Dietary antioxidants and flavonoids intake, and their association with inflammation and oxidative stress parameters in asthmatic women: a case-control study

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Asthma is more prevalent and severe in women, especially after puberty. Studies suggest a potential link between dietary antioxidants, inflammation, and oxidative stress. This study aimed to compare the dietary intake of antioxidants in asthmatic and healthy women, evaluating their potential associations with inflammation and oxidative stress. This study analyzed 30 asthmatic and 30 healthy women's lung function, anthropometry, biochemical parameters, and dietary antioxidant intake using a 161-itemized semi-quantitative food frequency questionnaire. Additionally, the study explored connections between serum inflammatory markers and oxidative stress indicators in relation to dietary intake of antioxidant nutrients and flavonoids. Asthmatic women exhibited higher serum IL-6 levels and lower total antioxidant status compared to healthy controls. Nevertheless, no significant differences were observed in dietary antioxidant micronutrient intake. Healthy controls demonstrated a notably higher intake of anthocyanidins compared to asthmatic women. Furthermore, the study identified a negative correlation between flavonol intake and serum total oxidant status, as well as between flavan-3-ols intake and serum oxidative stress index. Dietary differences in flavonoid and flavonoid-rich foods intake among asthmatic women may affect their serum IL-6 levels and oxidative stress. Promoting a diverse diet rich in flavonoids could benefit women with asthma by mitigating inflammation and oxidative stress.

***Key Words*: dietary antioxidants, flavonoids, asthma, adult, systemic inflammation**

Asthma is a chronic respiratory condition characterized by persistent inflammation of the airways with reversible airway hyperresponsiveness.[1] Recent reviews have described gender differences in asthma's prevalence and severity, with women exhibiting higher rates of the disease after puberty. The underlying mechanisms for these differences remain unclear, but immunological, hormonal, and environmental factors have been proposed.[2,3] Gender-based differences in body composition and fat distribution are known to exist and may contribute to the observed variations in lung mechanics.[4] Dietary habits may play a role in the development and progression of asthma.[1,5] Women generally consume less energy than men and prefer healthier diets with lower energy-dense foods, such as fruits and vegetables.[6] Misso *et al.*[7] revealed that women have higher intakes of vitamins and minerals like vitamin C and carotene than men. Poor dietary habits in adult women, low in fiber and high-fat intake, are related to an increased risk of asthma exacerbations during pregnancy.[8] Unintended pregnancies, associated with adverse maternal and fetal health, are still common.[9] Therefore, evaluating the dietary differences between asthmatic and healthy women of reproductive age will affect fetal growth and development.

Oxidative stress is a clinically relevant factor in asthma, leading to systemic and airway inflammation.[5,10] Inflammation and oxidative stress do not exist separately in asthma, but coexist and influence each other.[11,12] One of the recent studies has shown that inhibiting the release of inflammatory factors through the transcription of inflammatory genes, lincRNA-Cox2, can prevent airway inflammation. This inhibition can be achieved by activation of the antioxidant signaling pathway.[11] Women with asthma have been shown to have higher dietary antioxidant intake but lower plasma levels, possibly due to increased oxidative stress and inflammation.[7] Evidence suggests that increasing consumption of antioxidant-rich fruits and vegetables may positively affect asthma and lung function.[13,14] Comprehensive reviews suggest that consuming dietary antioxidants, such as vitamins like A (retinol and carotenoids), C, and E (tocopherols), as well as trace elements like zinc, copper, magnesium, and selenium, crucial for antioxidant enzyme function in adults, could have potential links to asthma.[5,15,16] Recent research has emphasized the potential advantages of flavonoids, a subgroup of polyphenols present in various foods, including fruits, vegetables, chocolate, olive oil, nuts, seeds, legumes, and beverages like tea, coffee, and wine, for airway diseases owing to their anti-allergic, anti-inflammatory, and antioxidant features.[16] While some studies have evaluated the associations between flavonoid groups and asthma, only a few have explored the association between dietary flavonoid intake and asthma, and the results remain uncertain.[13,17,18]

Research on adult asthmatics' dietary intake of antioxidant nutrients, including flavonoids and their relation to antioxidant status and systemic inflammation markers, is limited. As such, we hypothesized that asthmatic women may have a lower dietary intake of antioxidant nutrients and flavonoids, which may be related to increased systemic inflammation and oxidative stress parameters. This study aims to compare the dietary antioxidant

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nutrient and flavonoid intake of asthmatics to that of healthy controls and to assess the possible associations between dietary antioxidants, systemic inflammation, and oxidative stress parameters.

Materials and Methods

Study population and design. This study recruited 30 individuals diagnosed with asthma at least one year prior who had been admitted to the Pulmonology Outpatient Clinic of the Antalya Training and Research Hospital, as well as 30 healthy controls, between May 2019 and October 2021. Sample size was calculated using G*Power, ver. 3.1, considering results from previous studies, with an error rate of 0.05 and power of 0.90. The two groups were similar in terms of age and body mass index (BMI). Inclusion criteria were as follows: women who are aged between 19 and 50 years, non-smokers. Exclusion criteria were as follows: under 18 and over 50 years, smoking, pregnancy, breastfeeding, menopause, respiratory tract infection in the past four weeks, malignancy, or chronic diseases other than asthma, regular antioxidant dietary supplement use, unreliable nutritional information, and lack of voluntary participation. The majority of the asthmatic women (83.4%) were on inhaled corticosteroid treatment, and patients using systemic corticosteroids or in exacerbation, which might affect food intake and pulmonary functions, were excluded.[19]

All procedures performed in this study involving human participants were by the regional ethics committee of the Antalya Training and Research Hospital, University of Health Sciences, Türkiye (Decision number: 12/29, Date: 02.05.2019) and 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics approval was obtained from the University of Health Sciences, Antalya Training and Research Hospital's Clinical Ethics Committee before conducting this research. Demographic data, including age, marital status, total education time, alcohol use, and physical activity were collected by a survey.

Lung function. Pulmonary functions were evaluated using a ZAN-GPI 3.00 spirometer (Nspire Health GmbH, Oberthulba, Germany), and a healthcare specialist recorded the best value from 3 maneuvers as an absolute value. The forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were presented as a percentage of predicted values adjusted for age, sex, and height.

Anthropometry. The anthropometric measurements such as height, waist circumference, and hip circumference were taken using a stretch-resistant tape, and an electronic scale sensitive to 0.1 kg (Premier "PWS 2039" scale, Nasmina Electronic, Zhongshan Guangdong, China). Height was measured using stretch resistant tape, without shoes, and on a Frankfort plane position. Waist and hip circumference were obtained following the protocol established by the World Health Organization (WHO).[20] Following the WHO guidelines, the participants' BMI (kg/m^2) and waist-hip ratio were calculated and classified accordingly.[20,21]

Biochemical analysis. After an overnight fast of at least 8 h, blood samples were collected from the participants. Eosinophil and immunoglobulin E (Ig E) levels were determined using the laboratory procedures of the hospital. The serum levels of IL-6 and TNF-α were measured using commercial ELISA kits from Elabscience Inc. (Houston, TX) (Catalog nos. E-EL-H0102 and E-EL-H0109, respectively). The turbidimetric method was used to identify high-sensitivity CRP parameters (Catalog no. OSR6299) with Beckman Coulter Au5811. The levels of plasma total antioxidant status (TAS) and total oxidant status (TOS) were measured using a method developed by Erel.[22,23] TAS results were expressed as μmol Trolox equiv./L, and TOS results were expressed as μmol H_2O_2 equiv./L. The oxidative stress index (OSI) was calculated using the formula: [TOS (μmol H_2O_2 equiv./L) × 100/TAS (μmol·Trolox·equiv/L)]. All tests were conducted in duplicate according to the manufacturer's guidelines.

Dietary intake assessments. A 161-itemized semi-quantitative food frequency questionnaire (FFQ) was utilized by a research dietitian to estimate the participants' dietary data through face-to-face interviews. Portion sizes were determined using a photographic atlas,[24] and daily intake was calculated by multiplying consumption frequency by standard portion size weight. Daily dietary energy and antioxidant micronutrients were calculated using BEBİS 8.1 (Nutrition Information System) program.[25] Flavonoid intake was assessed using the expanded USDA Flavonoid Database for the Assessment of Dietary Intakes (FDB-EXP)[26] and the USDA Flavonoid Content of Selected Foods 3.3,[27] while excluding animal-based products; however, including eggs in isoflavone intake calculations due to the potential contribution of soybean meal in poultry.[28] The intake of flavonoids was calculated by multiplying the consumption frequency of each food by the flavonoid content of the specified portion size, and the total flavonoid consumption was calculated as the sum of all flavonoid subclasses (isoflavones, anthocyanidins, flavan-3-ols, flavanones, flavones, and flavonols)[24] from the 119 kinds of foods and beverages commonly consumed by the FFQ.

Energy-adjustment calculation. To control for potential confounding effects of differences in energy intake, we used the residuals method described by Willet *et al.*[29] to analyze the association between energy-adjusted dietary antioxidants and the risk of asthma. Linear regression equations were established for each dietary antioxidant group, where the dependent variable was nutrient or flavonoid intake, and the independent variable was total energy intake. The energy-adjusted intake for each antioxidant was computed by adding the mean dietary intake of the study population to the residual of the regression analysis.

Statistical analysis. The data were reported using means ± SD, median (interquartile range), frequency, and percentage (%). Chi-square tests were used to analyze categorical data, while the Mann–Whitney *U* test and Student *t* test were employed for continuous and numerical data, respectively, based on their appropriateness after verifying normal distribution. Due to the non-normal distribution of serum inflammation and antioxidant parameters, the correlation between dietary antioxidants and serum parameters was analyzed using Spearman correlation analysis. Multivariate logistic regression was used to investigate dietary intake differences between the two groups, adjusting for potential confounding factors such as total education time, alcohol intake, and waist circumference. IBM SPSS ver. 23 was used for statistical analysis with a significance set at $p<0.05$.

Results

Table 1 presents the general characteristics of the study. Although asthma cases and healthy controls had similar age and BMI ranges, asthmatic women exhibited a significantly higher mean waist circumference ($p = 0.035$) and lower total education time, alcohol use, and physical activity levels ($p = 0.001$, $p = 0.003$, and $p = 0.033$, respectively). Asthmatic women also demonstrated worse lung function and higher levels of blood eosinophils %, Ig E, and IL-6, while having a lower serum TAS than healthy controls ($p = 0.018$, $p = 0.004$, $p = 0.001$, and $p = 0.037$, respectively). No significant differences were found in the dietary intake of antioxidant nutrients or other serum inflammatory markers or oxidative stress parameters. Notably, only one asthmatic woman in the study consumed alcohol, while healthy women exhibited a significantly higher alcohol consumption rate. Additionally, healthy women preferred wine, although this was not shown in Table 1.

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Table 1. Baseline characteristics and biochemical variables of the asthma cases and control groups

Variables	Asthma cases (n = 30)	Healthy controls (n = 30)	p*
Age (years)	35.00 (22.75, 42.25)	30.00 (28.75, 37.00)	0.888[a]
Marital Status			
Married	19 (63.3)	17 (56.7)	0.598[b]
Single	11 (36.7)	13 (43.3)	
Total education time	12.30 ± 4.39	16.07 ± 3.44	<0.001[c]
Alcohol use	1 (3.3)	10 (33.3)	0.003[b]
Physical activity	3 (10.0)	11 (36.7)	0.033[d]
Weight (kg)	67.68 ± 10.40	64.89 ± 10.06	0.296[c]
BMI (kg/m^2)	25.65 (21.48, 28.90)	24.60 (21.50, 26.73)	0.255[c]
Waist circumference (cm)	87.9 ± 12.52	81.45 ± 10.59	0.035[c]
Waist circumference evaluation			
Healthy	9 (30.0)[a]	15 (50.0)[a]	0.059[e]
Increased risk	6 (20.0)[a]	9 (30.0)[a]	
Substantially increased risk	15 (50.0)[a]	6 (20.0)[b]	
Waist/Hip ratio	0.84 ± 0.06	0.81 ± 0.08	0.105[c]
Respiratory Function			
FEV_1 % predicted	94.07 ± 12.13	101.37 ± 10.98	0.018[c]
FVC % predicted	96.67 ± 11.40	101.03 ± 7.87	0.090[c]
FEV_1/FVC %	102.07 ± 8.97	104.50 ± 7.75	0.266[c]
Biochemical variables			
Eosinophils %	2.40 (1.68, 3.48)	1.50 (1.28, 2.28)	0.004[a]
Immunoglobulin E (IU/ml)	97.05 (30.75, 190.50)	19.50 (18.90, 35.15)	<0.001[a]
IL-6 (pg/ml)	17.87 (15.33, 38.56)	14.02 (11.43, 19.40)	0.037[a]
TNF-α (pg/ml)	13.42 (6.45, 41.60)	14.80 (5.27, 29.21)	0.668[a]
hs-CRP (mg/L)	1.85 (0.65, 6.90)	0.84 (0.19, 2.36)	0.085[a]
TAS (mmol/L)	1.26 (1.16, 1.30)	1.35 (1.20, 1.44)	0.029[a]
TOS (μmol/L)	4.61 (3.92, 5.56)	3.99 (2.77, 5.80)	0.169[a]
OSI	0.37 (0.32, 0.44)	0.32 (0.19, 0.45)	0.107[a]

Data were presented as mean ± SD, n (%), or median (Interquartile range), where appropriate. BMI, body mass index; IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha; hs-CRP, high-sensitivity C-reactive protein; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index. *The detailed explanation of p values were is as follows: [a]Mann–Whitney U test, [b]chi-square test, [c]Independent t test, [d]Yate's continuity correction in chi-square test, [e]Fisher–Freeman–Halton test.

The dietary intake of antioxidant vitamins and minerals did not differ significantly between asthma cases and healthy controls. However, asthmatic women had a significantly higher total energy intake, while anthocyanidin intake was significantly lower compared to healthy controls. No differences were found in other flavonoid subgroups or total flavonoid intakes (Table 2). After adjusting for potential confounding factors, participants with higher anthocyanidin intake demonstrated a significantly lower risk for asthma (OR = 0.975, 95% CI: 0.954, 0.998). However, after further adjustments for Ig E (Model 2), the association attenuated (OR = 0.981, 95% CI: 0.954, 1.009).

In the total sample, we found significant negative correlations between IL-6 and dietary vitamin E intake, and TNF-α and magnesium, respectively (Fig. 1). Figure 2 illustrates a negative correlation between flavonols and serum TOS, flavan-3-ols, flavonols and serum OSI in asthma cases (p<0.05). Additionally, in healthy controls, a significant negative correlation between IL-6 and vitamin C was observed (p<0.05) (the figure is not shown).

In Table 3, the dietary intake of food groups is presented for both asthma cases and healthy controls. Asthma cases demonstrated higher legume intake and lower coffee consumption compared to healthy controls. Regression analysis indicated a significant association between coffee consumption and asthma risk when adjusted for potential confounding factors (Model 1) (OR = 0.991, 95% CI: 0.983, 1.000). However, after further adjustments for Ig E (Model 2), this association weakened to non-significance (OR = 0.989, 95% CI: 0.975, 1.003). Conversely, in Model 2, asthma was found to be significantly associated with olive oil consumption (OR = 0.809, 95% CI: 0.679, 0.963) (Table 3).

Discussion

Our study investigated the differences in dietary antioxidants in asthmatic women compared to healthy women of reproductive age. No significant differences were found in dietary antioxidant nutrients between asthmatic women and healthy controls. However, asthmatic women had a lower intake of anthocyanidins, a subclass of flavonoids, compared to healthy controls. A higher intake of anthocyanidin was associated with a decreased risk of asthma in women. In addition, asthmatic women exhibited elevated plasma IL-6 levels and decreased plasma TAS levels in comparison to healthy controls.

The relationship between dietary intake of antioxidant nutrients and adult asthma remains uncertain due to conflicting findings in the literature.[15,16] Although certain studies have stated significant differences in antioxidant intake[30–32] and plasma antioxidant levels[33,34] between asthmatics and healthy individuals, others have not. Previous studies[7,35,36] showed no significant differences in the intake of ascorbic acid, vitamin E (tocopherols), and vitamin A (carotene, and retinol), magnesium,

Table 2. Logistic regression analysis of daily dietary energy and energy-adjusted antioxidants intake in asthma cases compared with healthy controls

Variables	Asthma cases (n = 30)		Healthy controls (n = 30)		p*	Adjusted Model 1			Adjusted Model 2		
						Odds ratio‡	p	95% CI	Odds ratio‡	p	95% CI
Energy (kcal)	1,975.88	(1,858.04, 2,224.82)	1,829.63	(1,583.44, 1,918.79)	0.001[b]	1.003	0.040*	1.000, 1.006	1.005	0.100	0.999, 1.010
Vitamin A (μg)	1,784.92	(1,310.93, 2,278.55)	1,709.91	(1,365.76, 1,974.52)	0.965[b]	1.000	0.940	0.999, 1.001	0.999	0.440	0.998, 1.001
Retinol (μg)	451.53	(356.87, 847.78)	467.20	(408.46, 733.47)	0.690[b]	1.000	0.865	0.999, 1.001	0.999	0.475	0.998, 1.001
Carotene (mg)	6.79	(4.83, 10.27)	7.63	(5.79, 9.65)	0.615[b]	0.959	0.668	0.791, 1.162	0.918	0.561	0.689, 1.224
Vitamin C (mg)†	210.40	77.33	207.10	63.51	0.858[a]	1.001	0.769	0.993, 1.010	0.996	0.608	0.983, 1.010
Vitamin E (mg)	21.61	(18.51, 25.53)	20.54	(17.79, 23.46)	0.554[b]	1.047	0.465	0.925, 1.186	1.082	0.310	0.929, 1.261
Zinc (mg)†	10.08	1.58	10.55	1.81	0.296[a]	1.067	0.456	0.900, 1.264	1.115	0.442	0.845, 1.470
Magnesium (mg)†	365.24	62.70	366.14	78.47	0.961[a]	1.008	0.136	0.997, 1.019	1.004	0.593	0.989, 1.019
Selenium (mg)	11.32	(8.24, 22.09)	11.75	(5.17, 22.19)	0.848[b]	1.003	0.938	0.938, 1.072	0.911	0.145	0.804, 1.033
Copper (mg)†	2.08	0.31	2.03	0.39	0.611[a]	3.350	0.205	0.516, 21.743	1.051	0.971	0.017, 15.817
Manganese (mg)†	4.70	1.14	4.74	1.21	0.899[a]	1.504	0.182	0.826, 2.740	1.060	0.904	0.413, 2.721
Total flavonoids (mg)	690.40	(471.97, 1,409.84)	810.86	(492.56, 1,350.47)	0.906[b]	1.000	0.639	0.999, 1.001	1.000	0.679	0.998, 1.001
Isoflavonoids (mg)	0.05	(0.04, 0.06)	0.05	(0.04, 0.06)	0.701[b]	1.029	0.850	0.767, 1.380	1.152	0.631	0.646, 2.053
Anthocyanidins (mg)	31.74	(18.63, 56.69)	52.50	(33.32, 97.99)	0.019[b]	0.975	0.032*	0.954, 0.998	0.981	0.183	0.954, 1.009
Flavan-3-ols (mg)	704.28	(449.44, 1,591.84)	798.11	(393.39, 1,339.66)	0.988[b]	1.000	0.510	0.999, 1.001	1.000	0.833	0.999, 1.001
Flavonols (mg)†	52.66	19.92	52.70	24.19	0.993[a]	1.007	0.605	0.980, 1.036	0.990	0.606	0.952, 1.029
Flavanones (mg)	33.55	(13.28, 52.84)	22.89	(13.09, 38.92)	0.209[b]	1.025	0.073	0.998, 1.054	1.007	0.726	0.971, 1.044
Flavones (mg)	32.25	(18.82, 51.32)	35.99	(11.95, 58.05)	0.918[b]	0.997	0.712	0.978, 1.015	0.980	0.213	0.948, 1.012

Data are median (interquartile range), †Data are mean ± SD unless otherwise indicated. Logistic regression analysis for each antioxidant compound included the following covariates in the Model 1: total education time, alcohol intake, waist circumference, Model 2 also included that serum Immunoglobulin E. ‡Indicates a change in risk per unit of dietary intake.

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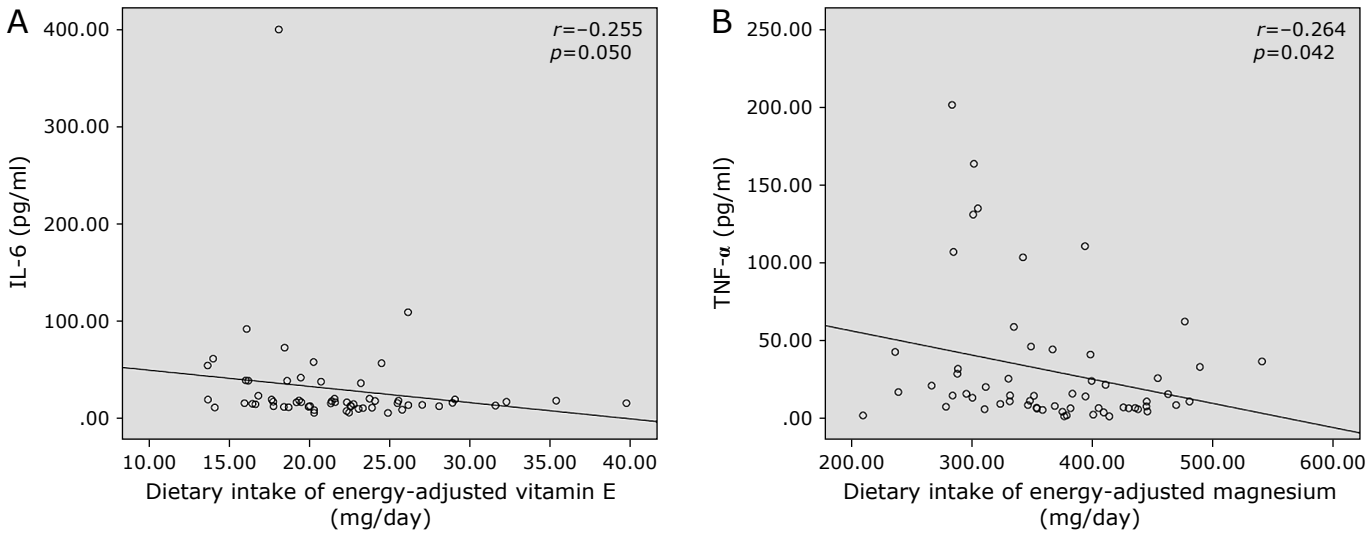


Fig. 1. Correlations between (A) IL-6 and dietary intake of energy-adjusted vitamin E and (B) TNF-α and dietary intake of energy-adjusted magnesium in total sample. This relationship revealed that greater serum IL-6 with a lower dietary intake of vitamin E and greater serum TNF-α with lower dietary intake of magnesium in total sample.

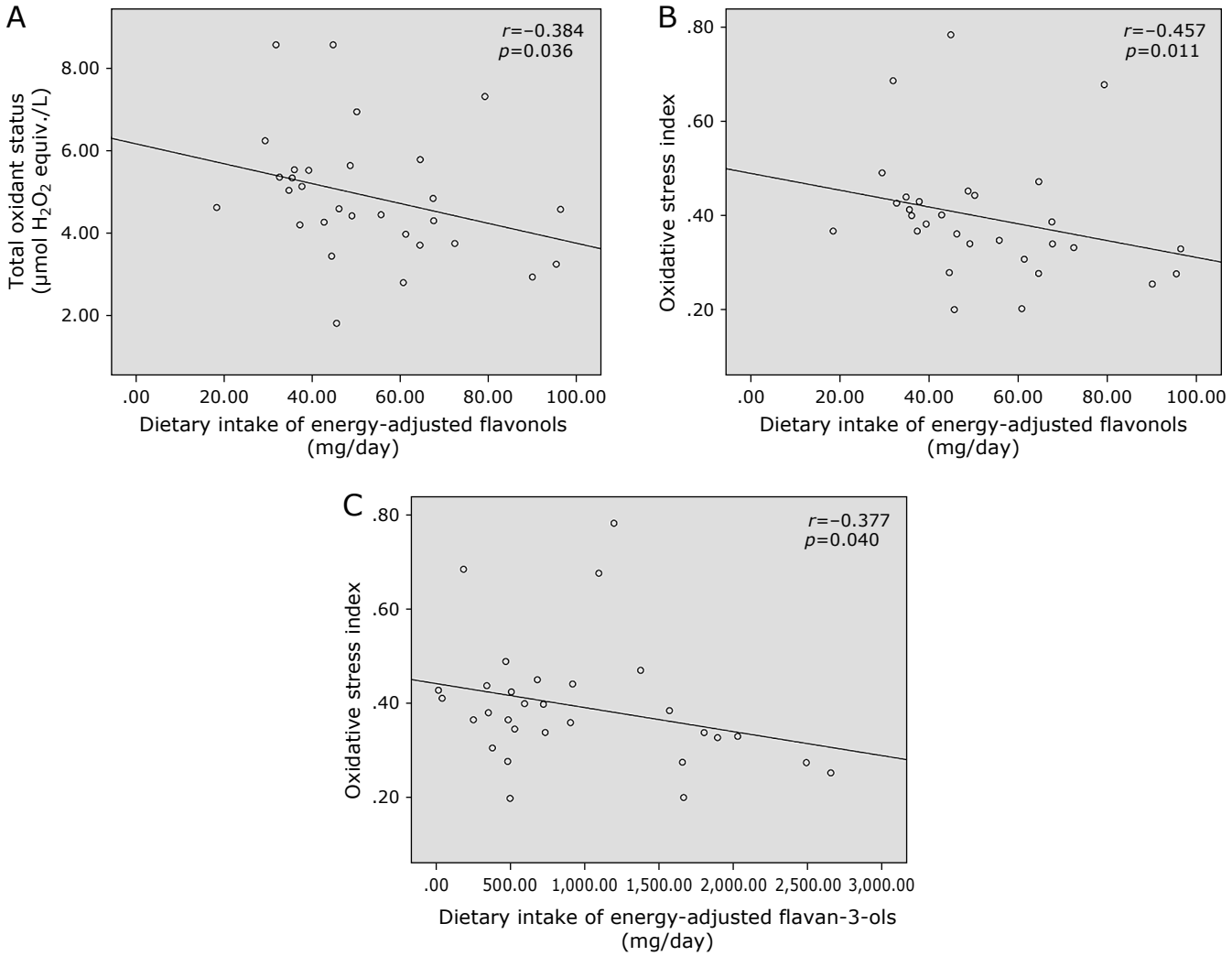


Fig. 2. Correlations between (A) serum total oxidant status and dietary intake of energy-adjusted flavonols, and the oxidative stress index and (B) dietary intake of energy-adjusted flavonols, and (C) flavan-3-ols in asthma cases. The results indicated that a higher dietary intake of energy-adjusted flavonols was significantly related to a lower serum TOS and OSI, and a higher dietary intake of energy-adjusted flavan-3-ols were significantly associated with a lower serum OSI.

Table 3. Logistic regression analysis of daily intake of flavonoid-rich food groups in asthma cases compared with healthy controls

Daily intake of food groups (g/day)	Asthma cases (n = 30)		Healthy controls (n = 30)		p*	Adjusted Model 1			Adjusted Model 2		
						Odds ratio	p	95% CI	Odds ratio	p	95% CI
Fruits (g/day)†	380.03	123.15	355.43	123.61	0.443[a]	0.995	0.159	0.989, 1.002	0.996	0.372	0.987, 1.005
Vegetables (g/day)†	423.37	96.60	388.00	130.85	0.238[a]	1.002	0.474	0.996, 1.009	1.001	0.855	0.992, 1.010
Nuts and Seeds (g/day)	28.50	(18.25, 50.25)	22.50	(10.25, 34.50)	0.174[b]	1.000	0.982	0.962, 1.041	1.007	0.844	0.941, 1.077
Legumes (g/day)	17.00	(10.75, 26.00)	9.00	(6.00, 19.00)	0.030[b]	1.046	0.160	0.982, 1.113	1.099	0.083	0.988, 1.222
Chocolate (g/day)	5.50	(1.75, 12.25)	4.00	(1.00, 11.00)	0.656[b]	1.053	0.096	0.991, 1.119	1.009	0.868	0.913, 1.114
Olive oil (g/day)	20.00	(9.00, 26.25)	20.00	(10.00, 22.50)	0.821[b]	0.960	0.226	0.899, 1.025	0.809	0.017*	0.679, 0.963
Olives (g/day)	20.00	(6.25, 31.25)	24.00	(9.00, 32.50)	0.520[b]	0.964	0.058	0.927, 1.001	0.935	0.084	0.867–1.009
Tea (ml/day)	380.18	(216.49, 822.80)	380.35	(191.81, 601.78)	0.684[b]	1.000	0.538	0.999, 1.002	1.000	0.873	0.998, 1.003
Coffee (ml/day)	30.00	(12.90, 70.43)	121. 25	(40.03, 257.25)	0.001[b]	0.991	0.038*	0.983, 1.000	0.989	0.115	0.975, 1.003

Data are median (interquartile range). †Data are $\bar{X} \pm SD$ unless otherwise indicated. *The p values show the difference between asthma cases and healthy control groups, and the detailed explanation is as follows: [a]Independent sample t test and [b]Mann–Whitney U test. Logistic regression analysis for each food group included the following covariates in the Model 1: total education time, alcohol intake, waist circumference, and total energy intake and Model 2 also added immunoglobulin E.

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zinc, copper, or manganese between asthmatics and controls. Our study aligns with these previous findings and suggests that flavonoids, rather than micronutrients, might be involved in the association between dietary antioxidants and asthma.

Over the past decade, the immunomodulatory, anti-inflammatory, anti-allergic, and antioxidant properties of flavonoids in asthma have been emphasized.[16,37] Flavonoids are known to reduce inflammation and exert immunomodulatory effects by inhibiting histamine release, enzymes in arachidonic acid metabolism, cytokine production, and regulating transcription factors.[38] They also have antioxidant effects due to their ability to scavenge reactive substances and regulate antioxidant enzymes.[13,38,39] While earlier studies indicate that a higher intake of flavonoids is linked with a reduced risk of asthma,[18,35] other studies have shown no association.[13,17] Our study revealed that asthmatic women had a lower energy-adjusted intake of anthocyanins compared to healthy women, which may be explained by their lower berries and wine consumption. Our results also revealed that energy-adjusted flavonols intake and flavan-3-ols related to TOS and OSI. The conflicting results of previous studies on the dietary intake of flavonoids could be attributed to variations in the types of flavonoids examined, databases utilized for flavonoid calculation,[37] and differences in consumption of flavonoids based on geographical location and cultural factors.[13,17,18,40]

Anthocyanins, responsible for the colors of foods, can reduce cyclooxygenase gene activation, a key factor in the inflammatory reaction, associated with the pathogenesis of asthma. A recent experimental study showed that anthocyanins inhibited the NF-κB pathway, leading to reduced airway hyperresponsiveness and Ig-E-related inflammation.[41] However, after adjusting for Ig E, the relationship between dietary anthocyanidin intake and asthma risk became non-significant, possibly due to flavonoids' assumed anti-allergic property. Studies on the link between higher consumption of fruit, vegetables, wine, and tea and a reduced risk of asthma have produced mixed results.[17,35,42,43] Recent studies suggest that coffee and wine consumption may also be related to asthma risk,[44,45] possibly due to their other parameters like methylxanthines, phenolic acids, or stilbenes, which can promote stable gut microbiota and reduce inflammation linked to allergic conditions.[46] Although controlling for serum Ig E concentration attenuated the association between coffee consumption and asthma risk, adjusting for all covariates, including Ig E, revealed a significant inverse association between consuming olive oil and asthma risk. Olive oil's antioxidant and anti-inflammatory properties, as well as its content of fatty acids, vitamin E and polyphenolic compounds such as tocopherols, oleuropein, and hydroxytyrosine, may be responsible for its protective effect on asthma/atopy.[47] In a study by Cazzoletti *et al.*[48] reported that olive oil consumption was associated with reduced asthma risk in adults, which aligns with our own findings.

Our study has some strengths. Firstly, we evaluated the dietary intake of antioxidants alongside systemic inflammatory and antioxidant/oxidant parameters. Secondly, using six subclasses of flavonoids calculated from current USDA databases that provide updated information on the flavonoid content of foods and beverages, we examined the association between asthma and flavonoid intake. This data enabled us to quantify flavonoid intake with more robust evidence than in previous studies. Finally, our FFQ included an extensive list of fruits and vegetables and other dietary sources known to be flavonoid-rich.

Determining whether the observed differences in dietary antioxidants and systemic inflammation and oxidative stress parameters are a cause or a consequence of asthma is limited by the cross-sectional case-control design of our study. We cannot conclude whether asthma causes an altered dietary intake of flavonoids or *vice versa*. Furthermore, the role played by the colonic microbiota in metabolizing these antioxidants makes it difficult to interpret these results. To clarify these findings, further large case-control and cohort studies with other inflammatory and oxidative stress parameters are needed.

This study indicates that women with asthma in reproductive age have similar dietary intake of antioxidant nutrients but may differ in their intake of flavonoids and flavonoid-containing foods, which could be linked to serum IL-6 and antioxidant status. The literature supports increasing dietary intake of flavonoid-rich groups, such as fruits and vegetables, to benefit clinical practice. Encouraging a diverse and colourful diet to increase flavonoid intake may have potential benefits for asthma in women.

Author Contributions

All authors contributed to the conception and design of the study. GS, OK, and İÖK carried out the collection, analysis, and interpretation of data. GS wrote the first draft of the manuscript. AA was the supervisor of the present study and participated in drafting, revising the manuscript, and approving the final version. All authors read and approved the final version of the manuscript and declare that the contents have not been published elsewhere. This research is part of the PhD thesis of the corresponding writer, GS.

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Ethical Approval

All procedures performed in this study involving human participants were by the regional ethics committee of the Antalya Training and Research Hospital, University of Health Sciences, Türkiye (Decision number: 12/29, Date: 02.05.2019) and 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethics approval was obtained from the University of Health Sciences, Antalya Training and Research Hospital's Clinical Ethics Committee before conducting this research.

Conflict of Interest

No potential conflicts of interest were disclosed.

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