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Ultra-processed foods intake in relation to metabolic health status, serum brain-derived neurotrophic factor and adropin levels in adults

Donya Poursalehi[1,2], Shahnaz Amani Tirani[1,2], Farnaz Shahdadian[3], Zahra Hajhashemy[1,2], Parisa Rouhani[4] and Parvane Saneei[2*]

Abstract

Background In recent years, there has been a lot of discussion over the impact of ultra-processed foods (UPFs) intake on overall health of subjects. However, the association between UPFs intake and metabolic unhealthy (MU) status is still in a state of ambiguity. The current study assessed the relationship between UPFs intake and MU status with regard to brain-derived neurotrophic factor (BDNF) and adropin levels.

Methods A sample of Iranian adults (aged 20–65 years) was selected to participate in this cross-sectional study using a multistage cluster random-sampling method. UPFs intake was assessed by a validated food frequency questionnaire and NOVA classification. Concentrations of metabolic parameters, BDNF and adropin were determined through fasting blood samples. MU status was assessed according to the criteria proposed by Wildman.

Results The overall prevalence of MU phenotype among study participants ($n=527$) was 42.5%. Higher intake of UPFs was associated with elevated odds of MU status in multivariable-adjusted model ($OR_{T3\ vs.\ T1}=1.88$; 95%CI: 1.02–3.45). Moreover, a positive association was observed between UPFs intake and hypertriglyceridemia after controlling all confounders ($OR_{T3\ vs.\ T1}=2.07$; 95%CI: 1.15–3.73). However, each tertile increase in UPFs intake was not significantly associated with serum BDNF ($\beta=0.15$; 95%CI: -0.05, 0.34; $P=0.14$) and adropin ($\beta=-1.37$; 95%CI: -6.16, 3.42; $P=0.58$) levels in multivariable-adjusted linear regression models.

Conclusion Our findings suggested that higher consumption of UPFs was related to increased likelihood of MU status among a sample of Iranian adults. Further longitudinal studies are needed to verify the directionality and generalizability of the results to all adult populations.

Keywords Ultra-processed foods, Metabolic health status, Brain-derived neurotrophic factor, Adropin, Adults

*Correspondence:
Parvane Saneei
saneeip@yahoo.com; saneei@nutr.mui.ac.ir
[1]Students' Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Community Nutrition, School of Nutrition and Food Science, Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, PO Box 81745-151, Isfahan, Iran
[3]Department of Clinical Nutrition, School of Nutrition and Food Science, Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

Introduction

Overweight and obesity are known as serious global health concerns, considering their dramatic increasing trend in both developed and developing nations [1]. According to the latest statistics published by the World Health Organization (WHO), the global prevalence of overweight and obesity among adult individuals were estimated as 39% and 13%, respectively [2]. The excessive accumulated fat in the body is the major risk factor for developing chronic diseases such as cardiovascular diseases [3], respiratory diseases [4] and certain types of cancers [5]. It also affects self-esteem and life expectancy, negatively [6]. However, this condition does not apply to all individuals with overweight/obesity. Such that a group of adults with overweight or obesity has a favorable metabolic profile, regardless of their weight status [7]. In return, some adults with normal weight may have several metabolic disorders [7]. Therefore, metabolic status could be a more comprehensive and accurate definition of the health status of subjects compared with their weight alone.

Brain as a central nervous system has multidirectional relationships with other body organs through bioactive factors including hormones to promote health status against external cues. Brain-derived neurotrophic factor (BDNF) and adropin are among these hormones. Despite the decisive role of these bioactive molecules in brain growth and development, they are involved in metabolic profile by mediating energy and hemostasis [8, 9]. Several studies documented the significant association between these peptide hormones and metabolic disorders [10–12]. It has also been discovered that circulating levels of these hormones would be influenced by environmental factors including diet [13, 14]. However, data in this regard are insufficient. Therefore, evaluating various dietary intakes in relation to BDNF and adropin levels could broaden our knowledge about improving these hormones and thus, decreasing metabolic disorders.

There has been a global surge in the consumption of pre-made or ready-made products which are known as ultra-processed foods (UPFs) [15]. UPFs consist of a combination of various components, which are predominantly comprised of specialized industrial-grade processing substances [16]. Food processing serves to improve flavor, aroma and color profiles of foods, increases the longevity of food products, and decreases the amount of time required for their preparation [17]. In addition, these products have found a special place in people's diets, due to their affordable cost [18]. The variety and availability of UPFs have substantially grown in food markets which first appeared in high-income nations and then, were spread to middle-income countries [19]. This transition to a highly processed diet raises major health concerns at a global scale.

UPFs might change the taste and dietary behavior of individuals and reduce their desire for organic and unprocessed foods. Also, UPFs typically exhibit limited nutritional values, characterized by a high energy density, inadequate fiber and vitamins composition, and elevated levels of added sugars, saturated fatty acids (SFAs), trans fatty acids (TFAs), sodium, additives and neo-formed chemicals that make subjects susceptible to endocrine disorders [20]. It has been shown that UPFs intake was associated with increased odds of metabolic syndrome (MetS) in American adult populations [21]. However, this association was not significant among Brazilian individuals [22]. Positive relationships between UPFs and other cardiometabolic abnormalities including dyslipidemia, diabetes and hypertension were also documented in different societies [23–25]. However, most of these studies were conducted in Western countries where economic status and dietary habits are different from our culture. Also, there is a lack of data addressing the potential association between UPFs with metabolic health status, as a recent proposed concept, and BDNF and adropin, as metabolic determinant hormones. Given the roles of BDNF and adropin in metabolic regulation and limited evidence regarding the relation between diet and these markers, we hypothesized that high UPF consumption could be negatively related to BDNF and adropin levels, thereby could contribute to the development of an unhealthy metabolic status. Thus, this study was designed to assess UPFs intake in relation to metabolic health status, as well as BDNF and adropin in a sample of Iranian adults.

Methods and materials

Study design and participants

This cross-sectional study was performed in 2021, on a sample of Iranian adults (20 to 65 years old) living in Isfahan, a large central city of Iran. Participants were recruited from employees of 20 schools in different education districts of the city, using a multistage cluster random-sampling approach. Adults with various job categories in schools (managerial, educational, assistantship or service roles) were included. The sample size was calculated based on a previous report on the frequency of MU phenotype in Iranian adults [26]. Considering type 1 error of 0.05 (confidence interval (CI) of 0.95), precision (d) of 4.5%, and power of 80%, a minimum sample size of 474 subjects was estimated for this study. However, 600 individuals were invited to participate in the survey, given the high prevalence of covid-19 pandemic and its probable impact on data collection. Individuals with a history of type 1 diabetes, cardiovascular diseases, stroke, cancer, pregnant or lactating women, and those who followed a special diet (weight loss or weight gain diets) were not included in the study. Then, participants who left more than 70 items on the food frequency questionnaire (FFQ)

unfilled, or reported an energy intake outside of the 800–4200 kcal/d range, or refused blood draw were excluded. Finally, a total of 527 adults met the eligible criteria for participating in this study. The local Ethics Committee of Isfahan University of Medical Sciences approved the protocol of this study. The objectives of the study were explained to each participant and a written informed permission was obtained.

Dietary intakes and UPFs intake estimation

Dietary intakes of individuals were collected by a Willett-format semi-quantitative 168-item FFQ. The results of this FFQ validation study among the Iranian population demonstrated reasonable correlations between the estimated intakes by FFQ and those estimated by 24-hour dietary recalls [27]. One year test-retest reliability of the questionnaire was also approved by the mentioned validation study. A registered dietitian provided detailed instructions on completing the FFQ for all participants. Afterward, household measures were used to convert the portion size of consumed foods to grams per day [28]. For a final estimate of energy and nutrient intake, the Nutritionist IV program was applied.

The NOVA (a name, not an acronym) classification was used to detect UPFs in the present study. The mentioned system categorizes foods based on the nature, extent, and purpose of food processing into four groups of unprocessed or minimally processed, processed culinary, processed, and ultra-processed foods [29]. UPFs were subjected to the most advanced level of processing and manufactured as complex industrial formulations consisting of many components [29, 30]. The UPFs in the present study were thirty-two food items and beverages classified into 7 groups of sweets (jam, gaz, sohan, candy, chocolate, cream caramel, sesame halva, and noghl), industrial breads and cakes (French bread, toast bread, biscuits, cakes (including Yazdi, homemade, other cakes), pastries, creamy pastries and donuts), processed meats and fast foods (canned tuna, hamburger, sausage, pizza), potato chips and salty snacks (crackers, puffs, and potato chips), dairy beverages (cocoa milk, chocolate milk, traditional ice cream, non-traditional ice creams), non-dairy beverages (soft drinks), and oil and sauces (mayonnaise, tomato sauce, margarine). The daily intakes of these thirty-two food items and beverages were summed up to determine the daily UPFs intake of each subject.

Anthropometry and blood pressure

Anthropometric indices (weight, height, and waist circumference (WC)) were assessed based on standard procedures by two skilled dietitians. Weight was measured to the nearest 0.1 kg by a body composition analyzer (Tanita MC-780MA, Tokyo, Japan). Height was measured to the nearest 0.1 cm by a tape measure fixed on the wall. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). WC was also measured to the nearest 0.1 cm by an unstretched flexible tape, after a normal breath with no outside pressure on the body. The blood pressure (BP) of participants was measured after a five-minute rest using a digital sphygmomanometer (OMRON, M3, HEM-7154-E, Japan). BP was measured twice, with an interval of 5–10 min, and the average of two measurements was reported as the final value.

Biochemical parameters

An overnight 12-hour fasting blood sample was drawn from each participant for biochemical assessments. Concentrations of triglyceride (TG), fasting blood glucose (FBG), and high-density lipoprotein cholesterol (HDL-c) were assessed using a Biosystem A15 auto-analyzer with specific enzymatic colorimetric methods. Additionally, serum levels of other biochemical parameters including high sensitive C-reactive protein (hs-CRP) (turbidimetry kit, latex enhanced turbidimetric method, Delta. DP), insulin (Monobined Inc. Lake Forest, CA 92630, USA), BDNF (Zellbio, Veltlinerweg, Germany), and adropin (Zellbio, Veltlinerweg, Germany) were measured by using the commercial enzyme-linked immunosorbent assay (ELISA) kits. Homeostasis Model Assessment Insulin Resistance (HOMA-IR) formula was used to estimate insulin resistance (IR) [31].

Metabolic health status

Diagnostic criteria proposed by Wildman et al. were applied to determine the metabolic health status of participants [32]. By this definition, individuals with normal weight ($18.5 < BMI < 25$) or overweight/obesity ($BMI > 25$) were respectively determined as metabolically unhealthy normal-weight (MUNW) and metabolically unhealthy overweight/obese (MUOW), if they had two or more than two of the following risk factors: (a) high FBG levels (defined as $FBG \geq 100$ mg/dL); (b) decreased HDL-c levels (defined as HDL-c < 40 mg/dL for males or < 50 mg/dL for females); (c) elevated TG levels (defined as TG levels ≥ 150 mg/dL); (d) high BP (defined as BP ≥ 130/85 mmHg); (e) increased IR (defined as HOMA-IR > 90th percentile or > 3.99); (f) elevated inflammatory protein hs-CRP levels (defined as hs-CRP > 90th percentile, or > 6.14 mg/L). Normal-weight and overweight/obese participants with less than two of the above-mentioned risk factors were classified as metabolically healthy normal-weight (MHNW) and metabolically healthy overweight/obese (MHOW), respectively. In this study, the sample size was calculated for metabolic status regardless of body weight status. Therefore, we combined MUNW and MUOW as well as MHNW and MHOW to have two groups of individuals (metabolically unhealthy vs. metabolically healthy).

Other variables

A self-administered checklist was used to collect data on sex, age, education, approximate income per month, marital and smoking status. A validated International Physical Activity Questionnaire-short form (IPAQ-SF) was used to collect data on physical activity (PA) [33]. This tool evaluates the duration and frequency of walking, moderate-intensity activities, and vigorous-intensity activities as well as physical inactivity during the preceding week. The data collected by IPAQ-SF were converted to Metabolic Equivalent Task (MET) per week and participants were classified as inactive (<600 MET.min/wk), minimally active (≥600 to <3000 MET.min/wk), or active (≥3000 MET.min/wk).

Statistical analysis

The residual method was used to estimate the energy-adjusted intake of UPFs and then participants were categorized into tertiles of intake. Continuous and categorical variables were respectively reported as mean (±SD/SE) and percentage across UPFs tertiles. The comparison of participants' basic characteristics across UPFs tertiles was performed by one-way ANOVA (for continuous variables) and chi-square test (for categorical variables). Additionally, age, sex, and energy-adjusted dietary intakes of individuals were compared across UPFs tertiles through ANCOVA. Binary logistic regression was used to detect the probable relationship between intake of UPFs with metabolic health status and its components, considering the first tertile of UPFs intake as the reference category. Confounding roles of age, sex, and energy intake were controlled in the 1st model. Further adjustments for education, approximate income per month, marital status, smoking status, and PA were done in the 2nd model. BMI was additionally controlled in the 3rd model. UPFs tertiles were considered as an ordinary variable in logistic regression models to evaluate trends. Multivariable-adjusted linear regression were applied to detect the link between serum BDNF values across UPFs tertiles by controlling confounding role of age, sex, PA, high BP, high TG, and high FBG. Linear regression analysis was also used to provide β regression coefficient for serum adropin values in UPFs tertiles by adjustment of covariates (including age, sex, energy intake, PA, and BMI). SPSS software version 26 (IBM, Chicago, IL) was used for all analyses, and P-values < 0.05 were considered to be statistically significant.

Results

Among 527 individuals participated in this study, 241 (45.7%) were female. Mean age of participants was 42.66±11.19 years and their BMI ranged from 16.60 to 59.80 kg/m^2. The average intake of UPFs among participants was 140.74±5.28 (SE) grams per day. General characteristics of participants across energy-adjusted tertiles of UPFs intake are shown in Table 1. Individuals in the highest tertile of UPFs intake were more likely to be male, younger, had lower approximate income per month, lower prevalence of hyperglycemia, and lower circulating adropin levels, in comparison with those in the first tertile. Nevertheless, no significant differences were found in other demographic and cardiometabolic features across energy-adjusted tertiles of UPFs.

Table 2 provides dietary intakes of participants across energy-adjusted tertiles of UPFs intake. Adults in top tertile of UPFs intake had lower dietary quality (lower Alternative Healthy Eating Index (AHEI) score), energy and protein intake compared to those at the bottom tertile. In reverse, fat intake was higher in subjects with highest intake of UPFs. However, intake of carbohydrates did not differ substantially across tertile of UPFs. Dietary intakes all UPFs components including cookies and cakes, dairy beverages, potato chips and salty snacks, processed meat and fast foods, oils and sauces, sweets and nondairy beverages were significantly higher in the last tertile compared to the first tertile of UPFs intake.

Among all study participants, 42.5% had an MU phenotype; of whom 20.5% was normal weight and 79.5% was overweight/obesity. Prevalence of MU status among energy-adjusted tertiles of UPFs intake was 46.3 (first tertile), 40.9 (second tertile) and 40.3% (third tertile) (P_{value}=0.46). Multivariable-adjusted ORs for MU status across energy-adjusted tertiles of UPFs intake are illustrated in Table 3. In crude model, no substantial association was found between UPFs intake and odds of MU status ($OR_{T3\ vs.\ T1}$=0.79; 95% CI: 0.51–1.20). However, by controlling all potential confounders, subjects in the highest tertile of UPFs intake had an increased likelihood of MU status in comparison with the reference group ($OR_{T3\ vs.\ T1}$=1.88; 95% CI: 1.02–3.45). A significant increasing trend was also observed for MU status across tertiles of UPFs intake in multivariable-adjusted model (P_{trend}=0.04).

Table 4 demonstrates multivariable-adjusted ORs for metabolic components across tertiles of UPFs intake. Individuals with the highest consumption of UPFs had elevated odds of hypertriglyceridemia in the first model by controlling age, sex and energy intake ($OR_{T3\ vs.\ T1}$=1.90; 95% CI: 1.16–3.12). After adjusting all confounding variables, this association was strengthened ($OR_{T3\ vs.\ T1}$=2.07; 95% CI: 1.15–3.73). Nevertheless, UPFs intake was not significantly related to other metabolic components including hyperglycemia, hypo-HDL-cholesterolemia, hypertension, insulin resistance and high hs-CRP levels, in the first or in the multi-adjusted models.

Mean concentrations of serum BDNF and adropin values among subjects were 1.25±0.07 (SE) ng/mL and 56.59±1.80 (SE) pg/mL, respectively.

Table 1 Demographic and cardiometabolic features of participants across energy-adjusted tertiles of ultra-processed foods intake ($n=527$)[1]

Variables	Tertiles of energy-adjusted ultra-processed foods intake [2]			*P*-value [3]
	T1 ($n=175$)	T2 ($n=176$)	T3 ($n=176$)	
Age (year)	48.32 ± 10.96	42.32 ± 10.25	37.36 ± 9.55	**< 0.001**
Body weight (kg)	75.92 ± 14.84	74.17 ± 14.14	77.23 ± 14.70	0.14
BMI (kg/m^2)	27.02 ± 4.62	26.82 ± 4.33	26.88 ± 4.37	0.91
WC (cm)	93.89 ± 11.62	91.51 ± 10.77	92.59 ± 11.99	0.15
Sex				**0.03**
Male	61.1	47.2	54.5	
Female	38.9	52.8	45.5	
Education				0.16
≤ Diploma	13.3	12.6	7.4	
> Diploma	86.7	87.4	92.6	
Marital status				0.14
Single or divorced	17.3	13.7	21.8	
Married	82.7	86.3	78.2	
Smoking				0.39
Non-smoker	91.7	94.4	94.7	
Ex-smoker	5.1	3.1	1.3	
Smoker	3.2	2.5	3.9	
Approximate income				**0.01**
Low	8.6	16.7	16.4	
Moderate	60.1	63.7	69.1	
High	31.3	19.6	14.5	
Physical activity				0.53
Inactive	52.3	57.7	60.0	
Minimally active	39.7	33.1	33.7	
Active	8.0	9.1	6.3	
High BP (≥ 130/85 mmHg)	54.9	43.2	43.8	0.05
High TG (≥ 150 mg/dL)	33.7	35.8	40.3	0.42
Low HDL-C (< 40 mg/dL for male/50 mg/dL for female)	9.1	10.8	14.8	0.24
High FBG (≥ 100 mg/dL)	27.4	15.3	16.5	**0.01**
High HOMA-IR (> 90th percentile)	10.3	10.8	8.5	0.76
High hs-CRP (> 90th percentile)	9.1	12.5	8.0	0.33
BDNF (ng/ml)	1.17 ± 0.04	1.28 ± 0.13	1.30 ± 0.16	0.73
Adropin (pg/ml)	53.51 ± 2.14	63.05 ± 4.06	53.25 ± 2.79	**0.04**

Abbreviations BDNF: Brained Derived Neurotrophic Factor; BMI: Body Mass Index; BP: Blood Pressure; FBG: Fasting Blood Glucose; HDL: High Density Lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; hs-CRP: High-sensitivity C -reactive protein; T: tertile; TG: Triglycerides; WC: Waist Circumference

[1] Quantitative variable are expressed as means ± standard deviation (SD) except for BDNF and adropin which are means ± standard error (SE) and qualitative variables are displayed as percentage

[2] Ultra-processed foods intake was adjusted for energy intake based on residual method

[3] Obtained by ANOVA for quantitative variables and chi-square test for categorical variables. Bold values indicate P<0.05.

Multivariable-adjusted linear regressions for BDNF and adropin levels are depicted in Figs. 1 and 2, respectively. Each tertile increase in UPFs intake was not significantly associated with BDNF levels in crude model (β=0.07; 95% CI: -0.11, 0.24; P_{value}=0.46). After adjustments of all confounders, this association was strengthened, but still remained insignificant (β=0.15; 95% CI: -0.05, 0.34; P_{value}=0.14). In case of adropin levels, an insignificant inverse linear association was seen in both crude (β=-0.17; 95% CI: -4.51, 4.16; P_{value}=0.94) and multivariable-adjusted (β=-1.37; 95% CI: -6.16, 3.42; P_{value}=0.58) models. Stratified analysis by age group (age $\leq$ 40 vs. >40 years) showed no significant association for BDNF or adropin values in younger vs. older participants (Supplemental Table S1).

Discussion

This population-based study on adult participants revealed that high consumption of UPFs was positively associated with increased odds of MU status. A direct association was also seen between UPFs intake and likelihood of hypertriglyceridemia. However, UPFs intake was

Table 2 Multivariable-adjusted intakes of selected food groups and nutrients of study participants across energy-adjusted tertiles of ultra-processed foods intake ($n=527$)[1]

Variables	Tertiles of energy-adjusted ultra-processed foods intake [2]			*P*-value [3]
	T1 ($n=175$)	T2 ($n=176$)	T3 ($n=176$)	
Ultra-processed foods intake (g/d)	< 90.81	90.81-157.43	> 157.43	
Alternative Healthy Eating Index-2010[4]	57.31 ± 8.26	55.31 ± 7.29	52.40 ± 8.21	< 0.001
Energy (Kcal/d)	2497.85 ± 51.99	2057.94 ± 49.54	2276.39 ± 51.57	**< 0.001**
Nutrients				
Proteins (% of energy)	14.62 ± 0.23	14.35 ± 0.22	13.77 ± 0.22	**0.03**
Carbohydrates (% of energy)	61.53 ± 0.64	61.34 ± 0.61	59.85 ± 0.64	0.14
Fats (% of energy)	25.94 ± 0.53	26.21 ± 0.50	28.26 ± 0.52	**0.01**
Ultra-processed foods components (g/d)				
Cookies and cakes	18.46 ± 3.20	37.40 ± 3.05	64.54 ± 3.12	**< 0.001**
Dairy beverages	5.89 ± 1.97	12.58 ± 1.88	24.08 ± 1.92	**< 0.001**
Potato chips and salty snacks	2.13 ± 0.84	4.96 ± 0.81	8.51 ± 0.82	**< 0.001**
Processed meat and fast foods	8.60 ± 1.61	18.04 ± 1.53	30.17 ± 1.57	**< 0.001**
Oils and sauces	2.79 ± 0.68	6.00 ± 0.65	10.42 ± 0.67	**< 0.001**
Sweets	7.05 ± 2.41	18.40 ± 2.30	28.69 ± 2.35	**< 0.001**
Nondairy beverages	0.87 ± 6.43	26.82 ± 6.14	85.31 ± 6.27	**< 0.001**

[1] Values are means ± standard error (SE). Energy intake and macronutrients were adjusted for age and sex; all other values were adjusted for age, sex and energy intake

[2] Ultra-processed foods intake was adjusted for energy intake based on residual method

[3] P-value obtained from ANCOVA. Bold values indicate P<0.05.

[4] Alternate Healthy Eating Index-2010 score ranged from 10 to 100 and included 10 components: fruits, vegetables, whole grains, nuts and legumes, long-chain n-3 fatty acids, polyunsaturated fatty acids (PUFAs), red and processed meats, sugar-sweetened beverages and fruit juices, trans fatty acids, sodium

Table 3 Multivariable-adjusted odds ratio for metabolic unhealthy status across energy-adjusted tertiles of ultra-processed foods intake ($n=527$)[1]

	Tertiles of energy-adjusted ultra-processed foods intake [2]			
	T1 ($n=175$)	T2 ($n=176$)	T3 ($n=176$)	P_{trend} [3]
Cases (n)	81	72	71	
Crude	1.00	0.80 (0.53–1.23)	0.79 (0.51–1.20)	0.26
Model 1	1.00	1.44 (0.88–2.35)	**1.72 (1.04–2.86)**	**0.04**
Model 2	1.00	1.54 (0.89–2.68)	**2.00 (1.11–3.61)**	**0.02**
Model 3	1.00	1.47 (0.83–2.57)	**1.88 (1.02–3.45)**	**0.04**

[1]All values are odds ratios and 95% confidence intervals (bold values indicate statistically significant associations). Model 1: Adjusted for age, sex, energy intake. Model 2: More adjustments for physical activity, approximate income per month, education, marital status, smoking status. Model 3: Further adjustment for BMI

[2] Ultra-processed foods intake was adjusted for total energy intake based on residual method

[3] P_{trend} was obtained by the use of tertiles of ultra-processed foods intake as an ordinal variable in the model. Bold values indicate P<0.05.

not significantly associated with serum BDNF and adropin concentrations.

Unfavorable metabolic status is closely linked to the risk of developing chronic diseases such as cardiovascular disease, type 2 diabetes, and obesity. The current study highlights the importance of dietary intakes in the management of metabolic disorders. Given the growing prevalence of UPFs in modern diets, our findings indicate that reducing UPF consumption could be an important part of dietary guidelines aiming at improving metabolic health. Also, further community programs of promoting UPF reduction in daily diets could play vital roles in mitigating chronic disease risk. While UPF was not significantly related to BDNF and adropin levels, these biomarkers are still of interest, due to their roles in neuroplasticity, energy homeostasis, and metabolic regulation. It is recommended for future studies to investigate such an association in larger sample sizes to determine the potential direct and indirect role of these biomarkers in the relation between diet and metabolic health.

In this cross-sectional study, we found a positive association between UPFs intake and odds of MU profile. Similar to our findings, each 10% increase in energy intake from UPFs was positively associated with an MU phenotype in both normal-weight and overweight/obese subjects in a prospective study in Tehran, Iran [34]; while only normal weight individuals in the highest quartile of UPFs intake (vs. the lowest quartile) had significantly

Table 4 Multivariable-adjusted odds ratio for metabolic components across tertiles of ultra-processed foods intake

	Tertiles of energy-adjusted ultra-processed foods intake [2]			P_{trend} [3]
	Tertile 1 ($n=175$)	Tertile2 ($n=176$)	Tertile3 ($n=176$)	
Hyperglycemia (FBG ≥ 100 mg/dL)				
Age, sex, energy-adjusted	1.00	0.75 (0.42–1.36)	1.19 (0.65–2.18)	0.64
Multivariable-adjusted [4]	1.00	1.18 (0.61–2.31)	1.54 (0.74–3.22)	0.25
Hypertriglyceridemia (TG ≥ 150 mg/dL)				
Age, sex, energy-adjusted	1.00	1.49 (0.92–2.42)	**1.90 (1.16–3.12)**	**0.01**
Multivariable-adjusted [4]	1.00	1.51 (0.87–2.62)	**2.07 (1.15–3.73)**	**0.02**
Low HDL-cholesterolemia (< 40 mg/dL for male/< 50 mg/dL for female)				
Age, sex, energy-adjusted	1.00	1.18 (0.56–2.49)	1.68 (0.81–3.49)	0.15
Multivariable-adjusted [4]	1.00	1.10 (0.47–2.57)	1.68 (0.71–3.98)	0.23
Hypertension (BP ≥ 130/85 mmHg)				
Age, sex, energy-adjusted	1.00	1.07 (0.66–1.75)	1.46 (0.88–2.42)	0.14
Multivariable-adjusted [4]	1.00	1.14 (0.66–1.99)	1.59 (0.88–2.89)	0.12
Insulin resistance (HOMA-IR score ≥ 3.99)				
Age, sex, energy-adjusted	1.00	1.18 (0.57–2.45)	0.95 (0.43–2.09)	0.90
Multivariable-adjusted [4]	1.00	1.01 (0.44–2.28)	0.87 (0.35–2.12)	0.75
High hs-CRP (> 6.4)				
Age, sex, energy-adjusted	1.00	1.74 (0.84–3.63)	1.18 (0.52–2.67)	0.69
Multivariable-adjusted [4]	1.00	1.93 (0.83–4.47)	1.71 (0.66–4.43)	0.26

Abbreviations BP, Blood Pressure; FBG, Fasting Blood Glucose; HDL, High-Density Lipoprotein; HOMA-IR, Homeostasis Model Assessment Insulin Resistance, hs-CRP, high sensitive C-reactive protein; T, tertile; TG, Triglycerides

[1] All values are odds ratios and 95% confidence intervals (bold values indicate statistically significant associations).

[2] Ultra-processed foods intake was adjusted for total energy intake based on residual method

[3] P_{trend} was obtained by the use of tertiles of ultra-processed foods intake as an ordinal variable in the model. Bold values indicate P<0.05.

[4] Further adjustments for physical activity, approximate income per month, education, marital status, smoking status and BMI

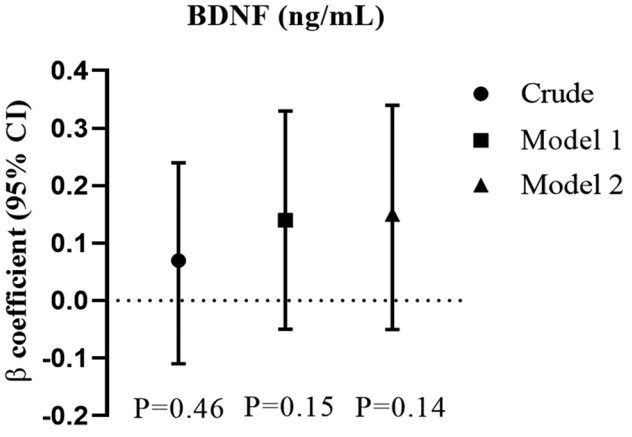

Fig. 1 Linear association between tertiles of ultra-processed foods (UPFs) intake and serum brain-derived neurotrophic factor (BDNF) levels. Values are β regression coefficients (and 95% confidence intervals) for BDNF concentration per one tertile increase in UPFs intake. Model 1: Adjusted for age, sex; Model 2: More adjustments for physical activity, history of high blood pressure, high triglyceride and high fasting blood glucose

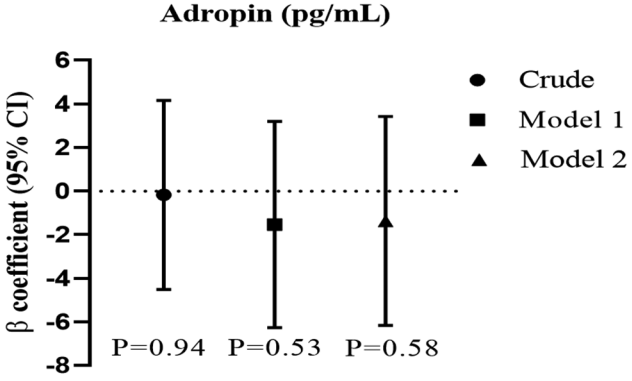

Fig. 2 Linear association between tertiles of ultra-processed foods (UPFs) intake and serum adropin levels. Values are β regression coefficients (and 95% confidence intervals) for adropin concentration per one tertile increase in UPFs intake. Model 1: Adjusted for age, sex, and energy intake; Model 2: More adjustments for physical activity and BMI

higher risk of MU. A review of studies with different designs also suggested adverse effects of UPFs on metabolic health, particularly among adults [35]. The plausible mechanism behind the relationship of UPFs with MU status or its components might be related to exposition to cosmetic additives during preparing and processing of these foods such as preservatives, emulsifiers, thickeners, stabilizers, artificial sweeteners, coloring and flavoring agents that might be associated with elevated risk of cardiometabolic disorders [36]. In addition, as our results documented, those with higher UPFs intake had lower dietary quality and unbalanced nutritional characteristics with high levels of fats and refined sugars vs. minimal

levels of protein, fiber and micronutrients [20]. It seems that high amounts of added sugars, sodium, SFAs, and TFAs, as major components of UPFs, would directly or indirectly lead to different metabolic disorders. Also, sophisticated packaging of these foods and its contaminated materials such as bisphenols and phthalates might be associated with dyslipidemia through disturbances in TG, HDL-c and high-density lipoprotein cholesterol (LDL-c) levels [37, 38].

More than half of all UPFs is refined sugar-based. Free sugar has a high glycemic index (GI) which leads to weight gain through a raise in appetite and desire, and also increases odds of cardiometabolic disorders by enhancing oxidative stress, inflammation and endothelial dysfunction [39]. Consuming an excessive amount of salt, as another significant element of UPFs, is linked to an elevated likelihood of developing hypertension, a key risk factor for heart disease and stroke. It has been documented that high sodium intake would be linked to high BP by disrupting renal and extra-renal homeostasis and neuro-hormonal pathways and also through direct impact on blood vessels [40]. In addition, UPFs include high levels of fats, particularly SFAs and TFAs, which make them more palatable. However, TFAs, which mostly present in hydrogenated oils, and SFAs have unfavorable effects on lipid profile including hypo-HDL cholesterolemia and hypertriglyceridemia [41]. Considering the evidence regarding no beneficial effects of reducing SFAs from some dietary sources such as dairy and dark chocolate, it should be noted that the effects of SFAs could be modulated by the interacting the food components and whole food matrix [42].

In this study, no significant associations were observed between UPFs intake and concentrations of serum BDNF and adropin. Considering previous related studies, diet has a role in determining these peptide hormones levels [13, 14]. Although UPFs intake has not been assessed in this relation, some other dietary factors showed different results regarding BDNF and adropin levels. An intervention study on overweight/obese adults revealed that an 8-week weight loss diet (very low energy diet (VLED)) with or without exercise could significantly decrease the circulating levels of BDNF only among women [43]. Another study among older adults with depression lived in Spain showed higher levels of BDNF in those followed the Mediterranean diet (MD) [44]. Negative associations were also seen between carbohydrate and fat intakes and blood levels of adropin [45, 46]. However, we failed to find a substantial relationship between UPFs intake with BDNF and adropin levels. Our limited sample size (due to the financial restrictions) and plausible effects of residual confounders might justify the observed findings. Nevertheless, there are inadequate human studies regarding diet in relation to BDNF and adropin levels and most of previous studies in this regard conducted on animals that might have a different physiological condition from humans. Findings of this study could broaden insights for further studies to determine nutritional factors related to concentrations of these hormones and the rationale behind these relationships.

Considering high consumption of UPFs among most societies and their detrimental effects on health status, finding practical strategies to reduce the intake of these foods would be vital. Media has a strong power in stimulation to increase consumption of UPFs. According to the research conducted in Brazil, UPFs accounts for 60.7% of all advertisements in television [47]. Therefore, special attention should be paid to the content of television programs and their advertisements. In addition, increasing community awareness about detrimental impacts of high UPFs intake on health as long as facilitating access to the healthier foods could be other beneficial strategies to reduce UPFs intake [48]. In general, all these solutions require the government's assistance in changing the existing infrastructure and increasing people's facilities.

This study was one of the first studies that evaluated UPFs intake in relation to MU status, BDNF and adropin levels in a somehow representative sample of Iranian adults. Applying validated questionnaires and tools to assess exposure and outcomes of interest strengthened the findings of the study. Also, adjusting several potential confounders enhanced the internal validity of the study. Nevertheless, the results of our study should be described with considering the following limitations. It was not possible to establish a causal relationship between intake of UPFs and MU phenotype, BDNF and adropin levels, due to the cross-sectional design of the study. In addition, self-administrated nature of the questionnaires increased the likelihood of recall bias and thus, misclassification among individuals. Residual confounding variables might also affect the obtained findings.

Based on our findings, UPFs intake was a threatening factor for MU phenotype among Iranian adults. Our findings could have invaluable importance for public health strategies and dietary recommendations aiming at managing metabolic disorders. Additional related investigations, especially with a prospective design, are required to provoke government agencies to revise public policies in order to prevent chronic diseases.

Abbreviations

AHEI	Alternative Healthy Eating Index
BP	Blood Pressure
BMI	Body Mass Index
BDNF	Brain-Derived Neurotrophic Factor
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
FBG	Fasting Blood Glucose
FFQ	Food Frequency Questionnaire
GI	Glycemic index
HDL-c	High-density lipoprotein cholesterol

HOMA-IR	Homeostasis Model Assessment Insulin Resistance
hs-CRP	High sensitive C-Reactive Protein
IR	Insulin Resistance
IPAQ-SF	International Physical Activity Questionnaire-Short Form
LDL-c	Low-density lipoprotein cholesterol
MD	Mediterranean Diet
MET	Metabolic Equivalent
MetS	Metabolic Syndrome
MHNW	Metabolically Healthy Normal-Weight
MHOW	Metabolically Healthy Overweight/Obese
MU	Metabolically Unhealthy
MUNW	Metabolically Unhealthy Normal-Weight
MUOW	Metabolically Unhealthy Overweight/Obese
ORs	Odds Ratios
PA	Physical Activity
SD	Standard Deviation
SE	Standard Error
SFAs	Short Chain Fatty Acids
SE	Standard Error
T	Tertile
TFAs	Trans Fatty Acids
TG	Triglycerides
UPFs	Ultra-Processed Foods
VLED	Svery low energy diet
WC	Waist Circumference
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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Author contributions
DP, SAT, FS, ZH, PR, and PS contributed in conception, design, data collection, data interpretation, manuscript drafting, approval of the final version of the manuscript, and agreed for all aspects of the work.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study procedure was performed according to declaration of Helsinki and STROBE checklist. All participants provided informed written consents. The study protocol was approved by the local Ethics Committee of Isfahan University of Medical Sciences.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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