BMC Medical Genomics

RESEARCH

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# Interaction of genetics risk score and fatty acids quality indices on healthy and unhealthy obesity phenotype

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## Abstract

**Background** The growth in obesity and rates of abdominal obesity in developing countries is due to the dietary transition, meaning a shift from traditional, fiber-rich diets to Westernized diets high in processed foods, sugars, and unhealthy fats. Environmental changes, such as improving the quality of dietary fat consumed, may be useful in preventing or mitigating the obesity or unhealthy obesity phenotype in individuals with a genetic predisposition, although this has not yet been confirmed. Therefore, in this study, we investigated how dietary fat quality indices with metabolically healthy obesity (MHO) or metabolically unhealthy obesity (MUO) based on the Karelis criterion interact with genetic susceptibility in Iranian female adults.

**Methods** In the current cross-sectional study, 279 women with overweight or obesity participated. Dietary intake was assessed using a 147-item food frequency questionnaire and dietary fat quality was assessed using the cholesterol-saturated fat index (CSI) and the ratio of omega-6/omega-3 (N6/N3) essential fatty acids. Three single nucleotide polymorphisms-MC4R (rs17782313), CAV-1 (rs3807992), and Cry-1(rs2287161) were genotyped by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique and were combined to produce the genetic risk score (GRS). Body composition was evaluated using a multi-frequency bioelectrical impedance analyzer. Participants were divided into MHO or MUO phenotypes after the metabolic risk assessment based on the Karelis criteria.

**Results** We found significant interactions between GRS and N6/N3 in the adjusted model controlling for confounding factors (age, body mass index, energy, and physical activity) (β = 2.26, 95% CI: 0.008 to 4.52, *P* = 0.049). In addition, we discovered marginally significant interactions between GRS and N6/N3 in crude (β = 1.92, 95% CI: -0.06 to 3.91, *P* = 0.058) and adjusted (age and energy) (β = 2.00, 95% CI: -0.05 to 4.05, *P* = 0.057) models on the MUH obesity phenotype. However, no significant interactions between GRS and CSI were shown in both crude and adjusted models.

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**Conclusion** This study highlights the importance of personalized nutrition and recommends further study of widely varying fat intake based on the findings on gene-N6/N3 PUFA interactions.

**Keywords** Genetic risk score, Obesity, Gene-by- environment interaction, Lipids

## Introduction

Obesity is widespread and occurs rapidly worldwide [1, 2]. Notably, the number of people with overweight or obesity globally is estimated at nearly 2.1 billion [3]. Inflammation-related illnesses, hypertension, dyslipidemia, diabetes mellitus (DM), cardiovascular diseases (CVDs), and other metabolic disorders are all strongly correlated with obesity [4]. However, not all obese individuals exhibit metabolic dysfunction [5]. It is well known that certain obese individuals have a suitable metabolic profile, including blood pressure, a good lipid and hormone balance, insulin sensitivity, and a lower risk of CVDs [6]. This subgroup is termed metabolically healthy obesity (MHO). This phenotype results from a complex interaction of genetic, environmental, lifestyle, and dietary factors [5]. The metabolically unhealthy obesity (MUO) phenotype is linked to at least two or more metabolic abnormalities and an increased risk of CVDs [7]. In this study, MHO was defined using the Karelis criteria [8], which states that an individual cannot be classified as MHO unless they meet at least four proposed criteria [9].

Not much is known about the causes of the MHO phenotype [10]. MHO can be hereditary, but recent studies have shown that lifestyle variables, such as diet and physical activity (PA), can also play a significant role in its development [11]. Furthermore, certain dietary patterns may predispose individuals with MHO to a transition to a less favorable metabolic phenotype over time [12, 13]. Given the importance of diet in influencing metabolic health, it is essential to explore the relationship between dietary patterns and MHO, as this information may aid in developing strategies to improve metabolic health in overweight or obese individuals.

As a primary energy source, dietary fats play a critical role in the body [14–16]. While past research has often focused on the quantity of fat consumed, emerging evidence suggests that the type of dietary fat may significantly impact health and quality of life [17]. In this context, the Cholesterol-Saturated Fat Index (CSI), developed by Connor et al. [18], offers a novel approach to assessing dietary fat quality. Additionally, Simopoulos emphasized the importance of the omega-6 to omega-3 (N6/N3) essential fatty acids (EFAs) ratio [19], suggesting that a balanced N6/N3 EFA ratio may be vital for preventing and managing chronic diseases. A cross-sectional study by Ramos-Lopez et al. [20] found that total dietary fat consumption was linked to a greater risk of metabolically unhealthy overweight/obesity (MUHO) among 298 Spanish adults with overweight or obesity. Similarly, Mirzabaabei et al. [21] reported that an "unhealthy" diet pattern—characterized by high-fat dairy, organ meats, and trans fats—was positively associated with MUHO.

Several studies suggest a link between dietary fat intake and obesity phenotypes. Large-scale genome-wide association studies (GWAS) of body fat percentage (BFP) identified multiple genetic variants associated with the MHO phenotype, indicating that certain genetic profiles may predispose individuals to greater adiposity with lower cardiometabolic risk [22]. Other studies have examined genetic variants linked to insulin resistance in the metabolically obese normal weight (MONW) phenotype, finding that these variants can influence metabolic health independently of body weight [23].

In both children and adults, the MC4R (melanocortin 4 receptor) rs17782313 variation has been linked to increased body mass index (BMI) [24]. The C allele of this variant has been linked to an increased likelihood of obesity, inflammation, and cardiovascular risk factors such as insulin resistance and hypertension [25]. In adipocytes, which have many caveolae [26], caveolin-1 (CAV-1) is a key structural protein [27]. Over the past decade, research has associated the CAV-1 genetic variant with a higher risk of atherosclerosis, dyslipidemia, and hypertension [28, 29]. Additionally, the Cry-1 gene, which regulates circadian rhythms, has been implicated in metabolic functions like glucose homeostasis [30]. The Cry-1 rs2287161 C allele has also been associated with a higher BMI [31]. Given that each of these genetic variants has been linked to an increased risk of obesity in certain populations [32], examining their combined impact through a genetic risk score (GRS) is crucial.

It is crucial to look into the GRS of these genes since studies have linked MC4R [33], Cav 1 [34], and CRY1 [35] genetic variants to obesity. Moreover, recent studies suggest that single nucleotide variants (SNVs) may interact with dietary fat consumption to influence metabolic health outcomes. Although the precise molecular mechanisms underlying this interaction have not been fully elucidated, it is hypothesized that genetic variants could affect lipid metabolism, fat storage, and inflammatory responses. For instance, SNVs in genes related to fat metabolism may alter how individuals process different types of dietary fats, potentially leading to variations in the risk of developing MUO [36, 37]. Understanding these mechanisms is crucial for establishing targeted dietary recommendations based on genetic profiles [38]. In order to study this link, the pros and cons of various fats and fatty acids in the diet and the role of genetics in

obesity and its phenotypes should be looked at. To our knowledge, there hasn't been any research on this subject, and our study is the first to look at how GRS, CSI, and N6/N3 affect healthy and unhealthy obesity phenotypes.

## Methods

### Study population

This cross-sectional study includes 279 women with overweight or obesity in Tehran, Iran, who were referred to the medical services of the Tehran University of Medical Sciences (TUMS). The research population was drawn using a multistage cluster sampling technique. Participants were identified by age 18–48 years, BMI of 25–40 kg/m$^2$, the absence of an active weight loss program, and the use of weight loss supplements. Participants who had CVDs, thyroid disease, diabetes, acute or chronic disease, cancer, kidney disease, menopause, were pregnant or lactating, or were taking lipid-lowering, antidiabetic, antihypertensive, or weight-loss medications were excluded from the study. All participants signed an informed written consent before entering the study. The current study was authorized by the Ethics Committee of TUMS (assigned number: IR.TUMS.VCR.REC.1399.636).

### Body composition analysis and anthropometric indices

Anthropometric measurements were performed using a multi-frequency bioelectrical impedance analyzer (BIA), the InBody 770 (Inbody Co., Seoul, Korea) scanner. These measurements included weight, BMI, body free mass (BFM), bone mineral content (BMC), visceral fat area (VFA), fat-free mass (FFM), fat-free mass index (FFMI), body fat percentage (BF%), and visceral fat area [39]. With an accuracy of 0.5 cm, the participants' waist (WC), hip circumferences, and heights were measured [40]. The waist-to-hip ratio (WHR) was then calculated using the method. Aditional informations are in previous studies [41–43].

### Biochemical and hormonal determination

All blood samples were collected after 10–12 h of fasting and placed in tubes containing 0.1% EDTA. Samples were centrifuged as soon as possible for 10 min. At 3000 rpm, aliquoted, and stored at or below 80ºC until analysis. According to the manufacturer's procedure, a single assay was used to examine all of the samples. All of the samples were examined using an AutoAnalyzer BT1500 (Selectra2; Vital Scientific, Spankeren, Netherlands). Serum triglyceride (TG) was measured using the Glycerol-3-phosphate Oxidase Phenol 4-Aminoantipyrine Peroxidase (GPO-PAP) technique. An endpoint enzymatic technique was applied to determine total cholesterol. Both the direct technique and immunoinhibition were used to measure low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C). As an indicator of inflammation, the amount of High-sensitivity C-reactive protein (hs-CRP) was determined by the immunoturbidimetric technique. All kits were supplied by Pars Azmoon Company (Pars Azmoon Inc., Tehran, Iran). The following formula was used to calculate the Homeostatic Model Assessment; HOMA-IR: [fasting plasma glucose (mmol/l) * fasting plasma insulin (mIU/l)]. /22.5 [44]. The criteria for HOMA-IR were considered to be ≥ 1.95 [45]. In addition, serum insulin was measured by the enzyme-linked immunosorbent assay (ELISA) technique (Human Insulin ELISA Kit, DRG Pharmaceuticals, GmbH, USA).

### Dietary intake assessment

Food consumption was measured using a semi-quantitative food frequency questionnaire (FFQ) containing 147 foods, including a list of foods consumed in the previous year [46]. All participants were asked about the amount and frequency of each food consumed on a daily, weekly, or monthly basis. The recorded frequency of each food was then converted to grams per day. N4 software (First Data Bank, San Bruno, CA), which contains a database adapted for Iranian foods, was used to evaluate dietary nutrient consumption. In addition, this survey has high reliability and validity [46].

### Fatty acid quality indices

Indices of fat quality such as CSI and N6/N3 ratio are computed using their respective formulas.

CSI: Gives information about saturated fats and cholesterol levels, assisting a person in taking care of themselves to reduce their cholesterol levels [18].

$$CSI = \frac{cholesterol}{saturated\ fats}$$

N6/N3 ratio: Two important fats that fall within the PUFA category are omega 6 and omega 3. To calculate a ratio, the total amount of omega-6s and omega-3s is divided by one another [47].

$$N6/N3\ ratio = \frac{\sum_{N-6}}{\sum_{N-3}}$$

### Definition of metabolic health and its components

Metabolic health state was described using the Karelis criteria as follows: hs-CRP ≤ 3.0 mg/L, TG ≤ 1.7 mmol/L, HDL-C ≥ 1.3 mmol/L and no treatment, LDL-C ≤ 2.6 mmol/L and no treatment, and HOMA-IR ≤ 2.7 [48]. A metabolic health diagnosis is made when at least four of the symptoms are present. Thus, based on metabolic

health, individuals are divided into two groups, MHO and MUO.

### Physical activity assessment

Physical activity level was assessed using the International Physical Activity Questionnaire (IPAQ), which has been validated in adult Iranian women [49]. Participants were asked about time spent walking, and moderate and strenuous activity in the previous week. Then, each exercise duration was converted to minutes per week and the metabolic equivalent of the task (MET/minutes/week) was calculated. Based on a list of typical daily activities, scores were assigned based on how often and how long mild, moderate, high, and extremely high-intensity activities were performed.

### Genotyping and GRS

The salting-out approach was used for DNA extraction [50]. A 1% agarose gel was used to monitor DNA integrity and a Nanodrop 8000 spectrophotometer (Thermo Scientific, Waltham, MA, USA) was used to measure DNA concentration. SNPs were genotyped using the PCR-allele method, which is carried out by the TaqMan Open Array (Life Technologies Corporation, Carlsbad, CA, USA) [51]. Previous work [52] was used to guide the choice of the MC4R gene primer. Polymerase chain reaction (PCR) was utilized to detect MC4R (rs17782313) using the following primers: 5-AAGTTCTACCTACCA TGTTCTTGG-3 and 5-TTCCCCCTGAAGCTTTTCTT GTCATTTTGAT-3 are the forward and reverse primers, respectively. Then, fragments with the three genotypes CC, CT, and TT were identified. For CAV-1 (rs3807992), we used PCR with the forward primer 3′AGTATTGAC CTGATTTGCCATG 5′ and the reverse primer 5′GT CTTCTGGAAAAAGCACATGA 3′. Then, fragments with the three genotypes GG, GA, and AA were identified. We utilized the following PCR primers for Cry1 (rs2287161): forward primer 5′-GGAACAGTGATTGG CTCTATCT 3′ and reverse primer 5′-GGTCCTCGGT CTCAAGAAG-3′. Then, pieces with the three genotypes CC, GC, and GG were identified. MC4R (rs17782313), CAV-1 (rs3807992), and Cry-1 (rs2287161) were combined to form the GRS. For each SNP, genotypes were assigned as 0,1, or 2 according to risk alleles for increased BMI. In this method, the risk alleles from the three SNPs are used without weighting to generate the GRS. Each point on the GRS scale, which runs from 0 to 6, represents one risk allele. On the GRS scale, higher scores are interpreted as indicating a stronger genetic propensity to higher BMI [53].

### Statistical analyses

P values less than 0.05 were considered statistically significant using SPSS software, version 26. P values between 0.05 and 0.07 were considered marginally significant. The Kolmogorov-Smirnov test was used to determine whether quantitative variables were normally distributed (P value > 0.05). Categorical variables were presented as numbers and percentages, and all data were reported as means and standard deviations (SD). Pearson's chi-square test was used to assess the Hardy-Weinberg Equilibrium and to compare categorical variables. One-way analysis of variance (ANOVA) was used to assess the relationship between eating indices, anthropometric measurements, and biochemical measurements. Analysis of covariance (ANCOVA) was applied to eliminate confounding results. A generalized linear model (GLM) was used to estimate the interactions between GRS and fatty acid quality indices in both crude and adjusted models. Results were adjusted for energy intake, age, BMI, and PA.

## Results

### Descriptive characteristics of the study sample

The current study was carried out in 279 women with overweight or obesity participated. Individuals' age, weight, BMI, CSI, and N6/N3 mean and SD were $36.48 \pm 8.45$ years, $79.99 \pm 10.88$ kg, $30.73 \pm 3.72$ kg/m$^2$, $12.65 \pm 5.29$, and $12.65 \pm 0.10$, respectively.

### General characteristics of the study population according to tertile categories of CSI and N6/N3 in women with overweight or obesity

The main characteristics of the study population in relation to tertile categories of CSI and N6/N3 in women with overweight or obesity are presented in Table 1. Before adjustment for age, BMI, total energy intake, and PA, a significant difference across CSI for age ($P = 0.02$) was found although no significant differences were found for other tertiles of CSI. No variables had a significant association with N6/N3 tertiles, but after controlling for, a marginally significant difference for hs-CRP was seen in individuals with higher N6/N3 ($P = 0.07$) (Table 1).

### General characteristics of the study population according to tertile categories of GRS in women with overweight or obesity

Apart from the significant difference for height ($P = 0.01$), there was a marginally significant difference for BMI ($P = 0.05$) in the crude model. After adjusting for age, BMI, PA, and total energy intake, the significant associations were not maintained. There were also no significant differences for the remaining parameters across GRS (Table 2).

**Table 1** General characteristics of study population according to tertile categories of CSI and N6/N3 in obese and overweight women ($n=279$)

| **Variables†** | **CSI** | | | | |
|---|---|---|---|---|---|
| | **Mean ± SD** | | | *P*-**value** | *P*-**value**$_b$ |
| | **$T_1$ ($n=99$)** | **$T_2$ ($n=104$)** | **$T_3$ ($n=76$)** | | |
| Age (years) | 37.97 ± 8.31 | 36.51 ± 8.23 | 34.48 ± 8.64 | **0.02** | 0.27 |
| PA (MET-min/week) | 855.11 ± 1067.64 | 1113.51 ± 1190.64 | 1003.86 ± 961.72 | 0.29 | 0.45 |
| **Anthropometric measurements** | | | | | |
| Weight (kg) | 78.78 ± 9.91 | 80.58 ± 11.53 | 80.76 ± 11.19 | 0.38 | 0.74[a] |
| Height (cm) | 160.57 ± 5.94 | 161.58 ± 5.69 | 161.94 ± 5.82 | 0.25 | 0.89[a] |
| WC (cm) | 97.45 ± 8.49 | 98.83 ± 9.80 | 99.07 ± 9.67 | 0.44 | 0.83[a] |
| WHR (ratio) | 0.92 ± 0.047 | 0.93 ± 0.054 | 0.93 ± 0.051 | 0.41 | 0.80[a] |
| BMI (kg/m$^2$) | 30.62 ± 3.54 | 30.80 ± 3.79 | 30.77 ± 3.89 | 0.94 | 0.97[a] |
| VFL (cm$^2$) | 17.16 ± 19.87 | 16.78 ± 13.49 | 15.67 ± 3.37 | 0.78 | 0.49[a] |
| FFMI | 17.82 ± 1.43 | 19.24 ± 12.86 | 17.80 ± 1.41 | 0.35 | 0.45[a] |
| FMI | 12.89 ± 2.99 | 12.89 ± 2.94 | 12.96 ± 3.06 | 0.98 | 0.92[a] |
| **Metabolic factors** | | | | | |
| TC (mmol/l) | 4.77 ± 0.807 | 4.76 ± 1.02 | 4.69 ± 0.93 | 0.85 | 0.66 |
| TG (mmol/l) | 1.39 ± 0.91 | 1.40 ± 0.79 | 1.27 ± 0.55 | 0.57 | 0.68 |
| HDL (mmol/l) | 1.22 ± 0.26 | 1.20 ± 0.31 | 1.19 ± 0.21 | 0.72 | 0.87 |
| LDL (mmol/l) | 2.45 ± 0.59 | 2.40 ± 0.65 | 2.44 ± 0.60 | 0.81 | 0.38 |
| HOMA index | 3.42 ± 1.40 | 3.17 ± 1.17 | 3.48 ± 1.27 | 0.26 | 0.42 |
| hs.CRP (mg/l) | 3.75 ± 4.31 | 3.99 ± 4.31 | 5.06 ± 5.29 | 0.20 | 0.23 |
| **Education%(*n*)** | | | | 0.20 | |
| Illiterate | 3 (3) | 0 (0) | 0.0 (0) | | |
| Primary education | 46 (6) | 30.8 (4) | 23.1 (3) | | |
| Intermediate Education | 52.9 (9) | 23.5(4) | 23.5(4) | | |
| High school education | 57.1 (4) | 14.3 (1) | 28.6 (2) | | |
| Diploma | 32.1 (26) | 43.2 (35) | 24.7 (20) | | |
| Postgraduate education | 48 (12) | 28 (7) | 24 (6) | | |
| Bachelor's degree and higher | 29.3 (39) | 39.8 (53) | 30.8 (41) | | |
| **Marriage%(*n*)** | | | | 0.33 | |
| Married | 35.9 (78) | 36.9 (80) | 27.2 (59) | | |
| Single | 35.2 (19) | 37 (20) | 27.8 (15) | | |
| Away from spouse for more than 6 months | 0.0 (0) | 100.0 (1) | 0.0 (0) | | |
| Dead spouse | 0.0 (0) | 0.0 (0) | 100.0 (2) | | |
| Divorce | 40 (2) | 60(3) | 0.0 (0) | | |
| **Obesity phenotype** | | | | 0.90 | |
| MH | 45.3 (29) | 37.5 (24) | 17.2 (11) | | |
| MUH | 32.7 (55) | 37.5 (63) | 29.8 (50) | | |
| **Variables†** | **N6/N3** | | | | |
| | **Mean ± SD** | | | *P*-**value** | *P*-**value$_b$** |
| | **$T_1$($n=99$)** | **$T_2$($n=104$)** | **$T_3$($n=76$)** | | |
| Age (years) | 35.95 ± 8.20 | 36.08 ± 8.45 | 37.40 ± 8.72 | 0.43 | 0.29 |
| PA (MET-min/week) | 960.36 ± 926.07 | 1192.29 ± 1445.85 | 812.75 ± 727.60 | 0.08 | 0.14 |
| **Anthropometric measurements** | | | | | |
| Weight (kg) | 81.12 ± 10.74 | 80.84 ± 11.89 | 78.01 ± 9.77 | 0.09 | 0.37[a] |
| Height (cm) | 162.02 ± 5.47 | 161.79 ± 5.77 | 160.15 ± 6.09 | 0.05 | 0.72[a] |
| WC (cm) | 98.81 ± 9.13 | 99.62 ± 10.11 | 96.79 ± 8.49 | 0.10 | 0.18[a] |
| WHR (ratio) | 0.92 ± 0.047 | 0.94 ± 0.055 | 0.92 ± 0.049 | 0.07 | 0.14[a] |
| BMI (kg/ m$^2$) | 30.90 ± 3.93 | 30.91 ± 3.63 | 30.37 ± 3.61 | 0.53 | 0.46[a] |
| VFA (cm$^{2)}$ | 15.58 ± 3.32 | 19.06 ± 24.55 | 15.20 ± 3.14 | 0.13 | 0.07a |
| FFMI | 17.91 ± 1.35 | 19.47 ± 13.52 | 17.63 ± 1.41 | 0.23 | 0.43a |
| FMI | 13.02 ± 3.14 | 12.86 ± 2.86 | 12.84 ± 2.97 | 0.90 | 0.92a |
| **Metabolic factors** | | | | | |

**Table 1** (continued)

| | | | | | |
|---|---|---|---|---|---|
| TC (mmol/l) | 4.61 ± 0.75 | 4.77 ± 0.97 | 4.85 ± 1.01 | 0.26 | 0.10 |
| TG (mmol/l) | 1.33 ± 0.76 | 1.36 ± 0.81 | 1.39 ± 0.79 | 0.88 | 0.23 |
| HDL (mmol/l) | 1.19 ± 0.26 | 1.22 ± 0.28 | 1.20 ± 0.27 | 0.72 | 0.81 |
| LDL (mmol/l) | 2.40 ± 0.52 | 2.44 ± 0.64 | 2.45 ± 0.66 | 0.83 | 0.89 |
| HOMA index | 3.22 ± 1.27 | 3.23 ± 1.27 | 3.54 ± 1.30 | 0.19 | **0.03** |
| hs.CRP (mg/l) | 4.64 ± 4.80 | 3.97 ± 4.61 | 3.98 ± 4.43 | 0.59 | 0.07 |
| **Education%(n)** | | | | 0.58 | |
| Illiterate | 0.0 (0) | 66.7 (2) | 33.3 (1) | | |
| Primary education | 30.8 (4) | 53.8 (7) | 15.4 (2) | | |
| Intermediate Education | 35.3 (6) | 23.5 (4) | 41.2 (7) | | |
| High school education | 28.6 (2) | 42.9 (3) | 28.6 (2) | | |
| Diploma | 37.0 (30) | 32.1 (26) | 30.9 (25) | | |
| Postgraduate education | 16 (4) | 40 (10) | 44 (11) | | |
| Bachelor's degree and higher | 35.3 (47) | 30.8 (41) | 33.8 (45) | | |
| **Marriage%(*n*)** | | | | 0.59 | |
| Married | 32.7 (71) | 33.6 (73) | 33.6 (73) | | |
| Single | 33.3 (18) | 33.3 (18) | 33.3 (18) | | |
| Away from spouse for more than 6 months | 0.0 (0) | 0.0 (0) | 100.0 (1) | | |
| Dead spouse | 100.0 (2) | 0.0 (0) | 0.0 (0) | | |
| Divorce | 40.0 (2) | 40.0 (2) | 20.0 (1) | | |
| **Obesity phenotype** | | | | 0.82 | |
| MH | 29.7 (19) | 32.8 (21) | 37.5 (24) | | |
| MUH | 33.9 (57) | 31 (52) | 35.1 (59) | | |

CSI: cholesterol to saturated fat index; BMI: body mass index; HDL: high-density lipoprotein; HOMA; homeostatic model assessment; hs-CRP: high-sensitivity C-reactive protein; SD: standard deviation T: tertile; TC: total cholesterol; TG: triglyceride; VFL: visceral fat level, MH: metabolic healthy; MUH: metabolic unhealthy; IPAQ: International Physical Activity Questionnaires; FFMI: fat-free mass index; FMI: fat mass index, WC: waist circumference; WHR: waist to hip ratio

Values are represented as means (SD)

Categorical variables: % (*n*)

† Calculated by analysis of variance (ANOVA)

b: ANCOVA was performed to adjust potential confounding factors (age, BMI, energy intake, physical activity)

a: BMI is considered as a collinear variable for anthropometric measurements and these variables are adjusted for Age, physical activity, and total energy intake

$p < 0.05$ was considered significant

### Dietary intake of the study population according to tertile categories of CSI and N6/N3 in women with overweight or obesity

Greater CSI was associated with higher amounts of refined grains, vegetables, fish, poultry, egg, red meat, protein, carbohydrate, total fat, cholesterol, polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), linoleic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Significant differences were also observed between higher tertile of N6/N3 and lower consumption of fruits, monounsaturated fatty acids (MUFA), PUFA, oleic acid, and linoleic acid (Table 3).

### The interactions between GRS and CSI and N6/N3 on obesity phenotype

Using the GLM, the interactions between GRS with CSI and N6/N3 on the obesity phenotype were examined. In a multivariate-adjusted model 2 controlling for confounders such as age, BMI, energy, and PA, we found a significant interaction between GRS and N6/N3 (β = 2.26, 95% CI: 0.008 to 4.52, $P = 0.049$); higher N6/N3 adherence was more related to a higher MUH obesity phenotype among individuals with greater GRS. Marginally significant interactions were also seen between GRS and N6/N3 in the crude model (β = 1.92, 95% CI: -0.06 to 3.91, $P = 0.058$) and multivariate-adjusted model 1 controlling for the covariates including age and energy (β = 2.00, 95% CI: -0.05 to 4.05, $P = 0.057$). In both crude and adjusted models, no significant interactions between GRS and CSI were detected (Table 4).

## Discussion

To the best of our knowledge, the present study is the first to investigate the interaction between GRS and CSI and N6/N3 indices in women with healthy and unhealthy obesity phenotypes. Our study shows that the higher tertile of dietary N6/N3 intake is associated with a higher HOMA index, suggesting a link to insulin resistance, and a slight decrease in CRP, a marker of inflammation. Additionally, higher N6/N3 intake was associated with lower intakes of fruits, MUFA, PUFA, oleic acid, and linoleic acid. Our study indicates a significant interaction

**Table 2** General characteristics of the study population according to tertile categories of GRS in obese and overweight women ($n=279$)

| Variables† | GRS | | | | |
|---|---|---|---|---|---|
| | Mean ± SD | | | *P*-value | *P*-value $_b$ |
| | Low genetic risk score ($n=114$) | Moderate genetic risk score ($n=64$) | High genetic risk score ($n=101$) | | |
| Age (years) | 35.98 ± 8.74 | 36.65 ± 8.48 | 36.94 ± 8.15 | 0.69 | 0.90 |
| **Anthropometric measurements** | | | | | |
| Weight (kg) | 80.00 ± 10.32 | 78.55 ± 11.12 | 80.90 ± 11.35 | 0.40 | 0.81 [a] |
| Height (cm) | 162.56 ± 5.51 | 160.77 ± 6.29 | 160.27 ± 5.66 | **0.01** | 0.12 [a] |
| WC (cm) | 97.71 ± 9.01 | 98.05 ± 9.19 | 99.44 ± 9.73 | 0.37 | 0.40 |
| BMI (kg/ $m^2$) | 30.22 ± 3.54 | 30.53 ± 3.44 | 31.43 ± 4.00 | **0.05** | 0.18 |
| BF% | 40.55 ± 4.89 | 41.79 ± 4.81 | 41.75 ± 6.00 | 0.17 | 0.10 |
| **Blood pressure** | | | | | |
| SBP (mmHg) | 110.50 ± 11.88 | 111.12 ± 15.20 | 111.98 ± 14.24 | 0.73 | 0.86 |
| DBP (mmHg) | 77.34 ± 9.74 | 77.64 ± 10.09 | 77.76 ± 9.22 | 0.95 | 0.76 |
| **Metabolic factors** | | | | | |
| FBS (mg/dl) | 87.05 ± 9.04 | 86.03 ± 7.44 | 88.34 ± 11.53 | 0.37 | 0.69 |
| TC (mg/dl) | 187.07 ± 34.38 | 184.49 ± 39.12 | 179.23 ± 35.01 | 0.34 | 0.25 |
| TG (mg/dl) | 122.10 ± 67.92 | 109.47 ± 51.66 | 128.08 ± 81.78 | 0.29 | 0.30 |
| HDL (mg/dl) | 47.04 ± 9.85 | 48.43 ± 12.41 | 45.06 ± 9.98 | 0.16 | 0.24 |

SD: Standard deviation; GRS: Genetic risk score; BMI: Body mass index; WC: Waist circumference; BF: Body fat; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TG: Triglyceride; TC: Total cholesterol ; HDL: High density lipoprotein

† Calculated by analysis of variance (ANOVA)

b: Adjusted for age, BMI, physical activity, and total energy intake

a: BMI is considered collinear and this variable is adjusted for Age, physical activity, and total energy intake

$P<0.05$ was considered significant

between GRS and dietary N6/N3 intake, where women consuming higher amounts of N6/N3 have a higher genetic risk of the unhealthy phenotype of obesity.

In our study, significant interactions were found between the 3-SNP GRS including MC4R, CAV-1, and CRY, and an intake of N6/N3 on obesity. It has been shown to be associated with an increased risk of morbidity and mortality [54, 55]. We found significant interactions between GRS and N6/N3, where a higher N6/N3 intake was found to be associated with greater obesity in individuals. This suggests that women consuming higher amounts of n-6 fatty acids may have a higher genetic risk for developing an unhealthy obesity phenotype. Thus, dietary fatty acid composition may play a critical role in modulating genetic susceptibility to obesity.

Despite numerous studies examining dietary fat, the results have often been inconsistent. For instance, a study of 124 adults living in the UK found a negative correlation between plasma n-3 PUFA concentrations and anthropometric measurements [56], while another study involving 7,983 women living in the US reported positive associations [57]. Furthermore, an RCT involving lean fish (3150 g portions of cod per week) and fatty fish (3150 g portions of salmon per week) demonstrated weight loss in participants consuming these diets [58]. However, results from a meta-analysis indicated that n-3 PUFAs had no significant effect on reducing body weight and BMI in overweight/obese subjects [59]. Results of a six-week RCT of 195 UK adults showed no differences in anthropometric measures between three intervention diets containing specific fatty acid compositions (SFA-rich diet, MUFA-rich diet, or omega-6 PUFA-rich diet) [60]. Conflicting evidence regarding dietary fat intake and its effect on obesity traits highlights the importance of considering both genetic and lifestyle factors. This is particularly relevant in diverse populations, as genetic heterogeneity may influence how dietary fat affects obesity risk [61]. Investigating gene-diet interactions is crucial for understanding the underlying mechanisms of obesity and its phenotypes [62].

Moreover, our findings align with previous research linking dietary fat to obesity phenotypes. A study involving obese adolescents with fatty liver disease indicated that a lower intake of N6/N3 PUFA could improve metabolic phenotypes [63]. In childhood obesity studies, MUO was associated with higher n-6 and n-9 fatty acids, while MHO correlated with higher n-3 fatty acid concentrations [64]. Further research on 171 metabolically obese and non-obese adults revealed that those with MUO had higher total PUFA and n-6 PUFA intakes, while n-3 PUFA intake was lower in these individuals [65].

The conflicting evidence regarding dietary intake's impact on obesity traits may be attributed to genetic heterogeneity and the gene-diet interactions in diverse ethnic groups. Therefore, a comprehensive understanding of it's pathophysiology necessitates consideration of

**Table 3** Dietary intake of the study population according to tertile categories of CSI and N6/N3 in obese and overweight women ($n=279$)

| **Variables†** | **CSI** | | | |
|---|---|---|---|---|
| | **Mean ± SD** | | | ***p*-value*** |
| | **$T_1$ ($n=99$)** | **$T_2$ ($n=104$)** | **$T_3$ ($n=76$)** | |
| **Food groups** | | | | |
| Whole grains (g/d) | 53.24 ± 47.75 | 61.59 ± 54.19 | 77.42 ± 73.40 | 0.82 |
| Refined grains (g/d) | 331.80 ± 219.09 | 379.17 ± 191.55 | 397.52 ± 219.72 | **0.01** |
| Nuts (g/d) | 9.45 ± 10.99 | 14.59 ± 15.63 | 21.40 ± 20.64 | 0.25 |
| Legumes (g/d) | 42.47 ± 34.57 | 51.43 ± 42.42 | 46.40 ± 42.31 | 0.27 |
| Vegetables (g/d) | 288.84 ± 183.46 | 424.89 ± 241.68 | 445.77 ± 262.62 | **0.003** |
| Fruits (g/d) | 388.93 ± 312.69 | 510.63 ± 334.57 | 648.63 ± 34.94 | 0.92 |
| Fish (g/d) | 7.06 ± 6.33 | 12.59 ± 12.24 | 15.62 ± 15.97 | **< 0.001** |
| Poultry (g/d) | 23.03 ± 18.74 | 35.25 ± 26.63 | 50.75 ± 62.74 | **0.002** |
| Egg (g/d) | 12.60 ± 7.02 | 21.47 ± 9.40 | 33.85 ± 17.9 | **< 0.001** |
| Red meat (g/d) | 12.20 ± 8.51 | 22.38 ± 16.72 | 32.84 ± 23.24 | **< 0.001** |
| **Nutrient intake** | | | | |
| Energy (kcal/d) | 2136.53 ± 601.19 | 2650.61 ± 674.27 | 3151.67 ± 612.17 | - |
| Protein (g/d) | 66.53 ± 17.27 | 91.41 ± 20.92 | 112.36 ± 28.38 | **< 0.001** |
| Carbohydrate (g/d) | 305.72 ± 102.04 | 385.51 ± 120.18 | 435.97 ± 96.75 | **< 0.001** |
| Total fat (g/d) | 78.52 ± 29.67 | 91.87 ± 26.72 | 116.48 ± 30.52 | **0.03** |
| TC (g/d) | 158.47 ± 28.57 | 242.94 ± 25.18 | 387.88 ± 95.41 | **< 0.001** |
| MUFA (g/d) | 27.06 ± 11.69 | 29.95 ± 8.87 | 37.72 ± 10.50 | 0.05 |
| PUFA (g/d) | 18.96 ± 10.07 | 19.46 ± 7.35 | 21.64 ± 7.44 | **< 0.001** |
| SFA (mg/d) | 20.80 ± 6.43 | 26.59 ± 6.44 | 39.04 ± 12.35 | **< 0.001** |
| Trans fat (mg/d) | 0.0007 ± 0.002 | 0.0005 ± 0.001 | 0.001 ± 0.004 | 0.05 |
| Oleic acid (g/d) | 24.86 ± 11.50 | 26.86 ± 8.71 | 33.18 ± 9.97 | 0.06 |
| Linolenic acid (g/d) | 1.03 ± 0.66 | 1.19 ± 0.54 | 1.50 ± 0.61 | 0.46 |
| Linoleic acid (g/d) | 16.85 ± 9.56 | 16.76 ± 7.10 | 18.13 ± 7.14 | **< 0.001** |
| EPA (g/d) | 0.01 ± 0.02 | 0.03 ± 0.03 | 0.04 ± 0.04 | **< 0.001** |
| DHA (g/d) | 0.06 ± 0.06 | 0.11 ± 0.12 | 0.14 ± 0.13 | **< 0.001** |
| **Variables†** | **N6/N3** | | | |
| | **Mean ± SD** | | | ***P*-value*** |
| | **T1($n=93$)** | **T2($n=93$)** | **T3($n=93$)** | |
| **Food groups** | | | | |
| Whole grains (g/d) | 76.88 ± 67.78 | 70.52 ± 59.97 | 41.42 ± 38.36 | 0.17 |
| Refined grains (g/d) | 489.62 ± 239.45 | 340.17 ± 194.30 | 272.29 ± 117.29 | 0.46 |
| Nuts (g/d) | 21.11 ± 19.00 | 15.81 ± 17.75 | 6.95 ± 6.07 | 0.36 |
| Legumes (g/d) | 51.82 ± 40.69 | 52.32 ± 44.80 | 36.50 ± 31.08 | 0.18 |
| Vegetables (g/d) | 439.80 ± 243.54 | 417.86 ± 256.50 | 289.23 ± 183.76 | 0.06 |
| Fruits (g/d) | 750.11 ± 382.63 | 439.53 ± 243.73 | 325.48 ± 209.00 | **0.04** |
| Fish (g/d) | 13.75 ± 15.65 | 11.24 ± 11.07 | 9.36 ± 8.81 | 0.99 |
| Poultry (g/d) | 45.60 ± 55.96 | 31.70 ± 29.99 | 28.12 ± 23.10 | 0.32 |
| Egg (g/d) | 25.27 ± 17.06 | 22.53 ± 13.63 | 17.38 ± 10.67 | 0.38 |
| Red meat (g/d) | 31.64 ± 20.16 | 20.75 ± 19.16 | 12.47 ± 8.39 | 0.05 |
| **Nutrient intake** | | | | |
| Energy (kcal/d) | 3468.72 ± 402.67 | 2545.52 ± 190.36 | 1799.81 ± 271.01 | - |
| Protein (g/d) | 114.98 ± 24.09 | 87.51 ± 17.49 | 62.37 ± 13.30 | 0.58 |
| Carbohydrate (g/d) | 502.95 ± 82.83 | 353.96 ± 47.13 | 255.92 ± 53.31 | 0.09 |
| Total fat (g/d) | 122.50 ± 27.88 | 95.28 ± 20.53 | 63.74 ± 15.19 | 0.09 |
| MUFA (g/d) | 39.10 ± 9.87 | 32.22 ± 9.23 | 21.80 ± 6.55 | **0.03** |
| PUFA (g/d) | 24.25 ± 7.54 | 21.12 ± 8.80 | 14.24 ± 5.48 | **0.02** |
| SFA (mg/d) | 37.54 ± 11.27 | 27.37 ± 6.58 | 18.86 ± 5.14 | 0.38 |
| Trans fat (mg/d) | 0.001 ± 0.002 | 0.0007 ± 0.002 | 0.0008 ± 0.003 | 0.60 |
| Oleic acid (g/d) | 34.87 ± 9.55 | 29.18 ± 9.32 | 19.55 ± 6.46 | **0.02** |

**Table 3** (continued)

| | | | | |
|---|---|---|---|---|
| Linolenic acid (g/d) | 1.58 ± 0.55 | 1.26 ± 0.67 | 0.82 ± 0.40 | 0.07 |
| Linoleic acid (g/d) | 20.80 ± 7.42 | 18.44 ± 8.59 | 12.27 ± 5.34 | **0.03** |
| EPA (g/d) | 0.03 ± 0.04 | 0.03 ± 0.04 | 0.02 ± 0.02 | 0.83 |
| DHA (g/d) | 0.12 ± 0.13 | 0.10 ± 0.12 | 0.08 ± 0.08 | 0.94 |

CSI: Cholesterol to saturated fat index; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; MUFA; monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid; T: tertile; TC: total cholesterol

Values are represented as means (SD)

*P*-value*: ANCOVA was performed to adjust the potential confounding factor (energy intake)

$P < 0.05$ was considered significant

**Table 4** The interaction between GRS with CSI and N6/N3 on obesity phenotype in obese and overweight women ($n = 279$)

| Variable | GRS*CSI | | | GRS*N6/N3 | | |
|---|---|---|---|---|---|---|
| | MUH | | | MUH | | |
| | B | 95% CI | *P*-value | B | 95% CI | *P*-value |
| **Crude** | -0.01 | -0.07 to 0.04 | 0.60 | 1.92 | -0.06 to 3.91 | **0.058** |
| **Model1** | -0.01 | -0.07 to 0.04 | 0.61 | 2.00 | -0.05 to 4.05 | **0.057** |
| **Model2** | -0.01 | -0.07 to 0.05 | 0.76 | 2.26 | 0.008 to 4.52 | **0.049** |

GLM was performed to identify the interaction between GRS and CSI and N6/N3 on obesity phenotype. MUH: metabolically unhealthy phenotype

Model 1 = adjusted for potential confounding factors including (age and Energy)

Model 2 = adjusted for potential confounding factors including (age, BMI, energy, and physical activity)

$P < 0.1$ was considered significant

Metabolically healthy was considered as reference

both genetic and lifestyle factors [66]. Some experimental designs have successfully investigated the gene-environment interactions that could explain the "missing heritability" linked to complex obesity phenotypes.

It is proven some experimental designs investigate the interaction of gene-environment to explain the "missing heritability" related to the complex obesity phenotypes [67]. Several studies have demonstrated that long-chain n-3 PUFA intake may affect adiposity phenotypes [68, 69]. For instance, a study indicated that those with higher obesity-related GRS were more likely to accumulate fat when consuming n-3 PUFAs. Moreover, individuals with higher obesity-related GRS were at risk of fat accumulation when they consumed n-3 PUFAs [70]. Furthermore, other studies demonstrated that fish consumption of long-chain n-3 PUFAs moderate genetic influences on long-term BMI and weight changes, with significant correlations between GRS and weight loss among those with higher n-3 PUFA intake [71]. The result of a study on the interaction between dietary unsaturated fat consumption and GRS on body fat mass index (FMI) has been demonstrated [72].

Research suggests that genetic predisposition to obesity can interact significantly with saturated fat intake. One study found that individuals in the highest genetic predisposition quartile (Quartile 4) who consumed more SFA showed an increase of 1.8 kg/m² in BMI and an additional 3.7 cm in WC compared to those with lower SFA intake but the same genetic risk [73]. These findings indicate that reducing SFA consumption may help mitigate the genetic risk associated with central obesity [74]. Further, a 4-SNP GRS analysis revealed significant interactions between dietary fat types—including SFA, PUFA, and MUFA—and their impact on WC, suggesting that dietary fat composition could influence obesity-related outcomes based on genetic profiles [75]. Another study demonstrated that the balance between dietary polyunsaturated and saturated fats interacts with the FTO gene, where carriers of the A allele had a 0.43-fold higher obesity risk than TT allele carriers, regardless of their intake ratio [76]. These findings underscore the complex gene-diet interactions that may shape individual obesity risk and the potential for tailored dietary strategies to counteract genetic predispositions to obesity.

While limited studies have examined the interaction between GRS fatty acid intake concerning obesity phenotypes, it is critical to recognize that obesity's genetic influence is polygenic [61, 77]. Thus, larger-scale studies are necessary to replicate our findings regarding GRS-fat intake interactions. Systematic reviews indicate that reducing dietary intake of SFA, TFA, and n-6 PUFA while enhancing MUFA and n-3 PUFA consumption can effectively reduce obesity risk among genetically susceptible individuals [78].

The mechanisms underlying how obesity-related genes interact with n-3 PUFAs remained unclear. However, evidence suggests that regular consumption of n-3 PUFAs may help reduce adiposity in humans [79] by inhibiting adipogenesis [80] and stimulating fat oxidation [81]. Lipoprotein lipase (LPL), a key enzyme in lipid metabolism, plays a crucial role in lipid distribution in various tissues and is implicated in obesity progression [82, 83].

Additionally, cholesteryl ester transfer protein (CETP) mediates the transport of cholesteryl esters and triglycerides between lipoproteins and is more active in obese individuals [84]. Based on a study, increased CETP activity was observed in obese individuals [85]. Diets high in SFA have also been shown to reduce cholesterol efflux, further contributing to obesity development [86, 87].

### Strengths and limitations

Potential strengths of our study include the assessment of interactions between genes and diet in the Iranian population, comprehensive coverage of established BMI-associated genetic variants, and the use of well-validated dietary questionnaires. In addition, some limitations of this study need attention. First, our study was conducted only in the Iranian population, which limits its generalizability to other populations. Second, the N6/N3 PUFA*GRS interaction with adiposity phenotypes may have been influenced by total fat intake. These data revealed that the interactions between the GRS gene and N6/N3 PUFAs were not substantially confounded by total fat intake and that N6/N3 PUFA intake may modulate obesity susceptibility genes.

## Conclusion

The findings of this study suggest that a higher dietary N6/N3 PUFA intake may amplify the genetic risk of metabolically unhealthy obesity among Iranian adults with higher GRS. Specifically, those with a higher N6/N3 ratio appear more likely to exhibit obesity phenotypes when carrying metabolic risk alleles, highlighting the significance of gene-diet interactions in obesity risk and emphasizing the importance of individualized dietary advice based on each ethnic group. While the association between GRS and obesity phenotypes was observed with the N6/N3 ratio, no significant interactions were found between GRS and the CSI on obesity risk. This suggests that not all fat quality indices have the same impact when interacting with genetic risk, pointing to the specificity of N6/N3 PUFAs in this relationship. Given the study's focus on a limited number of SNPs, future research should extend to include a broader array of SNPs and polygenic risk scores (PRS) to deepen our understanding of how gene-diet interactions affect obesity susceptibility. Replicating these findings in diverse populations with varied dietary habits will provide a more comprehensive view and support the development of effective, personalized dietary recommendations.

#### Acknowledgements

The authors thank the Laboratory of Nutrition Sciences and Dietetics at Tehran University of Medical Sciences (TUMS). We are grateful to all of the participants for their contribution to this research. This study was approved by the Research Ethics Committee of the TUMS, Tehran, Iran, with ethics number IR.TUMS.MEDICINE.REC.1399.636. All participants signed a written informed consent that was approved by this committee prior to enrollment in the study.

#### Author contributions

Niloufar Rasaei and Khadijeh Mirzaei designed the search; Niloufar Rasaei and Khadijeh Mirzaei conducted the sampling; Fatemeh Gholami performed statistical analysis; Niloufar Rasaei, Seyedeh Fatemeh Fatemi, Mahsa Samadi, Mohammad Keshavarz Mohammadian and Elnaz Daneshzad and Khadijeh Mirzaei wrote the paper, Khadijeh Mirzaei primary responsibility for final content. All authors read and approved the final manuscript.

#### Funding

This study was supported by grants from the Tehran University of Medical Sciences, Tehran, Iran (Grant number: 99-3212-51715).

#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

#### Ethics approval and consent to participate

The study protocol has been approved by the ethics committee of the Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences (TUMS) with the following identification: IR.TUMS.MEDICINE.REC.1399.636. Each participant was completely informed about the study protocol and provided a written and informed consent form before taking part in the study. All methods were carried out in accordance with relevant guidelines and regulations, or the Declaration of Helsinki.

#### Consent for publication

Not applicable in the declarations section.

#### Competing interests

The authors declare no competing interests.

#### Conflict of interest

None of the authors have a conflict of interest.

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Received: 26 April 2024 / Accepted: 13 December 2024
Published online: 21 January 2025

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