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Association Between Dietary Flavonoid Intake and Cardiovascular Health in Cancer Survivors: A Cross-Sectional Study

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Purpose: Flavonoids are naturally occurring compounds with diverse health-promoting properties. The purpose of this study was to explore the associations between dietary flavonoid intake and cardiovascular health in cancer survivors.

Patients and Methods: We obtained data from the National Health and Nutrition Examination Survey (NHANES) 2007–2008, 2009–2010, and 2017–2018 cycles. Weighted linear regression and restricted cubic spline (RCS) were used to explore the correlation between dietary flavonoid intake and cardiovascular health (Life's Essential 8 (LE8) score) in cancer survivors. Then, weighted quantile sum (WQS) regression and quantile-based g-computation (qgcomp) models were performed to assess the mixed effects of the six flavonoid subclasses and to determine the major flavonoid types. Additionally, the protective effect of high flavonoid intake on cardiovascular health was further evaluated in different subgroups, and mediation analysis was used to explore mediating factors.

Results: After adjusting for all covariates, compared to those in the first quartile, participants in the fourth quartile of total flavonoids, anthocyanidins, flavonols, flavanones, and flavones intake exhibited increases in LE8 scores of 3.24% (95% CI: 0.45–6.03, *P* for trend=0.030), 6.25% (95% CI: 3.14–9.36, *P* for trend<0.001), 3.01% (95% CI: 1.33–4.69, *P* for trend= 0.003), 3.23% (95% CI: 0.18–6.27, *P* for trend=0.030), and 5.01% (95% CI: 2.42–7.61, *P* for trend<0.001), respectively. Meanwhile, significant non-linear relationships were supported by the RCS models. However, the weighted linear regression and RCS models did not reveal any clear correlations between isoflavone or flavan-3-ol intake and the LE8 score. Regarding mixed effects, anthocyanidin, flavonol, flavanone, and flavone intake were positively related to the LE8 score according to both the WQS and qgcomp models, and anthocyanidin intake was the major contributor.

Conclusion: Our study indicated that dietary flavonoid intake is positively associated with cardiovascular health in cancer survivors, among which anthocyanidin intake might provide the most benefit.

Keywords: weighted quantile sum, life's essential 8 score, restricted cubic spline, NHANES

Introduction

The population of cancer survivors is growing due to advances in early detection and treatment.[1] Cardiovascular disease (CVD) has emerged as a major cause of mortality in this population, with the risk of developing concurrent CVD being significantly greater than that in the general population.[2–4] The increased risk of developing CVD in cancer survivors might be associated with the side effects of cancer treatments and overlapping risk factors for cancer and CVD.[5,6] Consequently, the implementation of preventive measures aimed at enhancing cardiovascular health (CVH) in cancer survivors and addressing cancer treatment-related cardiotoxicity is critical for reducing CVD prevalence and alleviating CVD-related adverse outcomes.

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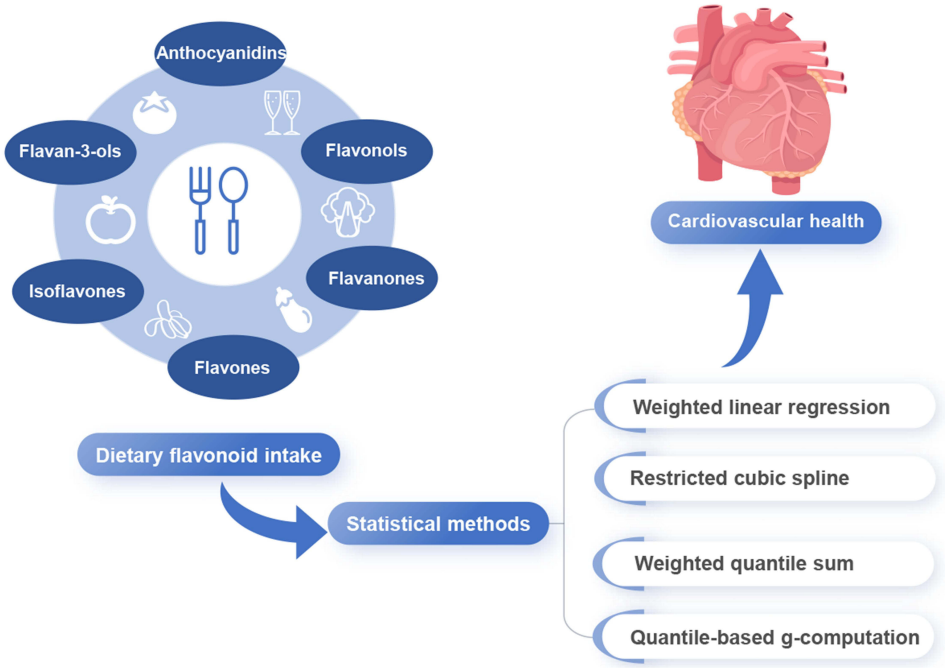
Graphical Abstract



Dietary interventions have demonstrated efficacy in preventing various diseases. Flavonoids, a class of natural polyphenols abundant in numerous plant-based foods, possess multiple beneficial antioxidant, anti-inflammatory, lipid metabolism, and cell protection properties that can alleviate or ameliorate a range of diseases. For example, studies revealed that flavonoids have neuroprotective effects and might reduce the risk of developing Alzheimer's disease, and a higher intake of dietary flavonoids was also related to lower odds of frailty onset in Oei S' study.[7–9] Furthermore, flavonoids have also been confirmed to increase the success of CVD treatment.[10–12] Recent studies have further hinted at flavonoids' protective influence on CVD by inhibiting lipid metabolism and regulating enzymes and transcription factors involved in inflammatory responses to suppress inflammation.[13,14]

Previous studies have highlighted the potential advantages of flavonoids for CVD and other diseases. However, these studies often focused on specific components and conditions and lacked comprehensive cross-sectional analyses in sizable populations, particularly among cancer survivors. Additionally, the American Heart Association (AHA) recently updated the Life's Essential 8 (LE8) score, which is used as a measure for quantifying CVH.[15,16] Therefore, the purpose of this study was to evaluate the associations between dietary flavonoid and flavonoid subclass intake and the LE8 score in cancer survivors using data from the National Health and Nutrition Examination Survey (NHANES).

Materials and Methods

Observational Research Design and Data Sources

The NHANES is a series of cross-sectional surveys designed to assess the health and nutritional status of the US population using a multistage stratified sampling method, which was carried out by the National Center for Health Statistics (NCHS). All survey data were approved by the NCHS Ethical Review Board (available on the website: https://www.cdc.gov/nchs/nhanes/). Given that dietary flavonoid data in the NHANES database is publicly available only for the 2007–2008, 2009–2010, and 2017–2018 cycles, only these three cycles were included in this study, comprising a total of 29,940 participants.[17] We excluded 12,238 participants for missing cancer survivor information, 15,918 non-cancer participants, 529 with missing LE8 score related data, 1 with missing education level, 154 lacking alcohol consumption

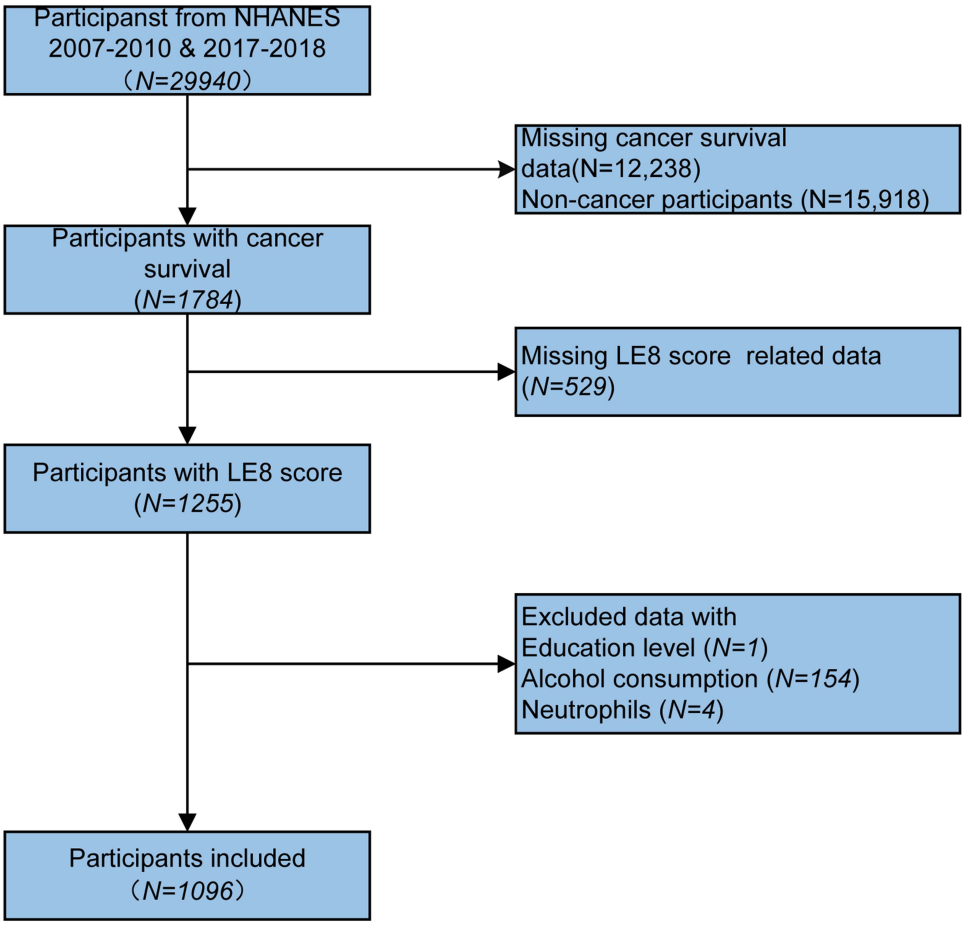


Figure 1 Flowchart of the NHANES database study.

data, and 4 with missing neutrophil (NEUT) data. Ultimately, 1096 participants were included in subsequent analyses. The details of the inclusion and exclusion process are displayed in Figure 1.

Quantification of CVH

CVH was quantified by the LE8 score, which is derived from 8 components: diet, tobacco/nicotine exposure, physical activity, sleep duration, BMI, non-high-density lipoprotein (HDL) cholesterol, blood pressure, and blood glucose.[18] Among them, dietary indicators were measured based on participants' 24-hour dietary recall and assessed using the Healthy Eating Index 2015 (HEI-2015).[19,20] In addition, self-report questionnaires were used to gather data on physical activity levels, smoking habits, sleep patterns, history of diabetes, and medication usage. Additionally, physical examinations were administered to measure participants' weight, height, and blood pressure, while blood samples were analyzed to assess blood lipids, glucose levels, and glycosylated hemoglobin. The score range of each CVH indicator is from 0 to 100 points, and the LE8 score is the average of the eight indicator scores (also ranging from 0 to 100).[21] Participants with LE8 scores were divided into 3 groups according to the recommendations of the American Heart Association: high (LE8 $\geq$ 80), medium (50 $\leq$ LE8 $<$ 80), and low (LE8 $<$ 50).[15,22]

Assessment of Dietary Flavonoid Intake

In the dietary intake interview section of the NHANES, we gathered dietary data from a two-day recall. Then, dietary flavonoid intake was estimated by computing the flavonoid content of each food product utilizing a comprehensive flavonoid database. The comprehensive flavonoid database used in this study was sourced from the USDA's Food and Nutrient Database for Dietary Studies (FNDDS), linked with NHANES data spanning the years 2007–2008, 2009–2010, and 2017–2018. As

shown in Table S1, this database encompasses a total of 29 flavonoids categorized into six main groups: anthocyanins, flavonols, flavanones, flavones, isoflavones, and flavan-3-ols. Consistent with methodologies employed in similar research, in this study, we defined total flavonoid intake as the aggregate of the means of these six flavonoid subclasses. Since 39.6% of individuals had zero intake of isoflavones, those with no isoflavone consumption were assigned to the first group, while the remaining individuals were divided into three equal groups. In contrast, with less than 33.3% of individuals reporting zero intake of total flavonoids, anthocyanidins, flavonols, flavanones, flavones, and flavan-3-ols, participants were grouped into quartiles, with cutoff values for each group provided in Table S2.

Assessment of Covariates

The demographic characteristics included age, race (Hispanic, non-Hispanic white, non-Hispanic black, other race), gender, and education level. First, the participants were divided into BMI categories: obesity (BMI $\geq$ 30.0 kg/m^2), overweight (30>BMI $\geq$ 25 kg/m^2) and normal weight or underweight (BMI < 25 kg/m^2).[23] Moreover, smoking status was categorized as never, former, or now, while alcohol consumption status included never, former, mild, moderate, or heavy drinkers.[24] Next, participants' educational backgrounds were assessed to ascertain their education levels, which were classified into three groups: less than high school, high school, and more than high school. A self-reported history of hypertension, the use of antihypertensive drugs, a mean systolic blood pressure of at least 140 mmHg and/or a mean diastolic blood pressure of at least 90 mmHg were all considered indicators of hypertension. Finally, we evaluated diabetes and hyperlipidemia based on self-reported information from the survey and criteria established in previous literature.[25]

Statistical Analysis

The intricate survey design of the NHANES was considered using the programs SDMVPSU and SDMVSTRA, while WTDR2D was utilized to provide weights for all the data to generate nationally representative estimates. Participant characteristics are presented as categorical variables, and characteristics among the three groups were compared using weighted chi-square tests. Subsequently, we analyzed the relationship between dietary flavonoid intake and the LE8 score through weighted linear regression. Moreover, restricted cubic spline (RCS) plot was generated with the R package "rms" to determine the corresponding dose–response relationship between dietary flavonoid intake and the LE8 score. We also implemented the weighted quantile sum (WQS) regression model to evaluate the mixed effects of six flavonoid subclasses and judge the dominant flavonoid types by calculating the WQS index. The WQS index ranged from 0 to 1 to assess the overall effect of exposure and the contribution of each ingredient in the mixture to the overall effect. However, WQS regression assumes by default that all exposure variables are associated with outcomes in the same direction (either positive or negative), so the quantile-based g-computation (qgcomp) model was further adopted for supplemental analysis. Unlike WQS, if directional homogeneity is not maintained, qgcomp will readjust the weights to either negative or positive, ensuring that the sums of the negative and positive weights are both equal to 1. Additionally, the R package "mediation" was used to investigate the mediating effects of BMI and neutrophil count on the association between dietary anthocyanin intake and the LE8 score. R software (version 4.3.1) was used for all the data analyses. P value < 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

As presented in Table 1, we included a total of 1096 participants, including 163 participants in the low-LE8-score group, 783 participants in the middle-LE8-score group, and 150 participants in the high-LE8-score group. Significant differences were observed among the three groups in terms of age, race, education, smoking status, BMI, diabetes, hypertension, total flavonoid intake, anthocyanidin intake, flavanone intake, flavone intake, isoflavone intake, and flavan-3-ol intake (P < 0.05).

Table 1 Characteristics of Participants in the NHANES 2007–2008, 2009–2010, and 2017–2018 Cycles Among Three Different Groups Classified by LE8 Score

Variable	LE8			*P*-value
	Low group (n=163)	Medium group (n=783)	High group (n=150)	
Age (years)				< 0.001
< 60	39(32.40)	201(34.92)	56(54.82)	
≥ 60	124(67.60)	582(65.08)	94(45.18)	
Gender				0.187
Female	94(59.50)	389(54.01)	88(65.33)	
Male	69(40.50)	394(45.99)	62(34.67)	
Race				0.002
Non-Hispanic Black	30(10.09)	98(5.34)	9(2.03)	
Non-Hispanic White	113(81.37)	552(85.28)	123(93.36)	
Other Hispanic	8(1.31)	47(3.36)	7(1.71)	
Other races	7(6.03)	26(3.09)	5(1.85)	
Mexican American	5(1.21)	60(2.94)	6(1.06)	
Education				< 0.001
Less than high school	66(32.96)	149(10.37)	14(7.02)	
High school	36(20.39)	195(23.86)	27(10.22)	
More than high school	61(46.64)	439(65.77)	109(82.76)	
Smoking Status				< 0.001
Never	49(29.67)	360(42.80)	103(75.81)	
Former	58(35.73)	322(42.50)	43(22.55)	
Now	56(34.61)	101(14.70)	4(1.64)	
Alcohol consumption				0.143
Never	22(14.00)	105(9.47)	18(12.24)	
Former	53(24.68)	151(16.24)	16(9.66)	
Mild	53(41.04)	368(47.10)	79(46.31)	
Moderate	20(11.35)	86(14.37)	25(22.15)	
Heavy	15(8.94)	73(12.82)	12(9.64)	
BMI				< 0.001
Underweight/Normal	17(8.85)	187(21.81)	80(54.46)	
Overweight	32(18.58)	292(36.24)	60(40.27)	
Obesity	114(72.57)	304(41.95)	10(5.28)	
Hypertension				< 0.001
Yes	131(80.73)	521(60.56)	40(15.45)	
No	32(19.27)	262(39.44)	110(84.55)	
Diabetes				< 0.001
Yes	80(45.27)	197(23.45)	8(6.92)	
No	67(44.71)	503(65.43)	138(91.29)	
Prediabetes	16(10.02)	83(11.12)	4(1.79)	
Hyperlipidaemia				< 0.001
Yes	149(95.32)	665(85.13)	95(58.73)	
No	14(4.68)	118(14.87)	55(41.27)	
Anthocyanidins				< 0.001
Q1	73(39.57)	194(25.06)	9(4.19)	
Q2	43(29.42)	202(22.68)	28(16.15)	
Q3	38(24.09)	190(23.62)	45(32.48)	
Q4	9(6.91)	197(28.65)	68(47.18)	

(*Continued*)

Table 1 (Continued).

Variable	LE8			*P*-value
	Low group (n=163)	Medium group (n=783)	High group (n=150)	
Flavonols				0.247
Q1	60(27.81)	196(21.33)	18(14.72)	
Q2	41(26.83)	201(25.55)	32(17.68)	
Q3	29(21.91)	193(25.41)	52(34.07)	
Q4	33(23.46)	193(27.70)	48(33.53)	
Flavanones				0.042
Q1	68(39.52)	187(22.77)	20(14.58)	
Q2	37(18.03)	201(27.69)	35(25.50)	
Q3	29(19.75)	205(25.79)	40(25.77)	
Q4	29(22.69)	190(23.75)	55(34.15)	
Flavones				0.030
Q1	62(29.89)	191(23.67)	24(15.76)	
Q2	43(26.17)	202(23.78)	27(14.44)	
Q3	32(23.60)	196(24.11)	45(24.76)	
Q4	26(20.33)	194(28.44)	54(45.03)	
Isoflavones				0.011
Q1	79(50.01)	317(38.68)	38(22.15)	
Q2	30(13.19)	164(21.42)	33(19.67)	
Q3	28(22.87)	154(19.40)	32(24.17)	
Q4	26(13.94)	148(20.50)	47(34.01)	
Flavan-3-ols				< 0.001
Q1	64(37.25)	199(24.44)	11(5.18)	
Q2	35(21.06)	189(19.91)	50(31.17)	
Q3	31(20.27)	188(23.53)	55(37.21)	
Q4	33(21.43)	207(32.12)	34(26.44)	
Total flavonoids				< 0.001
Q1	74(38.99)	188(23.03)	12(8.26)	
Q2	34(23.63)	199(22.81)	41(21.32)	
Q3	24(18.66)	189(22.23)	61(43.14)	
Q4	31(18.72)	207(31.93)	36(27.29)	

Weighted Linear Regression of Dietary Flavonoid Intake and the LE8 Score

We analyzed the relationship between dietary flavonoid intake and the LE8 score through weighted linear regression, as illustrated in Table 2. After adjusting for age, race, gender, education, BMI, smoking status, alcohol consumption, hyperlipidemia, diabetes, and hypertension, total flavonoid intake (*P* for trend = 0.030), anthocyanidin intake (*P* for trend < 0.001), flavonol intake (*P* for trend= 0.003), flavanone intake (*P* for trend = 0.030), and flavone intake (*P* for trend<0.001) were all positively correlated with the LE8 score. Moreover, compared to those in the first quartile, participants in the fourth quartile of total flavonoids, anthocyanidins, flavonols, flavanones, and flavones intake exhibited increases in LE8 scores of 3.24% (95% CI: 0.45–6.03), 6.25% (95% CI: 3.14–9.36), 3.01% (95% CI: 1.33–4.69), 3.23% (95% CI: 0.18–6.27), and 5.01% (95% CI: 2.42–7.61), respectively. However, isoflavone intake (*P* for trend = 0.250) and flavan-3-ol intake (*P* for trend = 0.180) were not significantly correlated with the LE8 score.

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Figure 2 illustrates that total flavonoid intake (*P* for nonlinearity < 0.001), anthocyanidin intake (*P* for nonlinearity < 0.001), flavonol intake (*P* for nonlinearity < 0.001), flavanone intake (*P* for nonlinearity = 0.005), and flavone intake (*P* for nonlinearity < 0.001) had significant dose-response relationships (nonlinear relationships) with the LE8 score, suggesting

Table 2 Weighted Line Regression Analysis of the Association Between Dietary Flavonoid Intake and the LE8 Score

Variable	Q1	Q2	Q3	Q4	*P* for trend
	β (95% CI)				
Anthocyanidins					
Model 1	Ref	5.70(1.47, 9.93)	8.87(5.36,12.38)	13.21(9.88,16.54)	<0.001
Model 2	Ref	5.99(1.91,10.06)	8.78(5.26,12.31)	12.99(9.65,16.34)	<0.001
Model 3	Ref	2.32(−0.18, 4.82)	4.51(1.89, 7.14)	6.25(3.14, 9.36)	<0.001
Flavonols					
Model 1	Ref	1.90(−2.31,6.11)	4.22(0.23,8.20)	4.95(0.72,9.19)	0.010
Model 2	Ref	2.42(−1.34, 6.18)	4.63(1.21, 8.06)	4.91(0.96, 8.86)	0.010
Model 3	Ref	1.95(0.22, 3.69)	3.67(1.76, 5.58)	3.01(1.33, 4.69)	0.003
Flavanones					
Model 1	Ref	4.99(1.90,8.08)	4.65(0.83,8.47)	6.15(2.60,9.70)	0.002
Model 2	Ref	4.96(1.99, 7.93)	4.35(0.70, 8.00)	6.15(2.61, 9.70)	0.002
Model 3	Ref	0.93(−1.66, 3.53)	1.34(−1.81, 4.50)	3.23(0.18, 6.27)	0.030
Flavones					
Model 1	Ref	3.35(−0.89, 7.58)	7.67(3.74,11.59)	8.47(4.65,12.28)	<0.001
Model 2	Ref	3.03(−1.39, 7.44)	7.39(3.71,11.06)	7.91(4.20,11.61)	<0.001
Model 3	Ref	1.43(−1.25, 4.10)	3.04(0.46, 5.63)	5.01(2.42, 7.61)	<0.001
Isoflavones					
Model 1	Ref	4.53(1.81, 7.25)	4.30(1.04, 7.56)	7.79(4.47,11.11)	<0.001
Model 2	Ref	4.81(2.11, 7.50)	4.30(1.04, 7.57)	7.14(4.34, 9.94)	<0.001
Model 3	Ref	1.37(−0.60, 3.35)	2.89(0.52, 5.26)	1.47(−0.95, 3.88)	0.250
Flavan-3-ols					
Model 1	Ref	7.77(4.69,10.85)	8.97(6.12,11.82)	6.49(2.89,10.09)	<0.001
Model 2	Ref	7.57(4.61,10.52)	8.95(5.88,12.02)	6.22(2.83, 9.61)	<0.001
Model 3	Ref	2.12(−0.64, 4.87)	2.01(−1.09, 5.12)	1.87(−0.58, 4.32)	0.180
Total flavonoids					
Model 1	Ref	7.25(2.60,11.91)	9.72(6.36,13.08)	7.26(3.13,11.40)	<0.001
Model 2	Ref	7.29(2.62,11.97)	9.83(6.23,13.43)	7.04(3.14,10.93)	<0.001
Model 3	Ref	3.41(0.69, 6.13)	4.45(1.03, 7.87)	3.24(0.45, 6.03)	0.030

Notes: Model 1: unadjusted model; Model 2: adjusted for age, gender, and race; Model 3: adjusted for age, gender, race, smoking status, alcohol consumption, education, BMI, diabetes, hypertension, and hyperlipidemia.

that the effects of flavonoids and these flavonoid subclasses on the LE8 score vary across different intake levels. In contrast, no dose-response relationships were found between the LE8 score and isoflavone intake (*P* for nonlinearity=0.257) or flavan-3-ol intake (*P* for nonlinearity = 0.123).

WQS and qgcomp Analysis

We explored the mixed effects of six flavonoid subclasses on LE8 scores through WQS and qgcomp models. The results suggested that the WQS index was positively associated with an increase in the LE8 score (β=3.09, 95% CI: (2.09–4.09), $P < 0.001$). Figure 3 shows that anthocyanins accounted for 60.2% of the mixed effects, followed by flavonols (14.8%) and flavanones (10.3%).

The qgcomp analysis results were consistent with those of the WQS model. As shown in Figure 4, qgcomp can detect both positive and negative weights for each flavonoid. Anthocyanidin intake (47.69%), flavonols intake (16.01%), flavanone intake (15.84%), flavone intake (15.03%), and isoflavone intake (5.42%) had positive weights, while flavan-3-ol intake had negative weight (100%).

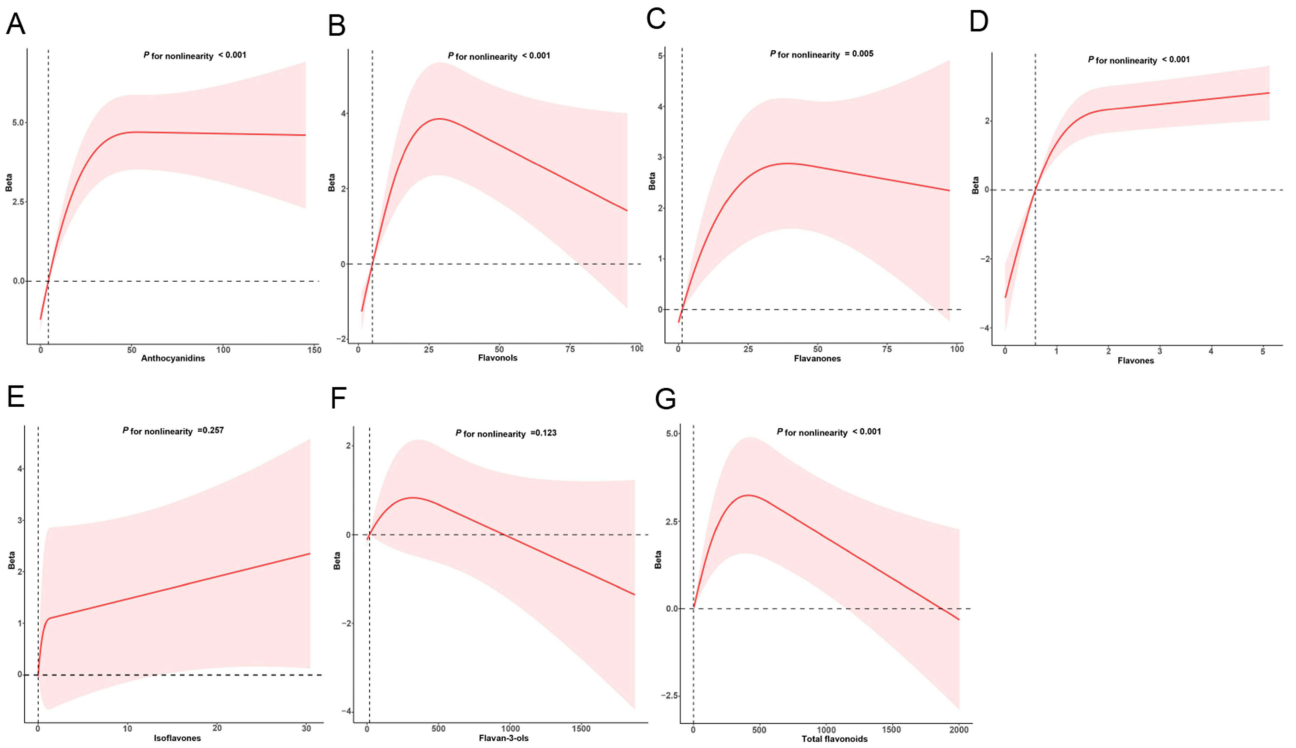

Figure 2 Restricted cubic spline model of the associations between the LE8 score and the intakes of different flavonoid subclasses: (**A**) anthocyanidins; (**B**) flavonols; (**C**) flavanones; (**D**) flavones; (**E**) isoflavones; (**F**) flavan-3-ols and (**G**) total flavonoids. All variables were adjusted for age, gender, race, education, BMI, smoking status, alcohol consumption, hypertension, diabetes, and hyperlipidemia.

Stratified Analysis

Tables S3–S5 show that there were no significant differences in the associations between dietary flavonoid intake and the LE8 score in the different age, gender, and race subgroups when the subgroups were stratified by age (< 60 and ≥ 60), gender (male and female), or race (non-Hispanic White and other).

Mediation Analysis

Our results revealed that anthocyanins were major contributors to the mixed effects. We further explored whether neutrophil count (NEUT) and BMI mediate the relationship between dietary anthocyanidin intake and the LE8 score in cancer survivors via three pathways. As shown in Figure 5 and Table S6, NEUT and BMI mediated 2.97% and 37.04%, respectively, of the associations between dietary anthocyanidin intake and the LE8 score in cancer survivors.

Discussion

This was the first cross-sectional study in which the association between dietary flavonoid intake and the LE8 score was investigated in a population of cancer survivors utilizing a nationally representative sample. We used four different models to explore single and mixed effects and showed that higher intakes of total flavonoids and their components (anthocyanidins, flavonols, flavanones, and flavones) were positively associated with the LE8 score after we adjusted for covariates, including age, race, gender, education, BMI, smoking status, alcohol consumption, hyperlipidemia, diabetes and hypertension.

Flavonoids are known for their diverse health-promoting properties and occur naturally in a variety of plant-based sources, such as fruits, teas, red wine, and herbs. A sustainable reduction in CVD risk has been observed among individuals with higher flavonoid intake.[26,27] Similarly, in a study on cell and animal models,[28] our team previously demonstrated that flavonoids can effectively inhibit ferroptosis and alleviate doxorubicin-induced cardiotoxicity. Researchers have suggested that the potential of flavonoids to promote heart health relies on their ability to balance

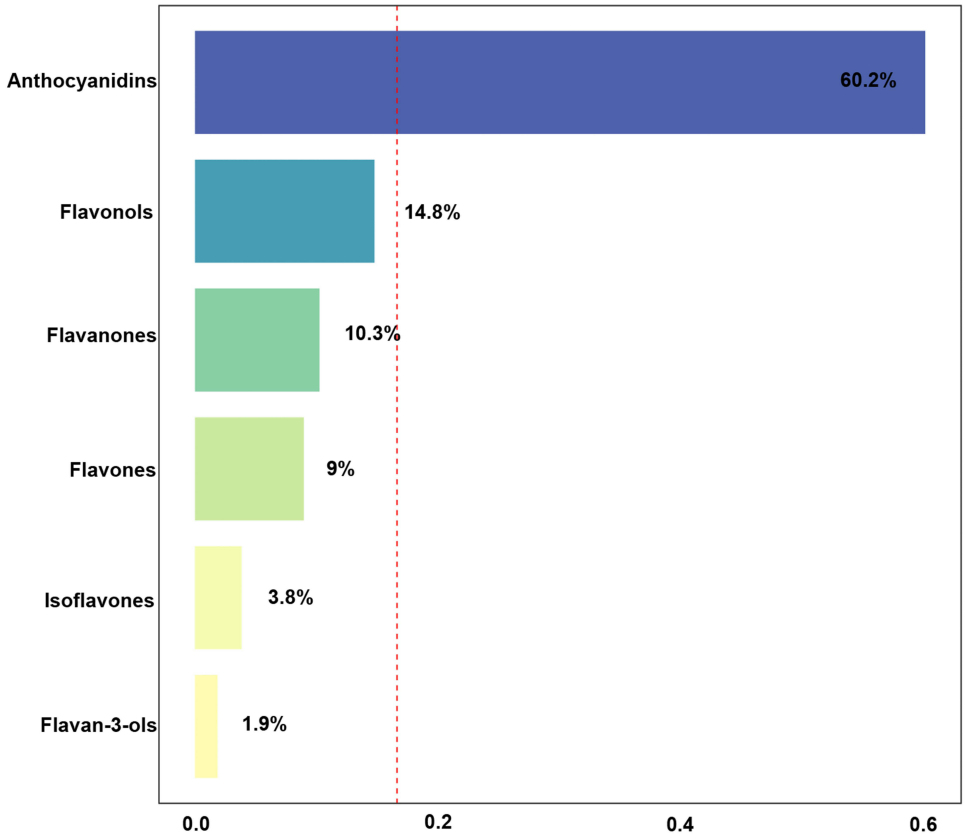

Figure 3 Weighted quantile sum model regression index weights for the LE8 score. The model was adjusted for age, gender, race, education, BMI, smoking status, alcohol consumption, hypertension, diabetes, and hyperlipidemia.

oxidative stress, combat inflammation, and regulate multiple intracellular signaling pathways.[29,30] Flavonoids have been shown to exert cardioprotective effects by inhibiting the synthesis of various proinflammatory mediators, reducing vascular inflammation, scavenging free radicals, reducing oxidative damage, and even regulating the intestinal flora.[31,32] In addition, some evidence has indicated that foods rich in flavonoids or specific flavonoid subclasses might counteract risk factors for CVD by regulating vascular smooth muscle contraction, improving endothelial dysfunction, lowering plasma lipid levels, reducing blood pressure, and ameliorating obesity, thereby enhancing CVH.[33,34]

After evaluating the effects of consuming different subclasses of flavonoids on the LE8 score in cancer survivors, anthocyanidins, flavonols, flavanones, and flavones were also found to have strong cardiovascular protective effects, which is consistent with the results of subsequent WQS and qgcomp analyses. There is strong evidence supporting these results. For instance, Yu LM et al[35] reported that flavanones can improve mitochondrial function and reduce cardiac damage following ischemia-reperfusion injury. Flavones, especially luteolin, protect against diabetic cardiomyopathy by activating antioxidant responses and inhibiting inflammation.[36] Our results were supported by another animal study, in which the heart–gut microbiota axis was shown to be regulated by flavonols, potentially providing cardioprotective benefits.[37] Interestingly, in the present study, the WQS and qgcomp models both indicated that anthocyanidin intake was the major contributor to the effects of mixture exposure, exhibiting the strongest positive correlation with the LE8 score in cancer survivors. Similarly, a British double-blind randomized controlled trial also revealed that consuming blueberries, which have high anthocyanin content, may increase the biomarkers of cardiometabolic function in individuals with metabolic syndrome.[38] We also performed a mediation analysis and found that NEUT and BMI mediated 2.97% and 37.04%, respectively, of the association between dietary anthocyanin intake and the LE8 score in cancer survivors. It is well known that anthocyanins can inhibit the invasion of inflammatory cells and decrease the levels of proinflammatory cytokines.[39] Thus, we believe that the anti-inflammatory properties of anthocyanins might be linked to their ability to

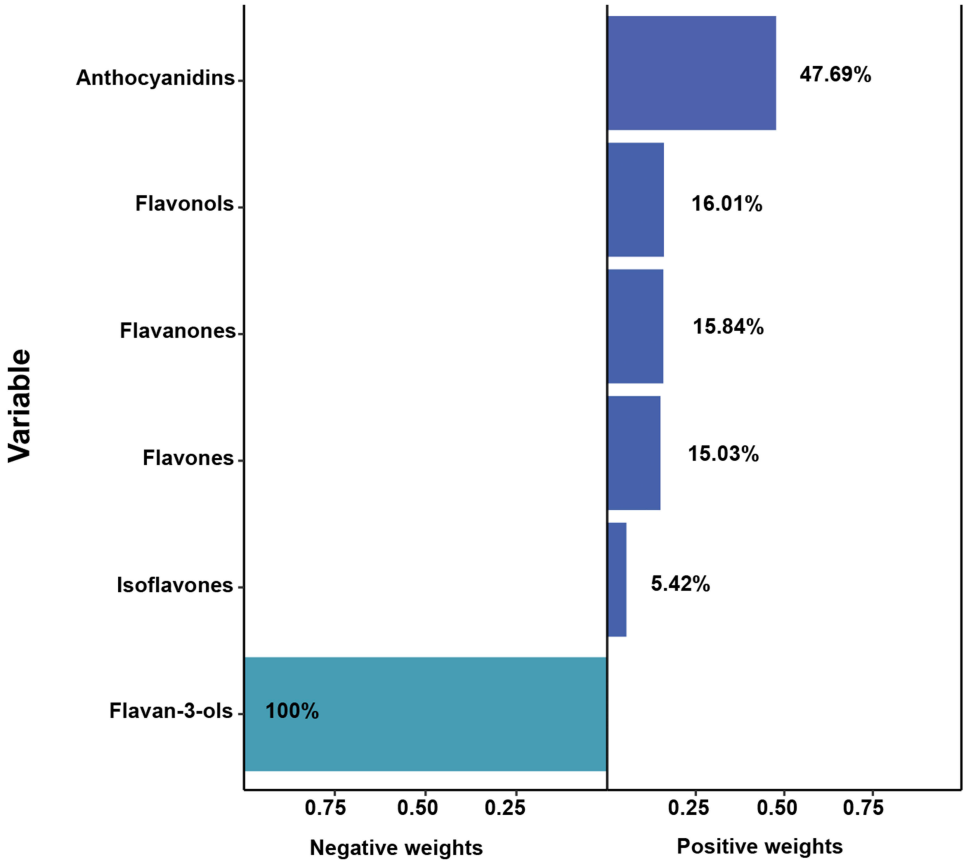

Figure 4 Quantile-based g-computation scaled weights for six flavonoid subclasses in the flavonoid mixture. The model was adjusted for age, gender, race, education, BMI, smoking status, alcohol consumption, hypertension, diabetes, and hyperlipidemia.

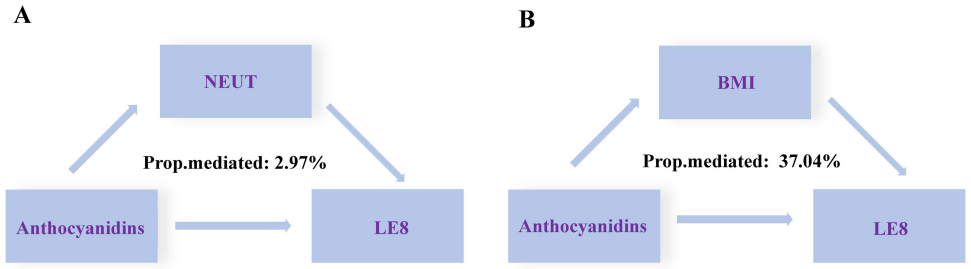

Figure 5 Mediating effects of the NEUT and BMI indicators on the association between dietary anthocyanidin intake and the LE8 score (**A**–**B**). Prop.mediated indicates the proportion of mediated effects (proportion of the total effect due to the mediator).

regulate CVH. Notably, an Australian 6-month double-blind controlled study revealed that anthocyanin intake might reduce BMI in individuals with obesity by regulating fatty acid biosynthesis and lipid metabolism.[40] Moreover, in a cohort study encompassing 37,672 participants, Claes Ohlsson et al[41] also reported that BMI is related to the risk of experiencing cardiovascular death, which is consistent with our finding that BMI is a mediating factor.

Isoflavones and flavan-3-ols are generally thought to be beneficial for treating CVD. Calycosin (a subclass of isoflavones) can reduce myocardial fibrosis in postmyocardial infarction mice and effectively attenuate isoproterenol-induced cardiac dysfunction, while flavan-3-ols can reduce arterial stiffness and improve blood lipid profiles.[42–45] However, no significant correlation was found between dietary isoflavone or flavan-3-ol intake and cancer survivors' LE8 scores according to our results. A possible and sensible interpretation of these results might be that they were caused

by differences in study subjects and sample sizes. Consequently, further large-sample prospective clinical trials may be needed in the future to explore the effects of isoflavone and flavan-3-ol intake on the CVH of cancer survivors.

This study has several advantages compared with previous findings. First, the most recent LE8 score was utilized as the outcome variable to assess the impact of dietary flavonoid intake on CVH in cancer survivors. Moreover, higher dietary flavonoid intake can effectively improve the CVH of cancer survivors, providing a reference for maintaining the CVH of cancer survivors. Finally, this study was based on a large population survey (NHANES) dataset, and four statistical models were simultaneously used to comprehensively explore the association between dietary flavonoid intake and CVH in cancer survivors from different perspectives, which greatly improved the accuracy of the results. Nevertheless, some limitations should be accounted for in this study. First, we used a cross-sectional study design, which cannot be used to determine a clear causative relationship or a temporal correlation between dietary flavonoid intake and CVH in cancer survivors. Second, two 24-hour dietary recalls were used to evaluate dietary patterns in this study. Despite being widely used in nutritional epidemiology studies, this approach might have some flaws. Future studies with more detailed dietary data will be valuable. Third, in our study, we did not account for all covariates that affected the outcome. Ultimately, the study sample comprised solely Americans and did not represent the global population, hence, the results may not be as broadly applicable as they may seem to be.

Conclusion

In summary, our study indicated that dietary flavonoid intake is positively associated with CVH in cancer survivors, among which anthocyanidin intake might play a predominant role. For cancer survivors, the consumption of flavonoid (anthocyanin)-rich foods may be beneficial for CVH.

Data Sharing Statement

Publicly available datasets were analyzed in this study. This data can be found here: www.cdc.gov/nchs/nhanes/.

Ethics Approval and Consent to Participate

The portions of this study involving human participants, human materials, or human data were conducted in accordance with the Declaration of Helsinki and the NCHS Research Ethics Review Committee reviewed and approved the NHANES study protocol. All participants signed written informed consent. Moreover, the study was conducted with approval from the Ethics Committee of Affiliated Nanping First Hospital, Fujian Medical University (NPSY202409024).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

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