

High-Quality Diets Are Associated With Reduced Risk of Hepatocellular Carcinoma and Chronic Liver Disease: The Multiethnic Cohort

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Hepatocellular carcinoma (HCC) and chronic liver disease (CLD) are major sources of morbidity and mortality globally. Both HCC incidence and CLD mortality are known to vary by race. There is limited research on the association between dietary measures and these outcomes in a diverse population. We prospectively investigated the associations between four diet quality index (DQI) scores (Healthy Eating Index-2010, Alternative Healthy Eating Index-2010, Alternate Mediterranean Diet [aMED], and Dietary Approaches to Stop Hypertension), HCC incidence, and CLD mortality in the Multiethnic Cohort. We analyzed data from 169,806 African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites, aged 45 to 75 years. DQI scores were calculated by using a validated food frequency questionnaire administered at baseline. During an average 17 years of follow-up, 603 incident cases of HCC and 753 CLD deaths were identified among study participants. Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) for each DQI were estimated using Cox regression. Higher aMED scores, reflecting favorable adherence to a healthful diet, were associated with a lower risk of HCC (quintile [Q]5 versus Q1 HR, 0.68; 95% CI, 0.51-0.90; trend, $P=0.02$). In racial/ethnic-specific analyses, there was no significant heterogeneity across groups (interaction, $P=0.32$); however, the association only remained statistically significant among Latinos (Q4 versus Q1 HR, 0.47; 95% CI, 0.29-0.79; trend, $P=0.006$). All DQI measures were inversely associated with CLD mortality, with no significant heterogeneity by race/ethnicity. **Conclusion:** Higher aMED scores were associated with a lower risk of HCC. A higher score of any DQI was associated with a lower risk of CLD mortality. These results suggest that better diet quality may reduce HCC incidence and CLD mortality. (*Hepatology Communications* 2019;3:437-447).

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide. Although incidence and mortality rates have declined for most cancers in the United States, HCC rates have continued to increase.⁽¹⁾ The health impact of the increasing incidence of HCC is compounded

Abbreviations: AARP, American Association of Retired Persons; AHEI, Alternative Healthy Eating Index; aMED, Alternate Mediterranean Diet Score; BMI, body mass index; CI, confidence interval; CLD, chronic liver disease; DASH, Dietary Approaches to Stop Hypertension; DPMP, Dietary Patterns Methods Project; DQI, diet quality index; HCC, hepatocellular carcinoma; HEI, Healthy Eating Index; HR, hazard ratio; ICD, International Classification of Diseases; MEC, Multiethnic Cohort; NAFLD, nonalcoholic fatty liver disease; NIH, National Institutes of Health; Q, quintile; QFFQ, quantitative food frequency questionnaire; ref, reference.

Received September 11, 2018; accepted December 19, 2018.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1313/supinfo.

Supported by the National Cancer Institute (grants U01CA164973 to L.L.M. and R01CA228589 to V.W.S.).

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DOI 10.1002/hep4.1313

Potential conflict of interest: Nothing to report.

by its dismal prognosis, with an overall 5-year survival of 18%. There are marked differences in HCC incidence by race/ethnicity, with disproportionate numbers among minority populations. In the Multiethnic Cohort (MEC), we showed striking racial/ethnic differences in HCC incidence, with Latinos having the highest incidence, followed by Native Hawaiians, African Americans, Japanese Americans, and whites.⁽²⁾ U.S.-born Latinos, particularly male adults, are at greater risk of HCC than foreign-born Latinos, suggesting an adverse acculturation effect.⁽³⁾

In the United States, chronic liver disease (CLD) is the sixth leading cause of mortality for individuals between 25 and 64 years of age. CLD has an estimated national prevalence of 1.5%, or 3.9 million,⁽⁴⁾ resulting in more than 40,000 deaths annually. CLD mortality differs dramatically among racial groups. It is the twelfth most common cause of mortality among non-Hispanic whites but the seventh among Hispanics and fourth among Hispanics between the ages of 45 and 64 years. Currently, CLD is the primary cause of more than 6,000 (3.4%) Hispanic deaths in the United States annually.

Several dietary factors have been associated with HCC,^(5,6) but in general the role of diet in HCC incidence, particularly in ethnically diverse populations, is poorly understood. Similarly for CLD, there is limited research on how diet affects disease incidence and death, specifically across different racial groups. Diet quality indexes (DQIs) have been developed to capture aspects of the entire diet and to better examine the complexity of foods and beverages as consumed. The Dietary Patterns Methods Project (DPMP), which was initiated by the National Cancer Institute,⁽⁷⁾ selected four DQIs to examine within three large U.S. cohorts, including the MEC. These DQIs were

the Healthy Eating Index-2010 (HEI-2010), the Alternative Healthy Eating Index-2010 (AHEI-2010), the Alternate Mediterranean Diet (aMED), and the Dietary Approaches to Stop Hypertension (DASH) index.⁽⁸⁾ The one and only study of DQIs, HCC incidence, and CLD mortality found HEI-2010 and aMED to be associated with reduced HCC incidence and CLD mortality in the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) cohort.⁽⁹⁾ However, this study was conducted in mostly non-Hispanic white individuals, and thus whether these findings apply to minority populations remains to be seen. Given there is considerable variation in HCC incidence and CLD mortality by race/ethnicity,^(3,10-13) there is a need to identify possible sources for this variation in risk. Diet is an important exposure to consider, given that it is known to differ by race/ethnicity.⁽¹⁴⁻¹⁶⁾

In the present study, we prospectively investigated the associations between four DQI scores, HCC incidence, and CLD mortality among ethnically diverse populations. We also examined whether the associations differed by sex and race/ethnicity.

Participants and Methods

STUDY POPULATION

The MEC is a prospective cohort of more than 215,000 men and women, aged 45 to 75 years, enrolled between 1993 and 1996. The cohort design and baseline characteristics have been described in detail.⁽¹⁷⁾ Potential participants were identified primarily through the Department of Motor Vehicles, voter registration lists, and Health Care Financing

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Administration data files. The response rates were highest in Japanese Americans (51%), whites (47%), and Native Hawaiians (42%) and lowest in African Americans (26%) and Latinos (21%). 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 analysis, we excluded participants who were not in the five main ethnic groups ($n = 13,987$), had any previous cancer reported on baseline questionnaire or from tumor registries ($n = 18,770$), had implausible dietary energy and macronutrient intakes ($n = 8,256$), or were missing covariate information ($n = 4,740$). The resulting cohort included 169,806 participants for the final analysis. The institutional review boards for the University of Southern California and the University of Hawaii approved this study. All participants provided consent at enrollment.

DIETARY ASSESSMENT AND CALCULATION OF DIETARY INDEXES

The MEC baseline questionnaire included a quantitative food frequency questionnaire (QFFQ) with >180 food items. This questionnaire was developed using data from 3-day measured dietary records completed by approximately 60 men and women from each ethnic group represented in the MEC.⁽¹⁷⁾ A calibration study showed satisfactory correlations for nutrients and for the MyPyramid Equivalent Database values used in the DQIs between the QFFQ and three repeated 24-hour recalls for all ethnic-sex groups.⁽¹⁸⁾ Daily nutrient intakes from the QFFQ were calculated by using food composition data developed and maintained at the University of Hawaii Cancer Center.

As described,^(8,19) four dietary indexes (HEI-2010, AHEI-2010, aMED, and DASH) have been calculated in the MEC as part of the DPMPs. In brief, the HEI-2010 was developed to quantify adherence to the 2010 Dietary Guidelines for Americans, with higher scores reflecting better quality and adherence. The AHEI-2010 was developed to identify dietary patterns consistently associated with a lower risk of chronic disease in clinical and epidemiologic investigations. The aMED score is an adaptation of the Mediterranean diet score, with consideration for eating behaviors

consistently associated with lower risks of chronic disease. The DASH score was designed to capture the diet tested in two feeding trials that examined the role of dietary patterns on blood pressure. The specific dietary components included in the indexes have been described.⁽²⁰⁾ The four DQI scores range as follows: HEI-2010, 0 (lowest adherence) to 100 (highest adherence); AHEI-2010, 0 (lowest adherence) to 110 (highest adherence); aMED, 0 (lowest adherence) to 9 (highest adherence); DASH, 8 (lowest adherence) to 40 (highest adherence). The distributions of the DQI scores by race/ethnicity in the cohort are shown in Supporting Table S1. All DQI scores were similar across racial/ethnic groups. Latinos consistently scored slightly lower than all other groups for HEI-2010, AHEI-2010, and aMED.

ENDPOINT ASCERTAINMENT

Incident HCC cases (International Classification of Diseases [ICD]-O-3 code C22.0 and morphology codes 8170-8175) were identified by annual linkage to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program tumor registries in Hawaii and California. Case ascertainment was complete through December 31, 2013. During an average of 17 years of follow-up, a total of 605 incident HCC cases were identified among study participants. Linkages to the National Death Index and death certificate files in Hawaii and California provided information on vital status as well as cause of death. Death from CLD was defined as ICD, Ninth Revision (ICD-9), 571; and ICD-10, K70-K76. Among all CLD deaths ($n = 753$) in the MEC, 79% were from alcoholic-related disease and liver fibrosis/cirrhosis. HCC deaths were excluded from CLD mortality endpoint analysis because we consider HCC incidence as a separate outcome in this study and death certificates can falsely include metastatic cancer to the liver as primary liver cancer.

STATISTICAL ANALYSIS

Cox proportional hazards models for HCC or CLD with age as the time metric were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). The period of observation was the age at cohort entry to the earliest of the following ages: age at HCC diagnosis, age at death, and age at end of

follow-up (December 31, 2013). DQIs were categorized into quintiles based on their distributions across the entire cohort, and indicator variables denoting quintile membership were included in the models. Trend variables for the indexes were assigned the sex- and ethnicity-specific median values for quintiles. In the race/ethnic-specific analyses, DQI quartiles were used because of the limited number of cases in certain groups. The proportional hazards assumption was tested by Schoenfeld residuals and was found to be met. Because the associations were similar between men and women, base models were fit for men and women combined, with adjustment for sex and race/ethnicity as strata variables and age at cohort entry as a covariate. Multivariate models further adjusted for body mass index (BMI) (<25, 25 to <30, and ≥ 30 kg/m²), smoking status (never, former, current), history of diabetes mellitus (yes/no), and total energy (log transformed kcal/day). For the HEI-2010 and DASH score models, alcohol consumption (g/day) was additionally adjusted; alcohol consumption is included as a factor in the scoring of AHEI-2010 and aMED. Tests for heterogeneity in the disease–dietary score associations between subgroups were based on the Wald statistics for cross-product terms of score trend variables and subgroup membership (sex and race/ethnicity). All statistical tests were two-sided. All analyses were performed by using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

The mean follow-up time of the 169,806 cohort members was 17 years, accumulating 3,081,687 person-years of follow-up time. There were 605 incident cases of HCC (88 African Americans, 40 Native Hawaiians, 201 Japanese Americans, 206 Latinos, 70 whites). The mean age of HCC diagnosis ranged from 70 for whites to 75 for Japanese Americans. The HCC incidence rates (age-adjusted to the U.S. 2000 standard population, per 100,000) were 14.2 for African Americans, 16.1 for Native Hawaiians, 13.7 for Japanese Americans, 18.3 for Latinos, and 6.4 for whites. During the follow-up period, there were 753 CLD deaths (93 African Americans, 44 Native Hawaiians, 114 Japanese Americans, 301 Latinos, 201 whites). The mean age of CLD death ranged from 70 for African Americans and Hawaiians to

77 for Japanese Americans. The CLD death rates (age standardized per 100,000) were 16.3 for African Americans, 16.5 for Native Hawaiians, 8.9 for Japanese Americans, 31.8 for Latinos, and 19.7 for whites.

The baseline characteristics of the study participants by lowest and highest quintiles of the four DQIs in the MEC are shown in Table 1. Across the DQIs, men and women in the highest quintiles were older, were more likely to have never been smokers, had lower BMI, and were less likely to have diabetes. Men and women in the highest quintile of HEI-2010 and AHEI-2010 reported lower energy intake, whereas those in the highest quintile of aMED and DASH reported higher energy intake.

The associations between DQIs and HCC incidence are shown in Table 2. In age-, sex-, and race/ethnicity-adjusted models, HEI-2010 (trend, $P = 0.003$), aMED (trend, $P = 0.048$), and DASH (trend, $P = 0.045$) were inversely associated with HCC incidence. After further adjustment for BMI, diabetes, smoking status, and total energy, the associations with HEI-2010 (trend, $P = 0.19$) and DASH (trend, $P = 0.29$) were no longer statistically significant. The association of HCC incidence with aMED scores remained statistically significant (quintile [Q]5 versus Q1 HR, 0.68; 95% CI, 0.51-0.90; trend, $P = 0.016$). Lag analyses, excluding the first 2 and 5 years of follow-up, yielded similar results (Supporting Table S2). The association between aMED and HCC was similar in men and women (heterogeneity, $P = 0.94$) (Supporting Table S3).

There was no significant heterogeneity in the association between aMED and HCC incidence across race/ethnic groups (interaction, $P = 0.32$) (Table 3). However, the association was strongest and most monotonic in Latinos (Q4 versus Q1 HR, 0.47; 95% CI, 0.29-0.79; trend, $P = 0.006$). In Latinos, we also observed an inverse association between AHEI-2010 scores and HCC incidence (Q4 versus Q1 HR, 0.55; 95% CI, 0.34-0.86; trend, $P = 0.0033$). These inverse associations were only observed among the U.S.-born Latinos (Supporting Table S4).

The relationship between each DQI and CLD mortality can be found in Table 2. In contrast to HCC, every DQI measure showed a significant decreasing trend for CLD mortality for the age-, sex, and race/ethnicity-adjusted models and the fully adjusted models (trend, $P < 0.0001$). A lag analysis excluding the first 2 and 5 years of follow-up yielded similar results

TABLE 1. BASELINE CHARACTERISTICS OF 169,806 PARTICIPANTS BY LOWEST (Q1) AND HIGHEST (Q5) QUINTILES OF THE FOUR DIET QUALITY INDEXES IN THE MULTIETHNIC COHORT STUDY

	HEI-2010			AHEI-2010			aMED			DASH		
	Q1	Q5	n	Q1	Q5	n	Q1	Q5	n	Q1	Q5	n
Men (n = 78,450)	n = 20,406	n = 11,162	n = 17,554	n = 15,122	n = 15,529	n = 19,552	n = 17,625	n = 17,764				
Age at cohort entry, years, mean (SD)	57.7 (8.6)	61.8 (8.6)	57.7 (8.6)	61.2 (8.8)	58.9 (8.7)	60.3 (8.8)	57.0 (8.5)	61.7 (8.6)				
Race/ethnicity, n (%) [*]												
African American	2,334 (11.4)	1,963 (17.6)	2,510 (14.3)	1,624 (10.7)	2,384 (15.4)	2,349 (12.0)	2,434 (13.8)	2,035 (11.5)				
Native Hawaiian	1,686 (8.3)	711 (6.4)	1,284 (7.3)	1,003 (6.6)	1,014 (6.5)	1,573 (8.0)	1,807 (10.3)	905 (5.1)				
Japanese American	6,447 (31.6)	3,005 (26.9)	4,457 (25.4)	5,850 (38.7)	4,197 (27.0)	6,568 (33.6)	7,315 (41.5)	4,201 (23.6)				
Latino	5,891 (28.9)	1,641 (14.7)	5,065 (28.9)	2,257 (14.9)	4,285 (27.6)	3,842 (19.7)	3,360 (19.1)	4,399 (24.8)				
White	4,048 (19.8)	3,842 (34.4)	4,238 (24.1)	4,388 (29.0)	3,649 (23.5)	5,220 (26.7)	2,709 (15.4)	6,224 (35.0)				
Body mass index, kg/m ² , mean (SD)	26.8 (4.2)	26.0 (3.8)	26.9 (4.2)	26.0 (3.8)	26.8 (4.1)	26.4 (4.0)	26.8 (4.2)	26.1 (3.8)				
Smoking status, n (%) [*]												
Never	4,820 (23.6)	4,225 (37.9)	4,539 (25.9)	4,971 (32.9)	4,168 (26.8)	6,531 (33.4)	4,145 (23.5)	6,534 (36.8)				
Former	9,318 (45.7)	6,110 (54.7)	8,008 (45.6)	8,643 (57.2)	7,339 (47.3)	10,579 (54.1)	8,136 (46.2)	9,689 (54.5)				
Current	6,268 (30.7)	827 (7.4)	5,007 (28.5)	1,508 (10.0)	4,022 (25.9)	2,442 (12.5)	5,344 (30.3)	1,541 (8.7)				
History of diabetes, n (%)	1,789 (8.8)	1,728 (15.5)	1,450 (8.3)	2,235 (14.8)	1,762 (11.3)	2,483 (12.7)	1,439 (8.2)	2,803 (15.8)				
Physical activity, METs/day, mean (SD)	1.66 (0.35)	1.69 (0.31)	1.66 (0.34)	1.68 (0.31)	1.64 (0.31)	1.69 (0.33)	1.65 (0.34)	1.69 (0.32)				
Alcohol intake, g/day, mean (SD)	23.4 (51.7)	9.0 (15.2)	24.8 (52.9)	10.9 (14.0)	15.9 (39.6)	13.5 (25.4)	18.7 (39.9)	11.3 (24.3)				
Energy intake, kcal/day, mean (SD)	2,541 (1,212)	2,187 (920)	2,343 (1,119)	2,481 (1,008)	1,792 (774)	3,070 (1,237)	2,184 (924)	2,671 (1,210)				
Women (n = 91,356)	n = 14,105	n = 22,388	n = 16,741	n = 18,811	n = 19,418	n = 21,592	n = 20,077	n = 20,560				
Age at cohort entry, years, mean (SD)	56.6 (8.5)	61.5 (8.5)	57.1 (8.7)	60.9 (8.7)	58.2 (8.9)	60.3 (8.7)	56.7 (8.6)	61.4 (8.5)				
Race/ethnicity, n (%) [*]												
African American	2,292 (16.2)	5,650 (25.2)	3,565 (21.3)	3,314 (17.6)	3,943 (20.3)	4,220 (19.5)	4,512 (22.5)	3,438 (16.7)				
Native Hawaiian	1,292 (9.2)	1,426 (6.4)	1,331 (8.0)	1,357 (7.2)	1,251 (6.4)	1,954 (9.0)	2,105 (10.5)	1,172 (5.7)				
Japanese American	3,544 (25.1)	5,897 (26.3)	3,606 (21.5)	6,861 (36.5)	4,706 (24.2)	6,681 (30.9)	6,766 (33.7)	4,779 (23.2)				
Latino	4,144 (29.4)	2,937 (13.1)	4,310 (25.7)	2,215 (11.8)	4,631 (23.8)	3,707 (17.2)	3,712 (18.5)	4,568 (22.2)				
White	2,833 (20.1)	6,478 (28.9)	3,929 (23.5)	5,064 (26.9)	4,887 (25.2)	5,030 (23.3)	2,982 (14.9)	6,603 (32.1)				
Body mass index, kg/m ² , mean (SD)	27.2 (5.9)	25.7 (5.1)	27.2 (5.8)	25.5 (5.2)	26.8 (5.6)	26.0 (5.4)	27.0 (5.7)	25.6 (5.1)				
Smoking status, n (%) [*]												
Never	6,832 (48.4)	1,3215 (59.0)	8,579 (51.2)	10,789 (57.4)	10,182 (52.4)	12,794 (59.3)	10,033 (50.0)	12,398 (60.3)				
Former	3,582 (25.4)	7,334 (32.8)	4,350 (26.0)	6,268 (33.3)	5,394 (27.8)	6,647 (30.8)	5,162 (25.7)	6,594 (32.1)				
Current	3,691 (26.2)	1,839 (8.2)	3,812 (22.8)	1,754 (9.3)	3,842 (19.8)	2,151 (10.0)	4,882 (24.3)	1,568 (7.6)				
History of diabetes, n (%)	1,190 (8.4)	2,674 (11.9)	1,343 (8.0)	2,369 (12.6)	1,992 (10.3)	2,321 (10.7)	1,730 (8.6)	2,469 (12.0)				
Physical activity, METs/day, mean (SD)	1.55 (0.28)	1.62 (0.26)	1.56 (0.28)	1.62 (0.26)	1.57 (0.27)	1.62 (0.27)	1.55 (0.27)	1.63 (0.27)				
Alcohol intake, g/day, mean (SD)	7.3 (27.7)	3.3 (8.3)	6.4 (24.3)	4.2 (8.6)	4.5 (17.5)	4.2 (12.5)	4.8 (18.5)	3.9 (12.5)				
Energy intake, kcal/day, mean (SD)	2,086 (1,093)	1,863 (829)	1,762 (893)	2,123 (876)	1,389 (580)	2,606 (1,094)	1,679 (733)	2,288 (1,065)				

^{*}Column percentages.
Abbreviation: MET, metabolic equivalent.

TABLE 2. DIETARY QUALITY INDEXES AND HEPATOCELLULAR CARCINOMA RISK AND CHRONIC LIVER DISEASE MORTALITY IN THE MULTIETHNIC COHORT STUDY, 1993-2013

Quintile (range)	Person-years	HCC			CLD		
		Cases	HR (95% CI)*	HR (95% CI) [†]	Cases	HR (95% CI)*	HR (95% CI) [†]
HEI-2010							
Q1 (13.5-57.4)	620,792	149	1.00 (ref.)	1.00 (ref.)	253	1.00 (ref.)	1.00 (ref.)
Q2 (57.5-64.3)	620,187	135	0.89 (0.71-1.13)	0.96 (0.76-1.21)	156	0.61 (0.50-0.74)	0.74 (0.60-0.91)
Q3 (64.4-70.2)	613,957	133	0.91 (0.72-1.15)	1.02 (0.80-1.31)	151	0.58 (0.47-0.71)	0.75 (0.61-0.93)
Q4 (70.3-76.7)	613,335	100	0.73 (0.56-0.94)	0.85 (0.66-1.11)	118	0.45 (0.36-0.56)	0.61 (0.48-0.77)
Q5 (76.8-99.9)	613,416	88	0.69 (0.53-0.91)	0.84 (0.64-1.12)	75	0.28 (0.22-0.37)	0.41 (0.31-0.54)
<i>P</i> value for trend [‡]			0.0027	0.1880		<0.0001	<0.0001
AHEI-2010							
Q1 (25.9-56.6)	621,559	122	1.00 (ref.)	1.00 (ref.)	226	1.00 (ref.)	1.00 (ref.)
Q2 (56.7-62.3)	613,270	136	1.07 (0.84-1.37)	1.08 (0.84-1.38)	173	0.74 (0.61-0.90)	0.76 (0.62-0.93)
Q3 (62.4-67.1)	613,619	116	0.92 (0.71-1.18)	0.92 (0.71-1.19)	142	0.62 (0.50-0.76)	0.63 (0.51-0.78)
Q4 (67.2-72.6)	612,285	121	0.96 (0.74-1.23)	0.97 (0.75-1.25)	127	0.56 (0.45-0.70)	0.57 (0.46-0.72)
Q5 (72.7-104.5)	620,954	110	0.85 (0.65-1.11)	0.87 (0.66-1.14)	85	0.38 (0.30-0.49)	0.39 (0.30-0.51)
<i>P</i> value for trend [‡]			0.1644	0.2307		<0.0001	<0.0001
aMED							
Q1 (0-2)	627,152	126	1.00 (ref.)	1.00 (ref.)	202	1.00 (ref.)	1.00 (ref.)
Q2 (3)	551,547	110	0.94 (0.73-1.21)	0.92 (0.71-1.19)	141	0.77 (0.62-0.96)	0.72 (0.58-0.89)
Q3 (4)	595,061	123	0.96 (0.74-1.23)	0.90 (0.70-1.17)	144	0.73 (0.59-0.91)	0.62 (0.50-0.78)
Q4 (5)	555,698	121	1.00 (0.78-1.28)	0.92 (0.70-1.20)	121	0.65 (0.52-0.82)	0.51 (0.40-0.65)
Q5 (6-9)	752,229	125	0.74 (0.58-0.95)	0.68 (0.51-0.90)	145	0.59 (0.48-0.73)	0.43 (0.34-0.56)
<i>P</i> value for trend [‡]			0.0479	0.0164		<0.0001	<0.0001
DASH							
Q1 (8-20)	690,493	133	1.00 (ref.)	1.00 (ref.)	181	1.00 (ref.)	1.00 (ref.)
Q2 (21-22)	452,577	101	1.05 (0.81-1.36)	1.11 (0.85-1.44)	128	0.91 (0.72-1.14)	0.97 (0.77-1.22)
Q3 (23-25)	771,075	157	0.93 (0.74-1.18)	0.99 (0.78-1.26)	207	0.79 (0.65-0.97)	0.89 (0.72-1.09)
Q4 (26-27)	473,065	90	0.86 (0.65-1.13)	0.92 (0.69-1.21)	108	0.64 (0.50-0.81)	0.73 (0.57-0.93)
Q5 (28-40)	694,477	124	0.80 (0.62-1.03)	0.89 (0.68-1.16)	129	0.50 (0.39-0.62)	0.60 (0.47-0.77)
<i>P</i> value for trend [‡]			0.0449	0.2863		<0.0001	<0.0001

*Adjusted for age at cohort entry, sex, and race/ethnicity.

[†]Additionally adjusted for BMI, history of diabetes, smoking status, and total energy. For HEI-2010 and DASH, models were further adjusted for alcohol consumption.

[‡]Trend variables were assigned the sex- and ethnicity-specific median values for quintiles.

(Supporting Table S2). The associations between the DQIs and CLD mortality were similar in men and women (Supporting Table S5). There were no significant differences in the associations of DQIs with CLD mortality across racial/ethnic groups (Table 4). Among Latinos, the associations of DQIs with CLD death were similar in U.S.-born and foreign-born Latinos (Supporting Table S4).

Discussion

To our knowledge, this is the first prospective study to use multiple DQI measures to examine the

association between diet, HCC incidence, and CLD mortality across multiple major racial/ethnic groups. Higher DQI scores, reflecting favorable adherence to a healthful diet, were associated with lower HCC incidence and CLD mortality.

In our study, we found higher aMED scores to be associated with a lower risk of HCC. When stratified by race/ethnicity, the association was strongest among Latinos. Only one previous study, the NIH-AARP Diet and Health study, has examined the association between adherence to two DQIs and risk of HCC.⁽⁹⁾ The NIH-AARP study included 509 HCC cases among 494,942 participants. This cohort is also part of the DPMP, meaning we used the same algorithm

TABLE 3. DIETARY QUALITY INDEXES AND HEPATOCELLULAR CARCINOMA RISK BY RACE/ETHNICITY IN THE MULTIETHNIC COHORT STUDY, 1993-2013

	African American (n = 28,076)				Native Hawaiian (n = 12,327)				Japanese American (n = 49,400)				Latino (n = 38,910)				White (n = 41,093)				P value for Heterogeneity		
	Cases		HR (95% CI)		Cases		HR (95% CI)		Cases		HR (95% CI)		Cases		HR (95% CI)		Cases		HR (95% CI)				
HEI-2010																							
Q1 (13.5-59.4)	24	1.00 (ref.)	12	1.00 (ref.)	59	1.00 (ref.)	77	1.00 (ref.)	17	1.00 (ref.)	17	1.00 (ref.)	17	1.00 (ref.)	17	1.00 (ref.)	17	1.00 (ref.)	17	1.00 (ref.)	17	1.00 (ref.)	
Q2 (59.5-67.2)	25	1.13 (0.64-2.00)	10	1.03 (0.44-2.42)	61	0.96 (0.66-1.38)	59	0.91 (0.64-1.29)	16	1.03 (0.51-2.06)	16	1.03 (0.51-2.06)	16	1.03 (0.51-2.06)	16	1.03 (0.51-2.06)	16	1.03 (0.51-2.06)	16	1.03 (0.51-2.06)	16	1.03 (0.51-2.06)	
Q3 (67.3-74.9)	18	0.77 (0.41-1.45)	13	1.60 (0.70-3.66)	40	0.70 (0.46-1.06)	42	0.81 (0.55-1.20)	17	1.07 (0.54-2.16)	17	1.07 (0.54-2.16)	17	1.07 (0.54-2.16)	17	1.07 (0.54-2.16)	17	1.07 (0.54-2.16)	17	1.07 (0.54-2.16)	17	1.07 (0.54-2.16)	
Q4 (75.0-99.9)	21	0.75 (0.40-1.41)	5	0.70 (0.23-2.09)	41	0.80 (0.53-1.23)	28	0.86 (0.55-1.35)	20	1.30 (0.65-2.60)	20	1.30 (0.65-2.60)	20	1.30 (0.65-2.60)	20	1.30 (0.65-2.60)	20	1.30 (0.65-2.60)	20	1.30 (0.65-2.60)	20	1.30 (0.65-2.60)	0.6416
P value for trend		0.2457		0.9466		0.1625		0.3461		0.4489		0.4489		0.4489		0.4489		0.4489		0.4489		0.4489	
AHEI-2010																							
Q1 (25.9-58.3)	21	1.00 (ref.)	10	1.00 (ref.)	39	1.00 (ref.)	77	1.00 (ref.)	19	1.00 (ref.)	19	1.00 (ref.)	19	1.00 (ref.)	19	1.00 (ref.)	19	1.00 (ref.)	19	1.00 (ref.)	19	1.00 (ref.)	
Q2 (58.4-64.7)	26	1.35 (0.76-2.40)	13	1.29 (0.56-2.98)	38	0.81 (0.51-1.27)	61	0.76 (0.54-1.07)	14	0.83 (0.41-1.66)	14	0.83 (0.41-1.66)	14	0.83 (0.41-1.66)	14	0.83 (0.41-1.66)	14	0.83 (0.41-1.66)	14	0.83 (0.41-1.66)	14	0.83 (0.41-1.66)	
Q3 (64.8-71.1)	24	1.35 (0.74-2.46)	7	0.62 (0.23-1.68)	59	1.04 (0.68-1.57)	43	0.65 (0.45-0.95)	19	1.12 (0.59-2.13)	19	1.12 (0.59-2.13)	19	1.12 (0.59-2.13)	19	1.12 (0.59-2.13)	19	1.12 (0.59-2.13)	19	1.12 (0.59-2.13)	19	1.12 (0.59-2.13)	
Q4 (71.2-104.5)	17	1.05 (0.54-2.03)	10	0.92 (0.37-2.28)	65	0.89 (0.59-1.36)	25	0.55 (0.34-0.86)	18	0.95 (0.49-1.85)	18	0.95 (0.49-1.85)	18	0.95 (0.49-1.85)	18	0.95 (0.49-1.85)	18	0.95 (0.49-1.85)	18	0.95 (0.49-1.85)	18	0.95 (0.49-1.85)	0.3552
P value for trend		0.8058		0.5548		0.8513		0.0033		0.9912		0.9912		0.9912		0.9912		0.9912		0.9912		0.9912	
oMED																							
Q1 (0-2)	19	1.00 (ref.)	6	1.00 (ref.)	35	1.00 (ref.)	53	1.00 (ref.)	13	1.00 (ref.)	13	1.00 (ref.)	13	1.00 (ref.)	13	1.00 (ref.)	13	1.00 (ref.)	13	1.00 (ref.)	13	1.00 (ref.)	
Q2 (3-4)	35	1.09 (0.61-1.93)	16	1.17 (0.45-3.05)	80	1.01 (0.67-1.51)	83	0.76 (0.53-1.09)	19	0.81 (0.39-1.66)	19	0.81 (0.39-1.66)	19	0.81 (0.39-1.66)	19	0.81 (0.39-1.66)	19	0.81 (0.39-1.66)	19	0.81 (0.39-1.66)	19	0.81 (0.39-1.66)	
Q3 (5)	18	1.22 (0.60-2.46)	8	0.98 (0.32-3.04)	39	0.91 (0.56-1.47)	40	0.72 (0.46-1.13)	16	1.38 (0.64-3.01)	16	1.38 (0.64-3.01)	16	1.38 (0.64-3.01)	16	1.38 (0.64-3.01)	16	1.38 (0.64-3.01)	16	1.38 (0.64-3.01)	16	1.38 (0.64-3.01)	
Q4 (6-9)	16	0.78 (0.36-1.68)	10	0.70 (0.22-2.22)	47	0.70 (0.43-1.15)	30	0.47 (0.29-0.79)	22	1.42 (0.66-3.07)	22	1.42 (0.66-3.07)	22	1.42 (0.66-3.07)	22	1.42 (0.66-3.07)	22	1.42 (0.66-3.07)	22	1.42 (0.66-3.07)	22	1.42 (0.66-3.07)	0.3195
P value for trend		0.9387		0.4890		0.1515		0.0060		0.2400		0.2400		0.2400		0.2400		0.2400		0.2400		0.2400	
DASH																							
Q1 (8-20)	17	1.00 (ref.)	9	1.00 (ref.)	52	1.00 (ref.)	40	1.00 (ref.)	15	1.00 (ref.)	15	1.00 (ref.)	15	1.00 (ref.)	15	1.00 (ref.)	15	1.00 (ref.)	15	1.00 (ref.)	15	1.00 (ref.)	
Q2 (21-24)	36	1.61 (0.89-2.89)	15	1.53 (0.65-3.57)	65	1.05 (0.72-1.52)	77	0.95 (0.64-1.40)	15	0.52 (0.25-1.08)	15	0.52 (0.25-1.08)	15	0.52 (0.25-1.08)	15	0.52 (0.25-1.08)	15	0.52 (0.25-1.08)	15	0.52 (0.25-1.08)	15	0.52 (0.25-1.08)	
Q3 (25-27)	18	1.24 (0.62-2.48)	11	1.50 (0.59-3.84)	56	1.32 (0.89-1.97)	37	0.53 (0.33-0.84)	18	0.67 (0.33-1.36)	18	0.67 (0.33-1.36)	18	0.67 (0.33-1.36)	18	0.67 (0.33-1.36)	18	0.67 (0.33-1.36)	18	0.67 (0.33-1.36)	18	0.67 (0.33-1.36)	
Q4 (28-40)	17	1.31 (0.63-2.72)	5	0.79 (0.24-2.55)	28	0.76 (0.46-1.23)	52	0.79 (0.51-1.25)	22	0.76 (0.38-1.54)	22	0.76 (0.38-1.54)	22	0.76 (0.38-1.54)	22	0.76 (0.38-1.54)	22	0.76 (0.38-1.54)	22	0.76 (0.38-1.54)	22	0.76 (0.38-1.54)	0.8700
P value for trend		0.6147		0.9853		0.7749		0.0892		0.7911		0.7911		0.7911		0.7911		0.7911		0.7911		0.7911	

Adjusted for age at cohort entry, sex, BMI, history of diabetes, smoking status, and total energy. For HEI-2010 and DASH, models were further adjusted for alcohol consumption.

TABLE 4. DIETARY QUALITY INDEXES AND CHRONIC LIVER DISEASE MORTALITY BY RACE/ETHNICITY IN THE MULTIETHNIC COHORT STUDY, 1993-2013

	African American (n = 28,076)				Native Hawaiian (n = 12,327)				Japanese American (n = 49,400)				Latino (n = 38,910)				White (n = 41,093)				P value for Heterogeneity
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)			
	HEI-2010	36	1.00 (ref.)	15	1.00 (ref.)	37	1.00 (ref.)	131	1.00 (ref.)	72	1.00 (ref.)	72	1.00 (ref.)	72	1.00 (ref.)	72	1.00 (ref.)	72	1.00 (ref.)	0.6010	
Q1 (13.5-59.4)	21	0.72 (0.41-1.27)	15	1.22 (0.58-2.55)	30	0.72 (0.44-1.19)	79	0.81 (0.61-1.09)	46	0.77 (0.52-1.13)	46	0.77 (0.52-1.13)	46	0.77 (0.52-1.13)	46	0.77 (0.52-1.13)	46	0.77 (0.52-1.13)			
Q2 (59.5-67.2)	21	0.64 (0.36-1.13)	11	1.06 (0.47-2.40)	25	0.61 (0.36-1.05)	58	0.75 (0.54-1.03)	53	0.82 (0.56-1.21)	53	0.82 (0.56-1.21)	53	0.82 (0.56-1.21)	53	0.82 (0.56-1.21)	53	0.82 (0.56-1.21)			
Q3 (67.3-74.9)	15	0.35 (0.18-0.66)	3	0.31 (0.09-1.13)	22	0.54 (0.31-0.96)	33	0.67 (0.45-1.01)	30	0.43 (0.27-0.68)	30	0.43 (0.27-0.68)	30	0.43 (0.27-0.68)	30	0.43 (0.27-0.68)	30	0.43 (0.27-0.68)			
Q4 (75.0-99.9)		0.0016		0.1537		0.0278		0.0223		0.001		0.001		0.001		0.001		0.001			
P value for trend																					
AHEI-2010	33	1.00 (ref.)	13	1.00 (ref.)	30	1.00 (ref.)	126	1.00 (ref.)	74	1.00 (ref.)	74	1.00 (ref.)	74	1.00 (ref.)	74	1.00 (ref.)	74	1.00 (ref.)	0.6875		
Q1 (25.9-58.3)	24	0.79 (0.47-1.34)	12	0.94 (0.43-2.09)	27	0.67 (0.39-1.13)	89	0.71 (0.54-0.94)	48	0.69 (0.48-1.00)	48	0.69 (0.48-1.00)	48	0.69 (0.48-1.00)	48	0.69 (0.48-1.00)	48	0.69 (0.48-1.00)			
Q2 (58.4-64.7)	15	0.48 (0.26-0.90)	10	0.72 (0.31-1.69)	28	0.52 (0.30-0.89)	59	0.58 (0.43-0.80)	47	0.67 (0.46-0.97)	47	0.67 (0.46-0.97)	47	0.67 (0.46-0.97)	47	0.67 (0.46-0.97)	47	0.67 (0.46-0.97)			
Q3 (64.8-71.1)	21	0.72 (0.40-1.27)	9	0.68 (0.28-1.65)	29	0.40 (0.23-0.69)	27	0.40 (0.26-0.61)	32	0.40 (0.26-0.61)	32	0.40 (0.26-0.61)	32	0.40 (0.26-0.61)	32	0.40 (0.26-0.61)	32	0.40 (0.26-0.61)			
Q4 (71.2-104.5)		0.1114		0.3276		0.0008		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001			
P value for trend																					
oMED	17	1.00 (ref.)	8	1.00 (ref.)	22	1.00 (ref.)	97	1.00 (ref.)	58	1.00 (ref.)	58	1.00 (ref.)	58	1.00 (ref.)	58	1.00 (ref.)	58	1.00 (ref.)	0.5899		
Q1 (0-2)	40	1.25 (0.70-2.24)	15	0.85 (0.35-2.05)	48	0.83 (0.50-1.40)	112	0.56 (0.42-0.74)	70	0.61 (0.42-0.87)	70	0.61 (0.42-0.87)	70	0.61 (0.42-0.87)	70	0.61 (0.42-0.87)	70	0.61 (0.42-0.87)			
Q2 (3-4)	20	1.23 (0.61-2.46)	10	0.93 (0.34-2.58)	20	0.58 (0.30-1.10)	39	0.37 (0.25-0.55)	32	0.49 (0.31-0.78)	32	0.49 (0.31-0.78)	32	0.49 (0.31-0.78)	32	0.49 (0.31-0.78)	32	0.49 (0.31-0.78)			
Q3 (5)	16	0.64 (0.30-1.39)	11	0.61 (0.21-1.78)	24	0.40 (0.21-0.77)	53	0.44 (0.30-0.64)	41	0.44 (0.28-0.69)	41	0.44 (0.28-0.69)	41	0.44 (0.28-0.69)	41	0.44 (0.28-0.69)	41	0.44 (0.28-0.69)			
Q4 (6-9)		0.1506		0.4144		0.0037		<0.0001		0.0001		0.0001		0.0001		0.0001		0.0001			
P value for trend																					
DASH	25	1.00 (ref.)	12	1.00 (ref.)	36	1.00 (ref.)	67	1.00 (ref.)	41	1.00 (ref.)	41	1.00 (ref.)	41	1.00 (ref.)	41	1.00 (ref.)	41	1.00 (ref.)	0.7344		
Q1 (8-20)	39	1.22 (0.73-2.03)	18	1.59 (0.75-3.39)	40	0.85 (0.53-1.34)	107	0.89 (0.65-1.21)	68	0.89 (0.60-1.32)	68	0.89 (0.60-1.32)	68	0.89 (0.60-1.32)	68	0.89 (0.60-1.32)	68	0.89 (0.60-1.32)			
Q2 (21-24)	15	0.71 (0.36-1.38)	12	1.46 (0.62-3.44)	22	0.65 (0.37-1.14)	68	0.73 (0.51-1.04)	54	0.77 (0.51-1.18)	54	0.77 (0.51-1.18)	54	0.77 (0.51-1.18)	54	0.77 (0.51-1.18)	54	0.77 (0.51-1.18)			
Q3 (25-27)	14	0.73 (0.36-1.49)	2	0.31 (0.07-1.47)	16	0.52 (0.28-0.97)	59	0.73 (0.50-1.07)	38	0.52 (0.32-0.83)	38	0.52 (0.32-0.83)	38	0.52 (0.32-0.83)	38	0.52 (0.32-0.83)	38	0.52 (0.32-0.83)			
Q4 (28-40)		0.2399		0.5946		0.0277		0.0569		0.0041		0.0041		0.0041		0.0041		0.0041			
P value for trend																					

Adjusted for age at cohort entry, sex, BMI, history of diabetes, smoking status, and total energy. For HEI-2010 and DASH, models were further adjusted for alcohol consumption.

to define DQIs, making our results comparable. Their study found risk of HCC to be inversely associated with closer adherence to both HEI-2010 (Q5 versus Q1 HR, 0.72; 95% CI, 0.53-0.97; trend, $P = 0.03$) and aMED (Q5 versus Q1 HR, 0.62; 95% CI, 0.47-0.84; trend, $P = 0.0002$). In our study, we found a 32% reduction in risk of HCC among those who adhered closest to the aMED diet (Q5 versus Q1 HR, 0.68; 95% CI, 0.51-0.90). In contrast to the NIH-AARP study, our first model showed a significant inverse trend for HEI-2010, but after further adjustment we observed an attenuation of the association and loss of statistical significance. Most of the NIH-AARP is composed of white men and women. Among whites in the MEC, we did not find any significant association of HEI-2010 or aMED with HCC incidence.

A second study, which pooled data from two separate hospital-based case-control studies in Greece and Italy (518 cases and 772 controls), found an inverse association between the traditional Mediterranean diet score and HCC (MED score ≥ 5 versus 0-3; odds ratio, 0.51; 95% CI, 0.34-0.75; trend, $P < 0.001$).⁽²¹⁾ Furthermore, this study showed that hepatitis B and C infection status did not modify the association (interaction, $P = 0.12$).

As mentioned, these prior studies contain more ethnic and racially homogeneous populations. In our study, we found no significant heterogeneity of associations between racial/ethnic groups; however, after stratification, only a significant trend for Latinos remained for AHEI-2010 and aMED. Further stratification among Latinos showed the association to only be present for those born in the United States. The persisting association of aMED and AHEI-2010 among U.S.-born Latinos likely results from differing diet compositions among those who do not adhere to these DQIs. National Health and Nutrition Examination Survey data have shown that U.S.-born Mexican Americans have a dietary pattern containing less beans, legumes, tomato-based products, tortilla, oil, rice, soups, and vegetables relative to Mexican-born Mexican Americans.⁽¹⁵⁾ Many of these dietary components overlap with aMED, making it likely that the observed association in U.S.-born Latinos is due to an altered diet within this ethnic group. In our DQI component analyses among Latinos, vegetable intake appeared to be the driving component of the inverse association between aMED and AHEI-2010 with HCC (data not shown). Because the incidence

rate of HCC is higher among Latinos than any other racial group in the MEC and in the United States, the possibility that overall diet quality may play a more central role in HCC among Latinos warrants further investigation.

There is limited information available on the association between DQIs and CLD mortality. The only other study available, the NIH-AARP Diet and Health study, reports CLD mortality to be inversely associated with aMED (Q5 versus Q1 HR, 0.52; 95% CI, 0.42-0.65; trend, $P < 0.0001$) and HEI-2010 (Q5 versus Q1 HR, 0.57; 95% CI, 0.46-0.65; trend, $P < 0.0001$).⁽⁹⁾ In our study, all DQIs showed a significant inverse association with CLD mortality. Closest adherence to these diets was associated with a 41% to 60% reduction in CLD mortality, which was similar to that found by the NIH-AARP study.

Most liver-related research on aMED focuses on nonalcoholic fatty liver disease (NAFLD). The dietary components of aMED are vegetables, fruit, nuts, legumes, fish, whole grains, low consumption of red or processed meat, moderate alcohol consumption, and a high ratio of monounsaturated fatty acid to saturated fatty acid.⁽²⁰⁾ Godos et al.⁽²²⁾ outlined the likely molecular mechanisms resulting in aMED's inverse association with NAFLD based on current supporting research. High levels of fish, nuts, and olive oil in aMED are associated with higher intakes of polyunsaturated and monounsaturated fatty acids, which are thought to result in lower liver inflammation, lipogenesis, steatosis, and oxidative stress. Whole grain consumption is hypothesized to lead to decreased liver inflammation and increased insulin sensitivity. Fruit and vegetable intake is associated with higher dietary vitamin E and D, with vitamin E influencing lower levels of liver steatosis and inflammation and vitamin D decreasing inflammation and increasing glucose and lipid metabolism. The inverse association between the Mediterranean diet and NAFLD reported by prior studies⁽²³⁻²⁸⁾ and with HCC incidence in the MEC Latinos in the current study is important to note given the high prevalence of NAFLD in Latinos^(29,30) and the large fraction of NAFLD-associated HCC among Latinos.⁽³¹⁾

There are some notable differences between the DQIs we examined. AHEI-2010 and aMED differ due to their dietary component of moderate alcohol consumption, which has been found to be inversely associated to HCC incidence and CLD

mortality.^(9,32,33) AHEI-2010, aMED, and DASH penalize for consumption of red and processed meats, which have been shown to increase the risk of both HCC incidence and CLD mortality.⁽³⁴⁾ DASH differs in that it uses a quintile-based scoring method. Although many dietary components of DASH are similar to aMED, the quintile-based scoring method allows for better precision in measurement relative to the median-based scoring of aMED. In contrast to aMED, DASH has dietary components for low consumption of sugar-sweetened beverages, sodium, and dairy. Of these additional components, sugar-sweetened beverages have been shown to increase the risk of HCC.⁽³⁵⁾ Lastly, all DQIs except DASH include dietary components for oils and fats. These DQIs favor unsaturated fatty acids in comparison to saturated fat, which has been associated with an increased risk of HCC incidence and CLD mortality.⁽³⁴⁾

There are several strengths to this study. The prospective nature of this design ensured temporal precedence of the exposure. The large multiethnic sample and detailed covariate data collected in the baseline survey made it possible to adjust for the most confounding variables. The diverse population with differing dietary patterns allowed us to examine the modification of diet by race and ethnicity, something which has not been done before. The dietary assessment was done using a comprehensive QFFQ, making it possible to collect detailed diet data on an ethnically and racially diverse sample. The QFFQ was compared against multiple 24-hour diet recalls and was shown to have a highly satisfactory correlation with these measures.⁽¹⁸⁾

There are several limitations to this study. Two DQIs, aMED and DASH, are based on sample-specific quantiles to determine diet adherence, whereas HEI-2010 and AHEI-2010 use mostly absolute measures and offer more concrete consumption guidelines for the public to follow. Additionally, nonadherence to a DQI is likely associated with different dietary patterns depending on the racial group. Assessment of diet using the self-administered QFFQ likely suffers from measurement error; however, this bias is expected to be nondifferential, resulting in an underestimation of observed association.⁽³⁶⁾ Although this study has a large sample size, there is data sparsity following stratification by race and adjustment of confounding variables. There was no information available on hepatitis B or C infection for all study participants. However,

prior research has shown little influence of hepatitis infection on the diet-HCC association.⁽²¹⁾ There was also no information on underlying etiology for HCC and CLD, and thus we were unable to examine DQI association for specific etiology. Lastly, because this study sample originated from California and Hawaii and we have low response rates in certain groups (i.e., African Americans and Latinos), our results may not be generalizable to other regions in the United States.

In conclusion, higher aMED scores were associated with a lower risk of HCC, particularly in Latinos, whereas all DQIs were associated with a decreased risk of CLD death across racial/ethnic groups. These results suggest that having a higher quality diet may reduce HCC incidence and CLD death in multiethnic populations. A healthy diet could be included as part of HCC and CLD prevention strategies and communicated in doctor-patient discussions about its importance.

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Supporting Information

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