Original Research

Dietary Phytochemical Index in Relation to Metabolic Health Status, Serum Adropin, and Brain-Derived Neurotrophic Factor Levels in Adults

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A B S T R A C T

Background: Little is known about the relationship between dietary intake of phytochemicals with metabolic health status and underlying mechanisms.

Objectives: Little is known about the relationship between dietary intake of phytochemicals with metabolic health status and underlying mechanisms. We hypothesized that dietary phytochemical index (DPI) improves metabolic health status by ameliorating serum concentrations of brain-derived neurotrophic factor (BDNF) and adropin.

Methods: A cross-sectional study was performed in 527 adults (286 males and 241 females). The dietary intakes of participants were collected by a 168-item food frequency questionnaire, and DPI was estimated as a percentage of energy intake derived from phytochemical-rich foods. Anthropometric variables, blood pressure, glycemic and lipid profiles, and biochemical variables were assessed. The metabolically unhealthy (MU) phenotype was determined based on the definition presented by Wildman et al.

Results: The MU phenotype was identified in 51.4% of male and 32.0% of female participants. Participants in the third tertile of DPI had 59% lower odds of MU than those in the first tertile (OR: 0.41; 95% CI: 0.19, 0.87) after considering potential confounders. Stratified analysis by sex and body mass index indicated that DPI was inversely related to MU phenotype in females (OR: 0.28; 95% CI: 0.08, 0.97) and normal-weight individuals (OR: 0.11; 95% CI: 0.02, 0.62). DPI was also inversely associated with hyperglycemia, hypertriglyceridemia, and chronic inflammation. Nonsignificant reduced odds of low BDNF (OR: 0.87; 95% CI: 0.42, 1.84) and adropin (OR: 0.75; 95% CI: 0.31, 1.79) were observed in individuals in the top tertile of DPI compared with those in the bottom tertile.

Conclusions: This study showed that individuals with higher dietary intake of phytochemicals had lower odds of MU, particularly females and normal-weight individuals. No significant relationship was observed between serum BDNF and adropin with phytochemical intake.

Keywords: metabolic health status, diet, dietary phytochemical index, brain-derived neurotrophic factor, adropin

Introduction

The global prevalence of obesity has increased significantly since 1980, such that approximately one-third of the world's population suffers from obesity and overweight [1]. Obesity is known as a major risk factor for noncommunicable diseases (NCDs), including type 2 diabetes mellitus, fatty liver, hypertension, cardiovascular diseases, myocardial infarction, and stroke [2]. However, risk of NCDs does not drastically increase in a subgroup of obese people known as metabolically healthy obese (MHO) [3]. Previous studies have also demonstrated that

normal-weight individuals with unfavorable metabolic health status, known as metabolically unhealthy (MU) normal-weight (MUNW), have higher risk of developing NCDs than metabolically healthy normal-weight (MHNW) individuals [4,5]. Therefore, metabolic health status could predict risk of future diseases better than obesity. The metabolic status is transient and the shifting condition from healthy to unhealthy is associated with an increased risk of NCDs [6–8]. Therefore, managing and maintaining metabolic health status throughout life via behavioral and medical strategies is of great importance.

Recent experimental and observational studies have discovered the metabolic role of some biomolecules, such as brain-derived neurotrophic factor (BDNF) and adropin. BDNF, a member of the nerve growth factor family, is mainly expressed in the central nervous system. This neurotrophic factor plays an important role in the growth, survival, and differentiation of neurons as well as synaptic plasticity [9,10]. Adropin, encoded by the energy homeostasis-associated gene (Enho), is a peptide hormone that is predominantly expressed in the liver but also found in other body tissues such as the central nervous system, pancreas, kidney, heart, and small intestine [11]. The findings of previous studies have demonstrated that BDNF and adropin play their metabolic roles by affecting body energy homeostasis and glucose and fatty acids metabolism [12,13]. Reduced serum BDNF and adropin concentrations have also been observed in individuals with obesity or abnormal metabolic profiles [14–17]. In addition, it seems that modifiable lifestyle factors such as dietary intake and physical activity can alter BDNF [18–20] and adropin [21–23] secretion.

Phytochemicals are bioactive substances in plant-based foods such as fruits, vegetables (except for potatoes), grains, and oilseeds, which have many health benefits [24,25]. The dietary phytochemical index (DPI), proposed recently by McCarty, is a simple and practical index for the assessment of total dietary phytochemical consumption. DPI is defined as the percent of energy intake derived from phytochemical-rich foods [26]. The association between DPI and metabolic syndrome (MetS) in Iranian adults was previously evaluated; higher adherence to DPI was associated with a reduced chance of MetS and some of its components, such as high blood pressure, central obesity, insulin resistance, and hypertriglyceridemia [27–29]. Additionally, a recent study in Switzerland reported that higher consumption of phytochemical-rich foods, indicated by higher DPI scores, has protective effects against cardiometabolic risk factors [30]. An inverse relationship was also reported between DPI and MU obesity (MUO) phenotype among 228 Iranian females with overweight or obesity [31]. A lower likelihood of MUO was also reported in adolescents with a higher intake of phytochemicals in a previous survey in Iran [32]. However, no prior study has investigated the relationship between DPI and metabolic health status, considering the possible role of BDNF and adropin. We postulated that DPI improves metabolic health status by ameliorating serum concentrations of BDNF and adropin. Thus, the present study examined the association between DPI and MU status, considering the probable role of BDNF and adropin.

Methods

Study design and participants

A cross-sectional study was undertaken among a somewhat representative sample of Iranian adults (aged 18–60 y) in 2021.

The sample size of the present study was estimated based on a previous study that reported a prevalence of 49.4% for MU among Iranian adults [33]. The minimum required sample size was estimated to be 474, considering a power of 80%, type I error of 0.05, desired confidence interval (CI) of 0.95, and precision (d) of 4.5%. A stratified multistage cluster sampling approach was applied to select participants from 20 schools in 6 different educational districts (3–4 schools from each district) of Isfahan, a large central city of Iran. Participants from various socioeconomic classes were recruited from various job categories in randomly chosen schools, including teachers, administrative and managerial employees, assistants, and crews. Complete information on the subjects' features, study design, and methodology was previously published [34]. Subjects were not included if they: *1)* were following a special diet, *2)* had a prior history of chronic diseases such as type 1 diabetes mellitus, cardiovascular diseases, stroke, and malignancy, or *3)* were pregnant or lactating females. In total, 543 invited individuals agreed to participate in the present study (response rate = 90.5%), of which 16 people were excluded from the study for 1 of the following reasons: *1)* left >70 items of the food frequency questionnaire (FFQ) blank (*n* = 4), *2)* reported a total energy intake outside the range of 800–4200 kcal/d (*n* = 3), *3)* had missing blood pressure values (*n* = 8), and *4)* did not accept blood draw for biochemical analysis (*n* = 1). Finally, 527 individuals were included in the present analysis. All participants signed a written informed consent, and the study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (no. 2401283).

Dietary assessment and DPI calculation

The usual dietary intake of participants was assessed by a validated Willet-format semiquantitative 168-item FFQ [35]. This questionnaire could provide reasonably valid measures for common dietary intakes of the Iranian adult population. The validation study of this FFQ demonstrated reasonable correlations between dietary intakes obtained from FFQ and those obtained from multiple 24-h dietary recalls (ranging from 0.11 to 0.60 in females and 0.24 to 0.71 in males). The reliability of this questionnaire was additionally evaluated by comparing nutrient intakes obtained from 2 FFQs administered 1 y apart. The mean energy-adjusted intraclass correlation coefficients were 0.59 and 0.60 for males and females, respectively [35]. The study participants were asked to report the frequency and amount of each consumed food item during the preceding year. Then, household measures were applied to convert portion sizes of consumed foods to grams per day [36]. Finally, daily intake of energy and all nutrients was obtained by Nutritionist IV software.

The following equation suggested by McCarty et al. [26] was applied to estimate DPI for each participant: DPI = [(dietary energy derived from phytochemical-rich foods (kcal)/total daily energy intake (kcal)) × 100]. Vegetables, fruits, natural vegetable and fruit juices, tomato sauces, whole grains, legumes, nuts, seeds, olives, and olive oil were considered as phytochemical-rich foods. Potato was not considered for DPI calculation, because of its limited content of phytochemicals.

Assessment of anthropometric indices and cardiometabolic risk factors: A trained dietitian measured anthropometric indices. All measurements were performed while individuals stood in light clothing and with no shoes. Weight (kg) was

measured with a body composition analyzer (Tanita MC-780MA), and height (m) was measured to the nearest 0.1 cm using a tape measure. Waist circumference (cm) was measured to the nearest 0.1 cm at the end of a normal respiratory expiration by measuring halfway between the lower rib margin and iliac crest using a nonstretchable tape measure. The mean of 2 measurements of waist circumference was recorded. BMI (in kg/m^2) was calculated by dividing weight by the height squared. Blood pressure was measured using a digital sphygmomanometer (OMRON, M3, HEM-7154-E) in the sitting position after a 5-min resting. For each subject, this measurement was repeated 2 times with a 5-min interval, and the mean of 2 measurements was used for the analyses.

Twelve-hour fasting venous blood samples were drawn to evaluate biochemical markers. Serum concentrations of fasting blood glucose (FBG), HDL cholesterol, and triglyceride (TG) were measured using an autoanalyzer (BioSystems). Moreover, serum concentrations of insulin (Monobined Inc.) and high-sensitivity C-reactive protein (hs-CRP) (turbidimetry kit, latex enhanced turbidimetric method) were assessed through commercial kits. Insulin resistance was evaluated based on the HOMA-IR by the use of the following formula: HOMA-IR = [(fasting insulin (mU/L) × FBG (mg/dL)]/405. The ELISA kits (Zellbio) were applied to measure serum concentrations of adropin and BDNF. The first decile of serum BDNF and adropin concentrations were considered as low serum BDNF and adropin values.

Defining metabolic health status

Participants were divided into 4 groups of metabolic health: MHNW, MHO/overweight (MHOW), MUNW, and MUO/overweight (MUOW), according to the method provided by Wildman et al. [37]. Based on this method, individuals with normal-weight ($18.5 \leq$ BMI < 25) and overweight or obesity (BMI ≥ 25) with ≥ 2 of the following risk factors were considered as MUNW and MUOW, respectively: *1)* increased FBG (≥ 100 mg/dL), *2)* decreased HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females, *3)* increased TGs (≥ 150 mg/dL), and *4)* increased blood pressure ($\geq 130/85$ mmHg), *5)* increased insulin resistance (HOMA-IR > 90th percentile, or > 3.99), *6)* increased inflammatory protein hs-CRP (> 90th percentile, or > 6.14 mg/L). Individuals with normal-weight and overweight or obesity with < 2 of the abovementioned risk factors were considered as MHNW and MHOW, respectively.

Assessment of other variables

A validated International Physical Activity Questionnaire-short form was applied to evaluate physical activity [38]. This questionnaire contains 7 questions reflecting the frequency (days per week) and duration (minutes per day) of walking, moderate intensity, and vigorous-intensity physical activities during the last week. Data from this tool was converted to metabolic equivalent minutes per week. Then, individuals were categorized into inactive, minimally active, or health-enhancing physical activity active.

The validated Persian version of the Hospital Anxiety and Depression Scale was used to assess depression among study participants [39]. This 14-item self-administered questionnaire encompasses 2 7-item subscales of anxiety and depression. Each item is scored on a 4-point Likert-type scale, and the final score of each subscale ranges from 0 to 21. Those with a final score of ≥ 8 were considered as having depression. Data regarding other covariates, including age, sex, smoking habits, marital and education status, and socioeconomic status, were collected by a self-reported questionnaire.

Statistical analyses

The normal distribution of quantitative data was assessed by the Kolmogorov-Smirnov test. Continuous and categorical variables were reported as mean $\pm$ SD or SE and percentages, respectively. Individuals were distributed in tertiles of DPI (T1: < 25.27, T2: 25.27–36.44, and T3: > 36.44). Then, continuous and categorical variables were compared across tertiles of DPI through the χ^2 test and 1-way analysis of variance. To report adjusted dietary intakes of individuals across DPI tertiles, the analysis of covariance was used. Energy and macronutrients intakes were adjusted for age and sex, whereas intake of other nutrients was adjusted for energy intake, age, and sex. Binary logistic regression was applied to evaluate the association between DPI and MU and its components by reporting odds ratios (ORs) and 95% CIs in crude and multivariable adjusted models. Based on previous literature [27,30,40], in model 1, age, sex, and energy intake were controlled. Physical activity, smoking, marital status, educational status, and socioeconomic status were additionally adjusted in model 2. The effect of BMI was additionally adjusted in model 3. The first tertile of DPI was considered as the reference category. DPI tertiles were considered as continuous variables in logistic regression models to determine trends. Furthermore, stratified analyses were performed based on sex (males compared with females) and BMI categories (those with normal-weight compared with those with overweight or obesity). Crude and multivariable adjusted ORs and 95% CIs were also used to estimate the odds of low BDNF and adropin values in DPI tertiles. All statistical analyses were done by Statistical Package for Social Sciences version 20 (SPSS Inc.). *P* values of < 0.05 were considered statistically significant.

Results

In total, 527 adults, comprising 286 males and 241 females with a mean age of 42.66 ± 11.19 (SD) y and a mean BMI of 26.91 ± 4.43, were included in the present study. Among them, 42.5% (147 males and 77 females) had an MU phenotype. Among normal-weight individuals, 20.5% had an MU phenotype, whereas 79.5 % of subjects with overweight or obesity were MU.

General characteristics of the study population across tertiles of DPI are presented in Table 1. A significant difference was observed in mean age ($P < 0.001$), weight ($P = 0.04$), and high hs-CRP values ($P = 0.01$) among tertiles of DPI. Participants with the highest adherence to DPI were more likely to be females ($P < 0.001$), have higher socioeconomic status ($P = 0.01$), and university level education ($P = 0.01$). No significant differences were observed for other subjects' characteristics across tertiles of DPI.

Dietary intakes of the study population across tertiles of DPI are reported in Table 2. Individuals in the highest tertile of DPI had a higher intake of energy, carbohydrates, fruits, vegetables, nuts, fiber, vitamin A, vitamin K, vitamin C, vitamin B6, folate, magnesium, and fructose and consumed a lower amount of total fat, SFA, MUFA, and PUFA than those in the lowest tertile. No

TABLE 1

General characteristics and cardiometabolic factors of study participants across tertiles of dietary phytochemical index[1]

	DPI tertiles			*P* value[2]
	T1 (*n* = 175) (<25.27)	T2 (*n* = 176) (25.27, 36.44)	T3 (*n* = 176) (>36.44)	
Age (y)	39.73±11.52	41.42±9.69	46.80± 11.09	<0.001
Sex, %				<0.001
Males	65.1	55.1	42.6	
Females	34.9	44.9	57.4	
Marital status, %				0.25
Single	20.8	11.9	16.2	
Married	78.0	86.9	82.1	
Divorced or widow	1.2	1.1	1.7	
Education status, %				0.01
Diploma or lower	16.0	5.1	12.1	
Higher than diploma	84.0	94.9	87.9	
Socioeconomic status [3], %				0.01
Low	43.0	25.0	25.5	
Moderate	30.6	35.3	29.6	
High	26.4	39.7	44.9	
Weight (kg)	76.55±15.01	77.25±14.40	73.53±14.15	0.04
BMI (kg/m^2)	26.50±4.42	27.27±4.17	26.95±4.69	0.27
Waist circumference (cm)	92.39±12.16	93.60±10.86	91.99±11.42	0.39
BMI categories, %				0.06
Normal-weight	38.9	27.3	30.7	
Overweight/obese	61.1	72.7	69.3	
Smoking, %				0.54
Nonsmoker	93.0	92.5	95.4	
Ex-smoker	2.5	3.8	3.3	
Current smoker	4.4	3.8	1.3	
Physical activity levels, %				0.14
Inactive	59.0	58.5	52.6	
Minimally active	30.1	35.8	40.6	
HEPA active	11.0	5.7	6.9	
High systolic blood pressure (mmHg)	24.0	24.4	33.0	0.10
High diastolic blood pressure (mmHg)	39.4	40.9	39.2	0.94
High fasting blood glucose (mg/dL)	20.0	18.8	20.5	0.92
High triglycerides (mg/dL)	37.7	39.2	33.0	0.45
Low HDL cholesterol (mg/dL)	9.7	12.5	12.5	0.64
High hs-CRP (>90th percentile)	16.0	4.5	9.1	0.01
High HOMA-IR index (>90th percentile)	9.1	9.7	10.8	0.87

Abbreviations: ANOVA, analysis of variance; DPI, dietary phytochemical index; HEPA, health-enhancing physical activity; hs-CRP, high-sensitivity C-reactive protein.

[1] Values are mean ± SD, unless indicated.

[2] Obtained from 1-way ANOVA and χ^2 test for quantitative and categorical variables, respectively.

[3] Socioeconomic status score was evaluated based on the job, family size, having a car in the family, having a computer/laptop, and having travel by using a validated questionnaire.

significant differences were observed in the consumption of protein, whole grains, cholesterol, vitamin E, thiamin, riboflavin, niacin, vitamin B12, and calcium among DPI tertiles.

The frequency of participants with an MU phenotype across DPI tertiles is presented in Figure 1. A MUNW phenotype was observed in 30.9%, 25.0%, and 24.1% of normal-weight individuals in tertiles 1, 2, and 3 of DPI (*P* = 0.65) (Figure 1A). In addition, 50.5%, 46.9%, and 52.5% of individuals with overweight or obesity were identified as MUOW in tertiles 1, 2, and 3 of DPI (*P* = 0.67) (Figure 1B).

Multivariate adjusted ORs and 95% CI for MU status across tertiles of DPI are presented in Table 3. In the crude model, there was no significant association between DPI tertiles and MU status (OR: 1.04; 95% CI: 0.68, 1.58). However, the association became significant in model 2 after adjustment for confounders (including age, sex, energy intake, physical activity, smoking, marital, educational, and socioeconomic status) (OR: 0.47; 95%

CI: 0.22, 0.98). In the fully adjusted model, participants in the highest tertile of DPI had 59% significantly lower odds of MU status than those in the lowest tertile (OR: 0.41; 95% CI: 0.19, 0.87). As shown in Table 3, stratified analysis by sex revealed no significant association between DPI categories and MU status among females in the crude model (OR: 0.92; 95% CI: 0.47, 1.81). Again, this relationship became significant in model 2, and after considering all potential cofounders, females in the third tertile of DPI had 72% significantly reduced odds for MU phenotype in comparison with those in the first tertile (OR: 0.28; 95% CI: 0.08, 0.97). No significant association was observed between DPI tertiles and MU status either in crude (OR: 1.58; 95% CI: 0.87, 2.84) or fully adjusted model (OR: 0.41; 95% CI: 0.13, 1.28) among males.

Stratified analysis by BMI showed that in normal-weight participants, there was no significant association between DPI tertiles and MU status in the crude model (OR: 0.71; 95% CI:

TABLE 2

Dietary intakes (energy, macro/micro nutrients, and food groups) of study participants across tertiles of dietary phytochemical index[1]

DPI tertiles			
	T1 (*n* = 175) (<25.27)	T2 (*n* = 176) (25.27, 36.44)	T3 (*n* = 176) (>36.44)	*P* value[2]
Energy (kcal)	2164.34±52.19	2304.09±50.88	2361.85±52.85	0.03
Protein, % of energy	14.44±0.22	14.46±0.21	13.85±0.22	0.10
Carbohydrate, % of energy	58.89±0.61	59.99±0.60	63.83±0.62	<0.001
Fat, % of energy	27.90±0.51	27.43±0.50	25.09±0.52	<0.001
Cholesterol (mg)	286.13±9.06	281.23±8.80	260.49±9.16	0.12
SFA (g)	24.28 ±0.59	22.49±0.57	20.16±0.60	<0.001
MUFA (g)	23.10±0.52	22.01±0.50	20.18±0.52	0.01
PUFA (g)	16.29 ±0.56	17.09±0.55	14.73±0.57	0.01
Vitamin A, (RAE)	940.23 ±65.91	1235.32 ±63.99	1823.41±66.62	<0.001
Vitamin E (mg)	6.53±0.24	6.94±0.23	7.16±0.24	0.19
Vitamin K (Ug)	119.86±6.88	153.31±6.68	182.61±6.96	<0.001
Vitamin C (mg)	134.75±6.77	191.75±6.57	268.48±6.84	<0.001
Thiamin (mg)	2.05±0.32	2.03±0.31	2.04±0.32	0.90
Riboflavin (mg)	1.92±0.05	2.02±0.04	2.01±0.05	0.26
Niacin (mg)	23.61±0.35	22.88±0.34	22.37±0.36	0.06
Vitamin B6 (mg)	1.55±0.04	1.79±0.03	2.06±0.04	<0.001
Folate (µg)	282.02±8.02	347.47 ±7.78	395.75 ±8.10	<0.001
Vitamin B12 (µg)	4.25±0.14	4.28±0.13	3.84±0.14	0.05
Magnesium (mg)	252.22±4.79	290.04±4.65	309.15±4.85	<0.001
Calcium (mg)	892.65±28.92	957.29±28.08	921.96±29.23	0.27
Fructose (g)	15.60±0.84	19.79±0.81	27.89±0.85	<0.001
Total fiber (g)	16.03±0.39	20.90±0.37	26.54±0.39	<0.001
Fruits (g)	336.23±20.58	533.40±19.98	797.16±20.80	<0.001
Vegetables (g)	247.53±16.29	326.00±15.82	450.40±16.47	<0.001
Whole grains (g)	120.63±6.21	108.12±6.03	108.83±6.27	0.28
Legumes (g)	30.84±2.81	44.24±2.73	42.63±2.85	0.01
Nuts (g)	7.28±0.95	13.18±0.92	15.02± 0.96	<0.001

Abbreviations: ANCOVA, analysis of covariance; DPI, dietary phytochemical index, RAE, retinol activity equivalents.

[1] Values are mean ± SE. Energy intake and macronutrients were adjusted for age and sex; all other values were adjusted for age, sex, and energy intake.

[2] *P* value obtained from ANCOVA test for adjustment of energy intake.

0.32, 1.59) (Figure 2A). However, after making adjustments for confounders, participants in the highest tertile of DPI showed an 89% significant reduced odds for MU phenotype compared with those in the bottom tertile (OR: 0.11; 95% CI: 0.02, 0.62). No significant association was observed between DPI and MU phenotype either in crude (OR: 1.08; 95% CI: 0.64, 1.82) or fully adjusted model (OR: 0.62; 95% CI: 0.24, 1.61) among individuals with overweight or obesity (Figure 2B).

Multivariate adjusted ORs and 95% CIs for components of metabolic health status across tertiles of DPI are presented in Table 4. No significant association was found between DPI and components of metabolic health in the crude model. However, after controlling for confounders, participants in the third tertile of DPI showed significantly decreased odds of high FBG (OR: 0.40; 95% CI: 0.17, 0.96), high TG (OR: 0.42; 95% CI: 0.20, 0.88), and high hs-CRP (OR: 0.24; 95% CI: 0.08, 0.72) compared with the first tertile.

The mean values of serum BDNF and adropin across different metabolic health phenotypes are depicted in Figure 3. Participants with an MHOW phenotype had the lowest serum BDNF values [1.12±0.04 (SE) ng/mL], and those with an MUNW phenotype had the highest serum BDNF concentration [1.79 ±0.61 (SE) ng/mL] (*P* = 0.05). Furthermore, MUOW individuals showed the lowest serum adropin concentration [54.91±2.50 (SE) pg/mL], whereas the highest serum adropin concentrations were observed in MHNW individuals [59.39±4.36 (SE) pg/mL] (*P* = 0.79).

Multivariate adjusted ORs and 95% CIs for low BDNF and adropin values (the first decile) across tertiles of DPI are presented in Table 5. In a fully adjusted model, 13% and 25% nonsignificant reduced odds for low BDNF and low adropin values were observed in individuals in the top tertile of DPI

A.

P =0.65

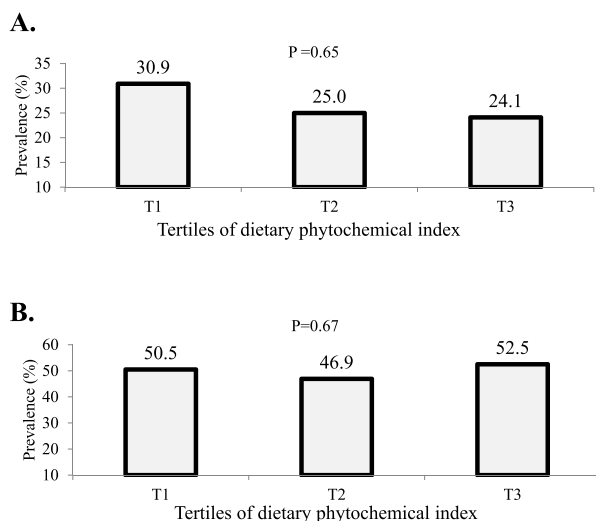30.9 25.0 24.1

B.

P=0.67

50.5 46.9 52.5

FIGURE 1. Prevalence of metabolically unhealthy phenotype in individuals with (A) normal-weight and (B) obesity or overweight in tertiles of dietary phytochemical index.

TABLE 3

Multivariable adjusted odds ratio and 95% confidence interval for metabolically unhealthy status across tertiles of dietary phytochemical index[1]

DPI tertiles				
	T1 (<25.27)	T2 (25.27, 36.44)	T3 (>36.44)	*P*-trend
All participants				
Cases/participants (*n*)	75/175	72/176	77/176	
Crude	1	0.92 (0.60, 1.41)	1.04 (0.68, 1.58)	0.87
Model 1[2]	1	0.85 (0.54, 1.33)	0.75 (0.46, 1.23)	0.25
Model 2[3]	1	0.69 (0.37, 1.30)	0.47 (0.22, 0.98)	0.04
Model 3[4]	1	0.56 (0.29, 1.08)	0.41 (0.19, 0.87)	0.02
Males				
Cases/participants (*n*)	54/114	49/97	44/75	
Crude	1	1.13 (0.66, 1.95)	1.58 (0.87, 2.84)	0.14
Model 1[2]	1	0.90 (0.50, 1.60)	0.87 (0.45, 1.69)	0.67
Model 2[3]	1	0.67 (0.30, 1.50)	0.55 (0.19, 1.61)	0.24
Model 3[4]	1	0.52 (0.22, 1.21)	0.41 (0.13, 1.28)	0.09
Females				
Cases/participants (*n*)	21/61	23/79	33/101	
Crude	1	0.78 (0.38, 1.60)	0.92 (0.47, 1.81)	0.89
Model 1[2]	1	0.78 (0.37, 1.64)	0.62 (0.30, 1.28)	0.20
Model 2[3]	1	0.67 (0.21, 2.13)	0.28 (0.08, 0.95)	0.04
Model 3[4]	1	0.59 (0.18, 1.93)	0.28 (0.08, 0.97)	0.04

[1] All values are odds ratios and 95% confidence intervals.
[2] Model 1: Adjusted for age, sex, and total energy intake. In stratified analysis by sex, adjusted for age and total energy intake.
[3] Model 2: Additionally adjusted for physical activity, smoking, marital status, educational status, and socioeconomic status.
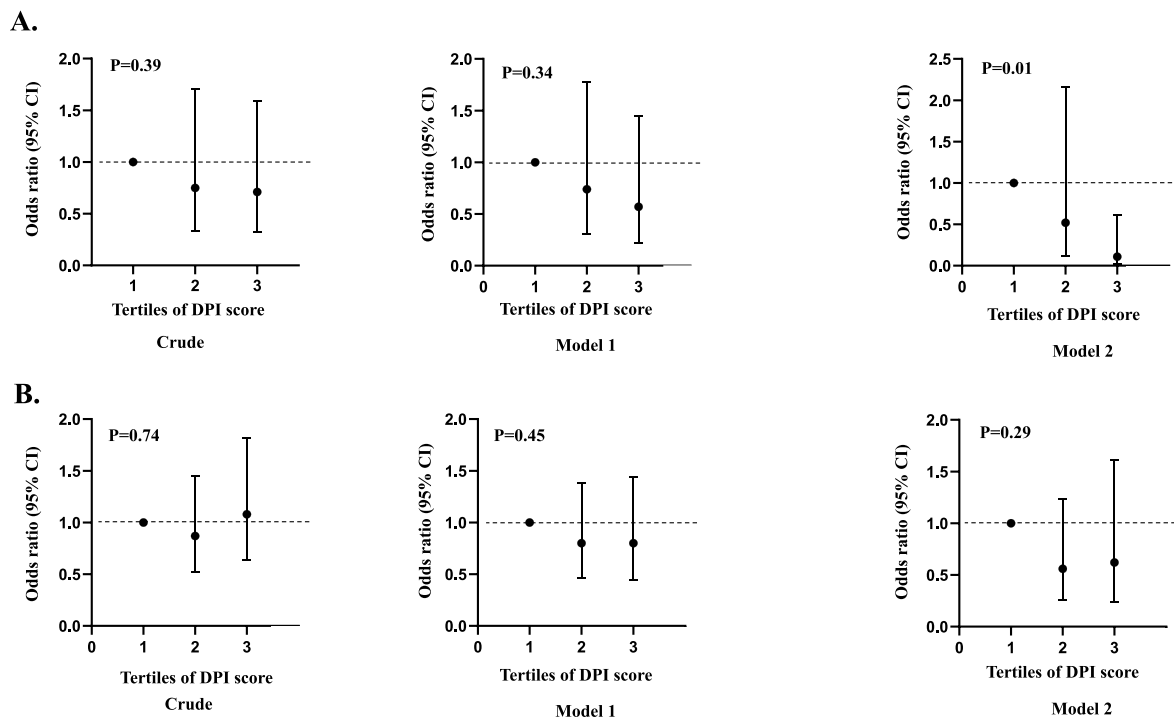[4] Model 3: Additionally adjusted for BMI.

FIGURE 2. Multivariate adjusted odds ratio and 95% confidence intervals (CIs) for the metabolically unhealthy phenotype in individuals with (A) normal-weight and (B) obesity or overweight. Model 1: adjusted for age, sex, and total energy intake; Model 2: further adjustment for physical activity, smoking, marital status, educational status, and socioeconomic status. DPI, dietary phytochemical index.

compared with those in the bottom tertile [(OR: 0.87; 95% CI: 0.42, 1.84); and (OR: 0.75; 95% CI: 0.31, 1.79), respectively].

Discussion

The results of this cross-sectional study showed that the prevalence of MU status was >40% among Iranian adults. This prevalence was significantly higher among individuals with overweight or obesity than those with normal-weight (79.5 compared with 20.5%). Higher adherence to DPI was significantly related to a reduced chance of MU phenotype, particularly in females and normal-weight individuals. Investigating the relationship between DPI and components of metabolic health status has additionally shown that higher dietary phytochemical

TABLE 4

Multivariable adjusted odds ratio and 95% confidence interval for metabolic components across tertiles of dietary phytochemical index[1]

DPI tertiles				
	T1 (<25.27)	T2 (25.27, 36.44)	T3 (>36.44)	*P*-trend
High blood pressure				
Crude	1	1.04 (0.68, 1.58)	1.16 (0.76, 1.77)	0.49
Fully adjusted model[2]	1	0.63 (0.32, 1.25)	0.65 (0.30, 1.41)	0.25
High fasting blood glucose				
Crude	1	0.92 (0.54, 1.57)	1.03 (0.61, 1.73)	0.91
Fully adjusted model[2]	1	0.53 (0.24, 1.16)	0.40 (0.17, 0.96)	0.04
High triglyceride				
Crude	1	1.07 (0.69, 1.64)	0.81 (0.52, 1.26)	0.35
Fully adjusted model[2]	1	0.68 (0.37, 1.26)	0.42 (0.20, 0.88)	0.02
Low HDL cholesterol				
Crude	1	1.33 (0.68, 2.60)	1.33 (0.68, 2.60)	0.42
Fully adjusted model[2]	1	1.24 (0.48, 3.21)	1.07 (0.37, 3.09)	0.91
High HOMA-IR				
Crude	1	1.06 (0.52, 2.18)	1.20 (0.60, 2.42)	0.60
Fully adjusted model[2]	1	1.32 (0.52, 3.35)	0.83 (0.29, 2.43)	0.76
High hs-CRP				
Crude	1	0.25 (0.11, 0.57)	0.53 (0.27, 1.01)	0.03
Fully adjusted model[2]	1	0.20 (0.07, 0.59)	0.24 (0.08, 0.72)	0.01

Abbreviation: hs-CRP, high-sensitivity C-reactive protein.

[1] All values are odds ratios and 95% confidence intervals.

[2] Fully adjusted model: Adjusted for age, sex, total energy intake, physical activity, smoking, marital status, educational status, socioeconomic status, and BMI.
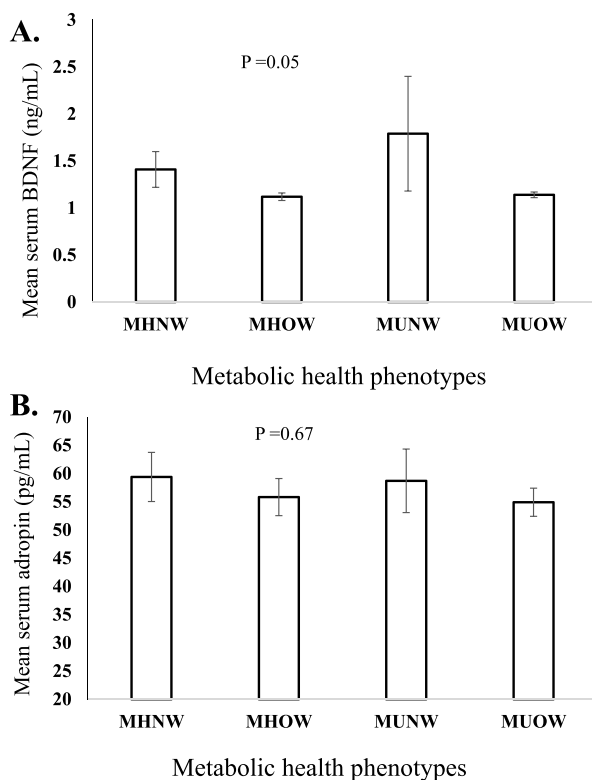

FIGURE 3. Mean serum concentrations of (A) brain-derived neurotrophic factor and (B) adropin across categories of metabolic health status. BDNF, brain-derived neurotrophic factor; MHNW, metabolically healthy normal-weight; MHOW, metabolically healthy obese/overweight; MUNW, metabolically unhealthy normal-weight; MUOW, metabolically unhealthy obese/overweight.

consumption was associated with lower odds of hyperglycemia, hypertriglyceridemia, and chronic inflammation. Furthermore, a nonsignificant inverse association was found between DPI with low BDNF and low adropin values.

NCDs are the leading causes of premature death and disability all around the globe, especially in developing countries where 80% of NCDs-related mortalities occur [41]. Metabolic and lifestyle risk factors are the most common causes of NCDs. Previous studies have shown that the prevalence of some NCDs, such as cardiovascular disease and chronic kidney disease, is higher in individuals with MUOW and MUNW phenotypes than in MHNW individuals [7,42]. Therefore, preventing shifting from a metabolically healthy status to MU status by dietary and lifestyle modifications can be beneficial in reducing the incidence of NCDs and correlated complications. Our results indicated that a higher dietary intake of phytochemical-rich foods such as fruits, vegetables, and nuts could be a beneficial approach to decrease the chance of MU, particularly in females and the normal-weight population. Therefore, the consumption of phytochemical-rich foods should be monitored in clinical settings; in case of insufficient consumption, relevant dietary education programs can be provided.

Although the beneficial role of phytochemicals on health has been indicated by various studies, few studies have investigated the relationship between dietary intake of these bioactive compounds and metabolic health status. DPI is an appropriate and simple tool to evaluate the intake of dietary phytochemicals and to investigate their effects on health in epidemiologic studies. The association between DPI and MetS and its components (such as hypertension, insulin resistance, and lipid profile disorders) has been investigated in previous research. Tehran Lipid and Glucose study [28] involving 2567 adult subjects reported that

TABLE 5
Multivariable adjusted odds ratio and 95% confidence interval for low brain-derived neurotrophic factor and adropin values across tertiles of dietary phytochemical index[1]

DPI tertiles				
	T1 (<25.27)	T2 (25.27, 36.44)	T3 (>36.44)	P-trend
Low BDNF				
Crude	1	0.83 (0.42, 1.64)	0.83 (0.42, 1.64)	0.59
Model 1[2]	1	0.81 (0.41, 1.62)	0.81 (0.39, 1.69)	0.57
Model 2[3]	1	0.85 (0.42, 1.71)	0.87 (0.42, 1.84)	0.66
Low adropin				
Crude	1	0.61 (0.28, 1.35)	1.00 (0.49, 2.03)	0.49
Model 1[4]	1	0.59 (0.26, 1.31)	0.90 (0.41, 1.94)	0.47
Model 2[5]	1	0.66 (0.29, 1.49)	0.74 (0.31, 1.76)	0.77
Model 3[6]	1	0.70 (0.30, 1.59)	0.75 (0.31, 1.79)	0.99

Abbreviation: BDNF, brain-derived neurotrophic factor.
[1] All values are odds ratios and 95% confidence intervals.
[2] Model 1: Adjusted for age and sex.
[3] Model 2: Additionally adjusted for physical activity, depression, hypertension, history of diabetes mellitus, and hyperlipidemia.
[4] Model 1: Adjusted for age, sex, and total energy intake.
[5] Model 2: Additionally adjusted for physical activity and smoking.
[6] Model 3: Additionally adjusted for BMI.

individuals in the highest DPI category showed reduced odds of hypertriglyceridemia and central obesity. However, no significant association was observed between DPI and other cardiometabolic risk factors [28]. The results of a prospective study in 1546 nonhypertensive Iranian adults indicated that higher adherence to DPI was associated with 48% reduced risk of incidence of hypertension [43]. Furthermore, the Korean National Health and Nutrition Examination survey involving 38,198 Koreans (≥30 y) reported an inverse association between DPI and hypertension prevalence [44]. In a longitudinal study, participants in the highest quartile of DPI had 86% reduced risk of incidence of hyperinsulinemia after 3 y of follow-up. The mentioned study has also indicated significant inverse relations between insulin resistance, insulin insensitivity, and DPI [29]. There were controversial findings regarding the association between DPI and lipid profiles. In a longitudinal study of 1983 adult subjects, significant inverse associations were found between DPI with total cholesterol, TG, and non-HDL cholesterol in males [45]. Another study in 235 patients with type 2 diabetes mellitus reported a significant positive association between DPI and HDL cholesterol; however, no significant association was observed between DPI with other lipid values [46]. To our knowledge, our study was among the first investigations that assessed the relationship between DPI and metabolic health status in Iranian adults. Similar to our results, Pourreza et al. [31] indicated that higher adherence to DPI was associated with a lower risk of MUOW phenotype in middle-aged females with overweight or obesity [31]. However, they have not assessed this linkage among males and normal-weight subjects. The mentioned study showed a significant relationship between DPI and HOMA-IR but not with other components of metabolic health status [31]. The differences in the findings of the above-mentioned studies are probably because of different study designs and populations.

Decreased concentrations of BDNF and adropin among individuals with metabolic disorders such as obesity and diabetes mellitus might be associated with the regulatory role of these molecules on the metabolism of macronutrients [47,48]. Limited evidence from interventional studies documented the effect of diet on the serum concentration of these biomarkers in humans [18,22,23,49]. In the present study, we evaluated for the first time the relationship between DPI with low serum concentrations of BDNF and adropin to figure out whether these biomarkers facilitate the favorable role of phytochemical-rich foods on metabolic health status. Our study showed that higher adherence to DPI might reduce the odds of low serum concentration of BDNF and adropin; however, the association was not statistically significant. Further large-scale prospective surveys are warranted to discover the effect of dietary phytochemicals on serum concentrations of BDNF and adropin and underlying mechanisms in human subjects.

The exact mechanisms explaining the relationship between DPI and metabolic health status are not well understood; however, some mechanisms are proposed. Oxidative stress and inflammation can be determinant factors in the etiology of MU phenotype [50,51]. Higher intake of phytochemical-rich foods may have favorable influences on metabolic health status through decreasing oxidative stress and inflammation. There is clear evidence about the effects of dietary phytochemicals such as phenolic acids, flavonoids, and carotenoids on reducing risk of cardiometabolic disorders through their antioxidant activity [24]. A growing body of in vitro and in vivo studies have suggested anti-inflammatory roles for phytochemicals from plant foods [52,53]; such that similar to our findings, a study in 18,699 Korean adults indicates an inverse trend between consumption of phytochemical-rich foods and inflammatory biomarkers such as high hs-CRP and white blood cell count [54].

The present study has several limitations that should be considered. First, it was not possible to establish a causal relationship between DPI and MU status, because of the cross-sectional design of the study. It should be considered that observed associations might be biased by reverse causation because individuals with cardiometabolic disorders might change their lifestyle behaviors. Thus, to explore a causal link between intake of phytochemicals and metabolic health status, well-designed prospective studies are needed. Second, although a validated FFQ has been used to collect usual dietary intakes, self-reported dietary intakes might be biased to recall bias and misclassification. Third, several

confounders were taken into account; however, the confounding role of some other confounders (such as muscle mass, sleep, and stress) on relationships remained to be considered. Fourth, the phytochemical content of food items with no calories, such as nonalcoholic beverages like tea and spices, or the bioavailability of phytochemicals, have been not considered in DPI estimation, which might affect the results. Fifth, there was no biomarker-based evidence for validation of DPI obtained from the applied FFQ; however, a number of previous studies reported the association between this index and chronic diseases [55–58]. Finally, although the sample examined in this study (in terms of general characteristics such as socioeconomic status, smoking, marital status, and physical activity) was similar to a previous large-scale survey conducted in Isfahan [59], a relatively small sample of adults was studied. Thus, extrapolation of these findings to the general adult population should be done with caution. The applied definition of metabolic health status (Wildman et al. [37] method) included hs-CRP as an inflammatory index besides insulin resistance and other traditional cardiometabolic risk factors. Finally, the evaluation of adropin and BDNF as biomarkers with limited dietary information in epidemiologic studies was the other strength of the study.

In conclusion, we found an inverse association between DPI and MU phenotype, particularly among females and normal-weight individuals. DPI was inversely associated with hyperglycemia, hypertriglyceridemia, and chronic inflammation. However, no significant association was found between serum concentrations of BDNF and adropin with phytochemical intake. Further prospective research in various populations is required to confirm these findings.

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Author contributions

The authors' responsibilities were as follows – SAT, KL, FS, ZH, PR, PS: contributed to the conception, design, data collection, data interpretation, manuscript drafting, and approval of the final version of the manuscript and agreed to all aspects of the work; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

The data that support the findings of the present study are available from the corresponding author upon request.

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