The interaction between rs 3,807,992 genotypes with the dietary inflammatory index on Leptin, Leptin resistance, and Galectin 3 in obese and overweight women

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Abstract

Objective: Obesity is related to increasing leptin and some inflammatory factors that are associated with low-grade inflammation. Moreover, several studies have shown Caveolin-1 (CAV1) genetic variations may be associated with dietary intake. The current study aimed to evaluate the interaction of CAV1 rs3807992 with types of the energy-adjusted dietary inflammatory index (EDII) in leptin, leptin resistance, and Galectin 3, as inflammatory factors.

Methods: This cross-sectional study was carried out on 363 overweight and obese females. Dietary intake and DII were obtained from a 147-item food frequency questionnaire (FFQ). The CAV-1 genotype was measured using the PCR-RFLP method. Anthropometric values and serum levels of leptin and Galectin 3 were measured by standard methods.

Results: Increased adherence to EDII in the interaction with CAV1 genotypes led to an increase in leptin level 79.15 (mg/l) (β = 79.15, CI = −1.23,163.94, \(P = 0.04\)) in model 3, after controlling for further potential confounders. By contrast, adherence to EDII in the interaction with the genotype including risk alleles showed no significant interaction, even after adjustment in model 3 (β = 0.55, CI = −0.99, 2.09, \(P = 0.48\)). Although, a marginal positive significant interaction was found between EDII and CAV1 genotypes on Galectin 3, after adjustment in model 3 (β = 31.35, CI = 0.13, 77.13, \(P = 0.05\)).

Conclusions: The present study indicates that a high adherence of EDII and CAV1 genotypes containing risk alleles may be a prognostic factor and increase both leptin and Galectin 3. However, it seems that the presence of interaction was not on leptin resistance. Further functional studies are necessary to elucidate the exact mechanism.

Keywords: Leptin, Leptin resistance, Galectin 3, Caveolin-1, Dietary inflammatory index, Interaction
physiological, and eating habits, which result in inflammation [3]. Inflammation is affected by a variety of influences, including lifestyle, nutrition, and physical exercise, as well as genetic [4], whilst adiposity is linked to a higher incidence of non-communicable diseases (NCDs) [5, 6]. This systemic and adipose tissue inflammation, which causes increases in the production of leptin and pro-inflammatory cytokines, is one of the pathways that could illustrate the connection between obesity and the progression of NCDs, with the cause of chronic low-grade inflammation [7–9]. The overabundance of leptin released by adipocytes to the amount of body fat [10] has a key role in homeostatic regulations of feeding and energy balance thus body weight management and also insulin sensitivity [11–13]. One of the related factors to energy balance thus body weight management and also has a key role in homeostatic regulations of feeding and released by adipocytes to the amount of body fat [10]. Leptin, in turn, plays a role in inflammation status, and interaction with genotype can influence the inflammatory response [14, 15].

Another factor that could affect inflammation is genotype, where there seems to be a relationship between leptin and rs 3807992 genotypes (Caveolin 1 (CAV1)), such that leptin upregulates CAV1 expression [16]. CAV1 is a transmembrane scaffolding protein that controls essential cell functions such as proliferation, apoptosis, cell division, and transcytosis via a variety of signaling pathways and the progression of atherosclerosis and obesity. On the other hand, according to recent research, CAV1 expression is increased in human obesity, suggesting that leptin can play a crucial role [17]. CAV1 works in the same way as the suppressor of the cytokine signaling family of proteins, which are components of the classic negative feedback circuit [6]. They are upregulated by cytokines, and, as a result, they block cytokine-induced signaling pathways in the cell. Also, some studies have shown that genetic variations in CAV1 can interfere with other risk factors, such as dietary intake [18, 19].

Diet, especially dietary patterns, plays a significant role in influencing obesity and circulating inflammatory markers in adults [8]. The Dietary Inflammatory Index (DII), developed by Shivappa et al., calculates the consumption of nutrient and non-nutrient components of the food and was recently introduced to measure the inflammatory properties of the diet, thus, it is considered as an overall picture of the inflammatory properties of the diet [20–22]. To our knowledge, there is only one report, from a cross-sectional study conducted in females, which found an interaction between the DII score and CAV1 on leptin and Galectin 3. The DII must be evaluated in different demographic environments, because dietary habits differ throughout societies and can have an effect on the DII quality. Furthermore, since other influences, such as climate, lifestyle, and genetic history, vary around population settings, the association between the DII score and inflammation status, and interaction with genotype can be influenced. Therefore, this study aimed to evaluate the variants in CAV1 (rs 3,807,992 genotypes) that could interact with the DII index for serum Leptin, Leptin resistance, and Galectin-3 Levels in an obese and overweight Iranian population.

Method
Research design and study population
To perform a multicenter unregulated cross-sectional study, this observational study used a multistage cluster random sampling approach. The sample size was calculated according to the following formula: \( N = \left( \frac{1}{(1 - \alpha + Z1 - \beta) \times \sqrt{1 - r 2/2 + 2}) \right) \times \sqrt{\frac{1}{2}} + \frac{1}{2} \), whit considering \( r = 0.35, \beta = 0.95, \) and \( \alpha = 0.05 \). The participants in this sample were 363 healthy obese and overweight women between the ages of 18 and 48 who had a body mass index (BMI) of 25–40 at Tehran University of Medical Sciences, who were referred to urban health centers. Those with a medical history, opioid, or nicotine usage or alcohol consumption, thyroid disorder, diabetes mellitus, cardiovascular diseases (CVDs), malignancies, hepatic or renal conditions, menopause, lactation, breastfeeding, acute or chronic infections, people following weight loss diets and specific nutritional therapies, such as insulin, and cardiovascular diets, as well as weight fluctuations in recent months, and the consumption of dietary supplements in the preceding three months, or estimated energy intakes of more than 4200 kcal/d or less than 800 kcal/d, were excluded [23]. This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (ID number: IR.TUMS.VCR.REC 1398.142). Before the start of the clinical screening tests, all patients were required to have written and informed consent. Grant ID: 97-03-161-41017.

Anthropometric measurements
The InBody 770 scanner, a multi-frequency bioelectrical impedance analyzer, was used to determine body composition, comprising weight, BMI, fat mass, and fat-free mass (FFM) (Inbody Co., Seoul, Korea). This electrical impedance analyzer measures the resistance of body...
tissue to the passage of an electrical signal emitted by both hands and feet. If the current passes more quickly through certain parts of the body, the amount and ratio of body fat-free mass and fat mass can be calculated, as per the manufacturer’s instructions. Height was measured on a Seca scale stadiometer with an accuracy of 0.5 cm following standard approaches. Waist circumference (WC) was measured in the narrowest part of the waist using a non-elastic tape with an accuracy of 0.5 cm while people were at the end of a normal exhalation. The largest part of the hip circumference (HC) was measured with an accuracy of 0.5 cm. The waist-to-hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). The waist-to-height ratio (WHtR) was measured by dividing the waist circumference (cm) by the height (cm). A trained dietician places a measuring tape across the neck, beginning 1 inch from the point where the neck and shoulders meet, which may be the lower portion of Adam’s apple, to determine neck diameter (NC). Leptin resistance is measured by the following formula: leptin (mg/l)/BMI (kg/m²); this index assesses leptin levels when accounting for the influence of BMI [24].

**Dietary measurements and EDII calculation**

To measure dietary consumption in the 12 months before the report, a 147-item semi-quantitative food FFQ was administered on a regular, weekly, annual, or yearly basis, a qualified researcher interviewed participants and collected their food intake number and frequency. A 147-item semi-quantitative FFQ validity and reliability has been confirmed by previous studies [25, 26]. Face-to-face interviews were used to assess dietary consumption using a standardized, reliable, and validated food-frequency questionnaire (FFQ) for Iran by a trained dietitian [27]. This evaluation was conducted by asking participants about the occurrence of food items consumed from a prepared list of foods. The servings and portion sizes reported by study subjects were converted to grams per day. Using household proportions, the portion sizes of the eaten items are translated to grams [28]. The NutriDay. Using household proportions, the portion sizes of reported by study subjects were converted to grams per day. A trained dietician places a measuring tape across the neck, beginning 1 inch from the point where the neck and shoulders meet, which may be the lower portion of Adam’s apple, to determine neck diameter (NC). Leptin resistance is measured by the following formula: leptin (mg/l)/BMI (kg/m²); this index assesses leptin levels when accounting for the influence of BMI [24].

After 15 minutes of rest, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times with a mercury sphygmomanometer. Participants were referred to the Nutrition and Biochemistry Laboratory of the School of Nutritional and Dietetics at Tehran University of Medical Sciences in this project. After a 10-12 hour overnight fast, venous blood samples were taken. Centrifuged for 15 minutes at 3000 rpm to isolate the EDTA anticoagulant plasma and serum samples, and the remaining blood was washed three times with 0.9 g/l NaCl solution. After serum isolation, the samples were instantly frozen at −80 °C for laboratory testing. Pars Azmoon laboratory kits were used to measure triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting blood pressure (FBS), and insulin levels in the blood (Pars Inc., Tehran, Iran). The active form of Galectin 3 was also measured using the ELISA-Quanti kit’s enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN). Industrial enzyme-linked immunosorbent assay kits were used to assess serum leptin concentrations (mg/l) (Mediagnost, Reutlingen, Germany). The homeostatic model assessment insulin resistance (HOMA-IR) was used to measure insulin resistance (mIU/ml), with the following equation: [fasting plasma glucose (mmol/l) and insulin (IU/l)] /22.5 [29]. After 15 minutes of rest, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times with a mercury sphygmomanometer.

**Genotyping**

Genotyping is the process of determining an individual’s DNA, which was isolated from whole blood using a Mini Columns package to genotype the CAV1 polymorphisms (Type G; Genall; Exgene). CAV1 polymorphisms (rs3807992) in gene fragments were investigated using the polymerase chain reaction-restriction fragment
length polymorphism (PCR-RFLP) technique (major allele G and minor allele A). The following primers were used for PCR: F:5′/AGAATTCAGGTCGCTGAACG/3′ and R:5′/GTTCCTTGAGAAAAAGCACTGA-3′. In a DNA thermocycler, PCR reactions were carried out in a volume of 20 μl, comprising 1 l isolated DNA, 1 μl Forward primers, 1 μl Reverse primers, 7 μl purified water, and 10 μl Taq DNA Polymerase Master Mix. The DNA templates were denatured for 3 minutes at 94 degrees Celsius, followed by 40 cycles of denaturation at 94 degrees Celsius, annealing at 42-50 degrees Celsius, and elongation at 72 degrees Celsius for 2 minutes. Amplified DNA was digested overnight at 37 °C with HinIII (NlaIII) restriction enzyme, then isolated on an agarose gel by electrophoresis (2%). Uncut homozygous AA (213bp), cut heterozygous GA (3 bands: 118, 95, and 213 bp), and cut homozygous GG genotypes of the CAV1 rs3807992 variant were identified (2 bands: 118 & 95 bp).

Other covariates assessment
Participants’ physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), where its validity and reliability has been verified. This questionnaire contains seven questions, each of which has two sections (number of exercises per week and length) that indicate the participants’ level of physical activity [30]. Other demographic characteristics, such as age, educational level, marital status, and income, were collected using standard questionnaires.

Statistical analysis
The Kolmogorov-Smirnov method was conducted to test the data’s normality (p > 0.05). The Hardy-Weinberg Equilibrium deviation among CAV1, G32124A allele frequencies were determined using Pearson’s chi-square test. The discrepancies between the two groups of the median of EDII and genotype according to risk allele were assessed using an independent sample t-test, Chi-square test expressed as mean and standard error (SE), and for categorical variables as numbers and percentages, respectively. Analysis of covariance (ANCOVA) was utilized to account for confounders. Linear regression was used to assess the association between leptin, leptin resistance, and Galectin 3 with EDII and genotypes, presented as B and 95% confidence interval (CI). A generalized linear model (GLM) was applied to obtain an estimate of interaction between EDII and Genotype on leptin, leptin resistance, and Galectin 3. SPSS v.25 program (SPSS Inc., IL, USA) was used for statistical analysis, and the significance level was set at a P-value < 0.05, whilst P-values 0.05, 0.06, and 0.07 were considered as marginally significant.

Results

Study population characteristics
General characteristics of participants, such as body composition, biochemical assessment, and others among lower vs higher than the median of EDII and genotypes, are presented in Table 1. A total of 363 women with BMI mean and SD 30.9 (3.90) kg/m² were divided into two groups, based on EDII median (0.07) lower (n=172) and upper than (n=191) median. The range of EDII was -3.83 to 3.19, and 70.8% of the study population were married. The level of leptin in individual’s serum had 27.7 (11.8) mg/l, and 4.02 (7.26) mg/l of Galectin3 (Table 1).

Association between population characteristics across rs 3,807,992 genotypes and median EDII score
Associations between population characteristics across rs 3807992 genotypes and median EDII score are shown in Table 1. Age of starting obesity and history of losing weight was higher in upper vs. median group of EDII, and after controlling potential confounders, including age, BMI, energy intake, and physical activity, there was a marginally significant mean difference among the median of EDII (P=0.05). In the crude model, significant mean differences were found for physical activity, starting obesity age (P<0.05), whilst for body composition and biochemical variables in terms of fat-free mass (FFM), skeletal muscle mass (SMM), soft lean mass (SLM), fat-free mass index (FFMI), and HDL, there were also significant mean differences (P<0.05). Categorical variables, such as economic and education status, were significantly different across the median of EDII (P<0.05), moreover all the mentioned factors had a higher mean in the lower median of EDII. Also, EDII was associated with body fat mass (BFM) (P=0.05) and BFM (%) (P=0.01), bone mineral content (BMC) (P=0.04), trunk fat (P=0.01), visceral fat (P=0.03), fat mass index (FMI) (P=0.01), and marginally significantly different for TG (P=0.06).

Association between population characteristics among genotype category
Subjects were divided into two groups according to risk alleles of CAV1 genotypes: GG (n=75) without risk alleles and AA+AG with risk alleles (n=198). A marginal significant mean difference was found in visceral fat (P=0.05) and FMI (P=0.07) and HC (P=0.06) among CAV1 genotypes category in the crude model. There was a significant difference was found for TG (P=0.04) after adjustment among genotype category groups. Also, a significant mean difference for HDL remained stable across models (P=0.04) (Table 1).
| Variables | EDII median <0.07 | P-value | p-value* | EDII median ≥0.07 | P-value | p-value* |
|----------|------------------|---------|----------|------------------|---------|----------|
|          | N = 172          |         |          | N = 191          |         |          |
| Mean ± SE |                  |         |          |                  |         |          |
| Age (years) | 36.74 ± 0.79    | 35.67 ± 0.78 | 0.33 | 0.08 | 36.33 ± 0.89 | 35.58 ± 1.08 | 0.40 | 0.59 |
| PA (MET-minutes/week) | 1544.81 ± 208.08 | 205.33 ± 205.33 | 0.007 | 0.04 | 1062.62 ± 193.41 | 947.60 ± 234.38 | 0.64 | 0.70 |
| Age of starting obesity | 20.97 ± 0.88 | 23.31 ± 0.81 | 0.10 | 0.05 | 22.46 ± 0.84 | 22.38 ± 0.89 | 0.08 | 0.94 |
| **Anthropometric variables** |                  |         |          |                  |         |          |
| Weight (kg) | 79.76 ± 0.90    | 78.49 ± 0.95 | 0.05 | 0.35 | 78.17 ± 0.70 | 76.51 ± 0.81 | 0.71 | 0.23 |
| Height (cm) | 161.84 ± 0.84   | 160.60 ± 0.93 | 0.68 | 0.35 | 161.41 ± 0.67 | 160.12 ± 0.59 | 0.24 | 0.56 |
| BMI (kg/m²) | 30.60 ± 0.57    | 30.00 ± 0.63 | 0.43 | 0.49 | 29.61 ± 0.39 | 30.51 ± 0.48 | 0.11 | 0.12 |
| **Body composition** |                  |         |          |                  |         |          |
| WC (cm) | 94.45 ± 1.18    | 93.23 ± 1.25 | 0.26 | 0.49 | 96.66 ± 0.64 | 153.90 ± 3.47 | 0.13 | 0.52 |
| HC (cm) | 112.08 ± 0.66    | 113.51 ± 0.70 | 0.60 | 0.15 | 104.56 ± 0.20 | 103.97 ± 0.24 | 0.35 | 0.06 |
| NC (cm) | 36.26 ± 0.36    | 36.93 ± 0.39 | 0.54 | 0.22 | 36.46 ± 0.27 | 36.64 ± 0.32 | 0.30 | 0.44 |
| WHR | 0.92 ± 0.00    | 0.93 ± 0.00 | 0.11 | 0.24 | 0.92 ± 0.00 | 0.92 ± 0.00 | 0.12 | 0.23 |
| WHRR | 0.58 ± 0.00    | 0.58 ± 0.00 | 0.14 | 0.78 | 0.59 ± 0.00 | 0.60 ± 0.00 | 0.04 | 0.16 |
| BFM (kg) | 31.91 ± 0.38    | 33.06 ± 0.40 | 0.27 | 0.05 | 31.70 ± 0.31 | 31.84 ± 0.36 | 0.10 | 0.64 |
| BFM (%) | 41.14 ± 4.99    | 42.22 ± 5.71 | 0.91 | 0.01 | 40.31 ± 0.40 | 40.79 ± 0.46 | 0.10 | 0.71 |
| FFM (kg) | 47.87 ± 0.85    | 45.46 ± 0.90 | 0.02 | 0.05 | 46.32 ± 0.56 | 45.34 ± 0.65 | 0.68 | 0.52 |
| SMM (kg) | 26.30 ± 0.50    | 24.91 ± 0.53 | 0.02 | 0.06 | 25.41 ± 0.33 | 24.78 ± 0.38 | 0.64 | 0.46 |
| SLM (kg) | 45.10 ± 0.79    | 42.85 ± 0.84 | 0.02 | 0.06 | 43.64 ± 0.52 | 42.76 ± 0.61 | 0.73 | 0.55 |
| BMC (kg) | 2.68 ± 0.36    | 2.61 ± 0.32 | 0.09 | 0.04 | 2.67 ± 0.03 | 2.59 ± 0.04 | 0.33 | 0.35 |
| Trunk fat(kg) | 15.77 ± 0.18    | 17.29 ± 0.19 | 0.26 | 0.01 | 15.16 ± 0.14 | 15.62 ± 0.16 | 0.08 | 0.47 |
| Visceral fat (kg) | 14.62 ± 0.29    | 15.54 ± 0.31 | 0.69 | 0.03 | 14.58 ± 0.20 | 14.91 ± 0.23 | 0.05 | 0.25 |
| FFMI | 18.21 ± 0.16    | 17.58 ± 0.17 | 0.004 | 0.01 | 17.76 ± 0.13 | 17.60 ± 0.11 | 0.78 | 0.52 |
| FMI | 12.21 ± 0.16    | 12.85 ± 0.17 | 0.35 | 0.01 | 12.23 ± 0.11 | 12.38 ± 0.13 | 0.07 | 0.55 |
| **Biochemical variables** |                  |         |          |                  |         |          |
| FBS (mg/dL) | 84.88 ± 1.55    | 86.85 ± 1.64 | 0.33 | 0.40 | 86.94 ± 1.01 | 86.85 ± 1.17 | 0.97 | 0.86 |
| TC (mg/dL) | 179.83 ± 5.49   | 174.49 ± 5.83 | 0.75 | 0.51 | 180.44 ± 3.35 | 172.32 ± 3.88 | 0.18 | 0.17 |
| TG (mg/dL) | 123.11 ± 12.10  | 132.78 ± 12.85 | 0.65 | 0.06 | 110.96 ± 6.7 | 130.53 ± 7.85 | 0.08 | 0.04 |
| HDL (mg/dL) | 47.66 ± 1.58    | 43.47 ± 1.67 | 0.04 | 0.07 | 48.08 ± 1.04 | 45.20 ± 1.20 | 0.02 | 0.04 |
| LDL (mg/dL) | 99.60 ± 3.92    | 92.87 ± 4.16 | 0.44 | 0.25 | 95.83 ± 2.37 | 93.55 ± 2.75 | 0.23 | 0.20 |
| **Categorical variables** |                  |         |          |                  |         |          |
| Economic status |                  |         |          |                  |         |          |
| Low level | 51(62.2) | 31(37.8) | 0.01 | 0.01 | 28(32.6) | 58(67.4) | 0.31 | 0.20 |
| Moderate level | 72(43.4) | 94(56.6) | 46(26.3) | 129(73.7) | 24(22.9) | 81(77.1) |
| High level | 44(43.6) | 57(56.4) | | | | |
| Education level | | | | | | |
| Illiterate | 3(75) | 1(25) | 0.004 | 0.001 | 1(25) | 3(75) | 0.11 | 0.20 |
| Under diploma | 26(55.3) | 21(44.7) | 16(33.3) | 32(66.7) | 45(30.8) | 101(69.2) |
| Diploma | 78(56.1) | 61(43.9) | 45(30.8) | 101(69.2) | 37(20.6) | 143(79.4) |
| Master and higher | 65(38) | 106(62) | 37(20.6) | 143(79.4) | | |
| Marital status | | | | | | |
| Single | 124(48.1) | 134(51.9) | 0.80 | 0.91 | 28(26.2) | 79(73.8) | 0.99 | 0.86 |
| Married | 48(46.6) | 55(53.4) | | | 71(26.2) | 200(73.8) | | |
Although there was a significant mean difference among the EDII median for leptin ($P=0.03$), after further controlling with economic status and education, starting obesity age, there was no significant mean difference for leptin resistance ($P=0.21$). Moreover, a marginal significant mean difference was found for Galectin 3 ($P=0.06$) (Table 2). There was no significant mean difference among median of EDII in other variables ($P>0.05$). Food group intake of study population among EDII category are shown in Fig. 1.

### The association between EDII score and with the leptin, leptin resistance and Galectin3

The association between EDII score and rs 3807992 genotypes with the leptin, leptin resistance, and Galactin3 are presented in Table 3. Increased adherence to EDII yielded an increase of 16.73 mg/l in leptin level ($\beta=16.73$, 95% CI $=1.56, 39.3$, $P=0.04$) and 0.55 in leptin resistance ($\beta=0.55$, 95% CI $=0.00, 1.30$, $P=0.06$) in model 2, which was adjusted for, economic status, education level, age of starting obesity, weight loss history. By contrast, increased adherence to EDII in the association with that genotype showed no significant association in Galectin3 in model 2 ($\beta=0.91$, 95% CI $=-0.64, 2.48$, $P=0.24$) (Table 3).

### Table 2 Galectin-3, leptin, and leptin resistance across rs 3,807,992 genotypes and median EDII score in obese and overweight women ($n = 363$)

| Variables          | EDII median | P-value | p-value* | rs 3,807,992 genotypes | p-value | p-value* |
|--------------------|-------------|---------|----------|------------------------|---------|----------|
|                    | <0.07       | > = 0.07|          | GG                     |         |          |
|                    | $N = 172$   | $N = 191$|          | AA + AG                |         |          |
| Mean ± SE          |             |         |          | $N = 75$               |         |          |
|                    |             |         |          | $N = 198$              |         |          |
| Leptin (mg/l)      | 27.13 ± 3.45| 29.87 ± 3.01| 0.64 | 0.03 | 30.38 ± 2.82 | 26.69 ± 3.69 | 0.52 | 0.40 |
| Leptin resistance  | 0.81 ± 0.05 | 0.91 ± 0.05 | 0.17 | 0.21 | 0.81 ± 0.06 | 0.90 ± 0.05 | 0.72 | 0.31 |
| Galectin-3 (mg/l)  | 4.01 ± 1.88 | 4.99 ± 2.05 | 0.67 | 0.06 | 4.86 ± 1.43 | 2.73 ± 1.34 | 0.12 | 0.29 |

EDII energy-adjusted dietary inflammatory index, SE standard error

$P$-value: obtain from ANOVA

$P$-value*: obtain from ANCOVA; adjusted for age, physical activity, total energy intake, BMI, economic status and education, age of starting obesity

$P < 0.05$ consider as significant, $P = 0.06$, and 0.07 consider as marginally significant
The association between rs 3,807,992 genotypes with the leptin, leptin resistance and Galectin3

After adjustment, there were not any significant association between CAV1 genotypes with a risk allele in the association with leptin ($\beta=2.53$, 95%CI = -3.42,8.48, $P= 0.39$), leptin resistance ($\beta=0.08$, 95%CI= 0.00,0.28, $P=0.08$), and Galectin 3 ($\beta=1.08$, 95%CI= -3.40,5.58, $P=0.62$) (Table 3).

The interactions between adherence of EDII across rs 3,807,992 genotypes on the leptin, leptin resistance, and Galectin3

The interactions between adherence of EDII across rs 3807992 genotypes on leptin, leptin resistance, and Galectin 3 were presented in Table 4. A marginal positive interaction was observed between EDII and risk alleles group (AA+AG) genotype in model 2 further

Fig. 1 Food groups intakes among EDII categories in obese and overweight women
Table 3 The association between EDII across and rs 3,807,992 genotypes on the leptin, and Galectin3 in obese and overweight (n = 363)

| Variables                  | Models  | EDII score       | P-value** | rs 3,807,992 genotypes | P-value** |
|----------------------------|---------|------------------|-----------|------------------------|-----------|
|                            |         | β     | 95% CI    |            | β     | 95% CI    |
| Leptin (mg/l)              | Crude   | 2.34   | −22.52,27.21 | 0.85**    | 1.32 | −3.73,6.38 | 0.60    |
|                            | Model1  | 14.03  | −8.57,36.65  | 0.22**    | −0.71 | −5.43,9.11 | 0.76    |
|                            | Model2  | 16.73  | 1.56,39.32   | 0.04*     | 2.53 | −3.42,8.48 | 0.39    |
| Leptin resistance          | Crude   | 0.57   | −0.36,1.51   | 0.22**    | 0.02  | −1.24,0.17 | 0.72    |
|                            | Model1  | 0.49   | −0.24,1.23   | 0.18*     | −0.01 | −0.16,0.13 | 0.85    |
|                            | Model2  | 0.55   | 0.00,1.30    | 0.06*     | 0.08  | 0.00,0.28  | 0.08    |
| Galectin3 (mg/l)           | Crude   | 21.45  | −19.47,62.37 | 0.30*     | −0.80 | −3.93,2.31 | 0.60    |
|                            | Model1  | 0.82   | −0.59,2.25   | 0.25*     | 0.06  | −3.84,3.97 | 0.97    |
|                            | Model2  | 0.91   | −0.64,2.48   | 0.24*     | 1.08  | −3.40,5.58 | 0.62    |

EDII energy-adjusted dietary inflammatory index
Model 1: additionally adjusted for age, BMI, total energy intake, and physical activity
Model 2: additionally adjusted for economic status, education level, age of starting obesity, losing weight history
Model 3: further adjustment with the age of starting obesity, history of losing weight

* Significant level in the crude model
^ Significant level after adjustment by Model 1, 2
P < 0.05 consider as significant, P = 0.06, and 0.07 consider as marginally significant

Table 4 The interactions between adherence of EDII across rs 3,807,992 genotypes on the leptin, leptin resistance, and Galectin3 score in obese and overweight women (n = 363)

| Variables                  | Models  | EDII adherence* AA + AG | β     | 95% CI    | P-value |
|----------------------------|---------|-------------------------|-------|-----------|---------|
| Leptin (mg/l)              | Crude   | 14.73                   | −41.06,70.54 | 0.60    |
|                            | Model1  | 30.64                   | 15.03,75.13   | 0.05    |
|                            | Model2  | 18.94                   | 15.03,75.13   | 0.06    |
|                            | Model3  | 79.18                   | 13.23,163.94  | 0.04    |
| Leptin resistance          | Crude   | 0.57                    | −0.36,1.51   | 0.22    |
|                            | Model1  | 0.03                    | −1.94,2.01   | 0.97    |
|                            | Model2  | 0.92                    | 2.40,1.51    | 0.45    |
|                            | Model3  | 0.55                    | −0.99,2.09   | 0.48    |
| Galectin3 (mg/l)           | Crude   | 21.45                   | −19.47,62.37 | 0.30    |
|                            | Model1  | 24.16                   | −25.04,73.38 | 0.33    |
|                            | Model2  | 0.15                    | 0.01,1.03    | 0.07    |
|                            | Model3  | 31.35                   | 0.13,77.13   | 0.05    |

EDII energy-adjusted dietary inflammatory index
Model 1: additionally adjusted for age, BMI, total energy intake, and physical activity
Model 2: additionally adjusted for economic status, education level
Model 3: further adjustment with the age of starting obesity, history of losing weight

* Significant level in the crude model and after adjustment by Model 1, 2, and 3
P < 0.05 consider as significant, P = 0.06, and 0.07 consider as marginally significant

Discussion
To the best of our knowledge, the present study is the first cross-sectional study to investigate the interaction of EDII and CAV1 genotypes on leptin, leptin resistance, and Galectin 3 as outcomes. We found that, after taking into account confounding variables, increased adherence to EDII, in association with leptin level and leptin resistance, is associated with an increase in both variables. Also, our results suggest that EDII interacts positively...
with CAV1 genotypes including risk alleles (AA+AG) on leptin level and Galectin 3.

Leptin is considered a cytokine that is created by adipocytes, and it leads to the induction of inflammation. The pro-inflammatory properties of leptin have been proposed to be comparable to those of immune cell-derived cytokines, including interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [31, 32]. Present study has indicated EDII was associated with leptin, and leptin resistance. Similar to our study Muhammad et al. showed that the DII score was positively associated with plasma leptin concentration [33], which was not in line with a cross-sectional study in the USA that demonstrated the DII score was not related to leptin [34]. According to an observational study among children, exposure to a more pro-inflammatory diet in boys and girls is associated with an increase in leptin concentrations [35]. It has been illustrated that leptin resistance may depend on the variety of nutrients consumed from the diet, supporting the hypothesis of the vital role of an accurate distribution in the dietary pattern. Recent studies have contributed to recognizing the mechanisms regarding the impaired response to leptin, and desensitization of leptin receptor, down-regulation of its intracellular signaling and inflammation are regarded as key routes involved [36]. The DII not only includes micronutrients and macronutrients, but also includes general intake of bioactive components containing flavonoids, spices, and tea. The whole score takes into account the complete diet, not just separate nutrients or foods [21]. Thus, inflammatory factors are affected by bioactive components [37]. Unclear processes appear underlie how a pro-inflammatory diet causes obesity. Previous research has shown that early in the process leading to weight gain, substantial amounts of inflammatory biomarkers are present. In Duncan et al., it was discovered that during a 3-year period in middle-aged people, fibrinogen, leukocytes, and other indicators of chronic low-grade inflammation engendered weight gain [38, 39]. Increased levels of inflammation-sensitive plasma proteins in middle-aged men from the cohort of the Malmo Preventive Study indicated weight increase, even in middle-aged and older participants’ inflammatory indicators, were directly linked to weight increase [40–42]. Moreover, in Ramallal. et al, the authors indicated the risk of acquiring new-onset overweight or obesity and yearly weight gain were both significantly increased by proinflammatory diet [43]. Uncertain processes underlie how a proinflammatory diet promotes obesity, however, there is some evidential mechanism in the tendency to acquire weight. Proinflammatory cytokines including IL-6, IL-1, and TNF-a may increase appetite, resulting in an increase in caloric intake and fat storage, B-adrenergic receptors brought on by persistent peripheral sympathetic nervous system stimulation brought on by adiposity signals like leptin and insulin, which are linked to the inflammatory

Fig. 2 Interaction between rs 3,807,992 genotypes (GG consider as the reference group) with EDII on leptin and Galectin3 (A, B respectively). Vertical lines in every column are error bar, that have shown standard error. A Leptin (The P-value for AG + AA genotype: 0.02; P-value for adherence of EDII: 0.05; P-value for interaction between AG + AA genotype and Leptin: 0.65). B Galectin3 (The P-value for AG + AA genotype: 0.31; P-value for adherence of EDII: 0.02; P-value for interaction between AG + AA genotype and Galectin3:0.24)
process [44–46]. Moreover, excess consumption of some nutrients may also produce hypothalamus inflammation, and impact of nutrition on alterations in the gut microbiota, which come before the low-grade inflammation that encourages adiposity, represent another putative mechanism [47–49]. Blood leptin levels and body fat are shown to be associated, where more adiposity equates to higher leptin levels. This appears to represent the start of the defect loop of inflammation by diet in the increment of leptin level [50]. In the present study, due to the non-significance of the mean difference weight among median of EDII, but the percentage BFM weight was higher in subjects with more adherence of EDII, which can highlight the role of this mechanism. Leptin resistance is a broad-based pathophysiological condition. The leptin axis interacts in a useful way with factors involved in metabolism, such as insulin, and inflammation, including innate immune system mediators, such as interleukin-6. Leptin resistance is reported to be caused by a physical interaction between leptin and C-reactive protein [51]. Therefore, it seems that following an inflammatory diet with its effect on the state of inflammatory factors and insulin resistance can be effective in creating leptin resistance [52]. The present study demonstrates that increased adherence to EDII in the association leptin and leptin resistance leads to an increase in leptin level and leptin resistance; however, there was no impact on Galectin 3. Galectin 3 is a crucial component of several physiological processes, including cell adhesion, proliferation, apoptosis, signal transduction, and the control of immunological and inflammatory responses [53, 54]. Numerous types of human cells, including immunological and inflammatory cells, fibroblasts, endothelium, and epithelium, are highly expressed in this protein [55]. Galectin-3’s function in determining nutritional status has not previously been investigated.

In the present study, there was no association between CAV1 and leptin, leptin resistance, and Galectin 3. CAV1 is considered a key factor with cellular functions including pinocytosis and regulation of cell signaling [56]. Singh et al. present a feedback loop of CAV1 mediated downregulation of leptin signaling [16]. The significant and novel findings pointed out that there is a strong association between leptin and CAV1, so it contributes to raising CAV1 expression which impairs the signaling of leptin. Also, the associated mechanisms need to be ascertained [57]. In line with our findings, Schroeter et al. found that Caveolin deficiency was associated with the lack of leptin in vivo [58]. In this study, we found no association between caveolin with leptin, leptin resistance, and Galectin 3; by contrast, some studies have demonstrated that Galectin 3 induces integrin function and Caveolin phosphorylation, suggesting that Galectin 3 may be related to Caveolin [59, 60].

We found that, after taking into account confounding variables, increased adherence to EDII in the interaction with CAV1 genotype including risk alleles (AA+AG) leads to a positive interaction on leptin level and Galectin 3. Inflammatory stimuli can lead to raised Caveolin expression by inhibiting upstream regulators of antioxidant defense enzymes; Caveolin expression can further intensify the inflammatory reaction. Caveolae nutritional modulation may apply an opportunity to upset inflammatory signaling events; indeed, DI1 has strong anti-inflammatory effects which occur through modifications to the lipid microenvironment [61].

The major strength of this investigation is that it is the first study to evaluate the interaction of EDII and CAV1 genotypes on leptin, leptin resistance, and Galectin 3. These interactions remained significant across multiple testing, despite the high correlations among the outcomes of interest. Additionally, demographic characteristics and FFQ were measured/colllected by a trained dietitian. Moreover, the knowledge gained from this study may be applied to clinical practice and contribute to personalized therapies for the prevention and treatment of metabolic disorders.

Limitations of this investigation include the use of cross-sectional design, which precludes causal inferences. Longitudinal epidemiologic studies and biochemical experimentally based research are required to elucidate and strengthen the findings from this study. Furthermore, whether this interaction relates to changes in CAV1 genotypes has not been explored. Besides, the pathway linking dietary inflammatory index to this CAV1 gene is unknown. Also, FFQ was used for recording the subject’s food, which is subject to memory and recall bias. Although the FFQ is typically used to examine long-term dietary consumptions, its closed structure with limited response options limits its ability to determine between-person variations, so there can be some misclassification. Residual confounding for is another limitation. Moreover, we did not measure cytokines in participants, and only measured leptin and Galectin-3. Because in the initial approach, we did not have a presupposition for this kind of influence, and our null hypothesis only pertained to the presence or absence of association and interaction between rs 3807992 genotypes with the dietary inflammatory index on leptin, leptin resistance, and Galectin 3, and not the mechanism of effect or the investigation of the cause of this influence. However, it seems that there is a need to conduct more studies in this field to investigate these inflammatory factors and the serum levels of these cytokines and It is their effectiveness.
Conclusion
We found that there may be an association between DII and leptin and leptin resistance, and that high adherence of EDII and CAV1 genotypes containing risk alleles have prognostic value and are associated with increases in both leptin and Galectin3, but not leptin resistance.

Nevertheless, prospective investigation of the interaction between EDII and CAV1 genotypes should be a priority in further study of this interaction.

Abbreviations
NCDs: Non-communicable diseases; CAV1: Caveolin1; DII: Dietary Inflammatory Index; CVDs: Cardiovascular diseases; BMI: Body mass index; FFM: Fat-free mass; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WHR: Waist-to-height ratio; NC: Neck diameter; EDII: Energy-adjusted DII; FFQ: Food frequency questionnaire; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FBS: Fasting blood pressure; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; ELISA: Enzyme-linked immunosorbent assay; HOMA: Homeostatic model assessment; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; IPAQ: International Physical Activity Questionnaire; SD: Standard deviation; ANCOVA: Analysis of covariance; SMM: Skeletal muscle mass; SLM: Soft lean mass; ECW: Extracellular water; ICW: Intraocular water; FFMI: Fat-free mass index; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-alpha.

Acknowledgments
We are grateful to all of the participants for their contribution to this research. This study was supported by grants from the Tehran University of Medical Sciences, Tehran, Iran.

Authors’ contributions
FSH, MF, CC, Sh and NR wrote the paper, CC revised the manuscript, KhM had full access to all of the data in the study and took responsibility for the integrity and accuracy of the data. All authors read and approved the final manuscript.

Funding
This study is funded by grants from the Tehran University of Medical Sciences (TUMS). (Grant ID: 97-03-161-41017).

Availability of data and materials
The data that support the findings of this study are available from the corresponding author but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author.

Declarations
Ethics approval and consent to participate
Ethics approval for the study protocol was confirmed by The Human Ethics Committee of Tehran University of Medical Sciences (Ethics Number: IR.TUMS.VCR.REC.1398.142). Each participant was completely informed about the study protocol and provided a written and informed consent form before taking part in the study. This study was approved by the research council. We confirmed that all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Each participant was completely informed about the study protocol and provided a written and informed consent form before taking part in the study.

Competing interests
All authors declared that they have no competing interests.

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Received: 31 March 2022 Accepted: 19 August 2022
Published online: 23 September 2022

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