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Greater flavonoid intake is associated with improved CVD risk factors in US adults

Kijoon Kim, Terrence M. Vance and Ock K. Chun*

Department of Nutritional Sciences, University of Connecticut, Storrs, CT 06269, USA

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Abstract

Epidemiological studies have reported that diets high in flavonoids are associated with a reduced risk of CVD. However, evidence on the association of dietary flavonoid intake with CVD risk factors is still scarce. The present study aimed to investigate the association of dietary flavonoid intake with CVD risk factors among US adults in the National Health and Nutrition Examination Survey (NHANES) 2007–2012. A total of 4042 US adults aged 19 years and older from the NHANES 2007–2012 participated in this cross-sectional, population-based study. Intakes of total and individual flavonoids were estimated from 2-d 24-h diet recall data by matching with the expanded US Department of Agriculture flavonoid, isoflavone and proanthocyanidin databases. After adjusting for covariates, increased HDL-cholesterol was associated with higher total flavonoid intake (0·54 % change). TAG and TAG:HDL-cholesterol ratio were inversely associated with anthocyanidin (−1·25 % change for TAG; −1·60 % change for TAG:HDL-cholesterol ratio) and total flavonoid intakes (−1·31 % change for TAG; −1·83 % change for TAG:HDL-cholesterol ratio), respectively. Insulin and homoeostasis model assessment for insulin resistance (HOMA-IR) were inversely associated with flavone (for insulin, −3·18 % change; 95 % CI −5·85, −0·44; for HOMA-IR, −3·10 % change; 95 % CI −5·93, −0·19) and isoflavone intakes (for insulin, −3·11 % change; 95 % CI −5·46, −0·70; for HOMA-IR, −4·01 % change; 95 % CI −6·67, −1·27). BMI was negatively associated with anthocyanidin intake (−0·60 % change). This study showed that higher flavonoid intake was associated with improved CVD risk factors. Further research is warranted to confirm the findings from this study as these associations were moderate in strength.

Key words: Flavonoids: Atherogenesis: Blood: Lipids: National Health and Nutrition Examination Survey: CVD

CVD is the leading cause of death worldwide[1]. Abnormal levels of lipids in the blood are risk factors for CVD. High levels of LDL-cholesterol and TAG and low levels of HDL-cholesterol lead to atherosclerosis and stroke, increasing the risk of CVD[2,3]. Metabolic risk factors such as large waist circumference, high blood pressure, high TAG, high fasting blood glucose and low HDL-cholesterol have been used to assess CVD risk[4]. Other risk factors include overweight and obesity, elevated LDL-cholesterol and insulin resistance[5,6].

Diet is a modifiable risk factor for reducing the risk of CVD. Greater consumption of fruits and vegetables is associated with reduced risk of CVD[7], and flavonoids found in these foods may contribute to this risk reduction[8]. Flavonoids are polyphenolic phytochemicals commonly found in fruits, vegetables, herbs and teas[9]. There is evidence that flavonoids may reduce the risk of CVD by inhibiting LDL oxidation[10], reducing endothelial wall damage and preventing atherosclerosis[11,12].

Although dietary flavonoids have been reported to reduce the risk of CVD[13,14], findings from studies on the effects of specific flavonoid compounds or flavonoid-rich foods are still inconsistent[15,16]. Hooper *et al.*[17] provided a comprehensive review of 133 randomised-controlled trials, which confirmed significant heterogeneity by different effects among flavonoid subclasses or foods. Furthermore, there have been no validated investigative tools or flavonoid food composition tables available for estimating flavonoid intake in observational studies. As the US Department of Agriculture (USDA) has released an updated flavonoid database[18–20], several studies have been conducted to estimate flavonoid intake based on this database[21,22]. One study observed an inverse association between intake of anthocyanins and anthocyanin-rich foods and incidence of type 2 diabetes[22,23]. Another study reported that the higher intake of anthocyanins was associated with reduction in risk of hypertension[21]. Several epidemiological studies have focused on flavonoid intake and CVD events or mortality[24–27]. However, studies on the association of flavonoid intake with comprehensive CVD risk factors including blood lipid profile, blood pressure and anthropometric measures are lacking. Therefore, in this study, we aimed to investigate the association of dietary flavonoid intake with CVD risk factors among US adults by utilising the National Health and Nutrition Examination Survey (NHANES) 2007–2012.

Abbreviations: HOMA-IR, homoeostasis model assessment for insulin resistance; NHANES, National Health and Nutrition Examination Survey; USDA, US Department of Agriculture.

* **Corresponding author:** O. K. Chun, fax +1 860 486 3674, email ock.chun@uconn.edu

Methods

Study population

This study utilised data from 4042 US adults aged 19 years and older from the NHANES 2007–2012[28–30]. Exclusion criteria included the following: subjects who reported fasting for <8 h (*n* 9859), pregnant or breast-feeding women (*n* 112), those with dietary recalls coded as unreliable or incomplete (*n* 1086), those whose dietary recalls were coded as 'much more than usual' or 'much less than usual' or those who answered yes to 'Are you currently on any kind of diet, either to lose weight or for some other health-related reason?', because these might affect biomarkers of interest (*n* 2256).

Estimation of dietary flavonoid intake

This study used databases on flavonoid, isoflavone and proanthocyanidin contents of US foods: the USDA Database for the Flavonoid Content of Selected Foods, version 3.1[18], containing values for 506 food items of twenty-six dietary flavonoid compounds classified by flavonoid subclasses such as flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins; the USDA Database for the Isoflavone Content of Selected Foods, version 2.0[19], containing values for individual isoflavone compounds for 557 foods; and the USDA Database for the Proanthocyanidin Content of Selected Foods, containing values for proanthocyanidins for 205 food items[20]. These three databases were combined to a single database: flavonols (isorhamnetin, kaempferol, myricetin, quercetin), flavones (apigenin, luteolin), flavanones (eriodictyol, hesperetin, naringenin), flavan-3-ols (flavan-3-ol monomers ((+)-catechin, (+)-gallocatechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin 3-gallate, (−)-epigallocatechin 3-gallate); flavan-3-ol derived compounds (theaflavin, theaflavin-3-gallate, theaflavin 3′-gallate, theaflavin 3,3′-digallate, thearubigins); proanthocyanidins (dimers, trimers, 4-6mers, 7-10mers and polymers)), anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin) and isoflavones (daidzein, genistein, glycitein). Flavan-3-ols intake was estimated by summing three subclasses of flavan-3-ol monomers, flavan-3-ol derived compounds and proanthocyanidins (dimer to polymers). As the analytical values were available for cooked or processed foods in the USDA flavonoid database, retention factors for processed or cooked foods based on the Phenol-Explorer database were applied only for expansion process of the flavonoid database[31]. The flavonoid contents in USDA databases are expressed as aglycone. The flavonoid and isoflavone databases were expanded to include additional foods as described in other publications[32]. This significantly improved the coverage of the flavonoid database by increasing the proportion of major food sources having flavonoid composition data from 36 to 67 %[33]. Average daily food intake was calculated from 2-d 24-h dietary recall data in the NHANES 2007–2012. Dietary flavonoid intake was estimated by combining the flavonoid, isoflavone and proanthocyanidin databases with the food consumption data of the NHANES 2007–2012. Total flavonoid intake was determined by summing the daily intake of individual flavonoid compounds.

CVD risk factors

Waist circumference, height, weight and blood pressure were measured in the mobile examination centre[34]. BMI values were calculated using measured height and weight values (kg/m^2). Serum total cholesterol (TC), HDL-cholesterol, TAG, fasting plasma glucose and insulin were measured as described in the NHANES Laboratory Procedures Manual[34]. LDL-cholesterol was calculated by the following equation: $LDL = TC - HDL - 0{\cdot}2 \times TAG$[34]. Homoeostasis model assessment for insulin resistance (HOMA-IR) is a method used to quantify insulin resistance and was calculated as (fasting serum glucose (mg/dl) × insulin (μU/ml))/405[35]. High ratios of TAG:HDL-cholesterol and TC:HDL-cholesterol have been reported as better predictors of CVD risk than changes in their absolute levels[36,37].

Statistical analysis

All the statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc.), using SAS survey procedures and the appropriate weight, strata, domain and cluster variables to account for the complex survey design. Dietary flavonoids were log-transformed and adjusted for average energy intake using the residual method[38].

Participants were grouped into quartiles based on flavonoid intake, and the means of CVD risk factors and proportion of subjects by socio-demographic and lifestyle variables were calculated across quartiles of flavonoid intake. For descriptive statistics, poverty income ratio (PIR) was classified as ≤1·3 and >1·3. Physical activity was expressed as metabolic equivalence of tasks (MET) based on weekly minutes of walking/bicycling and moderate/vigorous recreational activities by multiplying the number of days per week by the average minutes of activities on a typical day[39]. MET-min/week were determined by multiplying weekly minutes of activities by the assigned MET values. Subjects who reported no walking/bicycling or moderate/vigorous recreational activities were defined as inactive. Alcohol consumption was defined based on the number of drinks of any type of alcoholic beverage per day, with consumption of no drinks as none, no more than 2 drinks/d for men and no more than 1 drink/d for women as moderate and more than two drinks for men and more than one drink for women as high intake[40]. Positive smoking status was defined as smoking 100 cigarettes/year, with current smokers defined as those who had not quit and former smokers as those who had reported quitting by the time of the interview.

In regression models, after inspecting residual plots, all CVD risk factors were log-transformed. A simplified representation of the model for a given CVD risk factor and flavonoid can be described by the following regression equation:

$$\log_e(\text{CVD risk factor}) = \beta_0 + \log_e \text{flavonoid}\,\beta_1.$$

As the model was fit with both the predictor and the outcome on the logarithmic scale, the slope from the regression model above was used to calculate the % change in CVD risk factor for a 100 % increase in flavonoid intake (the choice of percentage is arbitrary):

$$\%\ \text{Change in CVD risk factor} = (2^{\beta_1} - 1) \times 100.$$

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To determine both statistical significance and precision, the 95 % CI of the % change determined above was calculated using the standard error of β_1 (95 % CI = % change $\pm (2^{1.96 \times SE_{\beta_1}} - 1)$). Multivariate models were adjusted for the following variables: age, sex, ethnicity, PIR, alcohol consumption, smoking status, physical activity, educational level, BMI, SFA, fibre and vitamin C intakes, and blood pressure medication and insulin use. A multivariate model of BMI was adjusted for all variables except BMI. All *P*-values reported are two sided ($\alpha = 0{\cdot}05$).

Results

The socio-demographic and lifestyle characteristics of study participants by quartiles of total flavonoid intake from the NHANES 2007–2012 are shown in Table 1. Age, PIR and education level were positively associated and smoking status was inversely associated with total flavonoid intake. Women in the lowest quartile of flavonoid intake had higher waist circumference. Subjects in the lowest quartile of flavonoid intake

Table 1. Socio-demographic and lifestyle characteristics by quartiles of total dietary flavonoid intake among US adults in the NHANES 2007–2012 (Ranges and mean; numbers and percentages; *n* 4042)

			Quartiles (Q) of total flavonoid intake (mg/d)							
			Q1 (*n* 978)		Q2 (*n* 1003)		Q3 (*n* 1035)		Q4 (*n* 1026)	
			Range	Mean	Range	Mean	Range	Mean	Range	Mean
	Total		0–55·0	12·5	15·9–197·8	59·0	50·5–549·0	197·6	167·7–7990·2	585·5
Intake	*n*	%*	*n*	%*	*n*	%*	*n*	%*	*n*	%*
Sex										
Men	2072	50·8	539	55·0	531	53·2	490	48·7	512	46·9
Women	1970	49·2	439	45·0	472	46·8	545	51·3	514	53·1
Age (years)										
19–30	775	20·2	236	25·4	210	23·0	184	18·5	145	14·7
31–50	1335	37·7	345	40·6	322	37·9	328	33·9	340	38·4
51–70	1268	30·9	264	25·6	298	26·9	336	34·6	370	35·9
70+	664	11·1	133	8·4	173	12·2	187	13·0	171	11·0
Ethnicity										
White	2019	72·8	526	74·7	457	70·0	468	68·8	568	76·9
Black	664	9·0	187	10·3	190	10·4	167	9·5	120	6·2
Mexican-American	623	7·6	110	6·2	158	7·8	208	10·4	147	6·0
Others	736	10·6	155	8·8	198	11·8	192	11·3	191	10·9
PIR										
≤1·3	1162	20·7	330	26·2	284	19·8	282	19·8	266	17·2
>1·3	2544	79·3	577	73·8	613	80·2	668	80·2	686	82·8
Alcohol consumption†										
None	1488	30·5	390	36·1	380	29·8	356	26·9	362	29·2
Moderate	1309	36·6	271	28·1	294	33·4	381	45·1	363	39·4
High	1245	32·9	317	35·8	329	36·8	298	28·0	301	31·4
Current smoking‡										
Never	2183	58·1	451	52·6	557	61·5	612	59·6	563	58·9
Former	1014	26·0	232	24·4	225	23·2	263	27·8	294	28·2
Current	615	15·9	217	23·0	155	15·3	109	12·6	134	12·9
Physical acitivity§										
Inactive	1572	35·4	444	43·8	371	32·5	377	31·3	380	34·0
<500 MET-min/week	506	12·5	133	14·0	124	12·8	120	12·2	129	11·2
≥500 MET-min/week	1962	52·0	400	42·2	508	54·7	538	56·5	516	54·8
Education										
Less than high school	995	15·9	263	20·3	259	15·4	254	14·6	219	13·5
High school equivalent	929	22·5	278	28·2	213	20·5	208	19·1	230	21·8
College or higher	2112	61·6	436	51·5	530	64·1	571	66·3	575	64·7
Blood pressure medication‖										
Yes	1314	29·1	311	27·6	302	26·3	356	31·1	345	31·1
No	2728	70·9	667	72·4	701	73·7	679	68·9	681	68·9
Insulin use¶										
Yes	257	4·5	64	5·9	66	4·3	56	3·0	71	4·8
No	3785	95·5	914	94·1	937	95·7	979	97·0	955	95·2

PIR, poverty income ratio; MET, metabolic equivalence of task.
* Percentage is weighted percentage considering the complex sampling design in the National Health and Nutrition Examination Survey.
† Alcohol consumption: no consumption of any type of alcoholic beverage per day was defined as none, no more than two drinks for men and no more than one drink for women as moderate and more than two drinks for men and more than one drink for women as high intake.
‡ Current smoking: former meant to have smoked at least 100 cigarettes in their entire life but do not smoke cigarettes now. Current meant to have smoked at least 100 cigarettes in their entire life and still smoke.
§ Physical activity: inactive meant not walking/bicycling or performing moderate/vigorous recreational activities for at least 10 min continuously in a typical week.
‖ Blood pressure medication: yes meant taking prescribed medicine for high blood pressure.
¶ Insulin use: yes meant taking insulin or medication to control blood glucose levels.

Table 2. CVD risk factors according to the quartile (Q) of dietary flavonoid intake among US adults in the National Health and Nutrition Examination Survey (NHANES) 2007–2012
(Ranges and mean; mean values with their standard errors; *n* 4042)

	Q1 (*n* 978)		Q2 (*n* 1003)		Q3 (*n* 1035)		Q4 (*n* 1026)		
	Range	Mean	Range	Mean	Range	Mean	Range	Mean	
	0–55·0	12·5	15·9–197·8	59·0	50·5–549·0	197·6	167·7–7990·2	585·5	
Intake	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	$P_{for\ trend}$*
Waist circumference (cm)									
Men	102·3	0·9	98·8	0·8	100·8	1·0	102·1	0·9	0·38
Women	96·3	1·0	92·8	1·1	93·2	1·0	94·7	0·9	0·73
BMI (kg/m^2)	29·1	0·3	27·7	0·3	27·8	0·3	28·5	0·3	0·60
TAG (mg/dl)	138·8	4·3	132·1	4·3	125·0	4·0	123·9	3·4	<0·05
HDL-cholesterol (mg/dl)									
Men	46·0	0·5	49·0	0·6	50·8	0·7	49·0	1·0	0·27
Women	56·1	0·8	59·3	0·9	60·6	0·8	60·0	0·8	0·28
Blood pressure (mmHg)									
Systolic	119·3	0·7	119·1	1·0	120·7	0·7	119·5	0·6	0·95
Diastolic	69·7	0·6	68·6	0·8	68·8	0·5	69·2	0·5	0·61
Fasting glucose (mg/dl)	106·2	1·1	102·4	0·8	103·0	0·7	103·8	0·9	0·76
Insulin (pmol/l)	82·7	2·5	70·4	2·7	72·2	2·1	78·8	3·9	0·63
TC (mg/dl)	193·3	1·9	195·4	1·9	197·7	2·0	197·7	1·8	0·61
LDL-cholesterol (mg/dl)	115·6	1·5	115·7	1·6	117·3	1·7	118·5	1·6	0·38
TAG:HDL-cholesterol ratio	3·2	0·1	3·0	0·2	2·7	0·1	2·7	0·1	<0·05
TC:HDL-cholesterol ratio	4·1	0·1	3·9	0·1	3·8	0·0	3·9	0·1	0·23
HOMA-IR	3·9	0·2	3·1	0·1	3·2	0·1	3·5	0·2	0·75

TC, total cholesterol; HOMA-IR, homoeostasis model assessment for insulin resistance.
* Test for linearity of the trend was carried out after adjusting for age, sex, ethnicity, physical activity, poverty income ratio, smoking status, alcohol consumption, education level, BMI, blood pressure medication and insulin use, and vitamin C, SFA and fibre intakes (model of BMI was adjusted for all variables except BMI).

had higher fasting glucose, insulin and HOMA-IR and lower HDL-cholesterol than those in the higher quartile of flavonoid intake (Table 2). Subjects with higher flavonoid intake had lower TAG:HDL-cholesterol ratio and TAG levels than those with lower flavonoid intake.

Serum TAG and TAG:HDL-cholesterol ratio were inversely associated with total dietary flavonoids after adjusting for age, sex, ethnicity, physical activity, PIR, smoking status, alcohol consumption, education level, BMI, SFA, fibre and vitamin C intakes, and blood pressure medication and insulin use (Table 3). The % changes in TAG for a 100 % increase in anthocyanidins and total flavonoid intakes were −1·25 % (95 % CI −2·44, −0·04) and −1·31 % (95 % CI −2·34, −0·26), respectively. TAG:HDL-cholesterol ratio was inversely associated with anthocyanidins (−1·60 % change; 95 % CI −3·12, −0·04) and total flavonoid intake (−1·83 % change; 95 % CI −3·03, −0·62). Increased HDL-cholesterol was associated with higher total dietary flavonoid intake (0·54 % change; 95 % CI 0·14, 0·94). Serum insulin and HOMA-IR were inversely associated with flavone (for insulin, −3·18 % change; 95 % CI −5·85, −0·44; for HOMA-IR, −3·10 % change; 95 % CI −5·93, −0·19) and isoflavone intakes (for insulin, −3·11 % change; 95 % CI −5·46, −0·70; for HOMA-IR, −4·01 % change; 95 % CI −6·67, −1·27). We observed that the % changes in TAG and TAG:HDL-cholesterol ratio for a 100 % increase in flavone intake were −2·15 % (95 % CI −4·70, 0·47) and −2·62 % (95 % CI −5·80, 0·66), respectively. However, they were not statistically significant. BMI was found to be negatively associated with anthocyanidin intake (−0·60 % change; 95 % CI −1·03, −0·16) after adjusting for all variables except for BMI.

Discussion

In spite of accumulating evidence that dietary flavonoids have effects on improving CVD risk factors in experimental studies[41–43], a few observational studies have reported the association between flavonoid intake and CVD risk factors[21,22]. Furthermore, even though studies have reported the protective effects of flavonoid-rich foods such as red wine, tea, chocolate, cocoa and soya products on CVD risk[44,45], it is still not clear whether the observed health benefits are attributed to flavonoids themselves rather than other ingredients. Established flavonoid composition databases for foods are essential for the reliable estimation of flavonoid intake and studies on flavonoids and disease prevention. Recently, two cross-sectional studies have documented the associations of higher consumption of flavonoids with improved metabolic syndrome or lipid profile by utilising flavonoid data from the Phenol-Explorer database or published composition database for estimation of flavonoid intake in the Chinese population[46,47]. Our research group has developed an investigative research tool by which we could expand the number of foods covered by the USDA flavonoid database[32], and using these data from the NHANES 1999–2002 we documented an inverse association between dietary flavonoid intakes and serum C-reactive protein concentrations in US adults[48].

In this cross-sectional investigation using NHANES 2007–2012 data, we found some associations between flavonoid intake and CVD risk factors. BMI was inversely associated with greater consumption of anthocyanidins. Although epidemiological studies on the effect of anthocyanidins on obesity are scarce, a

Table 3. Association between flavonoid intake and CVD risk factors among US adults in the National Health and Nutrition Examination Survey (NHANES) 2007–2012 (Percentages and 95 % confidence intervals; *n* 4042)†

	% Change predicted in CVD risk factors with a 100 % increase in flavonoid intake													
	Flavonols		Flavones		Flavanones		Flavan-3-ols‡		Anthocyanidins		Isoflavones		Total flavonoids	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
Waist circumference	−0·04	−0·24, 0·15	−0·21	−0·43, 0·02	0·00	−0·09, 0·10	−0·06	−0·17, 0·05	0·02	−0·13, 0·17	0·09	−0·26, 0·44	−0·10	−0·21, 0·02
BMI§	0·52	−0·14, 1·19	−0·91	−1·92, 0·10	−0·24	−0·61, 0·14	−0·09	−0·41, 0·24	−0·60*	−1·03, −0·16	−0·63	−1·57, 0·32	0·01	−0·45, 0·47
TAG	−1·40	−3·23, 0·47	−2·15	−4·70, 0·47	−0·53	−1·55, 0·50	−0·21	−1·15, 0·74	−1·25*	−2·44, −0·04	−0·53	−3·04, 2·04	−1·31*	−2·34, −0·26
HDL-cholesterol	0·68	−0·35, 1·72	0·47	−0·64, 1·59	0·15	−0·36, 0·66	0·02	−0·40, 0·43	0·35	−0·29, 1·00	0·44	−1·03, 1·92	0·54*	0·14, 0·94
Blood pressure														
Systolic	0·33	−0·08, 0·75	−0·22	−0·95, 0·52	0·09	−0·19, 0·38	−0·08	−0·26, 0·10	−0·08	−0·34, 0·18	−0·23	−0·76, 0·30	0·06	−0·16, 0·28
Diastolic	0·43	−0·19, 1·05	−0·07	−0·90, 0·76	−0·15	−0·56, 0·26	−0·14	−0·38, 0·10	−0·13	−0·46, 0·21	−0·79	−1·70, 0·14	−0·03	−0·36, 0·30
Fasting glucose	−0·02	−0·46, 0·43	0·08	−0·59, 0·77	−0·04	−0·27, 0·18	−0·06	−0·34, 0·22	−0·02	−0·28, 0·25	−0·89	−1·78, 0·00	−0·11	−0·38, 0·15
Insulin	−0·52	−2·78, 1·80	−3·18*	−5·85, −0·44	0·26	−0·74, 1·27	0·39	−0·66, 1·45	−1·01	−2·30, 0·30	−3·11*	−5·46, −0·70	0·01	−1·03, 1·06
TC	0·55	−0·13, 1·23	0·21	−0·75, 1·18	−0·17	−0·61, 0·28	−0·14	−0·50, 0·22	−0·27	−0·73, 0·20	−0·02	−1·10, 1·07	0·05	−0·42, 0·52
LDL-cholesterol	0·85	−0·20, 1·92	0·67	−0·51, 1·87	−0·06	−0·78, 0·67	−0·17	−0·66, 0·31	−0·27	−0·90, 0·38	−0·15	−2·03, 1·77	0·17	−0·47, 0·82
TAG:HDL-cholesterol ratio	−2·06	−4·60, 0·54	−2·62	−5·80, 0·66	−0·67	−1·90, 0·57	−0·23	−1·38, 0·94	−1·60*	−3·12, −0·04	−0·96	−4·45, 2·66	−1·83*	−3·03, −0·62
TC:HDL-cholesterol ratio	−0·13	−1·14, 0·89	−0·26	−1·58, 1·08	−0·31	−0·85, 0·23	−0·16	−0·59, 0·28	−0·62	−1·24, 0·01	−0·45	−2·23, 1·36	−0·49	−1·03, 0·06
HOMA-IR	−0·60	−3·00, 1·87	−3·10*	−5·93, −0·19	0·23	−0·84, 1·31	0·35	−0·84, 1·55	−1·03	−2·46, 0·42	−4·01*	−6·67, −1·27	−0·12	−1·35, 1·12

TC, total cholesterol; HOMA-IR, homoeostasis model assessment for insulin resistance.
*$P < 0·05$.
† Multivariate linear regression analysis of cardiovascular risk factors. Values are changes in percentages of cardiovascular risk factors with a 100 % increase in flavonoid intake. Models were adjusted for age, sex, ethnicity, physical activity, poverty income ratio, smoking status, alcohol consumption, education level, BMI, blood pressure medication, insulin use, vitamin C, SFA and fibre intakes.
‡ Flavan-3-ol intake was estimated by the sum of intakes of flavan-3-ol monomers, flavan-3-ol derived compounds and proanthocyanidins (dimer to polymers).
§ Multivariate model of BMI was adjusted for all variables except BMI.

few animal studies showed that anthocyanidins have a significant advantage for preventing obesity by improving adipocyte dysfunction[49]. For HDL-cholesterol, a positive association was observed with total flavonoid intake, which is supported by a study that reported flavonoids-rich cocoa powder and orange juice increased HDL-cholesterol in human intervention trials[50,51]. We found that insulin and HOMA-IR were negatively associated with flavone intake, which may be explained by the fact that flavone reduced insulin resistance and ameliorated insulin resistance-related endothelial dysfunction by blocking inhibitor of nuclear factor κ-B kinase β/NF-κB activation, leading to the down-regulation of TNF-α and IL-6 gene expressions[52,53]. Insulin and HOMA-IR were also inversely associated with isoflavone intakes, which is in accordance with previous studies that reported isoflavones favourably altered insulin resistance[54,55]. Some studies have demonstrated that isoflavones have anti-diabetic effects mediated by increased β cell proliferation, reduced apoptosis and glucose-stimulated insulin release[56]. However, as other human studies have reported that isoflavones showed no significantly beneficial effects on CVD risk factors[57,58], further research is warranted.

TAG and TAG:HDL-cholesterol ratio were inversely associated with anthocyanidin and total dietary flavonoid intakes. These are consistent with the results from previous experimental studies that showed higher flavonoid consumption decreased TAG and TAG:HDL-cholesterol ratio[59,60]. These findings are also supported by the report that showed supplementation of anthocyanin or anthocyanin-rich foods reduced TAG in human intervention trials[61,62]. Blood TAG:HDL-cholesterol ratio has been identified to be a strong predictor for extensive CHD among subjects at high risk for the development of coronary disease[37], cardiometabolic risk[63] and major adverse cardiovascular events among patients with acute coronary syndrome[64]. Therefore, these results indicate that flavonoid intake may lower CVD risk by improving atherogenic blood lipid profile.

In Table 3, the changes in percentages of cardiovascular risk factors with a 100 % increase in flavonoid intake are presented. For example, a −3·18 % change in the association of flavones with insulin means that an insulin level of 80 pmol/l might be decreased by 2·5 pmol/l (3·18 %) if 1·2 mg/d average intake of flavones would be doubled to 2·4 mg/d.

This study has several strengths. First, we used a relatively large sample of the US population. Second, we used a modified flavonoid database in an effort to reduce the incompleteness of the database and provided better estimates of dietary flavonoid intakes[33]. However, this study also has several limitations. First, this study was based on cross-sectional data, which only allows showing statistical associations and cannot make causal inference. Second, we did not consider the bioavailability or metabolism of flavonoids. Third, flavonoid intake may have been underestimated because of the limited food composition data and the exclusion criteria for flavonoid intake used in this study. Fourth, the estimation of flavonoid intake was based on 2-d 24-h dietary recalls, which are limited by within-person variability and recall error. Fifth, the values of thearubigins in the USDA database are crude approximations using an indirect method. Sixth, there may still have been residual confounding, although we adjusted available confounding factors. As we tested a set of statistical inferences simultaneously, some significant results might be false positives due to chance.

In conclusion, higher dietary flavonoid intake was associated with improved blood lipid profile. Our findings may support the beneficial effects of dietary flavonoids on lowering CVD risk. However, further research is warranted to confirm the findings from this study as these associations were moderate in strength.

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None of the authors has any conflicts of interest to declare.

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