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Negative association of composite dietary antioxidant index with risk of hepatic fibrosis in individuals underwent cholecystectomy: a cross-sectional study

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Cholecystectomy increases the incidence of metabolic associated fatty liver disease and fibrosis. Dietary antioxidants protect the liver from oxidative stress and inhibit the development of metabolic dysfunction-associated steatotic liver disease (MASLD), yet the epidemiological evidence that links antioxidants intake to hepatic steatosis and fibrosis in patients underwent cholecystectomy is not available. Therefore, the present study aimed to investigate the association of composite dietary antioxidant index (CDAI) with the risk of hepatic steatosis and fibrosis in the cholecystectomy population. Data of 773 participants from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 were analyzed. Dietary and supplementary intake of antioxidants were collected to calculate CDAI. The controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) assessed by the vibration controlled transient elastography (VCTE) were used to identify hepatic steatosis and hepatic fibrosis, respectively. Weighted multivariate logistic regression and restricted cubic spline (RCS) regression were conducted to analyze the association. Weighted multivariate logistic regression analysis with full adjustment for confounding variables showed a negative association between CDAI and hepatic fibrosis in individuals underwent Scholecystectomy [OR (95%CI) = 0.87 (0.79, 0.94), *P* = 0.010], while non-significant association was found between CDAI and MASLD. Moreover, compared to the lowest quartile, the highest quartile of CDAI was associated with a lower risk of hepatic fibrosis [OR (95%CI) = 0.28 (0.13, 0.60), *P* = 0.007]. The RCS analysis further indicated a linear negative relationship between intake of CDAI, vitamin E, and selenium and the risk of hepatic fibrosis, whereas vitamin A was non-linearly negatively correlated with the risk of hepatic fibrosis (all *P* overall < 0.001). Our findings suggest that higher antioxidants intake, especially vitamin E, may be associated with a lower risk of hepatic fibrosis among individuals underwent cholecystectomy. Further studies are needed to validate current findings and explore the underlying mechanisms.

Keywords Nutrition intervention, Antioxidants, Cholecystectomy, Hepatic fibrosis, Vitamin E

Abbreviations

AASLD	American Association for the Study of Liver Disease
AHF	Advanced hepatic fibrosis
BMI	Body mass index
CAP	Controlled attenuation parameter
CDAI	Composite dietary antioxidant index
CDCA	Chenodeoxycholic acid
CI	Confidence intervals

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EASL	European Association for the Study of the Liver
FFAs	Free fatty acids
FXR	Farnesoid X receptor
GPX1	Glutathione peroxidase1
LSM	Liver stiffness measurement
MASLD	Metabolic dysfunction-associated steatotic liver disease
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NIAAA	National Institute on Alcohol Abuse and Alcoholism
n-3 PUFA	N-3 polyunsaturated fatty acids
OR	Odds ratio
RCS	Restricted cubic spline
RDA	Recommended dietary allowance
ROS	Reactive oxygen species
VCTE	Vibration-controlled transient elastography

Cholecystectomy has been regarded as the gold standard for the treatment of symptomatic cholelithiasis because of the faster recovery, shorter hospital stays, and decreased transformation into gallbladder cancer compared to conservative therapy. However, recent studies suggested that risk of hepatic steatosis and fibrosis might be increased in populations who underwent cholecystectomy, and this was independent from gallstone disease[1–4]. Although it was hypothesized that cholecystectomy might change the metabolism profile of biliary acids[5], the underlying mechanisms that contribute to hepatic steatosis and fibrosis post cholecystectomy have not been fully elucidated, and there are currently no efficient treatments. In this regard, a better understanding of the potential risk factors is needed to achieve prevention and treatment of hepatic steatosis and fibrosis post cholecystectomy.

It is generally believed that diet is an important common risk factor shared by both cholelithiasis and metabolic associated steatotic liver disease and fibrosis. However, evidence on different dietary nutrients and the development of hepatic steatosis and fibrosis post cholecystectomy is limited. Sunmin et al.[6] found that a high-fat diet significantly increased the levels of hepatic triglyceride and hepatic lipid peroxides in cholecystectomied mice compared with a low-fat diet. In another prospective study, cholecystectomy patients who ate more animal protein, cholesterol or eggs, and less vegetables suffered more symptoms after three months of follow-up. However, no significant association was found between fat intake and the risk postcholecystectomic symptoms[7]. A recent population-based study revealed that the diet pattern rich in whole grains, legumes, vegetables, fish, and fruit was negatively associated with the risk of non-alcoholic fatty liver disease (NAFLD) in patients who underwent cholecystectomy, and the authors suspected that it was due to the abundant intake of n-3 polyunsaturated fatty acids (n-3 PUFA) which improved erythrocyte fatty acid[8]. Thus, due to the conflicting literature and limited evidence, it remains unclear what kind of nutrients play key roles in mediating the development of hepatic steatosis and fibrosis post cholecystectomy.

Antioxidants can substantially reduce the incidence of chronic metabolic diseases by regulating lipid homeostasis and inflammation[9]. Recent literature has suggested that oxidative stress, resulted from overload of free fatty acids (FFAs) oxidation and subsequent imbalance of antioxidant defense system, is a key force in driving hepatic steatosis and fibrosis[10]. Thus, antioxidants may protect the liver from oxidative stress and inhibit the development of steatotic liver disease. The Composite Dietary Antioxidant Index (CDAI) is a valid and comprehensive tool proposed by Wright et al. to quantify overall antioxidant capacity of the nutrients form diet (including food and supplements)[11]. Current population-based studies have shown that CDAI may be associated with decreased occurrence of metabolic dysfunction-associated steatotic liver disease (MASLD) rather than hepatic fibrosis[12]. However, the relationship between CDAI and hepatic steatosis and fibrosis in individuals underwent cholecystectomy has not been studied. Thus, utilizing the U.S. database of National Health and Nutrition Examination Survey (NHANES) 2017–2020, the present study examined the impact of antioxidants intake on the risk of hepatic steatosis and fibrosis in the cholecystectomy population, with the ultimate aim of better controlling the prognosis of cholecystectomy through nutrition intervention.

Materials and methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey conducted by the National Center for Health Statistics (NCHS) to evaluate health and nutritional status of non-institutionalized population across the United States. In this study, we analyzed the data from the most recent cycle of NHANES, 2017–2020, where Vibration-Controlled Transient Elastography (VCTE) were conducted to assess the degree of hepatic steatosis and fibrosis in participants. Of 15,560 participants who completed the survey, 773 were eventually enrolled for further analysis. All participants in the present study were aged over 20 years old, non-pregnant and participants were excluded based on the following criteria: (1) with lacking data of cholecystectomy (N = 14535); (2) with lacking data of transient elastography (N = 170); (3) with lacking data of reliable or complete diet recall (N = 60); (4) with incomplete data of covariates and with implausible total energy intake (< 500 or > 5000 kcal/day, N = 22).

Definition of hepatic steatosis and fibrosis

The VCTE measurements were obtained in the NHANES MEC using the FibroScan model 502 V2 Touch equipped with a medium or extra-large wand (probe). Exams were considered reliable if participants fasted at

least 3 h before the exam, there were 10 or more complete measurements and an interquartile range/median LSM < 30%. All VCTE results were read by trained NHANES health technicians to ensure quality. The presence of hepatic steatosis and fibrosis were assessed using data obtained by VCTE. Based on previously published data, hepatic steatosis was defined as controlled attenuation parameter (CAP) ≥ 274 dB/m and hepatic fibrosis was defined as liver stiffness measure (LSM) ≥ 6.3 kPa[13]. For participants with hepatic steatosis, additional criteria were considered to determine MASLD[14], including the presence of at least 1 of 5 cardiometabolic risk factors and the lack of metabolic parameters or known causes that were deemed to have cryptogenic steatotic liver disease.

Evaluation of CDAI

Dietary intake information of each participant in NHANES was derived from the 24-h dietary recall interview conducted by the U.S. Department of Agriculture's Food Surveys Research Group. All participants underwent two 24-h dietary recall interviews: the initial interview took place at a mobile examination center (MEC), while the second interview was conducted over the phone within 3–10 days. Additionally, the questionnaire assessed the use of dietary supplements in the past month, encompassing frequency, dosage, and duration of consumption. To reduce study bias, the dietary information from the first recall interviews was used. CDAI, the mostly recognized index to quantify the potential dietary antioxidant capacity was used in this study to assess to the relationship between dietary antioxidants and hepatic steatosis and fibrosis post cholecystectomy. CDAI was calculated by a combination of the standardized dietary intake of vitamins A, C, and E, carotenoids, zinc, and selenium with the following formula: $\mathrm{CDAI} = \sum_{i=1}^{n=6} \frac{\text{Individual intake} - \text{Mean}}{\text{Standard Deviation}}$

Covariates

To eliminate other known confounding factors from interfering with the results, we also analyzed covariates which include gender, age, race, education level, marital status, body mass index (BMI), hepatitis, diabetes, hypertension, physical activity, smoking and alcohol consumption collected from self-reported questionnaires and examinations of the participants. Race was categorized as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black and other races. Education was categorized as above high school, high school or equivalent and less than high school. Marital status was classified as married, separated and unmarried. Hepatitis included both viral hepatitis and autoimmune hepatitis. Hypertension was defined as systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg and/or participants who received anti- hypertension drug therapy and/or diagnosed with hypertension. Diabetes was defined as Glycohemoglobin ≥ 6.5% or fasting blood glucose ≥ 7.0 mmol/L or on treatment for type 2 diabetes or reported that they had ever been told by a doctor or health professional that they have diabetes. Physical activity was defined as active and inactive (while vigorous activity as exceeding 75 min or moderate activity as exceeding 150 min considered to be active). Smoking status was defined as current, past, and never. Alcohol drinking was categorized as heavy (≥ 4 drinks per day for women, ≥ 5 drinks per day for men), and not heavy based on recommendations from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the National Institute of Health. BMI was categorized into three groups: under/normal weight (< 25.0 kg/m^2), overweight (25.0–29.9 kg/m^2) and obesity (≥ 30.0 kg/m^2) according to the World Health Organization classification[4].

Statistical analysis

Survey-weighted statistical models were employed for data analysis according to the analytical guidelines edited by NCHS to make sure the results accurately represent the target population from the complex survey design. Categorical variables corresponding to the baseline characteristics were compared using weighted χ^2 tests analysis, while continuous variables were assessed using weighted univariate logistic regression analysis. The relationship between CDAI score and risk of MASLD and hepatic fibrosis was analyzed by multivariable logistic regression. Multiple models adjusted for potential confounding factors in progressive degrees were constructed as follows: Crude model was not adjusted for any covariates; Model 1 was adjusted for age, sex, and race/ethnicity; and Model 2 was additionally adjusted for education level, marital status, BMI, smoking status, drinking status, hepatitis, hypertension, diabetes and physical activity. The results are reported as odds ratios (ORs) with 95% confidence intervals (CI). In addition, subgroup analyses were performed to estimate the presence of interactions of stratified factors with the association between CDAI and hepatic fibrosis, with the Bonferroni corrections used to reduce false positives for multiple comparisons. The multivariable models were adjusted for covariates using the same method as that used in the above analysis. In this study, continuous variables were presented as medians and quartiles (Q1, Q3), while categorical variables were conveyed as frequencies and proportions. All statistical analyses were performed using R 4.4.1 (http://www.R-project.org). All statistical tests were two-sided, and a $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics of participants based on hepatic fibrosis phenotypes

A total of 773 participants were eventually included in this study according to the inclusion and exclusion criteria (Fig. 1). As shown in Table 1, characteristics of participants was summarized according to the presence of hepatic fibrosis. Compared with participants of non-fibrosis, participants with hepatic fibrosis were more likely to suffer obesity (76.3% vs 52.6%). Similarities were found in the percentage of age, sex, hypertension, diabetes, and hepatitis between the two groups.

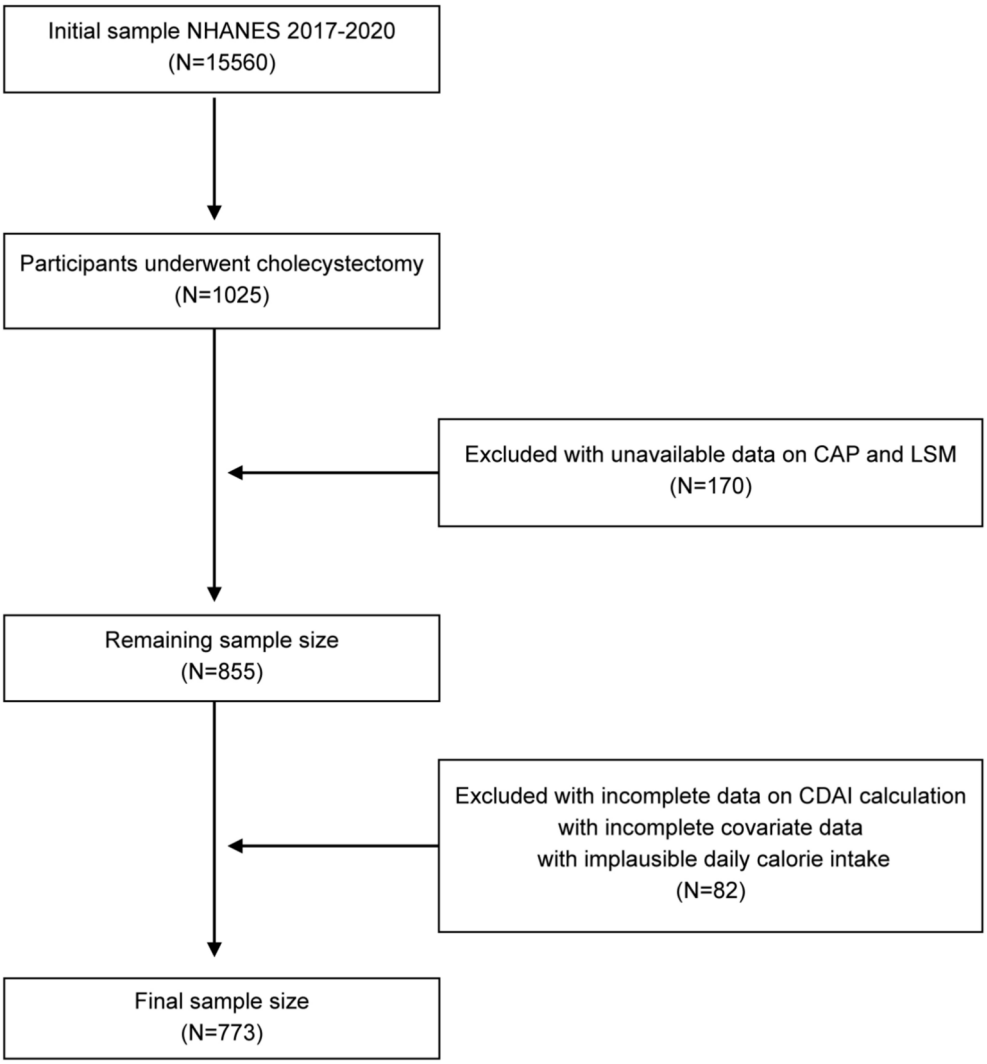

Fig. 1. Flowchart for participants recruitment.

Associations of CDAI and its components with prevalence of hepatic fibrosis in individuals underwent cholecystectomy

To further investigate the relationship between CDAI and prevalence of hepatic fibrosis, the weighted multivariate logistic regression analyses were performed. All participants were divided into four quartiles based on the CDAI scores to explore the effect of CDAI intake on the incidence of hepatic fibrosis. As shown in Table 2, in all three models, higher CDAI intake was correlated with a statistically significant decreased risk of hepatic fibrosis (OR = 0.28, *P* for trend = 0.010 after adjusting for covariates), presenting a linear dependence between CDAI intake and risk of hepatic fibrosis in individuals underwent cholecystectomy. Additionally, a statistically significantly negative association was observed between continuous CDAI and hepatic fibrosis before and after adjusting for potential confounders, with the adjusted OR (95% confidence interval) of 0.87 (0.79, 0.94) (*P* = 0.010), which further suggested that higher antioxidants intake was associated with a decreased risk of hepatic fibrosis in the cholecystectomy population.

Similarly, the relationship between CDAI intake and risk of MASLD was analyzed. The present results showed that there was no statistically significant association between categorical CDAI and risk of MASLD (*P* for trend = 0.217 after adjusting for covariates), although the adjusted OR of MASLD in the highest quartile of CDAI (OR = 0.59) was lower comparing to the lowest quartile of CDAI (Table S1).

The impacts of each CDAI component upon the risk of hepatic fibrosis were further analyzed. As shown in Table 3, lower intake of vitamin A (403.00 mg vs 471.50 mg) and vitamin E (6.89 mg vs 7.00 mg) and higher intake of selenium (90.80 mcg vs. 87.57 mcg) were seen in the hepatic fibrosis group, indicating that vitamin E, vitamin A and selenium may be correlated with the risk of hepatic fibrosis in individuals underwent cholecystectomy.

Characteristic	Non-fibrosis (N = 494)	Fibrosis (N = 279)	Overall (N = 773)	*P* value
Gender, %				0.474
male	122 (24.7)	76 (27.2)	198 (25.6)	
female	372 (75.3)	203 (72.8)	575 (74.4)	
Age, years, %				0.813
20-45 years	98 (19.8)	50 (17.9)	148 (19.1)	
45-60 years	140 (28.3)	68 (24.4)	208 (26.9)	
> 60 years	256 (51.8)	161 (57.7)	417 (53.9)	
Race/ethnicity, %				0.097
Mexican American	49 (9.9)	42 (15.1)	91 (11.8)	
Other Hispanic	52 (10.5)	25 (9.0)	77 (10.0)	
Non-Hispanic White	245 (49.6)	131 (47.0)	376 (48.6)	
Non-Hispanic Black	93 (18.8)	50 (17.9)	143 (18.5)	
Others	55 (11.1)	31 (11.1)	86 (11.1)	
Marital status, %				0.210
Married	281 (56.9)	174 (62.4)	455 (58.9)	
Separated	154 (31.2)	81 (29.0)	235 (30.4)	
Unmarried	59 (11.9)	24 (8.6)	83 (10.7)	
Education level, %				0.367
Less than high school	86 (17.4)	34 (12.2)	120 (15.5)	
High school or equivalent	135 (27.3)	90 (32.3)	225 (29.1)	
Above high school	273 (55.3)	155 (55.6)	428 (55.4)	
BMI, %				**0.006****
Normal weight	78 (15.8)	16 (5.7)	94 (12.2)	
Overweight	156 (31.6)	50 (17.9)	206 (26.6)	
Obesity	260 (52.6)	213 (76.3)	473 (61.2)	
Hypertension, %				0.131
No	172 (34.8)	112 (40.1)	284 (36.7)	
Yes	322 (65.2)	167 (59.9)	489 (63.3)	
Diabetes, %				0.269
No	338 (68.4)	172 (61.6)	510 (66.0)	
Yes	156 (31.6)	107 (38.4)	263 (34.0)	
Hepatitis, %				0.826
No	450 (91.1)	262 (93.9)	712 (92.1)	
Yes	44 (8.9)	17 (6.1)	61 (7.9)	
Drink, %				0.181
Not heavy	362 (73.3)	202 (72.4)	564 (73.0)	
Heavy	132 (26.7)	77 (27.6)	209 (27.0)	
Smoke, %				0.877
Current	81 (16.4)	42 (15.1)	123 (15.9)	
Past	149 (30.2)	87 (31.2)	236 (30.5)	
Never	264 (53.4)	150 (53.8)	414 (53.6)	
Physical activity, %				0.151
Not active	382 (77.3)	215 (77.1)	597 (77.2)	
Active	112 (22.7)	64 (22.9)	176 (22.8)	
CAP, %				0.176
< 274 dB/m	214 (43.3)	114 (40.9)	328 (42.4)	
≥ 274 dB/m	280 (56.7)	165 (59.1)	445 (57.6)	

Table 1. Baseline characteristics of the participants grouped by hepatic fibrosis. Categorical variables were presented as n (percentage) and the *P* values were calculated by weighted univariate logistic regression analysis. BMI, body mass index; CAP, controlled attenuation parameter. * *P* value < 0.05, ** *P* value < 0.01, *** *P* value < 0.001.

Dose–response analysis of CDAI with hepatic steatosis in individuals underwent cholecystectomy

Restricted cubic spline (RCS) was employed to further analyze the dose–response relationship between CDAI and hepatic fibrosis. As shown in Fig. 2, a significant linear and negative association was found between CDAI

CDAI		Crude model		Model 1		Model2	
		OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Continuous CDAI		0.88 (0.83, 0.94)	< 0.001***	0.88 (0.82, 0.94)	0.001***	0.87 (0.79, 0.94)	0.010*
Categorical CDAI	Q1	1.00	Reference	1.00	Reference	1.00	Reference
	Q2	0.55 (0.32, 0.97)	0.039*	0.57 (0.33, 1.01)	0.052	0.60 (0.31, 1.14)	0.098
	Q3	0.71 (0.43, 1.16)	0.162	0.69 (0.40, 1.21)	0.179	0.68 (0.36, 1.31)	0.199
	Q4	0.29 (0.16, 0.53)	< 0.001***	0.28 (0.14, 0.56)	0.001***	0.28 (0.13, 0.60)	0.007**
	P for trend	< 0.001***		0.002**		0.010*	

Table 2. Weighted logistic regression analysis on the association between CDAI and hepatic fibrosis. Data are presented as OR (95%CI). Crude Model: without adjusting for any covariates. Model 1: adjusted for age (continuous), sex (male or female), and race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black or Other); Model 2: adjusted for Model 1 plus education level (below high school, high school, or above high school), marital status (married, separated, or unmarried), BMI (normal weight, overweight, or obesity), smoking status (never smoker, former smoker, or current smoker), drinking status (heavy or not heavy drinker), hepatitis (yes or no), hypertension (yes or no), diabetes (yes or no), and physical activity (inactive, moderate, or vigorous). BMI, body mass index; CDAI, composite dietary antioxidant index; OR, odds ratio; CI, confidence interval. * *P* value < 0.05, ** *P* value < 0.01, ***P* value < 0.001.

Variables	Overall	Hepatic fibrosis		
		Non-fibrosis	Fibrosis	*P* value
CDAI	− 0.47 (− 2.40, 1.78)	− 0.44 (− 2.36, 2.02)	− 0.57 (− 2.49, 1.20)	< 0.001***
Vitamin A, mcg	452.00 (275.00, 751.00)	471.50 (287.75, 779.50)	403.00 (254.00, 685.50)	0.041*
Vitamin C, mg	44.50 (19.60, 96.10)	43.48 (20.13, 95.43)	45.30 (18.45, 98.27)	0.051
Vitamin E, mg	6.99 (4.41, 10.34)	7.00 (4.39, 10.82)	6.89 (4.47, 9.88)	0.002**
Zinc, mg	8.43 (5.90, 11.63)	8.42 (5.77, 11.62)	8.46 (6.05, 11.67)	0.152
Selenium, mcg	88.90 (62.80, 122.13)	87.57 (63.00, 129.83)	90.80 (62.60, 115.72)	0.018*
Carotenoid, mg	4.68 (1.67, 11.02)	4.94 (1.69, 11.58)	4.28 (1.53, 9.95)	0.319

Table 3. Dietary intake of each CDAI component grouped by fibrosis status. Data were presented as the median (Q1, Q3). The *P* values were calculated by weighted univariate logistic regression analysis. CDAI, composite dietary antioxidant index; MASLD, metabolic dysfunction-associated steatotic liver disease. * *P* value < 0.05, ** *P* value < 0.01, *** *P* value < 0.001.

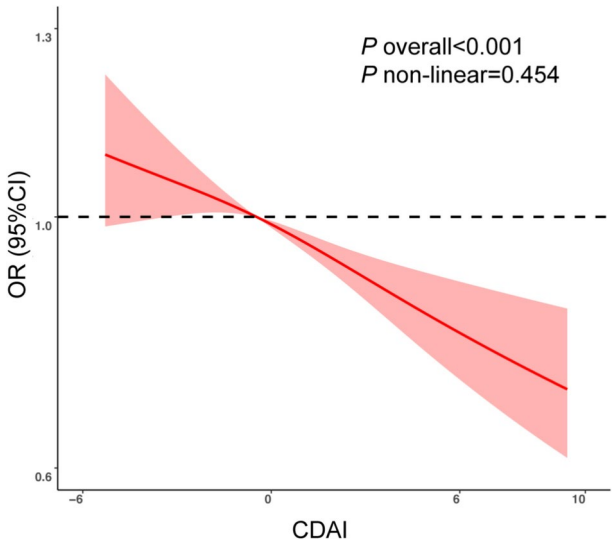

Fig. 2. The RCS curve of the association between CDAI and hepatic fibrosis in individuals underwent cholecystectomy. RCS regression was adjusted for age, sex, race, education levels, marital status, hepatitis, smoking, drinking, and physical activity. RCS, restricted cubic spline; CDAI, composite dietary antioxidant index; OR, odds ratio. * *P* value < 0.05, ** *P* value < 0.01, *** *P* value < 0.001.

and risk of hepatic fibrosis (*P* for overall < 0.001, *P* for non-linear = 0.454). Moreover, RCS curves displayed a non-linearly association between vitamin A and hepatic fibrosis. As shown in Fig. 3A, as intake of vitamin A increased, the OR of hepatic fibrosis exhibited a gradual decrease, but the protective effect appeared to stabilize beyond a certain value, suggesting the potential saturation effect at certain vitamin A intake (*P* for overall < 0.001, *P* for non-linear < 0.001). Furthermore, intake of vitamin E was found to be linearly and negatively correlated with hepatic fibrosis (*P* for overall < 0.001, *P* for non-linear > 0.05), with the intake of vitamin E corresponding to the inflection point in the curve being 6.93 mg (Fig. 3B). Although it showed a higher intake of selenium in the fibrosis group in Table 3, RCS curve showed a linear negative association between selenium intake and the risk of hepatic fibrosis, with the OR began to decline only when selenium intake exceeded 88.75 mcg (the inflection point, Fig. 3C), which suggested that adequate selenium intake also played a protective role in hepatic fibrosis. Further study is needed to explore the dose-dependent roles of the dietary antioxidants in the regulation of pathophysiology and treatment response of hepatic steatosis in individuals underwent cholecystectomy.

Subgroup analysis on the association of CDAI and the prevalence of hepatic fibrosis in individuals underwent cholecystectomy

We also conducted stratified analysis by dividing participants into subgroups according to sex, age, race, marital status, educational levels, drinking status, smoking status, physical activity, hypertension, diabetes, hepatitis, and BMI. As illustrated in Fig. 4, no significant interaction effects were observed between CDAI and any strata covariates with the risk of hepatic fibrosis (corrected significance threshold 0.004), indicating the association between CDAI and hepatic fibrosis remained stable across different subgroups.

Discussion

The main finding of the present study was that a higher CDAI score was associated with a decreased risk of hepatic fibrosis among individuals underwent cholecystectomy, highlighting a protective effect of dietary antioxidant intake on the cholecystectomy population. This is, to our knowledge, the first time to explore the relationship between CDAI and hepatic fibrosis specific for the cholecystectomy population. Moreover, in contrast to previous studies[12] that found no correlation between CDAI and hepatic fibrosis and a negative correlation with MASLD in the general population, we identified a notable linear negative association between CDAI and the risk of hepatic fibrosis, whereas no significant correlation with MASLD in the cholecystectomy population. The data also implied that the individuals underwent cholecystectomy may be more susceptible to oxidative stress and the resulting fibrotic degeneration. Thus, it is possible to suggest that the increase intake of dietary antioxidants is independently associated with reduced hepatic fibrosis in individuals underwent cholecystectomy.

Oxidative stress that contributes to hepatic fibrosis refers to an imbalance between reactive oxygen species (ROS) and the antioxidant defense systems. It occurs when the liver is overloaded with FFAs while endogenous antioxidant enzymes are unable to degrade the overproduced ROS. Moreover, the circulating levels of chenodeoxycholic acid (CDCA) after cholecystectomy were reduced, which leads to downregulated Farnesoid X receptor (FXR) and its downstream metabolic pathways, enhanced ROS production and increased oxidative stress[15]. Dietary derived antioxidants play a critical role for limiting oxidative stress and regulating the balance between ROS production and clearance[16,17], thus may help prevent the onset and progression of hepatic steatosis and fibrosis post cholecystectomy. In view of the scarcity of studies relating individual antioxidants to hepatic fibrosis post cholecystectomy, in the present study, we evaluate the 6 components of CDAI separately, and found a statistically significant negative correlation between vitamin E, vitamin A, and selenium respectively, and hepatic fibrosis among cholecystectomy participants, implying a predominant role of these antioxidants.

Vitamin E, which is widely found in corn, peanut, and soybean oil, is one of the well-known free radical scavengers and has been reported to ameliorate oxidative stress and inflammation either by neutralizing free

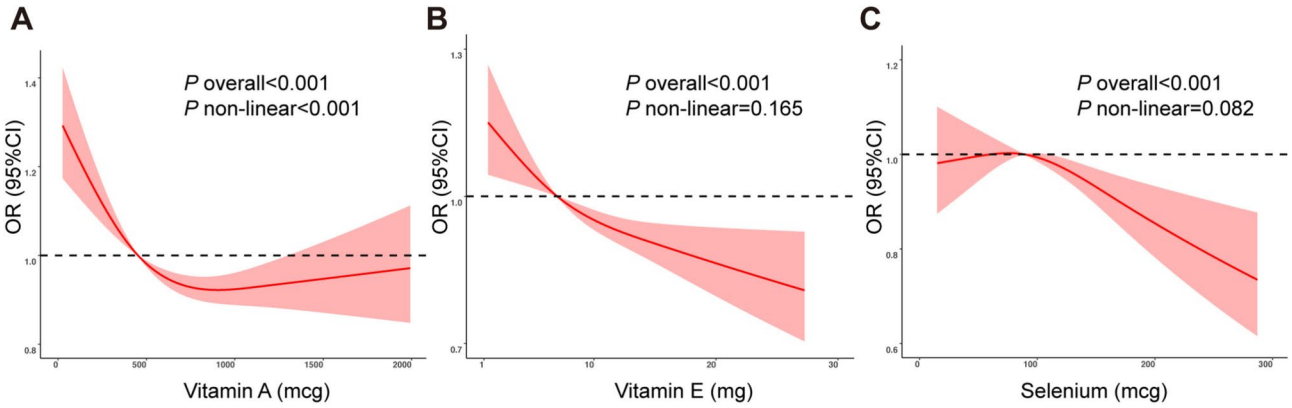

Fig. 3. The RCS curve of the association between intake of (**A**) vitamin A, (**B**) vitamin E, and (**C**) selenium and hepatic fibrosis in individuals underwent cholecystectomy. RCS regression was adjusted for age, sex, race, education levels, marital status, BMI, hypertension, diabetes, hepatitis, smoking, drinking, and physical activity. RCS, restricted cubic spline; CDAI, composite dietary antioxidant index; OR, odds ratio. * *P* value < 0.05, ** *P* value < 0.01, *** *P* value < 0.001.

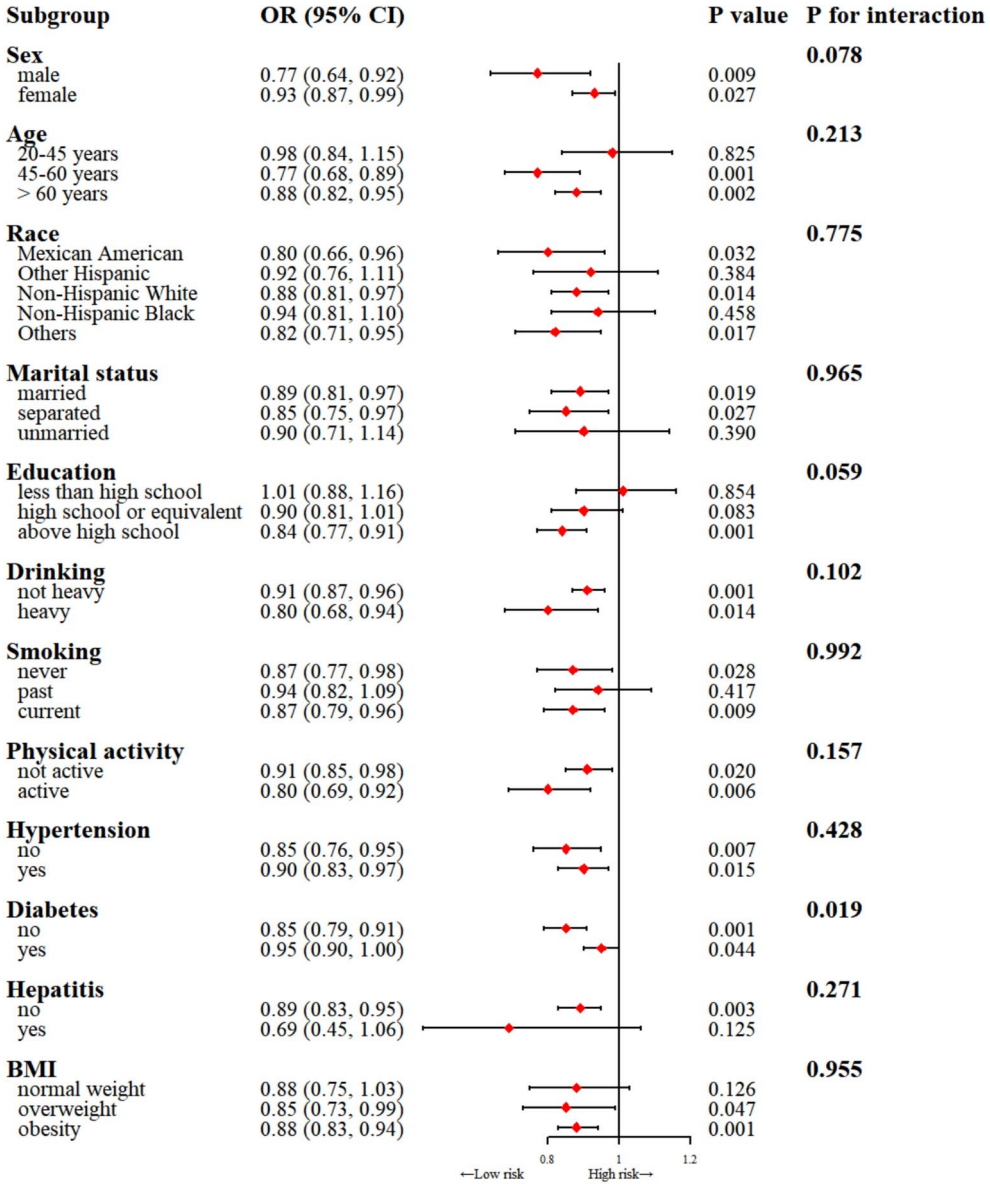

Fig. 4. Subgroup analysis for the association between CDAI and hepatic fibrosis in individuals underwent cholecystectomy. Analyses were stratified by sex (male and female), age (20–45 years, 45–60 years, and > 60 years), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Others), marital status (married, separated, unmarried), education (Above high school, High school or equivalent, Less than high school), drinking (not heavy or heavy), smoking (current, past, never), physical activity (active and not active), hepatitis (yes or no), hypertension (yes or no), diabetes (yes or no), and BMI (normal, overweight and obesity). CDAI, composite dietary antioxidant index; BMI, body mass index; OR, odds ratio. Corrected significance threshold 0.004.

radicals or by stimulating the action of other antioxidative enzymes[18]. Although it has been recommended by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) for patients with non-alcoholic steatohepatitis (NASH)[19,20], the effectiveness of vitamin E in the prevention and treatment of hepatic fibrosis remains a debatable topic. One study reported no significant improvement in NASH upon daily treatment of 800 IU vitamin E for 6 months[21]. However, another study showed that a dose of 300 mg/d vitamin E treated for more than 2 years was effective in ameliorating hepatic fibrosis[22]. Similar results were found in improving NASH by administration of vitamin E at a dosage of 800 IU for 18 months[23]. One possible factor contributing to the above difference is the dose and period of vitamin E administration. In our study, the negative correlation between vitamin E intake and hepatic fibrosis was linear and the upper limit of its effect was not seen, nevertheless, considering the toxicity of vitamin E overdose, intervention strategies of lower doses with longer durations should be considered. Recent evidence suggested that genetic variations in haptoglobin as well as *Fads1/Fads2* may be attributed to the different response of vitamin E treatment[24]. Furthermore, vitamin E has been found effective in interfering with fatty liver disease

as an adjunctive therapy in combination with other drugs or antioxidants[25]. In a word, vitamin E holds great promise for the prevention and treatment of hepatic fibrosis, while the effective and safe dose of vitamin E application needs more exploration.

Vitamin A has also been recognized for having potent antioxidant properties. Two population-based studies revealed that more intake of vitamins A or provitamin A were related to lower risk of NAFLD or NASH[26,27]. However, another study showed that participants with NASH had higher vitamin A intake than healthy subjects[28]. The contradictions may be explained by the finding in our study that the association between vitamin A intake and hepatic fibrosis was non-linear, and the optimal dose of vitamin A supplementation needs further exploration. Moreover, previous studies demonstrated a significant deficiency of serum or hepatic retinol level in NAFLD patients[29,30], whereas an increased concentration of serum vitamin A in their fibrogenic progression[31], which implied the different roles of vitamin A in mediating hepatic steatosis and fibrosis, respectively. In addition, vitamin A can be obtained both from carotenoids which mainly exists in carrots and green leafy vegetables and from retinyl esters which is enriched in animal sources like eggs, cheese and offal, and further studies are needed to identify the role and mechanism of vitamin A of different sources in the regulation of hepatic fibrosis.

Selenium are mainly obtained from meats and dairy products rather than plant-based foods[32]. Other epidemiological studies have shown that serum or blood levels of selenium are negatively associated with the prevalence of hepatic fibrosis[33,34], thus highlighting a protective role of selenium against hepatic fibrosis. Mechanically, for one thing, selenium is metabolized in the liver to synthesize selenoproteins, such as glutathione peroxidase1 (GPX1), which are used in hepatocytes to resist oxidative stress. Secondly, selenium exerts anti-inflammation property by suppressing the expression of pro-inflammatory cytokines. Moreover, selenium inhibits activation of hepatic stellate cells to mitigate excessive deposition of extracellular matrix, thereby leading to alleviation of hepatic fibrosis[35–37]. In the current study, we first found that the median intake of selenium was higher in the hepatic fibrosis group (90.80 mcg vs. 87.57 mcg, Table 3). However, when further applying the RCS analysis, we found a linear negative association between selenium intake and the risk of hepatic fibrosis, with the curve showing that the OR began to decrease only when selenium intake exceeded 88.75 mcg (the inflection point, Fig. 3C). The median selenium intake of the two groups was located on both sides of the inflection point, and the values were very close to each other. For one thing, this may be due to the small sample size, and for another thing, this may be attributed to the difference in the distribution of selenium intake between the two groups. So, in the present study, although the values of selenium intake appeared to be higher in the hepatic fibrosis group, it does not exclude a potential protective effect of selenium against hepatic fibrosis as shown by the RCS results. Based on these, we conclude that selenium has the potential to reduce the risk of hepatic fibrosis in patients underwent cholecystectomy, but further population-based large sample prospective studies and interventional studies are needed to validate the role and mechanism of selenium on hepatic fibrosis in cholecystectomy patients.

Our study has not revealed any correlation between vitamin C, zinc, and carotenoids and the risk of hepatic fibrosis. A previous study found a negative relationship between dietary intake of vitamin C and hepatic fibrosis[38]. In their study, the median dietary intake of vitamin C in the non-advanced hepatic fibrosis (AHF) group was 116.75 mg. However, in our study, the median dietary vitamin C intake for non-Fibrosis subjects was only 43.48 mg, which is much lower than the recommended dietary allowance (RDA) in the U.S. The explanation for the discrepancy between our study and others remains speculative, but it may indicate the importance of adequate intake of vitamin C. Although vitamin C is involved in the de novo lipogenesis pathways, the relationship between vitamin C intake and hepatic fibrosis remains controversial[39]. Current findings regarding the relationship between serum zinc levels and hepatic fibrosis are debatable, but the consensus is that there is no correlation between zinc intake and the odds of MAFLD[40,41], which is consistent with our study. There is currently little evidence from population-based studies on carotenoids and hepatic steatosis and fibrosis. Christensen et al. found that greater exposure to diet carotenoids was associated with lower odds of NAFLD [42], but in another study β-carotene intake was inversely associated with hepatic steatosis, while α-carotene was positively associated with hepatic fibrosis [43]. Furthermore, carotenoids are a class of lipid soluble phytochemicals that can be classified as provitamin A or non-provitamin A, and further studies are needed to explore the function of provitamin A and non-provitamin A, respectively.

This study has limitations that need to be noted and addressed in further research. Firstly, the outcome parameters CAP and LSM were measured by VCTE, which is a reliable measure, but also contributes to our limited sample size as these two parameters were only accessible from the 2017–2020 database. Moreover, although this study utilized CDAI, a composite indicator which has superior application advantages and validity to the traditional dietary antioxidant index, some recall bias could not be avoided in collecting dietary data. Thirdly, the results were not adjusted for potential confounders such as postoperative time, indications for cholecystectomy (such as stone type), and postoperative drug use (such as UDCA) as the study was a secondary analysis utilizing the established NHANES database. Lastly, this is a cross-sectional study, so we cannot conclude whether these is a causal relationship between CDAI and hepatic fibrosis, nor can we exclude whether there is reverse causality, and further validation in prospective studies is needed.

Conclusion

Findings from this study of US adults is the first time to suggest a significant negative association between CDAI and hepatic fibrosis among the cholecystectomy population. Notably, our results further found that adequate intake of vitamin E, vitamin A and selenium has the potential to reduce the risk of hepatic fibrosis in individuals underwent cholecystectomy, but further confirmation is needed in future studies. Taken together, our results provide a reference for subsequent prospective and interventional studies to refine nutritional strategies for this certain population in preventing disease progression.

Data availability

The dataset for this study was obtained from NHANES, which is publicly available and can be accessed at the following link: https://www.cdc.gov/nchs/nhanes/.

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Author contributions
S.H. design of the work; acquisition, analysis, and interpretation of data; drafted the work. W.Z. analysis, and interpretation of data and prepared figures. Y.S. data collection and analysis. M.M. design of the work and revision of the work. S.G. contribute to the conception and revision of the work.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The survey protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics, and written informed consent has been obtained from all the participants. Moreover, specific informed consent was not required for this secondary analysis of the publicly available data.

Additional information
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