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The mediatory role of inflammatory markers on the relationship between the NOVA classification system and obesity phenotypes among obese and overweight adult women: a cross-sectional study

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Background: Diet and inflammation both play important roles in the occurrence of obesity. We aimed to investigate the role of inflammation in the development of both metabolically healthy obese (MHO) and metabolically unhealthy obese (MUHO) individuals.

Methods: This cross-sectional study included 221 overweight and obese women aged 18–56 years. The study assessed the metabolic health phenotypes of the participants using the Karelis criterion score. Additionally, dietary intakes were evaluated using a 147-item semi-quantitative questionnaire and the NOVA classification system (comprising 37 food groups and beverages). The study also collected and analyzed the blood parameters, as well as biochemical and anthropometric indices, for all participants.

Results: Among the women included in the study, 22.9% had MHO phenotypes but 77.1% had MUHO phenotypes. A significant association between the third quartile of the NOVA classification system and the increased likelihood of having the MUHO phenotype was observed (OR = 1.40, 95% CI = 1.09−4.92, p = 0.04). Regarding the potential role of inflammatory markers, high-sensitivity C-reactive protein (hs-CRP) (p = 0.84), transforming growth factor-β (TGF-β) (p = 0.50), monocyte chemoattractant protein-1 (MCP-1) (p = 0.49), plasminogen activator inhibitor-1 (PAI-1) (p = 0.97), and homeostatic model assessment for insulin resistance (HOMA-IR) (p = 0.92) were found to be mediators.

Conclusion: We observed a significant positive association between ultra-processed food (UPF) consumption and the MUHO phenotype in overweight and obese women. This association appeared to be mediated by some inflammatory markers, such as hs-CRP, TGF-β, MCP-1, PAI-1, and HOMA-IR. Additional studies are needed to validate these findings.

1 Introduction

Obesity is associated with mild inflammation, and it is a state or condition that actively participates in regulating both physiological and pathological inflammatory processes by releasing pro-inflammatory cytokines, such as C-reactive protein (CRP) (1, 2). This inflammatory response can significantly increase the risk of morbidity and mortality (1, 3–5). The etiology of obesity is influenced by factors such as genetics, gender, lifestyle, and dietary intake (6–9). It was projected that, by 2030, the number of overweight adults will reach 2.16 billion and the number of obese adults will be approximately 1.12 billion (10). A study conducted on a population of 5,607 individuals reported an overall obesity prevalence of 57.2%, which was higher among women compared to men (11). However, not all obese individuals experience metabolic dysfunction, particularly cardiometabolic issues (12). Recent definitions classify obese individuals into metabolically healthy obese (MHO) and metabolically unhealthy obese (MUHO) groups based on their metabolic status. The MHO group (with a prevalence of 10–34%) is more prevalent in women and comprises individuals with specific metabolic profiles, such as higher insulin sensitivity, a lower incidence of hypertension, and optimal inflammation levels (13–16). Various indicators and definitions have been used to determine the metabolic health status, and in this study, the Karelis criterion was employed to categorize individuals into either the MHO or MUHO group (14, 15, 17, 18).

Dietary intake plays a crucial role in the development of overweight and obesity, and numerous studies have highlighted the significant impact of dietary patterns on obesity phenotypes (8, 19–21). Over the past few decades, there has been a notable increase in the consumption of processed foods due to the increasing availability of industrially processed products (22). Consequently, studies have reported associations between the consumption of processed foods, such as sugar (23), sugar-sweetened beverages (SSB) (24), fast food (25), and obesity, as well as unhealthy metabolic phenotypes (26–28). The energy-dense high-saturated fatty acid (SFA) diet enhances insulin resistance (IR), obesity, and metabolic syndrome (29, 30). Literature shows that ultra-processed food (UPF) intake affects inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) (31, 32). Several studies have been conducted on the relationship between inflammatory markers and obesity and how they activate the innate immune system in the adipose tissue, especially the visceral fat (33–35). However, regarding the relationship between UPF consumption and inflammatory markers, such as CRP, there are conflicting findings. In a cross-sectional study examining this relationship in both sexes, only a significant relationship was observed in women but not in men (36).

The NOVA classification system is a novel approach to assess the dietary patterns while grouping foods into four categories: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and UPFs (37). There was a significant association between UPF intake and an increased risk of chronic disorders such as diabetes and cardiovascular disease (CVD) (38–41). A prospective study in the Brazilian population showed more weight and waist circumference (WC) gains in the highest quartile of UPF consumption (42). Limited studies have reported an association between NOVA and increased inflammatory markers (31), which may be due to the consumption of SFAs, potatoes, hydrogenated fats, snacks, sugar, soft drinks, sweets, and desserts (43–46). However, there is currently a lack of studies exploring the relationship between UPF intake and inflammatory markers using the NOVA classification system among women. We aimed to investigate the mediating role of inflammatory markers in the relationship between the NOVA classification system and obesity phenotypes among women.

2 Subjects and methods

2.1 Participants

In this cross-sectional study, 221 overweight and obese women in the age range of 18–56 years participated. Participants with body mass index (BMI) between 25 kg/m² and 29.9 kg/m² were classified as overweight and those with BMI ≥30 kg/m² as obese. Participants were selected from those who attended the health clinics of Tehran University of Medical Sciences (TUMS), Tehran Province, Tehran, Iran. Participants were included in the study after signing a written informed consent. The study protocol entered the practical phase after being approved by the ethics committee of TUMS (Ethics ID: IR.TUMS.MEDICINE.REC. 1399.165). Participants having any history of disease, i.e., diabetes mellitus, CVD, hypertension, acute or chronic inflammatory disease, impaired renal and liver function, thyroid disease, autoimmune disease, malignancy, those who were pregnant and lactating, smokers, those with a regular use of drugs, including birth control pills, and those who consumed alcohol or had drug abuse, were excluded from the study. In addition, participants who had an energy intake of less than 800 kcal/day and more than 4,200 kcal/day, as well as those who had 5% weight fluctuations over the last year, were excluded from the study (47).

2.2 Assessment of dietary intakes

The dietary intakes were collected using a 147-item semi-quantitative food frequency questionnaire (FFQ) by a trained nutritionist. This validated and reliable questionnaire of Iranian adults (48, 49) includes a list of common foods consumed by the Iranian community, along with their standard portion sizes. Frequency of intake of each food item was asked and recorded as per daily, weekly, monthly, or annual consumption. After calculating the total energy intake (kcal/day), the data were analyzed using Nutritionist IV software (version 7.0; N-Squared Computing, Salem, OR, United States) (50). The standard portion size and items reported based on the household scale were collected and converted to grams using the home scale guide. Thus, the equivalent of grams consumed for each item and for each subject was calculated (51).

2.3 NOVA classification

The NOVA classification was used to assess the amount of UPF intake (52). NOVA classifies a total of 37 food items and beverages obtained from the FFQs as UPFs. These UPFs are further divided into seven distinct food groups as follows (Supplementary Figure S1):

(1) Group 1: Non-dairy drinks (industrial sweet drinks, cola, nectar, and coffee). Coffee torrefaction is often industrial in nature, and food technology specialists view it as a high-impact process whose elevated temperatures give rise to higher acrylamide levels (53).

(2) Group 2: Dairy drinks [ice cream (pasteurized and unpasteurized), cocoa milk, and chocolate milk].

(3) Group 3: Cakes and cookies [industrial bread, cakes, pancakes, noodles, toast, pasta, cookies, biscuits, and sweets (creamy and non-creamy)].

(4) Group 4: Fast food and processed meats (pizza, burger, sausage, and bologna).

(5) Group 5: Salty snacks (chips, puff pastry, and crackers).

(6) Group 6: Oil and sauce (mayonnaise, ketchup, and margarine).

(7) Group 7: Sweets (turmeric, nougat, chocolate, candy, stone candy, sweets, and jam) (54, 55). Candy and sweet ingredients that are used in Iran as UPFs include these items.

2.4 Measurement of biochemical parameters

The participants' blood samples after 8–12 h overnight fasting were collected with standard methods at the Nutrition and Biochemistry Laboratory of the School of Nutritional Sciences and Dietetics, TUMS (53). Triglyceride (TG), total cholesterol (T-Chol), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood sugar (FBS) levels were measured using glycerol-3-phosphate oxidase phenol 4-amino antipyrine peroxidase (GPO-PAP), enzymatic endpoint, direct enzymatic clearance, and glucose oxidase phenol 4-amino, respectively. Pars Azmoon laboratory kits (Pars Azmoon Inc., Tehran, Iran) were used to assess the serum levels of TG, T-Chol, HDL-C, LDL-C, glucose, and insulin. IR (mIU/ml) was calculated through the homeostatic model assessment (HOMA-IR) according to the following equation: [fasting plasma glucose (mmol/L) × fasting plasma insulin (μIU/L)]/22.5 (56). The enzyme-linked immunosorbent assay (ELISA) technique was used to evaluate the levels of inflammatory biomarkers. Levels of hs-CRP, monocyte chemoattractant protein-1 (MCP-1) (ZellBio GmbH, Ulm, Germany), transforming growth factor-β (TGF-β) (Human TGF-β1 Quantikine ELISA Kit, R&D Systems, United States), plasminogen activator inhibitor-1 (PAI-1) (Human PAI-1*96T ELISA Kit Crystal Company), galectin-3 (Gal-3), and interleukin-1β (IL-1β) were measured using an immunoturbidimetric test.

2.5 Anthropometry assessment

The body weight of the subjects was measured using a digital scale with a precision of 100 g. They were instructed to wear minimal clothing and no shoes during the measurements. Participant's height was recorded in a standing position with the normal position of the shoulders, without shoes. BMI was calculated by dividing the weight (kg) by the square of the height (m^2). We used a multi-frequency bioelectrical impedance analyzer [InBody 770 scanner (InBody Co., Ltd., Seoul, South Korea)] to assess the body composition, including the visceral fat level (VFL), body fat percentage (BF%), fat-free mass index (FFMI) and fat mass index (FMI), WC, waist-to-hip ratio (WHR), fat-free mass (FFM), fat trunk, and fat mass (FM). To record a more accurate result, participants were asked to be present with empty stomachs and bladders, without exercising before the session, and without their shoes, jackets, and coats. The output was printed out after 20 min of measurement.

2.6 Assessment of other variables

The assessment of physical activity (PA) levels was conducted using the International Physical Activity Short Form Questionnaire (IPAQ). This questionnaire was administered through interviews, with participants providing oral responses. PA was quantified as metabolic equivalent task minutes per week (MET-minutes/week) (57). Additionally, a demographic questionnaire was utilized to gather information on age, educational background, employment status, marital status, and economic status.

2.7 Definition of metabolic health and its components

The assessment of the metabolic health status in individuals was conducted using the Karelis criterion, which considers both insulin sensitivity and inflammatory profiles. According to the Karelis criterion, individuals are considered metabolically healthy if they meet four or more of the following five components: HOMA-IR ≤ 2.7, hs-CRP ≤ 3.0 mg/L, LDL-C ≤ 2.6 mmol/L without any treatment, HDL-C ≥ 1.3 mmol/L without any treatment, and TG ≤ 1.7 mmol/L (14).

2.8 Statistical analysis

Data analysis was conducted using SPSS version 26 (SPSS Inc.). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were reported as mean ± standard deviation (SD), and the categorical variables were reported as numbers and percentages. The mean and SD were reported by a one-way analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was used to examine the relationship between demographic variables (age, height, weight, PA, inflammatory parameters, food groups, macronutrients, and micronutrients) and the NOVA classification system while controlling for confounding variables, including age, BMI, and PA factors. The chi-square test was utilized to analyze the frequency of categorical variables, including education, economic status, marital status, employment status, and the NOVA classification system. Binary logistic regression analysis was employed to evaluate the association between NOVA classification scores and MUHO, with odds ratios (ORs) and 95% confidence intervals (CIs) reported. The analysis was performed in three models: crude, model 1, and model 2. The crude model did not include any confounding factors, with model 1 adjusted for age, BMI, energy intake, and PA and model 2 adjusted for age, BMI, energy intake, PA, economic status, supplement use, educational background, and marital status. In addition, to evaluate the mediatory role, Barrett's model was used, and inflammatory markers including hs-CRP, TGF-β, IL-1β, MCP-1, PAI-1, and HOMA-IR were included in the adjustment

models. value of *p*s of <0.05 were considered to be statistically significant, and value of *p*s of 0.05, 0.06, and 0.07 were considered marginally statistically significant.

3 Results

3.1 Study population and general characteristics

A total of 221 women who were overweight or obese were included in the analysis. The participants had a mean (SD) age of 36.22 (8.54) years, a body weight of 79.58 (10.89) kg, and a BMI of 30.55 (3.590) kg/m². Most participants were married (71.9%), employed (97.0%), and had a moderate economic status (42.4%). The mean (SD) values for the NOVA score, Karelis criterion score, and hs-CRP were 197.149 (136.80), 2.471 (1.11), and 4.532 (4.72) mg/L, respectively. Additionally, most participants (77.1%) were classified as MUHO.

3.2 General characteristics across quartiles of NOVA classification

Table 1 represents general characteristics and anthropometric variables across the quartiles of the NOVA classification. A significant difference was observed in mean age ($p = 0.03$), WHR ($p = 0.02$), and economic status ($p = 0.01$) in the crude model. However, after adjusting for confounding factors such as age, BMI, PA, and energy intake, no significant associations were found for these variables ($p > 0.05$). Other variables did not show any significant relationships among the NOVA quartiles (p > 0.05). Furthermore, after adjusting for confounders, a significant difference was observed in variables such as MCP-1 ($p = 0.06$), Gal-3 ($p = 0.03$), PAI-1 ($p = 0.024$), and supplement use (p = 0.03).

3.3 Dietary intake according to the NOVA quartiles

Table 2 displays the dietary intakes of the subjects categorized into NOVA classification system quartiles. The mean differences in protein, carbohydrate, SFA, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), linoleic acid, linolenic acid, vitamin A, vitamin C, vitamin E, vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B9, vitamin B12, biotin, calcium, iron, zinc, copper, manganese, selenium, chromium, fruit consumption, refined grain consumption, dairy consumption, and red meat intake were found to be significant among the NOVA quartiles in the crude model ($p < 0.05$). In the adjusted model, significant mean differences were observed for vitamin B6, total fiber intake, SSB consumption, processed food consumption, and vegetable consumption ($p < 0.05$).

3.4 Association between quartiles of NOVA classification and MUHO among overweight and obese women

The association between NOVA quartiles and MUHO in both the crude and adjusted models (model 1 and model 2) is represented in

Table 3. The results of our study demonstrate a 77% increase in the odds of MUHO in the third quartile compared to the first quartile in the crude model (OR = 1.77, 95% CIs = 1.02, 4.33, $p = 0.01$). This association remained significant after adjustment in model 1 (controlling for age, BMI, energy intake, and PA) (OR = 1.95, 95% CIs = 1.65, 5.79, $p = 0.04$) and model 2 (controlling for age, BMI, energy intake, PA, economic status, supplement use, educational background, and marital status) (OR = 1.40, 95% CIs = 1.09, 4.92, $p = 0.04$).

3.5 Association of MUHO across the quartiles of NOVA, mediated by inflammatory markers

The relationship between MUHO and the NOVA quartiles, mediated by inflammatory markers, in overweight and obese women is shown in Table 4. The potential role of inflammatory markers, such as hs-CRP ($p = 0.84$), TGF-β ($p = 0.50$), MCP-1 ($p = 0.49$), PAI-1 ($p = 0.97$), and HOMA-IR ($p = 0.92$), was found to be that of mediators.

4 Discussion

The current study investigated the associations between the mediating role of inflammatory markers and the relationship between the NOVA classification system and obesity phenotypes in obese and overweight adult women.

There was a positive association observed between the third quartile of the NOVA classification system and an increased likelihood of having the MUHO phenotype in women. Inflammatory markers such as hs-CRP, TGF-β, MCP-1, PAI-1, and HOMA-IR showed their mediatory role in Q3. This finding is consistent with a study by Yu et al., which found that the visceral adipose tissue (VAT) is independently associated with various inflammatory markers. Specifically, markers such as white blood cell (WBC) count and hs-CRP showed stronger correlations with VAT compared to other markers such as the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) [58]. Furthermore, another study reported a significant negative association between adherence to a healthy plant-based diet index (hPDI) and the MUHO phenotype among overweight and obese Iranian women. This association was found to be mediated by factors such as TGF-β, IL-1β, and MCP-1 [59]. Hosseininasab et al. indicated that there is a significant association between UPF consumption and TGF-β, atherogenic coefficient (AC), VFL, and the quantitative insulin sensitivity check index (QUICKI) [60]. In a systematic review and meta-analysis of 43 observational studies, there was an association between intake of UPF and an increased risk of obesity, overweight, abdominal obesity, and metabolic syndrome [61]. The higher consumption of dairy products, tea, and coffee compared to fast foods decreased the risk of developing an unhealthy phenotype [62]. In a systematic review and meta-analysis study, there was an association between increased UPF consumption and a cardiometabolic risk profile [63]. Exposure to bisphenol, an industrial chemical used in the plastic packaging of some UPFs, is related to an increased risk of cardiometabolic disease [64].

UPF intake must be cautiously adopted given the high proportion of artificial ingredients in their formulations [37], which are potentially harmful to human health, especially when consumed in excess. Excessive consumption of these foods is related to an increase

TABLE 1 General characteristics of the participants in the study among quartiles of the NOVA classification system in overweight and obese women (N = 221).

Variables		Quartiles of the NOVA classification system				Value of p	Value of p*
		Q1 (<109.41 gr) (n = 69)	Q2 (109.41–174.03 gr) (n = 51)	Q3 (>174.03–276.75 gr) (n = 51)	Q4 (>276.75 gr) (n = 50)		
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)		37.28 ± 8.08	38.17 ± 8.45	35.30 ± 9.5	33.64 ± 8.28	**0.03**	0.40
Height (cm)		160.14 ± 5.86	161.89 ± 5.92	162.18 ± 4.86	161.36 ± 5.61	0.19	0.89
Weight (kg)		77.78 ± 10.10	80.87 ± 9.89	80.75 ± 11.25	78.84 ± 10.78	0.30	0.55
BMI (kg/m²)		30.38 ± 3.48	30.74 ± 3.08	30.82 ± 3.61	30.44 ± 4.17	0.89	0.84
Body composition variables							
BFM (kg)		32.34 ± 6.63	32.77 ± 6.58	34.38 ± 7.28	33.10 ± 8.41	0.48	0.71
FFM (kg)		45.54 ± 5.59	47.85 ± 5.34	46.90 ± 5.44	46.14 ± 4.87	0.11	0.64
FFMI (kg/m²)		19.65 ± 15.84	18.22 ± 1.16	17.78 ± 1.54	17.70 ± 1.35	0.59	0.51
FMI (kg/m²)		12.78 ± 2.80	12.52 ± 2.50	13.04 ± 2.58	12.80 ± 3.36	0.83	0.90
BF (%)		41.28 ± 4.76	40.39 ± 4.53	41.80 ± 4.65	40.67 ± 6.62	0.51	0.64
WHR		0.92 ± 0.05	0.94 ± 0.04	0.93 ± 0.050	0.92 ± 0.05	**0.02**	0.08
WC (cm)		96.70 ± 8.81	99.63 ± 8.55	99.55 ± 8.91	97.37 ± 10.15	0.20	0.33
Visceral fat area (cm²)		157.22 ± 33.44	159.88 ± 34.50	167.01 ± 32.98	154.08 ± 44.21	0.31	0.60
Visceral fat level		15.11 ± 3.14	15.33 ± 3.17	16.03 ± 2.91	18.74 ± 27.59	0.48	0.51
Fat trunk (kg)		15.83 ± 3.02	16.35 ± 3.04	16.79 ± 3.10	16.24 ± 4.16	0.48	0.73
Fat trunk percentage		306.31 ± 59.54	304.34 ± 59.47	314.24 ± 53.14	305.52 ± 73.48	0.84	0.70
Blood parameters							
FBS (mg/dl)		87.40 ± 11.58	88.43 ± 8.96	87.90 ± 8.38	86.12 ± 8.73	0.66	0.38
T-Chol (mg/dl)		188.14 ± 36.92	186.11 ± 35.07	184.19 ± 40.44	180.24 ± 31.52	0.69	0.56
TG (mg/dl)		118.97 ± 58.50	126.62 ± 65.34	119.70 ± 57.48	109.22 ± 51.07	0.52	0.22
HDL-C (mg/dl)		47.53 ± 10.97	46.11 ± 10.35	43.78 ± 11.96	46.16 ± 8.55	0.29	0.89
LDL-C (mg/dl)		99.59 ± 23.96	95.76 ± 25.09	89.70 ± 22.89	93.38 ± 23.85	0.15	0.13
Inflammatory parameters							
MCP-1 (mg/L)		61.46 ± 115.36	48.29 ± 96.50	58.24 ± 101.35	48.33 ± 62.31	0.87	**0.06**
Gal-3 (mg/L)		5.37 ± 9.85	3.61 ± 4.89	4.45 ± 9.12	3.19 ± 3.98	0.80	**0.03**
PAI-1 (mg/L)		20.34 ± 41.73	10.71 ± 15.35 [a]	16.66 ± 27.00 [a]	16.07 ± 23.36	0.53	**0.02**
IL-1β (mg/L)		2.61 ± 0.86	2.87 ± 1.20	2.70 ± 0.88	2.85 ± 0.88	0.79	0.23
TGF-β (mg/L)		76.15 ± 43.83	88.63 ± 75.33	66.75 ± 17.42	84.95 ± 45.02	0.27	0.25
Hs-CRP (mg/L)		3.80 ± 4.50	4.88 ± 5.03	5.01 ± 5.20	4.52 ± 4.34	0.51	0.18
PA (METs-minutes/week)		1068.25 ± 1231.22	922.10 ± 1347.43	960.84 ± 882.06	1030.38 ± 1055.67	0.91	0.85
HOMA-IR		3.51 ± 1.57	3.38 ± 1.02	3.36 ± 1.16	3.26 ± 1.22	0.77	0.82
Insulin (mg/L)		1.19 ± 0.18	1.21 ± 0.26	1.248 ± 0.268	1.223 ± 0.226	0.67	0.84
Categorical variables		N	%	N	%	N	%	N	%	p-value	P-value*
Education status	Illiterate	0	0	1	33.3	2	66.7	0	0	0.30	0.36
	Under diploma	5	19.2	9	34.6	7	26.9	5	19.2		
	Diploma	32	36.8	19	21.8	20	23.0	16	18.4		
	Bachelor's degree and higher	31	30.1	22	21.4	22	21.4	28	27.2		
Economic status	Low level	17	31.5	17	31.5	11	20.4	9	16.7	**0.01**	0.47
	Moderate level	30	31.3	25	26.0	18	18.8	23	24.0		
	High level	20	35.1	6	10.5	15	26.3	16	28.1		
Marital status	Single	15	24.2	14	22.6	17	27.4	16	25.8	0.81	0.675
	Married	53	33.8	37	23.6	34	21.7	33	21.0		
Job status	Unemployed	1	100	0	0	0	0	0	0	0.70	0.54
	Employed	68	31.3	50	23.0	50	23.0	49	22.6		
Supplement	Yes	33	31.7	26	25	21	20.2	24	23.1	0.86	**0.03**
	No	22	31.9	11	15.9	17	24.6	19	27.5		

BMI, body mass index; BFM, body fat mass; FFM, fat-free mass; FFMI, fat-free mass index; FMI, fat-mass index; BF%, body fat percentage; WHR, waist to hip ratio; WC, waist circumference; FBS, fasting blood sugar; T-Chol, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; Gal-3, galectin-3; PAI-1, plasminogen activator inhibitor-1; IL-1B, interleukin-1 beta; TGF-β, transforming growth factor-β; hs-CRP, high-sensitive C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; PA, physical activity. Mean ± SD resulted from NOVA for continuous variables, and N (%) resulted from Q square for categorical variables. p-value, p-value for crude model; p-value*, p-value adjusted for age, BMI, energy intake, and PA. BMI is considered as a collinear variable for body composition and anthropometric measurements. p-values of < 0.05 were considered statistically significant, and p-value of 0.05, 0.06, and 0.07 were considered marginally significant. p-values of < 0.05 were considered statistically significant, and p-value of 0.05, 0.06, and 0.07 were considered marginally significant.

TABLE 2 Dietary intakes according to NOVA classification system quartiles in study participants (N = 221).

| Variables | Quartiles of the NOVA classification system | | | | p-value | p-value* |
| | Q1 (<109.41 gr) (n = 69) | Q2 (109.41–174.03 gr) (n = 51) | Q3(>174.03–276.75 gr) (n = 51) | Q4 (>276.75 gr) (n = 50) | | |
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Energy (kcal/d)	2042.15 ± 525.15	2558.11 ± 601.62	2717.52 ± 667.68	3215.88 ± 692.95	**<0.001**	—
Macronutrients						
Protein (g/d)	72.97 ± 23.79	84.64 ± 23.96	92.15 ± 21.32	107.55 ± 31.84	**<0.001**	0.62
Carbohydrate (g/d)	290.05 ± 88.87	364.99 ± 106.52	387.58 ± 109.66	463.18 ± 109.93	**<0.001**	0.90
Total fat (g/d)	72.71 ± 21.78	92.73 ± 30.65	97.72 ± 29.43	114.57 ± 30.24	**<0.001**	0.87
Subgroups of fat						
Chol (mg/d)	210.23 ± 70.16	241.36 ± 99.33	281.51 ± 95.74	284.05 ± 125.08	**<0.001**	0.28
SFA (mg/d)	21.73 ± 7.31	26.97 ± 11.38	30.68 ± 11.61	33.40 ± 11.39	**<0.001**	0.55
MUFA (g/d)	24.62 ± 8.65	30.99 ± 11.55	32.32 ± 10.21	36.29 ± 10.05	**<0.001**	0.76
PUFA (g/d)	16.44 ± 7.37	20.21 ± 9.44	19.61 ± 7.69	23.11 ± 7.97	**<0.001**	0.75
Linoleic acid (g/d)	14.03 ± 6.96	17.59 ± 8.95	16.96 ± 7.35	19.99 ± 7.72	**0.001**	0.76
Linolenic acid (g/d)	1.06 ± 0.64	1.32 ± 0.69	1.20 ± 0.52	1.38 ± 0.57	**0.02**	**0.06**
EPA (mg/d)	0.03 ± 0.04	0.02 ± 0.02	0.03 ± 0.03	0.03 ± 0.04	0.69	0.28
DHA (mg/d)	0.11 ± 0.12	0.09 ± 0.07	0.10 ± 0.09	0.11 ± 0.14	0.72	0.32
TFA (mg/d)	0.001 ± 0.003	0.001 ± 0.002	<0.001 ± 0.001	0.001 ± 0.002	0.52	0.36
Micronutrients and Vitamins						
Vitamin A (RAE)	682.35 ± 348.71	745.75 ± 408.17	837.83 ± 451.93	914.70 ± 437.27	**0.01**	0.64
B-carotene (mg/d)	4826.76 ± 3431.32	5223.90 ± 3596.27	5668.682 ± 4580.386	5779.42 ± 3317.88	0.49	0.29
Vitamin E (mg/d)	14.81 ± 7.81	16.55 ± 8.68	17.12 ± 8.56	19.10 ± 9.08	**<0.001**	0.99
Vitamin K (µg/d)	208.96 ± 151.93	217.04 ± 173.29	237.49 ± 326.88	218.36 ± 176.57	0.91	0.57
Vitamin C (µmol/L)	161.72 ± 100.81	189.06 ± 108.83	190.64 ± 107.73	256.60 ± 181.67	**0.001**	0.49
Vitamin B1(µg/d)	1.64 ± 0.47	2.09 ± 0.61	2.13 ± 0.60	2.46 ± 0.60	**<0.001**	0.40
Vitamin B2 (mg/d)	1.75 ± 0.59	2.10 ± 0.67	2.30 ± 0.64	2.77 ± 1.02	**<0.001**	0.37
Vitamin B3 (mg/d)	20.46 ± 6.68	24.02 ± 7.13	25.73 ± 6.83	30.85 ± 11.48	**<0.001**	0.66
Vitamin B5 (mg/d)	5.36 ± 1.71	6.29 ± 2.02	6.64 ± 1.83	7.97 ± 3.52	**<0.001**	0.77
Vitamin B6 (µg/d)	1.83 ± 0.57	2.14 ± 0.69	2.19 ± 0.61	2.56 ± 0.80	**<0.001**	**0.03**
Vitamin B9 (µg/d)	503.92 ± 153.74	624.28 ± 167.47	620.22 ± 156.23	693.46 ± 176.57	**<0.001**	0.08
Vitamin B12 (µg/d)	3.52 ± 1.74	4.04 ± 1.86	4.48 ± 1.42	5.77 ± 3.30	**<0.001**	0.14
Biotin (mg/day)	33.16 ± 14.32	36.52 ± 12.81	40.41 ± 14.85	46.64 ± 24.49	**<0.001**	0.64
Minerals						
Calcium (mg/d)	959.94 ± 357.03	1122.93 ± 396.33	1186.90 ± 372.93	1396.85 ± 430.55	**<0.001**	0.87
Iron (mg/d)	15.000 ± 4.83	18.77 ± 5.34	19.42 ± 5.50	22.53 ± 5.83	**<0.001**	0.37
Magnesium (mg/d)	387.74 ± 138.87	449.43 ± 138.89	490.02 ± 150.98	542.20 ± 129.30	**<0.001**	**0.03**
Zinc (mg/d)	10.51 ± 3.46	12.83 ± 4.36	13.74 ± 3.66	15.69 ± 4.15	**<0.001**	0.58
Copper (mg/d)	1.63 ± 0.55	2.01 ± 0.61	2.03 ± 0.59	2.47 ± 0.88	**<0.001**	0.69
Manganese (mg/d)	6.09 ± 3.15	7.02 ± 2.19	7.84 ± 3.02	7.90 ± 2.37	**0.001**	**0.06**
Selenium (mg/d)	94.19 ± 33.14	116.81 ± 32.45	131.17 ± 42.85	143.50 ± 41.41	**<0.001**	0.22
Chromium (mg/d)	0.09 ± 0.07	0.10 ± 0.07	0.13 ± 0.10	0.12 ± 0.08	**0.02**	0.11
Total fiber (g/d)	38.33 ± 17.28	47.24 ± 19.18	44.04 ± 16.96	50.89 ± 19.04	**0.002**	**0.01**
Food groups and other						
Whole grains (g/d)	8.20 ± 10.90	8.83 ± 11.35	6.37 ± 8.40	8.13 ± 12.38	0.69	0.22
Fruits (g/d)	419.20 ± 286.41	521.07 ± 327.56	542.11 ± 312.72	702.57 ± 423.02	**<0.001**	0.79
Vegetables (g/d)	445.71 ± 312.87	429.34 ± 237.19	401.70 ± 211.09	487.27 ± 288.93	0.44	**0.004**

(Continued)

TABLE 2 (Continued)

Variables	Quartiles of the NOVA classification system					
	Q1 (<109.41 gr) (n = 69)	Q2 (109.41–174.03 gr) (n = 51)	Q3(>174.03–276.75 gr) (n = 51)	Q4 (>276.75 gr) (n = 50)	p-value	p-value*
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Nuts (g/d)	12.52 ± 14.02	16.97 ± 22.36	14.83 ± 15.94	18.40 ± 17.19	0.28	0.21
Legumes (g/d)	51.06 ± 50.63	60.79 ± 43.43	54.81 ± 41.16	54.92 ± 36.56	0.69	0.32
Tea and coffee (ml/d)	680.71 ± 1225.10	663.14 ± 552.02	847.92 ± 493.90	887.19 ± 616.38	0.37	0.77
Refined grains (g/d)	318.91 ± 131.58	455.86 ± 247.79	461.25 ± 195.57	506.63 ± 268.62	**<0.001**	0.32
SSB (ml/d)	4.44 ± 8.74	8.84 ± 13.36	13.75 ± 18.98	64.78 ± 99.94	**<0.001**	**<0.001**
Dairy (ml/d)	320.36 ± 219.91	352.74 ± 218.64	386.42 ± 224.72	502.01 ± 300.83	**0.001**	0.55
Eggs (g/d)	18.90 ± 11.95	21.41 ± 12.05	25.11 ± 15.03	21.90 ± 16.78	0.12	0.29
Fish and seafood (g/d)	11.42 ± 12.08	9.77 ± 7.45	10.56 ± 8.26	12.87 ± 14.61	0.53	0.49
Meat (g/d)	52.70 ± 33.27	55.01 ± 33.36	64.77 ± 34.41	86.79 ± 74.83	**0.001**	0.34
White meat (g/d)	43.36 ± 34.19	36.83 ± 28.95	43.57 ± 29.18	56.22 ± 63.10	0.11	0.25
Red meat (g/d)	16.38 ± 12.88	21.25 ± 23.48	24.94 ± 19.98	29.91 ± 20.10	**0.002**	0.95
Processed food (g/d)	12.78 ± 12.74	16.58 ± 13.71	25.81 ± 21.02	46.86 ± 43.98	**<0.001**	**<0.001**
Caffeine (mg/d)	137.10 ± 245.06	133.02 ± 110.91	173.36 ± 98.99	182.87 ± 116.62	0.29	0.67

Chol, cholesterol; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; TFA, trans-fatty acid; SSB, sugar-sweetened beverages. Values are represented as means ± SD. p-value: p-value crude; ANCOVA (p-value*) was performed to adjust potential confounding factors (energy intake). p-values < 0.05 were considered statistically significant, and p-values of 0.05, 0.06, and 0.07 were considered marginally significant.

TABLE 3 Association between NOVA classification score and MUHO among overweight and obese women (N = 221).

MUHO	Q1 (n = 69)	Q2 (n = 51)			Q3 (n = 51)			Q4 (n = 50)			p-value*
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	
Crude model	Ref.	1.55	0.65, 3.71	0.31	1.77	1.02, 4.33	**0.01**	0.97	0.43, 2.20	0.95	0.85
Model 1		1.56	0.57, 4.29	0.38	1.95	1.65, 5.79	**0.04**	1.08	0.34, 3.44	0.88	0.66
Model 2		1.43	0.43, 4.70	0.55	1.40	1.09, 4.92	**0.04**	1.27	0.31, 5.19	0.73	0.67

The first quartile of the Nova classification score was considered the reference group. Metabolic healthy was considered as the reference group. Model 1 was performed to adjust for potential confounding factors (age, BMI, energy intake, and PA). Model 2 was performed to adjust for potential confounding factors (age, BMI, energy intake, PA, economic status, supplement usage, education status, and marital status). OR: odds ratio; CIs: confidence intervals. p-values of < 0.05 were considered statistically significant, and p-value of 0.05, 0.06, and 0.07 were considered marginally significant.

in the occurrence of NCDs (37, 65). Emerging evidence indicates that the consumption of UPF products contributes to an unhealthy dietary pattern (26). Furthermore, additives present in foods such as emulsifiers and non-caloric artificial sweeteners have been linked to various chronic disorders such as systemic inflammation, endothelial dysfunction, and disrupted immune response (66, 67). A study conducted in the United States revealed that UPF consumption was associated with increased exposure to phthalates (68), which have been suggested to be linked to obesity (69). Evidence suggests that abdominal obesity's origin can be associated with UPF intake, which delays satiety signals (37). UPF can also increase *ad libitum* energy intake by approximately 500 kcal/day, leading to higher weight gain compared to a minimally processed diet (70). Carrageenan, one of the commonly used additives, has been implicated in promoting IR and inhibiting insulin signaling in mice (71, 72), which may contribute to weight gain (73). On the other hand, a minimally processed diet has been shown to result in higher levels of peptide YY (an appetite suppressant hormone) compared to the UPF diet (70). Certain emulsifiers (such as carboxymethyl cellulose and polysorbate-80) have induced metabolic disturbances, alterations in the gut microbiota, and low-grade inflammation in mice (74).

The present study has its strengths. First, it is the first study to investigate the mediatory role of various inflammatory markers on the relationship between the NOVA classification system and obesity phenotypes among obese and overweight adult women. Second, the assessment of dietary intake was conducted using a validated and reliable questionnaire. Third, confounding factors were adjusted in the statistical models.

However, there are several limitations to be discussed. The observational design of the study restricts the ability to establish causality of associations. Nevertheless, an observational design is the most suitable approach to investigate these types of associations, as conducting longitudinal studies involving interventions targeting UPF intake could pose health risks and ethical concerns. Furthermore, the results cannot be extrapolated to the general population as the participants included in the study were overweight/obese Iranian women. In addition, the assessment of food intake using a FFQ is susceptible to measurement bias. Nevertheless, FFQs have been widely used as a tool in epidemiological studies since the 1990s (75). Finally, despite considering potential confounders, the possibility of residual confounding factors influencing the results cannot be entirely ruled out.

TABLE 4 Association of MUHO across the quartiles of NOVA, mediated by inflammatory markers.

Variables	Q1 (n = 69)	Q2 (n = 51)			Q3 (n = 51)			Q4 (n = 50)		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Metabolic unhealthy	Ref.									
hs-CRP (mg/L)		1.21	0.30, 4.92	0.78	0.86	0.20, 3.67	0.84	0.72	0.12, 4.007	0.70
TGF-β (mg/L)		1.47	0.28, 7.68	0.64	1.89	0.29, 12.39	0.50	0.66	0.10, 4.19	0.66
IL-1β (mg/L)		0.33	0.02, 5.10	0.43	0.09	0.001, 0.99	**0.02**	0.03	0.001, 1.37	**0.07**
MCP-1 (mg/L)		1.79	0.48, 6.63	0.38	1.58	0.42, 5.96	0.49	1.17	0.28, 4.89	0.82
PAI-1 (mg/L)		1.78	0.37, 8.48	0.46	1.03	0.20, 5.19	0.97	0.98	0.17, 5.60	0.98
HOMA-IR		0.97	0.21, 4.48	0.97	1.07	0.24, 4.67	0.92	1.19	0.22, 6.48	0.83

The first quartile of the Nova classification score was considered the reference group. Metabolic healthy was considered as the reference group. OR, odds ratio; CIs, confidence intervals; hs-CRP, high-sensitive C-reactive protein; TGF-β, transforming growth factor-β; IL-1B, interleukin-1beta; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1; HOMA-IR, homeostatic model assessment for insulin resistance. p-values of < 0.05 were considered statistically significant, and p-value of 0.05, 0.06, and 0.07 were considered marginally significant.

5 Conclusion

In conclusion, our findings indicate a significant positive association between the consumption of UPFs and the MUHO phenotype in overweight and obese women residing in Iran. This association appears to be mediated by inflammatory markers such as MCP-1, PAI-1, hs-CRP, TGF-β, and HOMA-IR. The results of this study suggest that UPF consumption may have detrimental effects on obesity-related characteristics and, consequently, on NCDs. The role of diet and nutritional status is crucial for improving human health. Identifying unhealthy dietary patterns and their association with obesity is essential for preventing chronic diseases and enhancing public health strategies. Further research is warranted to confirm and expand upon our findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethics approval for the study protocol was confirmed by The Human Ethics Committee of TUMS (Ethics Number: ID: IR. TUMS. MEDICINE. REC. 1399.165). All participants signed a written informed consent approved by the Ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MH and DH wrote the manuscript. FS performed the statistical analyzes. DH, YA, and SH revised the manuscript and improved its language. KM had full access to all the data in the study and took responsibility for the integrity and accuracy of the data. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1226162/full#supplementary-material

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Glossary

ANCOVA	Analysis of covariance
BF%	Body fat percentage
BMI	Body mass index
CVD	Cardiovascular disease
ELISA	Enzyme-linked immunosorbent assay
FBS	Fasting blood sugar
FFM	Fat-free mass
FFMI	Fat-free mass index
FFQ	Food Frequency Questionnaire
FMI	Fat mass index
FM	Fat mass
Gal-3	Galectin-3
HDL-c	High-density lipoprotein cholesterol
hs-CRP	High-sensitivity C-reactive protein
HOMA-IR	Homeostatic model assessment for insulin resistance
IR	Insulin resistance
LDL-c	Low-density lipoprotein cholesterol
MCP-1	Monocyte chemoattractant protein-1
MUHO	Metabolically unhealthy obese
MHO	Metabolically healthy obese
PAI-1	Plasminogen activator inhibitor-1
IL-1β	Interleukin-1beta
IL-6	Interleukin-6
TGF-β	Transforming growth factor-β
TG	Triglyceride
T-Chol	Total cholesterol
UPF	Ultra-processed food
WBC	White blood cells
WC	Waist circumference
WHR	Waist-to-hip ratio
OR	Odds ratio
CI	Confidence interval
VAT	Visceral adipose tissue