index	0.82	(0.24 – 2.79)	0.75	0.76	(0.23 – 2.56)	0.66
cholesterol	1.17	(0.22 – 6.14)	0.85	0.65	(0.17 – 2.43)	0.52
fiber	0.41	(0.06 – 2.59)	0.34	0.33	(0.07 – 1.59)	0.17
folate	2.13	(0.46 – 9.82)	0.33	1.07	(0.28 – 4.12)	0.92
retinol	1.43	(0.28 – 7.25)	0.67	0.58	(0.15 – 2.21)	0.42
B1-thiamin	0.18	(0.02 – 1.61)	0.12	0.64	(0.12 – 3.52)	0.61

	Lowest Daily Intake ##			Moderate Daily Intake ##		
	OR	95% CI	p-value	OR	95% CI	p-value
B2-riboflavin	1.36	(0.20 – 9.11)	0.75	0.74	(0.15 – 3.50)	0.70
B3-niacin	1.62	(0.18 – 14.42)	0.67	0.57	(0.11 – 3.08)	0.52
B6-pyridoxine	1.60	(0.23 – 10.90)	0.63	0.50	(0.12 – 2.13)	0.34
B12-cobalamin	1.40	(0.31 – 6.41)	0.66	1.75	(0.47 – 6.57)	0.41
vitamin C	1.21	(0.25 – 5.80)	0.81	0.38	(0.10 – 1.39)	0.14
vitamin D	1.57	(0.31 – 8.12)	0.59	0.48	(0.12 – 1.92)	0.30
vitamin E	4.16	(0.68 – 25.41)	0.12	6.24	(1.23 – 31.74)	0.03 [*]
glutathione-total	1.69	(0.26 – 11.13)	0.59	0.98	(0.24 – 4.01)	0.98
glutathione-reduced	1.93	(0.31 – 11.83)	0.49	1.00	(0.26 – 3.88)	0.99
alpha-carotene	1.34	(0.37 – 4.79)	0.66	0.95	(0.28 – 3.20)	0.93
beta-carotene	3.20	(0.74 – 13.72)	0.12	1.35	(0.38 – 4.78)	0.64
cryptoxanthin	1.55	(0.39 – 6.07)	0.53	1.55	(0.41 – 5.88)	0.52
lycopene	1.92	(0.42 – 8.69)	0.40	1.11	(0.27 – 4.45)	0.89
lutein	3.46	(0.85 – 14.12)	0.08 [^]	2.72	(0.75 – 9.82)	0.13
calcium	1.97	(0.29 – 13.39)	0.49	0.70	(0.15 – 3.19)	0.64
copper	1.34	(0.14 – 12.66)	0.79	0.45	(0.08 – 2.54)	0.37
iron	0.76	(0.10 – 5.50)	0.78	0.30	(0.06 – 1.50)	0.14
selenium	0.60	(0.05 – 7.24)	0.69	0.34	(0.05 – 2.33)	0.27
sodium	0.25	(0.02 – 2.77)	0.26	0.34	(0.05 – 2.43)	0.28
zinc	1.35	(0.19 – 9.74)	0.77	0.62	(0.13 – 2.91)	0.54
coffee (cups/day)	2.78	(0.69 – 11.12)	0.15	1.66	(0.46 – 6.06)	0.44

^{*} Significant at p<0.05;

[^] Approaching significance at 0.05 p 0.10.

[#] Adjusted for age at biopsy, ethnicity, pack-years smoking, current alcohol use, BMI, lag time between biopsy and survey and total calories.

^{##} Compared to those with highest daily dietary factor intake (upper tertile).

^{###} Nutrient intake as determined by self-reported answers to the Block Food Frequency Questionnaire.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; MUFA, mono-unsaturated fat; PUFA, polyunsaturated fat; OR, odds ratio.

Table 3B

Multivariate evaluation of daily dietary intake and risk of advanced HCV-related liver fibrosis (METAVIR F3-F4).[#]

Dietary Factor ###	Lowest Daily Intake ##			Moderate Daily Intake ##		
	OR	95% CI	p-value	OR	95% CI	p-value
calories	1.40	(0.44 – 4.43)	0.57	2.27	(0.72 – 7.11)	0.16
carbohydrate	0.27	(0.03 – 2.39)	0.24	0.24	(0.04 – 1.47)	0.13
protein	0.18	(0.02 – 1.43)	0.10 ^A	0.49	(0.10 – 2.45)	0.35
fat	2.04	(0.25 – 16.64)	0.50	1.88	(0.36 – 9.80)	0.45
saturated fat	0.88	(0.10 – 7.35)	0.90	1.28	(0.23 – 7.11)	0.78
omega 3	0.38	(0.05 – 2.66)	0.33	0.60	(0.12 – 3.16)	0.55
transfat	0.73	(0.18 – 2.98)	0.66	2.62	(0.75 – 9.14)	0.13
MUFA	0.64	(0.08 – 5.12)	0.68	0.47	(0.09 – 2.46)	0.37
PUFA	3.70	(0.59 – 23.25)	0.16	1.06	(0.23 – 4.83)	0.94
dairy (daily servings)	1.67	(0.45 – 6.26)	0.44	1.15	(0.34 – 3.90)	0.82
meat (daily servings)	0.73	(0.15 – 3.56)	0.70	0.40	(0.10 – 1.65)	0.21
fruit (daily servings)	0.43	(0.13 – 1.46)	0.17	0.53	(0.16 – 1.72)	0.29
vegetables (daily servings)	0.71	(0.20 – 2.51)	0.60	1.95	(0.55 – 6.92)	0.30
fat (daily servings)	4.02	(0.91 – 17.72)	0.07 ^A	4.10	(1.04 – 16.17)	0.04 [*]
grains (daily servings)	1.27	(0.26 – 6.13)	0.76	1.23	(0.32 – 4.78)	0.76
% calories carbohydrate	1.32	(0.41 – 4.27)	0.64	1.94	(0.60 – 6.21)	0.27
% calories protein	0.66	(0.22 – 1.99)	0.46	1.30	(0.42 – 3.98)	0.65
% calories fat	0.69	(0.20 – 2.30)	0.54	1.13	(0.36 – 3.51)	0.84
% calories sweets	4.52	(1.26 – 16.26)	0.02 [*]	1.03	(0.32 – 3.28)	0.96
glycemic index	1.32	(0.44 – 3.97)	0.62	0.95	(0.31 – 2.89)	0.93
cholesterol	1.33	(0.29 – 6.07)	0.71	1.33	(0.38 – 4.69)	0.65
fiber	0.13	(0.02 – 0.77)	0.02 [*]	0.17	(0.04 – 0.77)	0.02 [*]
folate	1.09	(0.26 – 4.51)	0.90	0.59	(0.16 – 2.15)	0.42
retinol	0.76	(0.18 – 3.22)	0.71	0.89	(0.26 – 3.06)	0.86
B1-thiamin	0.26	(0.02 – 3.02)	0.28	0.36	(0.05 – 2.43)	0.29

	Lowest Daily Intake ##			Moderate Daily Intake ##		
	OR	95% CI	p-value	OR	95% CI	p-value
B2-riboflavin	0.44	(0.08 – 2.49)	0.35	1.07	(0.24 – 4.73)	0.93
B3-niacin	0.42	(0.06 – 3.04)	0.39	0.52	(0.11 – 2.50)	0.41
B6-pyridoxine	0.26	(0.04 – 1.61)	0.15	0.22	(0.05 – 0.96)	0.04 *
B12-cobalamin	1.63	(0.39 – 6.89)	0.50	1.20	(0.35 – 4.09)	0.77
vitamin C	0.39	(0.10 – 1.56)	0.18	0.40	(0.12 – 1.33)	0.13
vitamin D	2.11	(0.48 – 9.31)	0.32	1.20	(0.33 – 4.40)	0.78
vitamin E	1.05	(0.21 – 5.38)	0.95	1.25	(0.35 – 4.49)	0.74
glutathione-total	0.17	(0.03 – 1.15)	0.07 ^	0.42	(0.11 – 1.68)	0.22
glutathione-reduced	0.26	(0.04 – 1.57)	0.14	0.48	(0.13 – 1.80)	0.27
alpha-carotene	0.51	(0.16 – 1.63)	0.25	1.11	(0.35 – 3.46)	0.86
beta-carotene	1.18	(0.33 – 4.24)	0.80	1.14	(0.34 – 3.81)	0.83
cryptoxanthin	0.95	(0.27 – 3.38)	0.94	1.02	(0.30 – 3.56)	0.97
lutein	1.68	(0.48 – 5.81)	0.41	1.69	(0.52 – 5.56)	0.39
lycopene	2.13	(0.54 – 8.40)	0.28	0.91	(0.24 – 3.42)	0.89
calcium	2.45	(0.41 – 14.64)	0.32	1.33	(0.31 – 5.76)	0.70
copper	0.07	(0.01 – 0.60)	0.02 *	0.14	(0.03 – 0.78)	0.02 *
iron	0.30	(0.05 – 1.80)	0.19	0.47	(0.11 – 2.00)	0.30
selenium	0.26	(0.03 – 2.44)	0.24	0.55	(0.10 – 3.11)	0.50
sodium	0.34	(0.04 – 2.89)	0.33	0.76	(0.13 – 4.35)	0.76
zinc	0.47	(0.08 – 2.86)	0.42	0.74	(0.18 – 3.09)	0.68
coffee (cups/day)	2.45	(0.70 – 8.64)	0.16	2.07	(0.62 – 6.93)	0.24

* Significant at $p < 0.05$;

^ Approaching significance at 0.05 $p = 0.10$.

Adjusted for age at biopsy, ethnicity, pack-years smoking, current alcohol use, BMI, lag time between biopsy and survey and total calories.

Compared to referent category of those with highest daily dietary factor intake (upper tertile with cut-points established based on mild disease controls).

Nutrient intake as determined by self-reported answers to the Block Food Frequency Questionnaire.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; MUFA, mono-unsaturated fat; PUFA, polyunsaturated fat; OR, odds ratio.

Table 3C

Multivariate evaluation of daily dietary intake and risk of advanced HCV-related liver steatosis (Brunt S2-S3).[#]

Dietary Factor ###	Lowest Daily Intake ##			Moderate Daily Intake ##		
	OR	95% CI	p-value	OR	95% CI	p-value
calories	2.43	(0.63 – 9.44)	0.16	1.13	(0.28 – 4.58)	0.16
carbohydrate	7.30	(0.42 – 27.23)	0.17	3.81	(0.42 – 34.40)	0.23
protein	2.06	(0.18 – 23.69)	0.56	3.14	(0.49 – 20.13)	0.23
fat	0.48	(0.23 – 6.57)	0.58	1.12	(0.17 – 7.37)	0.90
saturated fat	0.40	(0.03 – 5.89)	0.50	0.84	(0.12 – 5.90)	0.86
omega 3	2.26	(0.23 – 22.6)	0.49	0.82	(0.11 – 6.11)	0.85
transfat	0.82	(0.17 – 4.06)	0.82	0.93	(0.23 – 3.75)	0.92
MUFA	0.61	(0.05 – 7.49)	0.71	0.94	(0.15 – 5.95)	0.95
PUFA	0.28	(0.04 – 1.95)	0.20	0.21	(0.04 – 1.14)	0.07 ^A
dairy (daily servings)	0.33	(0.06 – 1.65)	0.18	0.94	(0.22 – 3.97)	0.94
meat (daily servings)	0.29	(0.04 – 2.35)	0.24	3.73	(0.66 – 21.32)	0.14
fruit (daily servings)	1.52	(0.37 – 6.22)	0.56	1.33	(0.30 – 5.89)	0.70
vegetables (daily servings)	0.65	(0.15 – 2.87)	0.57	1.15	(0.30 – 4.45)	0.84
fat (daily servings)	1.70	(0.34 – 8.39)	0.52	0.95	(0.20 – 4.43)	0.95
grains (daily servings)	2.11	(0.32 – 14.14)	0.44	3.49	(0.68 – 17.94)	0.13
% calories carbohydrate	4.14	(0.96 – 17.86)	0.06 ^A	2.14	(0.48 – 9.56)	0.32
% calories protein	0.55	(0.14 – 2.16)	0.39	1.56	(0.42 – 5.82)	0.39
% calories fat	0.44	(0.10 – 1.88)	0.27	0.76	(0.21 – 2.74)	0.68
% calories sweets	1.30	(0.35 – 4.89)	0.69	0.81	(0.20 – 3.31)	0.76
glycemic index	2.41	(0.61 – 9.53)	0.21	2.13	(0.52 – 8.78)	0.29
cholesterol	0.89	(0.15 – 5.29)	0.90	1.44	(0.31 – 6.58)	0.64
fiber	1.78	(0.26 – 12.28)	0.56	1.96	(0.40 – 9.64)	0.41
folate	0.91	(0.18 – 4.58)	0.90	0.75	(0.16 – 3.55)	0.71
retinol	0.81	(0.15 – 4.26)	0.81	0.60	(0.14 – 2.63)	0.50
B1-thiamin	2.48	(0.18 – 34.23)	0.50	0.56	(0.07 – 4.40)	0.58

	Lowest Daily Intake ##			Moderate Daily Intake ##		
	OR	95% CI	p-value	OR	95% CI	p-value
B2-riboflavin	4.38	(0.47 – 41.18)	0.20	6.54	(1.04 – 41.00)	0.04 *
B3-niacin	5.08	(0.39 – 65.63)	0.21	3.07	(0.43 – 21.87)	0.26
B6-pyridoxine	2.55	(0.31 – 20.85)	0.38	0.67	(0.13 – 3.55)	0.64
B12-cobalamin	0.91	(0.16 – 5.12)	0.91	1.59	(0.35 – 7.11)	0.55
vitamin C	1.13	(0.24 – 5.21)	0.88	0.38	(0.08 – 1.73)	0.21
vitamin D	0.80	(0.15 – 4.17)	0.79	0.56	(0.12 – 2.53)	0.45
vitamin E	0.60	(0.14 – 2.56)	0.49	0.80	(0.13 – 5.03)	0.81
glutathione-total	3.26	(0.34 – 31.97)	0.31	1.34	(0.25 – 7.16)	0.74
glutathione-reduced	4.68	(0.49 – 44.52)	0.18	1.10	(0.21 – 5.82)	0.91
alpha-carotene	0.92	(0.23 – 3.69)	0.91	1.23	(0.33 – 4.54)	0.76
beta-carotene	0.77	(0.18 – 3.37)	0.73	0.65	(0.15 – 2.82)	0.57
cryptoxanthin	1.16	(0.26 – 5.15)	0.84	0.98	(0.21 – 4.54)	0.98
lutein	1.04	(0.26 – 4.14)	0.96	0.66	(0.15 – 2.86)	0.57
lycopene	0.27	(0.05 – 1.54)	0.14	0.89	(0.21 – 3.78)	0.88
calcium	2.26	(0.26 – 19.42)	0.46	1.80	(0.31 – 10.49)	0.51
copper	0.30	(0.03 – 3.29)	0.32	0.69	(0.12 – 4.16)	0.69
iron	3.16	(0.38 – 26.16)	0.29	0.97	(0.17 – 5.63)	0.97
selenium	1.83	(0.15 – 22.01)	0.63	1.70	(0.24 – 12.04)	0.59
sodium	1.36	(0.11 – 16.41)	0.81	1.06	(0.15 – 7.48)	0.95
zinc	0.43	(0.05 – 3.37)	0.42	0.57	(0.11 – 2.88)	0.49
coffee (cups/day)	3.64	(0.76 – 17.6)	0.11	3.19	(0.71 – 14.21)	0.13

* Significant at $p < 0.05$;

^ Approaching significance at 0.05 $p < 0.10$.

Adjusted for age at biopsy, ethnicity, pack-years smoking, current alcohol use, BMI, lag time between biopsy and survey and total calories.

Referent category those with highest daily dietary factor intake in upper tertiles defined using dietary distribution in mild steatosis controls

Nutrient intake as determined by self-reported answers to the Block Food Frequency Questionnaire.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; MUFA, mono-unsaturated fat; PUFA, polyunsaturated fat; OR, odds ratio.

IPAQ-sf assessed weekly physical activity stratified according to degree of liver disease in chronically hepatitis C infected male veterans.

Table 4

BIOPSY-ASSESSED DEGREE OF LIVER DISEASE									
Physical Activity	Fibrosis			Steatosis			Inflammation		
	Advanced (N=43)		p-value	Mild (N=67)		p-value	Mild (N=27)		Advanced (N=64)
	Median MET minutes/week	(%)		Median MET minutes/week	(%)		Median MET minutes/week	(%)	
Walking	2770	2772	0.36	2774	1386	0.02*	2772	2784	0.55
Moderate Physical Activity	720	960	0.72	960	210	0.05^	720	940	0.66
Vigorous Physical Activity	0	60	0.09^	0	0	0.33	0	0	0.13
			p-value			p-value			p-value
Cumulative Physical Activity Level			0.21			0.07^			0.18
High	25 (58.1%)	35 (72.9%)		48 (71.6%)	12 (50.0%)		14(51.9%)	46 (71.9%)	
Medium	14 (32.6%)	8 (10.4%)		12 (17.9%)	10 (41.7%)		9 (14.8%)	13 (20.3%)	
Low	4 (9.3%)	5 (16.7%)		7 (10.5%)	2 (8.3%)		4 (33.3%)	5 (7.8%)	

* Significant at p<0.05;

^ Approach significance 0.05 p 0.10.

Abbreviations: IPAQ-sf, International Physical Activity Questionnaire (short-form); MET, metabolic equivalent of task.