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The Dietary Inflammatory Index and hepatic health in the US adult population

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Abstract

Background: There is limited evidence on the role of an anti-/pro-inflammatory diet in the prevention of non-alcoholic fatty liver disease (NAFLD). We aimed (i) to assess the anti-inflammatory diet profile and its association with transient elastography parameters, including liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), and (ii) to analyse the relationship between the anti-inflammatory diet and surrogate markers of liver disease in a multiethnic US population.

Methods: A cross-sectional study was conducted on a nationally representative population of 4189 US adults aged 20–80 years. A FibroScan® 502 V2 device (Echosens) was used to estimate the CAP and LSM. Liver markers, including the aspartate transaminase (AST) to alanine transaminase (ALT) ratio, fatty liver index (FLI) and fibrosis-4 score, were also calculated. The Dietary Inflammatory Index (DII) was calculated using a 24-h diet recall.

Results: Lower DII scores (anti-inflammatory diet) were associated with a lower AST:ALT ratio ($p < 0.001$) and FLI ($p < 0.036$) after adjusting for covariates. Linear regression analysis revealed that gamma-glutamyl transferase levels ($\beta = 1.702$, 95% confidence interval [CI] = 0.325–3.080, $p = 0.015$), ALT levels ($\beta = -0.616$, 95% CI = -1.097 to -0.135, $p = 0.012$), AST:ALT ratio ($\beta = 0.025$, 95% CI = 0.014–0.036, $p < 0.001$) and FLI ($\beta = 1.168$, 95% CI = 0.224–2.112, $p = 0.015$) were significantly associated with the DII in the multivariable-adjusted model. Participants in the highest anti-inflammatory tertile had the lowest odds ratio (OR) for NAFLD assessed by FLI in both unadjusted (OR = 0.652, 95% CI = 0.539–0.788, $p \leq 0.001$) and adjusted models (OR = 0.722, 95% CI = 0.537–0.972, $p = 0.032$). For the transient elastography parameters (LSM and CAP), no significant associations were identified.

Conclusions: There was no relationship between the transient elastography parameters and the anti-inflammatory diet profile, although our study showed an association between higher pro-inflammatory properties of diet and poorer hepatic health assessed by surrogate markers of liver disease. Therefore, strategies to promote an anti-inflammatory diet should be considered to prevent NAFLD in adults.

KEYWORDS
anti-inflammatory diet, diet, inflammation, liver, non-alcoholic fatty liver disease

> **Key points**
> - An anti-inflammatory diet was significantly associated with lower aspartate transaminase:alanine transaminase ratio and fatty liver index (FLI).
> - Higher pro-inflammatory properties of diet were associated with an increased risk of non-alcoholic fatty liver disease (NAFLD) assessed by FLI.
> - Strategies to promote an anti-inflammatory diet should be considered to prevent NAFLD in adults.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with varying amounts of fibrosis and cirrhosis.[1] The estimated prevalence has increased rapidly and, in the USA and Europe, it is approximately 30%.[1,2] Worryingly, it has been postulated that the overall NAFLD prevalence among the adult population is projected to be 33.5% in 2030.[3] NAFLD has been recognised as an important predictor of cardiovascular disease events because the presence of NAFLD is significantly associated with a 64% increased risk of coronary artery disease and stroke.[4] Moreover, a recent meta-analysis showed that NAFLD is a predictor of increased all-cause mortality.[5]

Considering the burden of disease, screening for NAFLD is important for preventing progression of the disease to advanced fibrosis. Although liver biopsy is considered the gold standard in the evaluation of NAFLD, it is neither practical, nor feasible to perform liver biopsies in large populations and therefore has been partially replaced by non-invasive methods. Transient elastography is a simple-to-perform imaging modality with high accuracy for assessing liver stiffness and hepatic fat deposition when performed by FibroScan, as recommended by the American Association for the Study of Liver Diseases.[6] Transient elastography estimates the liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), which are markers of hepatic fibrosis and steatosis, respectively.[7,8] Furthermore, other non-invasive markers of liver injury with high sensitivity and accuracy, such as the aspartate transaminase:alanine transaminase (AST:ALT) ratio,[9] the fatty liver index (FLI)[10] and the fibrosis-4 score (FIB4),[11] which include a combination of clinical and routine parameters, may be useful surrogate measures of NAFLD. These simple measurements might be indicated for screening to identify patients at high risk for fatty liver disease in the general healthy population.[12]

NAFLD is a complex disease that appears to be modulated by the interplay of diverse mechanisms, including metabolic, genetic, environmental and gut microbial factors.[13] Among the modifiable factors, it has been demonstrated that dietary factors are linked to hepatic health; however, there is limited evidence on the role of diet quality in the prevention of NAFLD. Considering that NAFLD has been associated with a systemic and hepatic proinflammatory state and that inflammatory cytokines and chemokines, including tumor necrosis factor-α, interleukin-6 and high-sensitivity C-reactive protein (hs-CRP), are increased in patients with NAFLD and NASH,[14] it should be hypothesised that an anti-inflammatory diet could lead to an improvement in liver status. Previous studies have shown that the inflammatory potential of the diet is associated with mortality, metabolic syndrome and hepatic markers and therefore might be an important predictor of NAFLD.[15–20] Furthermore, it has been shown that the Mediterranean diet, a diet characterised by an anti-inflammatory dietary pattern, might have a beneficial role in the onset and severity of NAFLD.[21–23] However, the relationship between the Dietary Inflammatory Index (DII), a literature-derived dietary index that was developed to predict inflammation,[24] and the LSM and CAP assessed by transient elastography has not been investigated previously.

Therefore, the present study aimed (i) to assess the anti-inflammatory diet profile measured by the DII and its association with transient elastography parameters, including LSM and CAP, and (ii) to analyse the relationship between the anti-inflammatory diet and surrogate markers of liver disease in a multiethnic US population using the population-based National Health and Nutrition and Examination Surveys (NHANES; https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overview.aspx?BeginYear=2017) from 2017 to 2018.

METHODS

Design and study population

This cross-sectional study used data from NHANES 2017–2018. The data were acquired from a stratified multistage probability sample of a non-institutionalised civilian population in the USA. Ethical approval was obtained through the National Center for Health Statistics Research Ethics Review Board (CDC, 2016) research ethics review board. Further approval was not sought for the study because the data used were free of personal identifiers. All procedures conformed to the tenets of the Helsinki Declaration of 1975 (revised in 2013) and written informed consent was obtained from all participants.

Participants

Of the 9952 participants in the NHANES (2017–2018) who were aged 0–80 years, 4907 (restricted >20 years old) were assessed according to the inclusion criteria: (i) complete metabolic and liver function parameters; (ii) a complete transient elastography test; and (iii) a complete 24-h recall. For analyses evaluating the FLI and the FIB4, we additionally excluded persons with missing data on one or more components of the FLI and FIB4 ($n = 426$). Additionally, we exclude participants with positive for HBsAg/IgG anti-HBc/anti-HCV/anti-HIV antibodies ($n = 237$) and pregnancy ($n = 55$). Data from 4189 participants were analysed.

$$FLI = (e^{0.953 * \log_e(\text{triglycerides}) + 0.139 * BMI + 0.718 * \log_e(GGT) + 0.053 * \text{waist circumference} - 15.745})$$

$$/(1 + e^{0.953 * \log_e(\text{triglycerides}) + 0.139 * BMI + 0.718 * \log_e(GGT) + 0.053 * \text{waist circumference} - 15.745}) * 100$$

Instrumentation and measurements

All measurement procedures were taken from the published guidelines and procedures used by NHANES (https://wwwn.cdc.gov/nchs/nhanes). Anthropometric data (body mass, height and waist circumference) were collected by trained health technicians. Body mass index (BMI) was calculated as weight (kg) divided by height (m)^2. Participants were tested on routine cardiometabolic parameters. Triglycerides, total cholesterol, high-density lipoprotein (HDL), glucose, glycated hemoglobin, total bilirubin, hs-CRP, ALT, AST and γ-glutamyl transferase (GGT) concentrations were measured on the Cobas 6000 (c501 module) analyser (Roche) using a standard protocol by highly trained medical personnel in the mobile examination centre (MEC). Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), according to the equation: fasting glucose (mmol L^{-1}) × fasting insulin (mU L^{-1})/22.5.

Comorbidity data including hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure 90 mmHg, or on treatment with an antihypertensive agent), low HDL cholesterol (defined as a HDL cholesterol <50 mg dl^{-1} for women and <40 mg dl^{-1} for men), obesity (defined as a value ≥30 kg m^{-2}) and diabetes (defined as a fasting plasma glucose ≥126 mg dl^{-1} or treatment with a hypoglycaemic agent or insulin) were also evaluated. Sociodemographic characteristics were all assessed by self-report during an in-home interview, such as age, sex, race/ethnicity (non-Hispanic White; non-Hispanic Black; Mexican American or other Hispanic; and other, including multiracial) and citizenship status (citizen by birth, citizen by naturalisation or non-citizen). Minutes sedentary activity was measured based on the World Health Organization (WHO)'s Global Physical Activity Questionnaire.[25] Smoking was based on self-reporting. For assessment of the diet, 24-h recall was applied by a skilled assessor throughout the MEC as described previously.[26] The level of alcohol intake was evaluated through the use of diet 24-h recall (drinkers were defined with respect to the consumption of ≥40 g).

Liver markers

The AST:ALT ratio was calculated by dividing the serum AST by the ALT. We used the published cut-off of AST/ALT ratio ≤1 cut-off for excluding advanced fibrosis.[9] The FLI score is an index that was designed to assess hepatic steatosis and was calculated using[10]:

Participants with FLI measurements of ≥60 were categorised in the hepatic steatosis group.[27] The FIB4 was calculated using: age (years) × AST [U L^{-1}]/(platelets [10^9 L^{-1}] × (ALT [U L^{-1}])$^{1/2}$). We used the cut-off value of 1.45 because it was shown to have a negative predictive value of 90% for advanced fibrosis.[11]

Transient elastography

The transient elastography measurements were obtained in the NHANES MEC, using the FibroScan® 502 V2 Touch (Echosens) equipped with a medium or extra-large wand (probe), approved by the Food and Drug Administration. Participants were excluded if they (i) were unable to lie down on the exam table; (ii) were pregnant (or unsure if pregnant) at the time of their exam, or a urine sample could not be obtained to test for pregnancy; (iii) had an implanted electronic medical device; or (iv) were wearing a bandage or had lesions on the right side of their abdomen by the ribs (where measurements would be taken). Liver tissue examination was performed with the subject lying supine. The device estimates liver fibrosis and steatosis assessed by LSM (kPa) and CAP (dB m^{-1}), respectively. LSM and CAP scores of each participant was obtained simultaneously in the examination. Results were included in the final analysis only if the following three criteria were met: fasting time of at least 3 h, 10 or more complete LMS measures and an interquartile range less than 30% of the median LSM value. A detailed description of quality assurance and quality control measures considered for this component can be found in the Procedures Manual (https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/manuals/2018.pdf). The diagnosis of NAFLD was based on CAP ≥ 233 dB m^{-1} and LSM ≥ 8.7 kPa, respectively.[28,29]

The DII

The DII has been described previously.[24] It is based on a review of the literature published up to 2010 linking diet and inflammatory markers. To calculate DII for the participants in the present study, the dietary data were first linked to the regionally representative world database, which provided a robust mean ± SD estimate for each parameter. These then became the multipliers for expressing an individual's exposure relative to the 'standard global mean' as a Z score. This was achieved by subtracting the 'standard global mean' from the amount reported and dividing this value by the SD. To minimise the effect of 'right skewing', this value was then converted to a centred percentile score. This score, for each food parameter for each individual, was then multiplied by the respective food parameter effect score, derived from the literature review, to obtain a food parameter-specific DII score for each individual. All the food parameter-specific DII scores are then added together to create each participant's global DII score. Overall, 26 food parameters, including energy, protein, carbohydrate, total fat, saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, cholesterol, fibre, vitamin E, vitamin A, beta carotene, niacin, riboflavin, thiamine, vitamin B_6, folic acid, vitamin B_{12}, vitamin C, vitamin D, magnesium, iron, zinc, selenium, caffeine and alcohol, to calculate the global DII. Positive values represent a pro-inflammatory diet, whereas negative values represent an anti-inflammatory diet. DII scores range from 3.09 (maximally pro-inflammatory) to −4.70 (maximally anti-inflammatory).

Statistical analysis

Data were analysed with SPSS, version 22.0 (IBM Corp.). The Kolmogorov–Smirnov test was used to verify data distribution normality. Data were expressed as the mean ± SD for continuous variables and as frequencies and percentage for categorical variables. The DII was analysed both as a continuous variable and a categorised variable based on tertiles. Unadjusted differences in clinical and demographic characteristics by DII tertiles characteristics were compared using a one-way analysis of variance for continuous variables, and chi-squared tests for categorical variables. Analysis of covariance was also used to examined differences in liver markers and LSM and CAP by DII tertiles after adjusting by sex, age, race, citizenship status, energy intake, alcohol intake, smoking, sedentary activity, hypertension, low HDL levels, obesity and type 2 diabetes mellitus. Linear regression analyses were conducted to determine the association of the continuous DII score with liver markers and transient elastography parameters unadjusted and adjusted for covariates. Furthermore, multivariable logistic regression analyses were used to estimate the odds ratios (OR) for NAFLD for participants with an anti-inflammatory diet vs. a pro-inflammatory diet (the reference category) in separate models, with one unadjusted and the other after adjusting for the aforementioned confounding factors. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the study population by DII tertiles

The mean ± SD age of the study participants was 50.96 ± 17.36 years and 50.9% were female. The clinical and demographic characteristics of the participants according to the DII tertiles are shown in Table 1. There were significant differences in the study variables according to these DII tertiles. A lower DII score (anti-inflammatory diet) was associated with better anthropometric data profiles, including lower body mass ($p = 0.012$), BMI ($p < 0.001$) and waist circumference ($p < 0.001$). For cardiometabolic factors, participants with lower DII scores had lower HOMA-IR and hs-CRP values ($p = 0.032$ and $p < 0.001$, respectively). In terms of liver markers, there were also significant differences in ALT values ($p = 0.002$), AST:ALT ratio ($p < 0.001$) and FLI ($p < 0.001$) between DII tertiles. Note that a lower DII score was associated with lower CAP values ($p = 0.004$). Statistically significant differences were also identified between the DII tertiles and race/ethnicities ($p < 0.001$), citizenship status ($p < 0.001$), the presence of low HDL levels ($p < 0.001$), obesity ($p < 0.001$) and diabetes mellitus ($p = 0.028$), as well as alcohol intake ($p < 0.001$) and smoking habits ($p = 0.004$). For dietary factors, higher intakes of energy ($p < 0.001$), proteins ($p < 0.001$), carbohydrates ($p < 0.001$), dietary fibre ($p < 0.001$) and fats ($p < 0.001$) were observed in the anti-inflammatory group than in the pro-inflammatory group.

Associations between liver markers, transient elastography and the DII

Differences in the DII tertiles on liver markers and LSM and CAP adjusted by sex, age, race, citizenship status, energy intake, alcohol intake, smoking, sedentary activity, hypertension, low HDL levels, obesity and diabetes mellitus are shown in Table 2. There were significant differences in the AST:ALT ratio ($p < 0.001$) and FLI ($p < 0.036$) between DII tertiles.

The beta estimates and 95% CI values for the association between the DII, liver markers and transient elastography parameters are presented in Table 3. Unadjusted linear regression analysis revealed that ALT levels ($\beta = -0.729$, 95% confidence interval [CI] = −1.090 to 0.367, $p < 0.001$), AST levels ($\beta = -0.362$, 95% CI = −0.638 to 0.087, $p = 0.010$), AST:ALT ratio

TABLE 1 Clinical and demographic characteristics of the study population by Dietary Inflammatory Index tertiles

Characteristics	Dietary inflammatory index									p value
	Tertile 1 (anti-inflammatory)			Tertile 2			Tertile 3 (pro-inflammatory)			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
DII score	1396	−1.531	0.795	1397	0.226	0.392	1396	1.593	0.488	**<0.001**
Men/women, n (%)	826 (40.2)/570 (26.8)			677 (32.9)/720 (33.8)			554 (26.9)/842 (39.5)			**<0.001**
Anthropometric										
Age (years)	1396	51.31	17.11	1397	50.72	17.20	1396	50.86	17.77	0.639
Body mass (kg)	1388	81.13	20.82	1390	83.40	22.64	1390	83.19	23.23	**0.012**
Height (cm)	1389	168.14	10.00	1391	166.57	10.06	1389	165.07	9.94	**<0.001**
Body mass index (kg m^{-2})	1386	28.59	6.44	1389	29.89	6.96	1389	30.46	7.87	**<0.001**
Waist circumference (cm)	1361	98.32	15.66	1366	101.02	16.92	1364	101.70	17.59	**<0.001**
Cardiometabolic										
Triglycerides (mg dl^{-1})	1316	148.04	122.13	1322	147.24	127.97	1328	141.68	105.42	0.324
Total cholesterol (mg dl^{-1})	1321	189.08	41.14	1330	189.45	40.15	1333	187.80	41.26	0.552
HDL cholesterol (mg dl^{-1})	1321	53.73	14.91	1330	53.21	15.57	1333	52.70	16.27	0.234
Glucose (mg dl^{-1})	1316	100.73	34.70	1322	102.86	36.79	1328	103.05	36.04	0.182
HbA1c (%)	1345	5.78	0.97	1358	5.87	1.13	1350	5.86	1.10	0.066
HOMA-IR	598	2.88	2.21	618	3.23	2.46	626	3.05	2.25	**0.032**
Total bilirubin (µmol L^{-1})	1317	8.00	4.75	1323	7.88	4.71	1327	7.77	4.52	0.435
hsC-reactive protein (mg L^{-1})	1313	3.12	6.36	1323	3.69	5.63	1329	5.07	9.33	**<0.001**
Liver markers										
Glutamyl transferase (IU L^{-1})	1317	30.27	33.80	1322	33.21	48.70	1328	32.56	52.21	0.220
Alanine aminotransferase (IU L^{-1})	1317	23.21	14.97	1322	22.68	16.67	1328	21.04	17.40	**0.002**
Aspartate aminotransferase (IU L^{-1})	1309	22.38	10.04	1318	21.78	12.81	1327	21.56	14.15	0.218
AST:ALT ratio	1309	1.09	0.36	1318	1.11	0.40	1327	1.17	0.41	**<0.001**
FLI	842	55.61	33.56	858	62.47	33.92	884	63.55	33.08	**<0.001**
FIB-4	1309	1.13	0.67	1318	1.10	0.75	1326	1.12	0.79	0.551
Liver ultrasound transient elastography										
LSM (kPa)	1396	5.78	4.45	1397	5.87	5.20	1396	6.02	4.77	0.400
Stiffnessinterquartile range (IQR)	1394	1.00	2.77	1395	1.00	2.06	1394	1.03	1.92	0.580
CAP (dB m^{-1})	1396	260.47	58.95	1397	266.75	59.14	1396	267.23	61.36	**0.004**
CAP interquartile range (IQR)	1394	38.21	20.07	1395	37.71	20.94	1394	37.53	19.69	0.851
Racelethnicities, n (%)										
Mexican American	212 (38.3)			204 (36.8)			138 (24.9)			**<0.001**
Other Hispanic	130 (34.1)			135 (35.4)			116 (30.4)			
Non-Hispanic White	480 (32.4)			501 (33.7)			504 (33.9)			
Non-Hispanic Black	269 (27.1)			300 (30.2)			423 (42.6)			
Other race, including multi-racial	305 (39.3)			257 (33.1)			215 (27.7)			
Citizenship status, n (%)										
Citizen by birth	1177 (32.3)			1192 (32.7)			1272 (34.9)			**<0.001**

(Continues)

TABLE 1 (Continued)

	Dietary inflammatory index									
	Tertile 1 (anti-inflammatory)			Tertile 2			Tertile 3 (pro-inflammatory)			
Characteristics	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*p* value
Citizen by naturalisation	214 (40.1)			199 (37.3)			121 (22.7)			
Non-citizen	2 (28.6)			3 (42.9)			2 (28.6)			
Comorbidities, n *(%)*										
Hypertension	145 (36.6)			129 (32.6)			122 (30.8)			0.278
Low HDL levels	308 (26.2)			407 (34.7)			459 (39.1)			**<0.001**
Obesity	701 (28.8)			845 (34.8)			884 (36.4)			**<0.001**
Diabetes mellitus	194 (29.1)			226 (33.9)			247 (37.0)			**0.028**
Lifestyle factors, n *(%)*										
Alcohol intake (≥40 g)	143 (43.6)			118 (36.0)			67 (20.4)			**<0.001**
Smoking	564 (31.7)			573 (32.3)			644 (36.2)			**0.004**
Minutes of sedentary activities, min	1387	327.4	193.4	1390	327.4	202.2	1381	332.7	202.0	0.723
Dietary factors										
Energy (kcal)	1396	2751.0	1187.5	1397	2088.2	761.9	1396	1491.3	635.7	**<0.001**
Protein (g)	1396	108.4	49.6	1397	78.11	32.00	1396	52.15	23.95	**<0.001**
Carbohydrate (g)	1396	321.9	148.4	1397	242.1	100.0	1396	178.2	90.2	**<0.001**
Dietary fibre (g)	1396	26.5	11.6	1397	15.6	6.6	1396	8.5	4.4	**<0.001**
Fat (g)	1396	110.0	59.9	1397	84.7	40.3	1396	60.0	31.8	**<0.001**

Note: In bold: *p* < 0.05 (comparison between lowest and highest DII).

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; CAP, controlled attenuation parameter; DII, Dietary Inflammatory Index; FLI, fatty liver index; FIB-4, fibrosis index based on four factors; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; IQR, interquartile rate; LSM, liver stiffness measurement.

(β = 0.024, 95% CI = 0.015–0.033, *p* < 0.001), FLI score (β = 2.489, 95% CI = 1.573–3.404, *p* < 0.001) and CAP (β = 1.969, 95% CI = 0.680–3.257, *p* = 0.003) were significantly associated with the DII. However, only GGT levels (β = 1.702, 95% CI = 0.325–3.080, *p* = 0.015), ALT levels (β = −0.616, 95% CI = −1.097 to −0.135, *p* = 0.012), AST:ALT ratio (β = 0.025, 95% CI = 0.014–0.036, *p* < 0.001) and FLI score (β = 1.168, 95% CI = 0.224–2.112, *p* = 0.015) remained significant after adjusting for potential covariables. For transient elastography parameters (LSM and CAP), no significant associations were identified.

Risk of NAFLD and DII

To further investigate the relationship between the DII and NAFLD using hepatic health indices, we tested multiple logistic regression models (Table 4). Associations between the DII tertiles and the risk of having NAFLD by the AST:ALT ratio (*p* < 0.001) and LSM (*p* = 0.045) were demonstrated; these associations did not persist after adjusting for confounding factors. Participants in the highest anti-inflammatory tertile had the lowest OR for NAFLD by FLI in both unadjusted (OR = 0.652, 95% CI = 0.539–0.788, *p* < 0.001) and adjusted models (OR = 0.722, 95% CI = 0.537–0.972, *p* = 0.032). No significant associations were found between the DII tertiles and the risk of having NAFLD assessed by LSM and CAP.

DISCUSSION

The present study was the first to evaluate the possible relationship of the anti-inflammatory diet profile measured by the DII and liver status assessed by LSM and CAP using transient elastography. Additionally, we examined the association between the DII and other non-invasive surrogate markers of liver disease (AST:ALT ratio, FLI score and FIB-4 score) in a multiethnic US population. Our findings revealed a lack of association between LSM and CAP parameters and the anti-inflammatory diet profile. However, we observed that an anti-inflammatory diet was significantly associated with a lower AST:ALT ratio and FLI after adjusting for potential covariables, supporting the influence of dietary inflammatory potential on liver status. Additionally, we

TABLE 2 Liver markers and transient elastography measures by Dietary Inflammatory Index tertiles adjusted by covariates

	Dietary inflammatory index[a]						
	Tertile 1 (anti-inflammatory)		Tertile 2		Tertile 3 (pro-inflammatory)		
Characteristics	Mean	SD	Mean	SD	Mean	SD	p value
Liver markers							
Glutamyl transferase (IU L^{-1})	30.25	32.72	31.76	45.15	33.19	56.26	0.095
Alanine aminotransferase (IU L^{-1})	23.21	15.08	22.52	16.48	21.08	17.91	0.198
Aspartate aminotransferase (IU L^{-1})	22.46	10.24	21.76	13.19	21.44	13.96	0.691
AST:ALT ratio	1.09	0.36	1.11	0.41	1.17	0.41	**0.001**
HOMA-IR	2.85	2.24	3.26	2.47	3.13	2.27	0.141
FLI	56.38	33.31	63.39	33.22	64.60	32.70	**0.036**
FIB-4	1.13	0.67	1.09	0.77	1.11	0.79	0.699
Liver ultrasound transient elastography							
LSM (kPa)	5.72	4.13	5.95	5.64	6.04	4.94	0.397
CAP (dB m^{-1})	261.91	58.98	267.32	59.09	267.83	61.80	0.337

Note: In bold: $p < 0.05$ (comparison between lowest and highest DII).

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; CAP, controlled attenuation parameter; DII, Dietary Inflammatory Index; FLI, fatty Liver Index; FIB-4, fibrosis index based on four factors; HOMA-IR, homeostatic model assessment-insulin resistance; LSM, liver stiffness measurement.

[a]The multivariable models were adjusted with sex, age, race, citizenship status, energy intake, alcohol intake, smoking, sedentary activity, hypertension, low HDL levels, obesity and diabetes mellitus.

TABLE 3 Beta estimates and 95% confidence interval (CI) for the association between Dietary Inflammatory Index, liver markers and transient elastography measures

	Dietary inflammatory index					
	Unadjusted			Adjusted[a]		
Clinical markers	β	95% CI	p value	β	95% CI	p value
Liver markers						
Glutamyl transferase (IU L^{-1})	0.818	−0.190 to 1.825	0.112	1.702	0.325–3.080	**0.015**
Alanine aminotransferase (IU L^{-1})	−0.729	−1.090 to −0.367	**<0.001**	−0.616	−1.097 to −0.135	**0.012**
Aspartate aminotransferase (IU L^{-1})	−0.362	−0.638 to −0.087	**0.010**	−0.294	−0.673 to 0.085	0.129
AST:ALT ratio	0.024	0.015–0.033	**<0.001**	0.025	0.014–0.036	**<0.001**
HOMA-IR	0.059	−0.015 to 0.133	0.118	0.077	−0.009 to 0.163	0.080
FLI	2.489	1.573–3.404	**<0.001**	1.168	0.224–2.112	**0.015**
FIB-4	−0.005	−0.022 to 0.011	0.549	0.003	−0.015 to 0.020	0.743
Liver ultrasound transient elastography						
LSM (kPa)	0.086	−0.018 to 0.190	0.104	0.138	−0.010 to 0.286	0.068
CAP (dB m^{-1})	1.969	0.680–3.257	**0.003**	0.974	−0.580 to 2.527	0.219

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; CAP, controlled attenuation parameter; FLI, fatty liver index; FIB-4, fibrosis index based on four factors; HOMA-IR, homeostatic model assessment-insulin resistance; LSM, liver stiffness measurement.

[a]The multivariable models were adjusted with sex, age, race, citizenship status, energy intake, alcohol intake, smoking, sedentary activity, hypertension, low HDL levels, obesity and diabetes mellitus. In bold: $p < 0.05$.

found that participants that consumed a proinflammatory diet had an increased risk of NAFLD assessed by FLI as a surrogate marker, suggesting that diet-induced inflammation may increase the development of NAFLD.

Limited studies have explored the role of the inflammatory potential of diet on non-invasive markers of NAFLD.[15–17] The FLI is a non-invasive and inexpensive measure of fatty liver that may be easily performed in a large population and has been previously validated in the

TABLE 4 Results from the logistic regression models that evaluated non-alcoholic fatty liver disease (NAFLD) using hepatic health indices by Dietary Inflammatory Index tertiles

| | NAFLD by AST-ALT ratio cut-off | | | | | |
| | Unadjusted | | | Adjusted[a] | | |
Dietary inflammatory index	OR	95% CI	*p* value	OR	95% CI	*p* value
Tertile 1 (anti-inflammatory)	0.689	0.588–0.807	**<0.001**	0.808	0.642–1.018	0.070
Tertile 2 (anti-inflammatory)	0.733	0.626–0.859	**<0.001**	0.858	0.702–1.050	0.137
Tertile 3 (pro-inflammatory)	1.0 (Reference)					
	NAFLD by FLI cut-off					
Tertile 1 (anti-inflammatory)	0.652	0.539–0.788	**<0.001**	0.722	0.537–0.972	**0.032**
Tertile 2 (anti-inflammatory)	0.991	0.819–1.200	0.929	1.011	0.777–1.317	0.934
Tertile 3 (pro-inflammatory)	1.0 (Reference)					
	NAFLD by FIB-4 cut-off					
Tertile 1 (anti-inflammatory)	1.009	0.846–1.204	0.920	1.081	0.796–1.466	0.618
Tertile 2 (anti-inflammatory)	0.866	0.723–1.037	0.117	0.831	0.634–1.087	0.177
Tertile 3 (pro-inflammatory)	1.0 (Reference)					
	NAFLD by LSM (kPa) cut-off					
Tertile 1 (anti-inflammatory)	0.763	0.586–0.994	**0.045**	0.702	0.482–1.021	0.064
Tertile 2 (anti-inflammatory)	0.817	0.629–1.059	0.127	0.766	0.559–1.049	0.097
Tertile 3 (pro-inflammatory)	1.0 (Reference)					
	NAFLD by CAP (dB/m) cut-off					
Tertile 1 (anti-inflammatory)	0.905	0.773–1.059	0.214	0.952	0.749–1.211	0.690
Tertile 2 (anti-inflammatory)	1.038	0.885–1.217	0.646	0.994	0.802–1.232	0.957
Tertile 3 (pro-inflammatory)	1.0 (Reference)					

Note: The multivariable models were adjusted with sex, age, race, citizenship status, energy intake, alcohol intake, smoking, sedentary activity, hypertension, low HDL levels, obesity and diabetes mellitus. In bold: $p < 0.05$.

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase; CAP, controlled attenuation parameter; CI, confidence interval; FLI, fatty liver index; FIB-4, fibrosis index based on four factors; HOMA-IR, homeostatic model assessment-insulin resistance; LSM, liver stiffness measurement.

multiethnic NHANES population.[12] Our results are re-inforced by the ATTICA population-based study conducted in 3402 adults from the Greek population, which showed that the dietary anti-inflammation index was inversely associated with NAFLD, when applying indices with NAFLD cut-offs including the FLI.[15] Cantero *et al.*[16] also showed that a higher DII was associated with a higher degree of liver damage assessed by a FLI >60 in adults within the PREDIMED study. Similarly, a previous study from the NHANES also demonstrated significant associations between increasing DII score and prevalent fatty liver evaluated by the FLI.[17] Additionally, we demonstrated that the ALT:AST ratio, an inexpensive and non-invasive liver marker, was also associated with the DII score. Similar to these data, the PREDIMED study found that a pro-inflammatory diet was positively associated with relevant liver markers such as ALT and AST levels.[16] Similarly, a prospective study showed a relationship between perceived high salt intake, which has been positively associated with inflammation, and a higher future risk of NAFLD.[30] Taken

together, data from the literature and our results indicate that subjects that consume a pro-inflammatory diet might be at risk for fatty liver.

To date, most previous work has focused on liver markers, which include a combination of clinical and routine parameters, whereas, to the best of our knowledge, the effect of dietary inflammatory potential on liver status assessed by LSM and CAP measures has not been previously investigated. We found that adults in the highest anti-inflammatory tertile had significantly lower CAP scores than those in the pro-inflammatory tertile, and CAP values were also significantly associated with DII scores. However, these associations did not remain significant after adjusting for multiple potential covariables. Although our results did not support a relevant role of the DII on CAP and LSM measures in a US study cohort, further studies in independent populations would be necessary to support these preliminary findings.

Our results highlight that evaluating the inflammatory potential of the diet might be essential for the early

prevention of NAFLD in adults to prevent its progression to advanced fibrosis. In agreement with our data, anti-inflammatory diets rich in omega-3 polyunsaturated fatty acids have been proposed as potential treatments for NAFLD because they might enhance hepatic β-oxidation, decrease endogenous lipid production, and reduce the expression of pro-inflammatory molecules and oxygen reactive species.[31] Interestingly, the results of a randomised double-blind placebo-controlled trial demonstrated that a combined treatment with α-tocopherol (vitamin E) and vitamin C, which are potent antioxidants with anti-inflammatory properties,[32] resulted in a significant improvement in the fibrosis scores of participants after 6 months of therapy.[33] Additionally, flavonoids, which act as potent antioxidants, have been shown to exert beneficial effects against NAFLD.[34] Their protective effects are ascribed to their capacity to increase fatty acid oxidation in the liver and inhibit nuclear factor-kappa B, thereby attenuating the release of inflammatory cytokines, which trigger insulin resistance, increase adiponectin, and improve insulin sensitivity and glucose tolerance.[35]

Similarly, in an analysis of participants in the Framingham Heart Study, Mat *et al.*[36] demonstrated that increasing diet quality, based on the Mediterranean-style diet score and Alternative Healthy Eating Index score, is associated with less liver fat accumulation and reduced risk for new-onset fatty liver. The protective effect of the Mediterranean dietary pattern, a well-known anti-inflammatory dietary pattern, against NAFLD may be driven by the high amounts of MUFAs and phenolic compounds in olive oil, which exert an anti-inflammatory effect that has been associated with a reduction in steatosis.[37–39] Taken together, our results suggest that an anti-inflammatory diet exerts beneficial effects on liver status. Thus, to slow the progression of fatty liver in adults and reduce the comorbidities associated with the disease, nutritional counseling and implementation of educational programs focused on the identification of anti-inflammatory and pro-inflammatory foods are especially relevant.

The present study has some limitations and strengths that should be addressed. First, because of its cross-sectional nature, causality cannot be determined. Therefore, longitudinal studies are necessary to analyse any effect of the DII on liver status. Second, dietary intake was assessed using a single 24-h recall. This tool has been proposed as a valuable method, although it may limit the ability to accurately describe individuals' habitual diets. In addition, the DII score was determined based on only 26 of the 45 food parameters in the original DII. Nevertheless, previous studies have shown that the absence of these missing components has no effect on DII scores because they are not typically consumed by most population populations.[40] Third, as a result of the lack of a liver biopsy for the diagnostic confirmation of transient elastography findings, we do not have the precise prevalence of NAFLD. Additionally, it should be noted that the association between the lowest DII tertile and the FLI or AST:ALT ratio may be related to changes in liver blood test results but does not necessarily change the risk of liver-related outcomes over time. Further longitudinal studies would be needed to clarify whether a lower DII changes the surrogate markers of liver status or the liver status itself. By contrast, the present study was strengthened by the inclusion of a large nationally representative ethnically diverse population and the use of transient elastography. The use of the highly standardised procedures of the NHANES study, which minimised measurement bias, was also a major strength.[41] Future studies should concentrate on enhancing the quality of the current topic.

In conclusion, there was no relationship between the transient elastography parameters and the anti-inflammatory diet profile, although an anti-inflammatory diet was significantly associated with a lower AST:ALT ratio and FLI score as surrogate measures of NAFLD after adjusting for covariables, supporting the influence of dietary inflammatory potential on liver status. Additionally, the present study showed an association between higher pro-inflammatory properties of diet and an increased risk of NAFLD assessed by the FLI. Strategies to promote an anti-inflammatory diet should be considered to prevent NAFLD in adults. Future intervention studies investigating the effect of dietary inflammatory potential on LSM and CAP are required.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

ETHICAL APPROVAL

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the National Center for Health Statistics Research Ethics Review Board (CDC, 2016). Written informed consent was obtained from all subjectspatients.

AUTHOR CONTRIBUTIONS

TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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