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Diet associations with nonalcoholic fatty liver disease in an ethnically diverse population: the Multiethnic Cohort

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Abstract

Epidemiological data on dietary risk factors for NAFLD from population-based studies, particularly in an ethnically diverse population, are scarce. We examined dietary factors in relation to NAFLD risk in African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites in the Multiethnic Cohort (MEC). A nested case-control analysis was conducted within the MEC, a large prospective study with >215,000 older-adult participants in Hawaii and California. NAFLD was identified using Medicare claims data, and controls were selected among participants without liver disease and individually matched to cases by birth year, sex, ethnicity, and length of Medicare enrollment. Diet was assessed at baseline via a validated quantitative food frequency questionnaire. Diet-NAFLD associations were quantified by odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable conditional logistic regression. The study consisted of 2,974 NAFLD cases (518 with cirrhosis; 2,456 without cirrhosis) and 29,474 matched controls. Red meat ($P_{\text{trend}}=0.010$), processed red meat ($P_{\text{trend}}=0.004$), poultry ($P_{\text{trend}}=0.005$) and cholesterol ($P_{\text{trend}}=0.005$) intakes were positively associated with NAFLD, while dietary fiber

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intake ($P_{\text{trend}}=0.003$) was inversely associated with risk. Stronger associations were observed between red meat and cholesterol and NAFLD with cirrhosis than without cirrhosis ($P_{\text{heterogeneity}}=0.014$). *Conclusion:* Dietary factors are independently associated with NAFLD and NAFLD-related cirrhosis in a multiethnic population. Decreasing the consumption of cholesterol, red and processed meat and poultry and increasing consumption of fiber may reduce the risk for NAFLD and related advanced liver disease.

Keywords

steatosis; cirrhosis; food; macronutrients; nutrition; prevention

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has an estimated global prevalence of 25.3% (1), and is the most common chronic liver disease (2). NAFLD represents a spectrum of disease severity, ranging from benign simple steatosis termed as nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH) which may lead to cirrhosis, hepatocellular carcinoma and liver decompensation (3–5). A key step in the pathogenesis of NAFLD is the development of insulin resistance (6), a condition related to excess body fat that occurs primarily in the liver, muscle, and adipose tissue (7). The association of insulin resistance and obesity with NAFLD highlights the importance of excess energy intake. However, diet composition can also contribute to the development of insulin resistance and NAFLD.

Two recent studies showed that high consumption of red and/or processed meat was associated with a greater risk for NAFLD and insulin resistance in a cross-sectional study of population attending Gastroenterology department for screening (8), and that high animal protein intake, pointing at meat, was a risk factor for NAFLD in aging white population (9). Other studies including ours have shown that diet quality (10–12) and specific foods or nutrients, such as coffee (13), sugar-sweetened beverages (14, 15) and saturated fat (16) are associated with NAFLD. However, large population-based studies of diet and NAFLD associations, particularly in diverse ethnic groups and high-risk minority populations, are lacking. To address this gap, we performed a comprehensive analysis of dietary risk factors for NAFLD overall and by cirrhosis status in African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the Multiethnic Cohort Study (MEC).

METHODS

Study design and population

We conducted a nested case-control analysis within the MEC. The MEC is a large prospective cohort with >215,000 men and women aged 45–75 years, living in Hawaii and California at cohort entry (1993–1996). The cohort participants have been followed for more than two decades. Cohort design and baseline characteristics have been previously described (17). The baseline mailed questionnaire assessed diet, lifestyle, anthropometry, family and personal medical history and, for women, menstrual and reproductive history and hormone use. For this study, we restricted the analyses to the Medicare fee-for-service (FFS)

participants in the MEC (n=123,196) (18). Figure 1 shows the exclusion criteria and selection of the study participants. We excluded participants who were not from the five major ethnic groups (n=7,511), had invalid dietary data based on implausible macronutrient intakes (n=4,498) and missing baseline information on the important relevant variables (*e.g.* body mass index, diabetes, vigorous physical activity) (n=5,756). A total of 105,431 eligible participants were available for nested case-control analysis.

NAFLD cases among eligible participants were identified using Medicare claims as previously described (2). Briefly, we first identified chronic liver disease (CLD) cases using one inpatient or two or more outpatient/carrier qualifying claims on different dates between 1999 and 2016. NAFLD was determined as the underlying CLD etiology for cases without any other causes [hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol-related conditions, hemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, HIV, alpha-1-antitrypsin deficiency and autoimmune hepatitis] identified using ICD codes and with a baseline BMI ≥ 30 kg/m², diabetes mellitus or NAFLD ICD-9 (571.8 and 571.9) and ICD-10 (K75.81, K760, K7689, K741, K769) codes. Using the American Association for the study of Liver Disease guidelines(19), NAFLD cases who reported >21 drinks/week (men) or >14 drinks/week (women) were reclassified as alcoholic liver disease. In a random subset of NAFLD cases with blood (n=319), we tested hepatitis C antibodies and hepatitis B surface antigen (Abbott Architect i2000 using Architect system reagent Anti-HCV and HBsAg Qualitative) to confirm the robustness of using ICD-9 codes for excluding HBV- and HCV-related liver disease; we found >99% of NAFLD cases did not test positive for chronic viral hepatitis. NAFLD cases were further stratified by cirrhosis status identified using the following ICD9/10 codes: cirrhosis with alcoholism with and without ascites (571.2, K7030, K7031), cirrhosis no mention of alcohol (571.5, K740, K7460, K7469), esophageal varices (456.0, 456.1, 456.20, and 456.21, I8501, I8500, I8511, I8510), spontaneous bacterial peritonitis (567.23, K652); hepatic encephalopathy (572.2, K7290, K7291) and hepatorenal syndrome (572.4, K767). Controls were selected among Medicare FFS participants without CLD and individually matched to cases (with a ratio up to 10:1) on birth year, sex, ethnicity, and length of FFS enrollment. Length of FFS enrollment is the duration study participants enrolled in the FFS Medicare system; the average was 10.2 years in this study. Because NAFLD was identified using Medicare FFS claims, we used duration of Medicare FFS coverage as one of the matching criteria to assure that cases and controls have the same coverage, and thus similar opportunities for being identified as a NAFLD case during the study period. A total of 2,974 NAFLD cases and 29,474 matched controls were included in the current study. The average number of controls per case was 9.9. The characteristics of NAFLD cases (n=133) among the excluded participants with missing covariate data are provided in Supplementary Table 1. The included and excluded cases had similar age at cohort entry, duration of Medicare coverage, average BMI, smoking status, and energy intake, but the included cases had higher proportion of men, Japanese Americans, Latinos, and higher education level.

The Institutional Review Boards for the University of Southern California and the University of Hawaii approved this study.

Diet and covariate assessment

Dietary intake at baseline (1993–1996) was assessed using a comprehensive and well-validated quantitative food frequency questionnaire (QFFQ) designed for use in this multiethnic population (17). A calibration study of the QFFQ was conducted using three 24-hour recalls from a random subsample of participants selected within sex–racial/ethnic groups (20); this study revealed a high correlation between the QFFQ and 24-hour recalls for energy-adjusted nutrient intakes. Daily nutrient intakes from the QFFQ were calculated by using the food composition data developed and maintained at the University of Hawaii Cancer Center. In this study we examined meat intake including red meat, processed red meat, poultry, processed poultry, vegetable, fruit and dietary fiber intakes measured by density (g/1,000 kcal/day). We also examined cholesterol intake and several macronutrients adjusted for energy (% of energy in kcal) including total fat, specific type of fats (saturated, monounsaturated, polyunsaturated) and carbohydrate. Detailed demographics (*i.e.* sex, race/ethnicity, education) and other covariate information (body weight and height, alcohol intake, physical activity, smoking status, physician-diagnosed type 2 diabetes, coffee and soda consumption, etc.) were obtained from the baseline questionnaire. The median time between baseline and the first NAFLD-related claim was 17.4 years.

Statistical analysis

To account for matching factors and potential confounders, multivariable conditional logistic regression analysis was used to examine associations between dietary factors and the outcome of NAFLD overall and NAFLD with and without presence of cirrhosis. Associations were quantified by odds ratios (ORs) with 95% confidence intervals (CIs). Matched sets (each with 1 case and 2–10 controls) were used as strata in the logistic models, which were also adjusted for factors known to be associated with NAFLD (21) including body mass index (kg/m², continuous), alcohol intake (ethanol g/day, continuous), coffee drinking (0, 1, 2–3, 4 cups/day), total soda consumption (0, 2, >2–10, >10 cans/week), vigorous physical activity (hours/day, quartiles) and energy (kcal/day, continuous). Further adjustment for education, smoking status and presence of cardiovascular disease did not change the results substantially, and thus we presented results without these adjustments. A series of models were conducted. First, dietary factors were analyzed using quartiles of daily intake based on values in controls with the lowest quartile as the reference. Then to test for trend, models were run where the quartile of dietary intake was assigned an ordinal score (1,2,..,4) and was modeled as a continuous variable. The slope for this trend variable is then interpreted as the change in the log odds ratio per increase in dietary quartile and the p for trend is a general assessment of the linearity in the odds ratios across quartiles. We next performed these models separately for each racial/ethnic group. Then we fit a model including all participants and interaction terms for each diet trend variable and race/ethnicity indicators to test heterogeneity in the interaction parameters for the diet trend variables by race/ethnicity using a global Wald test with 4 degrees of freedom to jointly test the equality of parameters across racial/ethnic groups. Note that the conditional logistic regression compares the association of diet within matched strata and therefore precludes the investigation of matching factors, such as race/ethnicity, and NAFLD; however, the association of diet and NAFLD can be studied within race/ethnic groups by inclusion of the interaction terms. Lastly, we wished to test heterogeneity in the diet trend parameters for the

outcomes of NAFLD with and without cirrhosis. This required a different approach as the subgroups here are defined by the outcome rather than an exposure variable. This test was made using case-only unconditional logistic regression for the outcome of cirrhosis (yes vs. no) with adjustment for the matching variables. All *P*-values are two-sided. Analyses were conducted with SAS 9.4 software.

RESULTS

Participant characteristics

The characteristics of NAFLD cases and matched controls are shown in Table 1. Mean age of cohort entry was 57.7 years $\pm$ SD 7.8 and 63% were women. The study population included 50% Japanese Americans, 21% Latinos, 16% whites, 7% African Americans, and 6% Native Hawaiians. Demographics and other baseline characteristics were similar between cases and controls, but cases had higher prevalence of type 2 diabetes, higher BMI and reported less alcohol intake and vigorous physical activity. Of the 2,974 NAFLD cases, there were 518 with cirrhosis and 2,456 without cirrhosis. Cases with NAFLD-cirrhosis were more often male, African American, Latino, and obese and had cardiovascular disease and type-2 diabetes at baseline.

Associations of meat, vegetable and fruit intakes with NAFLD

The BMI and lifestyle-adjusted associations of meat intakes with NAFLD are shown in Table 2. Total red meat (OR Quartile 4 vs. Quartile 1=1.15; 95% CI: 1.02–1.29; *P*trend=0.016), red meat excluding processed red meat (OR= 1.16; 95% CI: 1.04–1.30; *P*trend=0.010), and processed red meat (OR= 1.18; 95% CI: 1.05–1.32; *P*trend= 0.004) were associated with NAFLD. Total poultry intake was also associated with NAFLD (OR= 1.16; 95% CI: 1.04–1.30; *P*trend= 0.005), as was processed poultry intake (OR= 1.12; 95% CI: 1.01–1.24), although the trend was not statistically significant (*P*trend=0.139). Table 2 also shows the adjusted associations of fruits and vegetables with NAFLD. There was a significant inverse trend with increasing fruit intake and NAFLD (*P*trend=0.036), but none of the point estimates (ORs) were statistically significant. Vegetable consumption was not associated with NAFLD.

Stratified analyses by cirrhosis status showed a significant modifying effect of cirrhosis status. The association for total red meat was stronger (*P*heterogeneity=0.026) among NAFLD with cirrhosis (OR=1.43; 95% CI: 1.08–1.90; *P*trend=0.012) than those without (OR=1.10; 95% CI: 0.97–1.25; *P*trend=0.119). The association with red meat excluding processed red meat showed a similar pattern, *i.e.* stronger association with NAFLD-cirrhosis (*P*heterogeneity=0.014). The tests for heterogeneity by cirrhosis status suggested no significant differences in the associations of processed red meat, poultry, and fruits between NAFLD with and without cirrhosis. However, the associations were mainly observed among NAFLD without cirrhosis for processed red meat (OR=1.17; 95% CI: 1.03–1.32; *P*trend=0.010) and total poultry (OR=1.19; 95% CI: 1.05–1.35; *P*trend=0.003).

Associations of macronutrients with NAFLD

Table 3 shows the adjusted association of macronutrients as percent of energy intake with NAFLD. Total fat and types of fat (saturated, monounsaturated, and polyunsaturated) and carbohydrate intakes were not associated with NAFLD. Cholesterol intake was positively associated with NAFLD (OR=1.16; 95% CI: 1.03–1.29; $P_{\text{trend}}=0.005$). There were differences in the association by cirrhosis status ($P_{\text{heterogeneity}}=0.001$); cholesterol was associated with NAFLD with cirrhosis (OR=1.52; 95% CI: 1.15–2.01; $P_{\text{trend}}=0.002$), but not with NAFLD without cirrhosis (OR=1.09; 95% CI: 0.96–1.23; $P_{\text{trend}}=0.09$). Dietary fiber intake was inversely associated with NAFLD (OR=0.84; 95% CI: 0.74–0.95; $P_{\text{trend}}=0.003$), with no significant differences in the associations of dietary fiber between NAFLD with and without cirrhosis ($P_{\text{heterogeneity}}=0.650$).

Associations of diet with NAFLD by race/ethnicity

The race/ethnicity-specific results are shown in Supplementary Table 1. The associations with NAFLD were generally similar across racial/ethnic groups, except for poultry consumption ($P_{\text{heterogeneity}}=0.004$). The significant positive association between poultry and NAFLD was observed for whites ($P_{\text{trend}}=0.003$) and Native Hawaiians ($P_{\text{trend}}=0.005$) only. The associations of red meat and processed red meat with NAFLD were in similar direction across racial/ethnic groups, but were only statistically significant in whites (total red meat $P_{\text{trend}}=0.005$; processed red meat $P_{\text{trend}}=0.005$) and in Latinos (processed red meat $P_{\text{trend}}=0.022$). Cholesterol was significantly positively associated with NAFLD in whites ($P_{\text{trend}}=0.006$) and Native Hawaiians ($P_{\text{trend}}=0.036$), while fiber intake was significantly inversely associated with NAFLD in whites ($P_{\text{trend}}=0.028$) and Latinos ($P_{\text{trend}}=0.034$).

DISCUSSION

In this large population-based study of ethnically diverse populations in the US, we assessed various dietary factors in relation to NAFLD and NAFLD-related cirrhosis. We found that higher intakes of red meat, processed red meat, poultry, and cholesterol are risk factors for NAFLD, while dietary fiber is a protective factor. Importantly, the associations were generally similar across a wide spectrum of racial/ethnic groups, supporting the external validity of the observed associations. Moreover, certain dietary risk factors (*i.e.* red meat and cholesterol) were associated with NAFLD-related cirrhosis.

Our findings agree with previous studies investigating the association of meat intake with NAFLD (8, 9, 14). In a cross-sectional study of 349 participants from a general population, protein from all types of meat was significantly associated with an increased risk for NAFLD ($P_{\text{for trend}}=0.01$ for increasing quartiles) (14). More recently, a cross-sectional study of 789 participants by Zelber-Sagi *et al.* showed that high intakes of red meat and/or processed meat were associated with NAFLD. High intake of processed meat alone did not remain significantly associated with NAFLD after adjusting for physical activity and other factors (8). In that study, the association between processed meat was only observed with insulin resistance, and not with NAFLD. The authors attributed these observations to the possibility of a relatively low consumption of processed meat in their study population. In

the Rotterdam study of 3,882 (1,337 NAFLD cases) mostly elderly participants from Europe, a general association between total animal protein and NAFLD was observed only among overweight subjects(9). Our study confirmed and refined these associations; showing specific associations of red meat and processed red meat with both NAFLD and related cirrhosis, regardless of other risk factors including lifestyle characteristics.

Interestingly, we have found that poultry intake was also associated with NAFLD risk. Most previous studies did not specifically examine poultry consumption, as most focused on overall meat consumption or red and processed meat consumption. In a smaller case-control study of 280 Italians, Miele *et al*, demonstrated that a high consumption of white meat was associated with increased risk of NAFLD (22).

The association between meat intake, particularly red and processed meat, and NAFLD risk is not unexpected. Both have shown associations with diabetes, cardiovascular diseases, insulin resistance, chronic liver disease (CLD) and hepatocellular carcinoma (HCC) (23–25). Freedman *et al*. showed that red meat is associated with risk of CLD and HCC, both of which may lead or emerge with cirrhosis progression. The harmful effect of red meat has been partially attributed to the formation of heterocyclic aromatic amines (HAAs) during less healthy cooking methods such as frying and barbecuing to a level of very well done. HAAs have been shown to increase oxidative stress which is a key step in the pathophysiology of NASH and ultimately cirrhosis (26–28). Collectively, these findings highlight the possible harmful effects of red meat and their association with NAFLD. Indeed, the Mediterranean diet, which is low in red meat and processed red meat, was found to be beneficial in NAFLD, leading to decreased steatosis and improved insulin resistance (11, 29). In a recent prospective study of diet quality and NAFLD by genetic risk score, red meat was implicated as one of the driving components for the association between diet quality and changes in liver fat (12).

In our study, we found an inverse association between total dietary fiber and NAFLD. Only few, smaller observational studies reported that NAFLD patients consume less vegetables and dietary fibers than controls (30, 31). Randomized intervention studies have shown that fiber intake improves liver enzymes and non-invasive NAFLD scores among participants with NAFLD (32, 33). We found a significant inverse trend between fruit intake and NAFLD, and a previous study showed that fiber from fruits has a favorable effect on liver enzymes among obese individuals (33). While it has been previously suggested that a high fiber diet could have a preventive role in liver diseases, and indeed high fiber intake is one of the plausible molecular mechanisms for the beneficial effect of the Mediterranean diet in NAFLD (21, 34), more studies are warranted to confirm our findings and support this recommendation.

Although total fat and fat composition were not associated with NAFLD, cholesterol consumption was associated with NAFLD risk in our study. It is interesting to note that the association was mainly observed for NAFLD with cirrhosis. A prospective analysis using NHANES data (5 year follow up, 123 cirrhosis cases among 9,221 participants) showed similar findings; while total fat consumption was not associated with the risk of cirrhosis, cholesterol consumption was associated with higher risk (35). Dietary cholesterol is

suggested as an important risk factor for the progression to hepatic inflammation in diet-induced NASH (36). However, the role of cholesterol and severity of NAFLD has been established mostly in animal models and less consistently in human studies. A diet of normal-weight NASH patients as compared to age, gender and BMI matched controls, was richer in cholesterol (37), and similar finding was seen in the diet of normal-weight NAFLD patients as compared to obese NAFLD patients (38). Previous epidemiological studies, however, did not demonstrate an association between cholesterol intake and NAFLD (9, 14). Min *et al.* showed that HMG CoA reductase (HMGCR) expression was correlated with free cholesterol, LDL-cholesterol and histologic severity of NAFLD (39). Their data revealed that dysregulated cholesterol metabolism in human NAFLD may contribute to disease severity. In animal models, cholesterol rich diets have led to oxidative stress and progression from NAFLD to NASH (40, 41). Others have shown that mitochondrial free cholesterol loading (but not fatty acids or triglycerides) lead to mice being sensitized to tumor necrosis factor and Fas induced steatohepatitis (42). Studies in mice have also shown that free cholesterol accumulates in hepatic stellate cells, and high cholesterol diet aggravates liver fibrosis (43, 44). Altogether, these studies support our finding of an association between dietary cholesterol and NAFLD severity.

There are several strengths to our study including the large sample size, population-based design, inclusion of diverse and high-risk understudied populations, and detailed dietary and nutrient intake data with a well-validated questionnaire, in addition to available information on potential confounders. We also showed that >99% of NAFLD cases with blood samples did not have underlying viral hepatitis based on serum testing.

Nevertheless, there were several limitations that should be noted. Bias in self-reported diet is inevitable and may have led to some degree of non-differential misclassification of exposure, which could have attenuated the observed associations. In addition, diet was assessed at baseline and may have changed during follow up, but in the subset of participants with repeated QFFQ in 2003–2007 (~58% participants with an average of 11.0 years between measurements), an analysis using averaged nutritional intake values yielded similar results for overall NAFLD and by cirrhosis status. The case identification was based on Medicare claims without imaging data; thus, participants with undiagnosed NAFLD might have been inadvertently included in the control group which can lead to underestimation of the true associations. The prevalence of NAFLD in our study was also likely underestimated, but it was consistent with other epidemiological studies that did not use imaging data (45–47). In addition, NAFLD identification using CLD claims may have led to selection of cases with more severe disease. Inclusion of older Medicare participants (*i.e.* age 65 or older) limits the generalizability of our results to younger populations. It is also possible that medication use (*e.g.* metformin, statins) may modify the diet-NAFLD association; unfortunately, we did not collect this information at baseline, and thus we were unable to examine the drug's possible modifying effects. Finally, while we adjusted for several important potential confounders including lifestyle factors in our analyses, as in any observational study, residual confounding cannot be excluded completely.

To our knowledge, this is the first and largest study in an ethnically diverse population that investigates dietary factors associated with NAFLD. This is also the first study to present

dietary associations for NAFLD by cirrhosis status. Dietary recommendations remain the first step and cornerstone of NAFLD/NASH treatment. Our findings suggest that diets low in meat and cholesterol and high in fiber may reduce the risk for NAFLD and for related advanced liver disease. Finally, our study calls for detailed nutrients documentation in future NASH trials, especially those with long follow up duration (phase 3 and 4) as diet may influence disease progression and study results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
CI	confidence interval
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OR	odds ratio
SD	(standard deviation)

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Figure 1. Exclusion criteria and selection of study participants.

ALD (alcoholic liver disease); BMI (body mass index); CLD (chronic liver disease); FFS (Fee-for-service); HBV (hepatitis B virus); HCV (hepatitis C virus); MEC (Multiethnic Cohort Study); NAFLD (nonalcoholic fatty liver disease); PBC (primary biliary cholangitis); PSC (primary sclerosing cholangitis).

Table 1.
Demographic and selected baseline characteristics of NAFLD cases and controls in the Multiethnic Cohort

	All NAFLD Cases (N = 2,974)	NAFLD No Cirrhosis (N=2,456)	NAFLD with Cirrhosis (N=518)	Controls (N = 29,474)
Age at cohort entry				
Mean (SD)	57.7 (7.8)	57.2 (7.8)	59.9 (7.5)	57.8 (7.8)
Sex, n (%)				
Men	1,113 (37.4)	898 (36.6)	215 (41.5)	11,112 (37.7)
Women	1,861 (62.6)	1,558 (63.4)	303 (58.5)	18,362 (62.3)
Race/ethnicity, n (%)				
White	474 (15.9)	386 (15.7)	88 (17.0)	4,740 (16.1)
African American	206 (6.9)	156 (6.4)	50 (9.7)	2,060 (7.0)
Native Hawaiian	186 (6.3)	150 (6.1)	36 (6.9)	1,856 (6.3)
Japanese American	1,490 (50.1)	1,337 (54.4)	153 (29.5)	14,692 (49.8)
Latino	618 (20.8)	427 (17.4)	191 (36.9)	6,126 (20.8)
Study area, n (%)				
Hawaii	1,887 (63.4)	1,657 (67.5)	230 (44.4)	17,848 (60.6)
California	1,087 (36.6)	799 (32.5)	288 (55.6)	11,626 (39.4)
Education, n (%)				
High School	1,133 (38.1)	874 (35.6)	259 (50.0)	10,838 (36.8)
Vocational/some college	856 (28.8)	711 (28.9)	145 (28.0)	8,540 (29.0)
College or higher	958 (32.2)	851 (34.6)	107 (20.7)	9,855 (33.4)
Missing	27 (0.9)	20 (0.8)	7 (1.4)	241 (0.8)
Duration of Medicare coverage, n (%)				
< 5 years	648 (21.8)	484 (19.7)	164 (31.7)	6,562 (22.3)
5 to < 10 years	796 (26.8)	645 (26.3)	151 (29.2)	7,898 (26.8)
10 years	1,530 (51.4)	1,327 (54)	203 (39.2)	15,014 (50.9)
Smoking status, n (%)				
Never	1,494 (50.2)	1,262 (51.4)	232 (44.8)	14,822 (50.3)
Past	1,120 (37.7)	911 (37.1)	209 (40.3)	10,768 (36.5)
Current	330 (11.1)	260 (10.6)	70 (13.5)	3,557 (12.1)
Missing	30 (1.0)	23 (0.9)	7 (1.4)	327 (1.1)

	All NAFLD Cases (N = 2,974)	NAFLD No Cirrhosis (N=2,456)	NAFLD with Cirrhosis (N=518)	Controls (N = 29,474)
Energy intake (kcal/day)				
Mean (SD)	2,122 (1,000)	2,103 (973)	2,211 (1,117)	2,127 (985)
Alcohol intake, g/day				
Mean (SD)	2.8 (6.3)	2.8 (6.3)	2.7 (6.5)	6.7 (19.2)
Coffee intake, n (%)				
0 cups/day	890 (29.9)	735 (29.9)	155 (29.9)	8,161 (27.7)
1 cups/day	1,338 (45.0)	1,084 (44.1)	254 (49.0)	13,594 (46.1)
2-3 cups/day	617 (20.7)	525 (21.4)	92 (17.8)	6,257 (21.2)
4 cups/day	129 (4.3)	112 (4.6)	17 (3.3)	1,462 (5.0)
Total soda intake, n (%)				
0 cans/week	434 (14.6)	362 (14.7)	72 (13.9)	5,188 (17.6)
2 cans/week	1,012 (34.0)	853 (34.7)	159 (30.7)	10,307 (35.0)
> 2 to 10 cans/week	1,112 (37.4)	924 (37.6)	188 (36.3)	10,683 (36.2)
> 10 cans/week	416 (14.0)	317 (12.9)	99 (19.1)	3,296 (11.2)
Body mass index (kg/m²)				
Mean (SD)	27.4 (5.2)	26.9 (4.9)	29.8 (6.0)	25.7 (4.7)
Type-2 diabetes, n (%)	1,965 (66.1)	1,517 (61.8)	448 (86.5)	12,221 (41.5)
History of cardiovascular disease, n (%)	264 (8.9)	185 (7.5)	79 (15.3)	1,911 (6.5)
Vigorous physical activity, n (%)				
0 h/day	1,466 (49.3)	1,186 (48.3)	280 (54.1)	13,519 (45.9)
> 0 - 0.11 h/day	517 (17.4)	431 (17.5)	86 (16.6)	4,959 (16.8)
> 0.11 - 0.36 h/day	399 (13.4)	346 (14.1)	53 (10.2)	4,326 (14.7)
> 0.36 h/day	592 (19.9)	493 (20.1)	99 (19.1)	6,670 (22.6)

Table 2.
Adjusted associations between food groups* and NAFLD and related cirrhosis in the Multiethnic Cohort

	All NAFLD			NAFLD No Cirrhosis			NAFLD With Cirrhosis			P-value heterogeneity
	Cases/ controls	OR** (95% CI)	Cases/ controls	OR** (95% CI)	Cases/ controls	OR** (95% CI)	Cases/ controls	OR** (95% CI)		
Total red meat										
13.7	639/7,342	1.00 (ref.)	550/6,063	1.00 (ref.)	89/1,279	1.00 (ref.)			0.0276	
> 13.7 to 23.3	721/7,373	1.08 (0.96–1.21)	600/6,057	1.05 (0.93–1.19)	121/1,316	1.22 (0.91–1.64)				
> 23.3 to 34.0	779/7,384	1.12 (1.00–1.26)	640/6,140	1.09 (0.96–1.23)	139/1,244	1.36 (1.02–1.82)				
> 34.0	835/7,375	1.15 (1.02–1.29)	666/6,049	1.10 (0.97–1.25)	169/1,326	1.43 (1.08–1.90)				
P-value for trend		0.0159		0.1190		0.0121				
Red meat excluding processed meat										
9.3	647/7,375	1.00 (ref.)	554/6,079	1.00 (ref.)	93/1,296	1.00 (ref.)			0.0144	
> 9.3 to 16.2	726/7,399	1.08 (0.97–1.21)	608/6,126	1.06 (0.94–1.20)	118/1,273	1.22 (0.91–1.64)				
> 16.2 to 24.1	765/7,342	1.11 (0.99–1.24)	636/6,098	1.09 (0.96–1.23)	129/1,244	1.28 (0.96–1.71)				
> 24.1	836/7,358	1.16 (1.04–1.30)	658/6,006	1.10 (0.97–1.25)	178/1,352	1.52 (1.15–2.01)				
P-value for trend		0.0106		0.1223		0.0033				
Processed red meat										
3.0	661/7,377	1.00 (ref.)	552/6,062	1.00 (ref.)	109/1,315	1.00 (ref.)			0.6750	
> 3.0 to 6.1	713/7,416	1.03 (0.92–1.16)	579/6,058	1.02 (0.90–1.15)	134/1,358	1.12 (0.85–1.48)				
> 6.1 to 10.0	736/7,272	1.05 (0.94–1.18)	622/6,054	1.07 (0.95–1.22)	114/1,218	0.97 (0.72–1.29)				
> 10.0	864/7,409	1.18 (1.05–1.32)	703/6,135	1.17 (1.03–1.32)	161/1,274	1.31 (0.99–1.71)				
P-value for trend		0.0039		0.0097		0.1123				
Total poultry										
11.4	648/7,331	1.00 (ref.)	530/6,035	1.00 (ref.)	118/1,296	1.00 (ref.)			0.7955	
> 11.4 to 18.0	732/7,434	1.07 (0.96–1.20)	613/6,243	1.08 (0.95–1.22)	119/1,191	1.06 (0.81–1.40)				
> 18.0 to 27.6	783/7,370	1.15 (1.02–1.28)	646/6,109	1.15 (1.02–1.30)	137/1,261	1.11 (0.85–1.46)				
> 27.6	811/7,339	1.16 (1.04–1.30)	667/5,922	1.19 (1.05–1.35)	144/1,417	1.03 (0.79–1.35)				
P-value for trend		0.0054		0.0028		0.7717				
Poultry excluding processed poultry										
10.7	639/7,328	1.00 (ref.)	516/6,050	1.00 (ref.)	123/1,278	1.00 (ref.)			0.9244	

	All NAFLD			NAFLD No Cirrhosis			NAFLD With Cirrhosis			P-value heterogeneity
	Cases/ controls	OR** (95% CI)	Cases/ controls	OR** (95% CI)	Cases/ controls	OR** (95% CI)				
> 10.7 to 17.0	746/7,427	1.11 (0.99–1.24)	631/6,218	1.15 (1.02–1.30)	115/1,209	0.96 (0.73–1.26)				
> 17.0 to 26.2	782/7,357	1.16 (1.04–1.30)	650/6,096	1.20 (1.06–1.36)	132/1,261	0.99 (0.76–1.30)				
> 26.2	807/7,362	1.17 (1.05–1.31)	659/5,945	1.21 (1.07–1.38)	148/1,417	1.02 (0.78–1.33)				
P-value for trend		0.0047		0.0022		0.8070				
Processed poultry										
0.1	805/8,558	1.00 (ref.)	647/6,964	1.00 (ref.)	158/1,594	1.00 (ref.)				
> 0.1 to 0.4	594/5,666	1.12 (1.00–1.25)	502/4,688	1.15 (1.02–1.30)	92/978	0.96 (0.73–1.28)				
> 0.4 to 1.3	781/8,066	1.01 (0.91–1.12)	654/6,749	1.03 (0.91–1.15)	127/1,317	0.96 (0.74–1.24)			0.4842	
> 1.3	794/7,184	1.12 (1.01–1.24)	653/5,908	1.14 (1.01–1.28)	141/1,276	1.05 (0.81–1.35)				
P-value for trend		0.1392		0.1212		0.7827				
Total vegetables										
109.1	762/7,360	1.00 (ref.)	639/6,065	1.00 (ref.)	123/1,295	1.00 (ref.)			0.5263	
> 109.1 to 148.2	730/7,369	0.95 (0.85–1.06)	602/6,134	0.92 (0.81–1.03)	128/1,235	1.11 (0.85–1.46)				
> 148.2 to 199.3	729/7,379	0.94 (0.84–1.05)	598/6,131	0.91 (0.80–1.02)	131/1,248	1.16 (0.88–1.53)				
> 199.3	753/7,366	0.99 (0.88–1.10)	617/5,979	0.97 (0.86–1.09)	136/1,387	1.07 (0.81–1.41)				
P-value for trend		0.8068		0.5758		0.6352				
Total fruits										
74.2	766/7,363	1.00 (ref.)	629/6,123	1.00 (ref.)	137/1,240	1.00 (ref.)			0.5911	
> 74.2 to 139.4	792/7,375	1.02 (0.91–1.13)	665/6,113	1.04 (0.92–1.16)	127/1,262	0.91 (0.70–1.19)				
> 139.4 to 230.6	714/7,369	0.92 (0.82–1.03)	585/6,084	0.91 (0.81–1.03)	129/1,285	0.94 (0.72–1.23)				
> 230.6	702/7,367	0.91 (0.81–1.02)	577/5,989	0.91 (0.80–1.03)	125/1,378	0.93 (0.70–1.23)				
P-value for trend		0.0364		0.0422		0.6650				

* Intakes were measured in density (g/1,000 kcal/day).

* OR derived from conditional logistic regression using matched sets as strata (each stratum with 1 case and 2–10 controls) and adjusted for body mass index (continuous), alcohol intake (continuous), coffee intake (0, 1, 2–3, 4 cups/day), total soda intake (0, 2, > 2 to 10, > 10 cans/week), vigorous physical activity (continuous), and energy (kcal/day, continuous).

Dietary factors were analyzed using quartiles based on values in controls with the lowest quartile as the reference group.

P-values for trend were based on including the dietary variables where the category was assigned an ordinal score (1,2,3,...) and was modeled as a continuous variable.

P-values for heterogeneity for the diet trend parameters for the outcomes of NAFLD with and without cirrhosis were calculated using case-only unconditional logistic regression with the event being cirrhosis (yes vs. no) and adjusting for the matching variables.

Table 3.
Adjusted associations of macronutrients with NAFLD and related cirrhosis in the Multiethnic Cohort

	All NAFLD		NAFLD No Cirrhosis		NAFLD With Cirrhosis		P-value heterogeneity
	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)	
Total fat (% of energy)							
24.7	687/7,377	1.00 (ref.)	592/6,169	1.00 (ref.)	95/1,208	1.00 (ref.)	0.0613
> 24.7 to 29.5	735/7,298	1.02 (0.91–1.14)	626/6,121	1.01 (0.90–1.14)	109/1,177	1.06 (0.78–1.42)	
> 29.5 to 34.1	725/7,433	0.94 (0.84–1.05)	584/6,088	0.91 (0.80–1.03)	141/1,345	1.12 (0.84–1.49)	
> 34.1	827/7,366	1.02 (0.91–1.15)	654/5,931	0.99 (0.88–1.13)	173/1,435	1.21 (0.91–1.62)	
P-value for trend		0.9819		0.5333		0.1575	
Saturated fat (% of energy)							
6.8	689/7,210	1.00 (ref.)	597/6,144	1.00 (ref.)	92/1,066	1.00 (ref.)	0.0954
> 6.8 to 8.5	724/7,440	0.97 (0.86–1.08)	628/6,297	0.98 (0.87–1.10)	96/1,143	0.92 (0.68–1.25)	
> 8.5 to 10.3	756/7,513	0.95 (0.85–1.07)	619/6,160	0.95 (0.84–1.07)	137/1,353	1.01 (0.76–1.36)	
> 10.3	805/7,311	0.98 (0.87–1.10)	612/5,708	0.95 (0.84–1.09)	193/1,603	1.12 (0.83–1.50)	
P-value for trend		0.7018		0.4075		0.3265	
Monounsaturated Fat (% of energy)							
8.8	675/7,356	1.00 (ref.)	575/6,154	1.00 (ref.)	100/1,202	1.00 (ref.)	0.3161
> 8.8 to 10.7	720/7,459	0.99 (0.89–1.11)	610/6,210	1.00 (0.89–1.13)	110/1,249	0.95 (0.71–1.28)	
> 10.7 to 12.5	800/7,421	1.06 (0.94–1.18)	658/6,126	1.05 (0.93–1.18)	142/1,295	1.11 (0.84–1.47)	
> 12.5	779/7,238	0.99 (0.88–1.11)	613/5,819	0.98 (0.86–1.11)	166/1,419	1.09 (0.82–1.44)	
P-value for trend		0.8474		0.8995		0.3577	
Polyunsaturated Fat (% of energy)							
5.8	692/7,563	1.00 (ref.)	575/6,152	1.00 (ref.)	117/1,411	1.00 (ref.)	0.3673
> 5.8 to 6.9	695/7,040	1.01 (0.91–1.13)	563/5,800	0.99 (0.87–1.11)	132/1,240	1.12 (0.86–1.48)	
> 6.9 to 8.1	774/7,391	1.03 (0.92–1.15)	657/6,070	1.05 (0.93–1.19)	117/1,321	0.88 (0.67–1.17)	
> 8.1	813/7,480	1.02 (0.91–1.14)	661/6,287	0.99 (0.87–1.11)	152/1,193	1.21 (0.92–1.58)	
P-value for trend		0.6907		0.9352		0.4163	
Cholesterol (mg/1,000 kcal/day)							
75.4	665/7,384	1.00 (ref.)	574/6,164	1.00 (ref.)	91/1,220	1.00 (ref.)	0.0012

	All NAFLD			NAFLD No Cirrhosis			NAFLD With Cirrhosis			P-value heterogeneity
	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)				
> 75.4 to 97.3	689/7,350	0.99 (0.89–1.11)	584/6,139	0.98 (0.87–1.11)	105/1,211	1.05 (0.78–1.42)				
> 97.3 to 121.4	760/7,370	1.07 (0.95–1.19)	634/6,073	1.06 (0.94–1.20)	126/1,297	1.09 (0.81–1.46)				
> 121.4	860/7,370	1.16 (1.03–1.29)	664/5,933	1.09 (0.96–1.23)	196/1,437	1.52 (1.15–2.01)				
P-value for trend		0.0048		0.0889		0.0018				
Carbohydrate (% of energy)										
48.2	680/7,345	1.00 (ref.)	531/5,845	1.00 (ref.)	149/1,500	1.00 (ref.)			0.2075	
> 48.2 to 53.9	771/7,411	1.00 (0.89–1.11)	628/6,085	1.01 (0.89–1.14)	143/1,326	0.97 (0.75–1.26)				
> 53.9 to 59.8	767/7,366	0.97 (0.87–1.09)	654/6,166	1.01 (0.89–1.14)	113/1,200	0.82 (0.62–1.08)				
> 59.8	756/7,352	0.97 (0.86–1.09)	643/6,213	0.98 (0.86–1.12)	113/1,139	0.91 (0.68–1.22)				
P-value for trend		0.5125		0.7748		0.3259				
Dietary fiber (g/1,000 kcal/day)										
8.5	781/7,476	1.00 (ref.)	668/6,429	1.00 (ref.)	113/1,047	1.00 (ref.)			0.6497	
> 8.5 to 11.0	779/7,407	0.95 (0.85–1.05)	642/6,133	0.95 (0.84–1.07)	137/1,274	0.88 (0.66–1.16)				
> 11.0 to 14.0	727/7,264	0.89 (0.80–1.00)	587/5,964	0.88 (0.77–0.99)	140/1,300	0.94 (0.70–1.25)				
> 14.0	687/7,327	0.84 (0.74–0.95)	559/5,783	0.86 (0.75–0.98)	128/1,544	0.75 (0.55–1.02)				
P-value for trend		0.0034		0.0123		0.1018				

* OR derived from conditional logistic regression using matched sets as strata (each stratum with 1 case and 2–10 controls) and adjusted for body mass index (continuous), alcohol intake (continuous), coffee intake (0, 1, 2–3, 4 cups/day), total soda intake (0, 2, > 2 to 10, > 10 cans/week), vigorous physical activity (continuous h/day), and energy (kcal/day, continuous).

Dietary factors were analyzed using quartiles based on values in controls with the lowest quartile as the reference group.

P-values for trend were based on including the dietary variables where the category was assigned an ordinal score (1,2,3,...) and was modeled as a continuous variable.

P-values for heterogeneity for the diet trend parameters for the outcomes of NAFLD with and without cirrhosis were calculated using case-only unconditional logistic regression with the event being cirrhosis (yes vs. no) and adjusting for the matching variables.