

Interactions between Caveolin-1 polymorphism and Plant-based dietary index on metabolic and inflammatory markers among women with obesity

Abaj, F., Mirzababaei, A., Hosseinasab, D., Bahrampour, N., Clark, C. C. T. & Mirzaei, K.

Published PDF deposited in Coventry University's Repository

Original citation:

Abaj, F, Mirzababaei, A, Hosseinasab, D, Bahrampour, N, Clark, CCT & Mirzaei, K 2022, 'Interactions between Caveolin-1 polymorphism and Plant-based dietary index on metabolic and inflammatory markers among women with obesity', *Scientific Reports*, vol. 12, 9088.

<https://dx.doi.org/10.1038/s41598-022-12913-y>

DOI 10.1038/s41598-022-12913-y

ESSN 2045-2322

Publisher: Nature Research

This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.



OPEN

Interactions between Caveolin-1 polymorphism and Plant-based dietary index on metabolic and inflammatory markers among women with obesity

Faezeh Abaj¹, Atieh Mirzababaei¹, Dorsa Hosseininasab², Niki Bahrapour³, Cain C. T. Clark⁴ & Khadijeh Mirzaei^{1✉}

A series of recent studies have indicated that the Caveolin-1 (CAV-1) gene variant may be associated with metabolic and inflammatory markers and anthropometric measures. Furthermore, it has been shown that a plant-based dietary index (PDI) can elicit a positive impact on these metabolic markers. Therefore, we sought to examine whether PDI intakes may affect the relationship between CAV-1 (rs3807992) and metabolic factors, as well as serum inflammatory markers and anthropometric measures, in women with obesity. This current study consisted of 400 women with overweight and obesity, with a mean (SD) age of 36.67 ± 9.10 years. PDI was calculated by a food frequency questionnaire (FFQ). The anthropometric measurements and serum profiles were measured by standard protocols. Genotyping of the CAV-1(rs3807992) was conducted by the PCR-RFLP method. The following genotypic frequencies were found among the participants: GG (47.8%), AG (22.3%), and AA (2.3%). In comparison to GG homozygotes, risk-allele carriers (AA + AG) with higher PDI intake had lower ALT (P: 0.03), hs-CRP (P: 0.008), insulin (P: 0.01) and MCP-1 (P: 0.04). Furthermore, A-allele carriers were characterized by lower serum ALT (P: 0.04), AST (P: 0.02), insulin (P: 0.03), and TGF- β (P: 0.001) when had the higher following a healthful PDI compared to GG homozygote. Besides, risk-allele carriers who consumed higher unhealthful PDI had higher WC (P: 0.04), TC/HDL (P: 0.04), MCP-1 (P: 0.03), and galactin-3 (P: 0.04). Our study revealed that A-allele carriers might be more sensitive to PDI composition compared to GG homozygotes. Following a healthful PDI in A-allele carriers may be associated with improvements in metabolic and inflammatory markers and anthropometric measures.

Abbreviations

AST	Aspartate aminotransferase
BIA	Bioelectrical impedance analysis
BMI	Body mass index
bp	Base pair
BFM	Body fat mass
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DP	Dietary pattern
eNOS	Endothelial nitric oxide synthase
FMI	Fat mass index

¹Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), P.O. Box: 14155-6117, Tehran, Iran. ²Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran, Iran. ³Department of Nutrition, Science and Research Branch, Islamic Azad University (SRBIAU), Tehran, Iran. ⁴Centre for Intelligent Healthcare, Coventry University, Coventry CV1 5FB, UK. ✉email: mirzaei_kh@sina.tums.ac.ir

FFQ	Food frequency questionnaire
GLM	General linear model
GWAS	Genome-wide association studies
HDL	High-density lipoprotein cholesterol
IR	Insulin Receptor
hs-CRP	High sensitivity C-reactive protein
IPAQ	International physical activity questionnaire
LDL	Low-density lipoprotein
MA	Minor allele
PBD	Plant-based diet
PDI	Plant-based dietary index
PCR	Polymerase chain reaction
PDI	Plant-based dietary index
RFLP	Restriction fragment length polymorphism
SNP	Single nucleotide polymorphism
TC	Total cholesterol
TG	Triglyceride
WC	Waist circumference
WHO	World Health Organization

Obesity is defined by an excess in the accumulation of lipids in adipose tissue; this accumulation becomes detrimental when it happens in visceral fat¹. Indeed, waist circumference (WC) (an indirect measure of visceral fat accumulation) is correlated with the progression of particular metabolic disorders containing cardiovascular diseases (CVDs) and type 2 diabetes (T2DM)². The prevalence of obesity is universally higher in women³; additionally, women with high body mass index (BMI) are considered at greater risk of T2DM⁴, atherosclerotic cardiovascular disease⁵, hypertension⁶, dyslipidemia⁷, and endocrine disorders⁸. Moreover, increased levels of hepatic enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are common in obesity and their prevalence increases gradually with increasing BMI⁹. Numerous population studies show that low-grade and chronic inflammation is often augmented in patients with obesity¹⁰. This is characterized by incremented circulating levels of pro-inflammatory cytokines—particularly Interleukin-6 (IL-6)—and of the monocyte chemoattractant protein (MCP-1), both generated by the adipose tissue^{11–14}.

Diet is one of the most notable variables that have life-long effects on obesity and metabolic risk factors¹⁵. There is abundant evidence to suggest that dietary patterns are related to inflammatory mediators and obesity as an inflammatory-related disease^{16–19}; indeed, a review article demonstrated that a plant-based diet (PBD) could alleviate certain inflammatory markers, such as IL-6²⁰. This kind of dietary pattern has been described as possessing a high intake of vegetables, fruits, grains, and legumes, which could lead to reductions in both inflammation and obesity²¹. Also, dietary inflammatory index, in which the consumption of food items that can increase body inflammations, such as saturated fatty acid, trans fatty acids, and refined grains, were positively associated with fat mass and concentration of MCP-1²². Several dietary intervention studies have shown that healthy plant foods, such as flavonoids, can modulate inflammatory cytokines^{23–25}. Therefore, PBD may be associated with an improvement in obesity-related inflammatory profiles and inhibition of chronic diseases risks. Indeed, recent studies have revealed that there might be an interaction between specific genes such as Caveolin-1 and particular dietary patterns^{26,27}.

Caveolin-1 (CAV-1), is the major structural protein of caveolae, which is located on human chromosome 7 (7q31.1) and it includes 3 exons that select intronic single nucleotide polymorphisms (SNPs). CAV-1 works in a scaffolding capacity and has been involved in transmembrane signaling²⁸. CAV-1 is a vital constituent of the lipid raft that controls their activity and cooperates with numerous signaling pathways, including steroid receptors²⁹. Moreover, CAV-1 gene variants have been shown to be correlated with insulin resistance (IR), diabetes mellitus, dyslipidemia, and metabolic syndrome³⁰. Based on previous studies, the adipocyte seems to have higher concentrations of caveolae than any other cell^{31,32}. Additionally, some studies have shown that diets containing foods with antioxidant features such as PBD, can modulate CAV-1 levels and caveolin function for the debarment of chronic diseases^{33–36}.

Given the rising prevalence of obesity and the lack of studies performed on Caveolin-1 (rs3807992) and plant-based dietary index (PDI), as well as its association with metabolic and inflammatory markers among women, the present study sought to evaluate the interactions between Caveolin-1 (rs3807992) and PDI on metabolic and inflammatory markers in Iranian women with overweight and obesity.

Methods

Study population. This cross-sectional study, including 400 women with obesity, was conducted in the health care center of Tehran, Iran. The subjects were chosen via a random cluster random sampling method, where the inclusion criteria were: women with overweight (BMI ≥ 25 kg/m²) or obesity (BMI ≥ 30 kg/m²), aged above 18 years, before menopause, not being pregnant or lactating and smoker. The women who had any chronic disease (T2DM), CVDs, polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease, etc.), taking any supplements or medications (Atorvastatin, Cholestyramine, etc.), and weight loss program were excluded. The general characteristics of the participants were collected via a demographic questionnaire. The study protocol was approved by the Ethics Commission of Tehran University of Medical Sciences (IR.TUMS.VCR.REC. 97-03-161-41017)³⁷. Total calorie intake was accepted in the range between 800 and 4200 kcal per day, with intakes

outside of this range leading to exclusion from the study³⁸. All of the participants completed a written informed consent form before taking part in the study.

General, anthropometric and physical activity assessments. Height was measured using Seca 216 to the nearest 0.1 cm and weight of subjects was also assessed using Seca scale to the nearest 0.1 kg, with light clothes and unshod, in a standing position. WC was measured at the point of the smallest girth by a trained expert. BMI was calculated as $\text{weight}/(\text{height})^2$. In addition, other anthropometric variables were measured using a multi-frequency bioelectrical impedance analyzer InBody 770 scanner (Inbody Co., Seoul, Korea), with participants wearing light clothes without any metal subjects³⁹. In addition, physical activity (PA) was assessed via the validated International Physical Activity Questionnaire⁴⁰. All participants' blood pressure was monitored using an automatic sphygmomanometer according to established procedures (OMRON, Germany).

Dietary assessments and plant-based dietary intake. A validated 147-items semi-quantitative food frequency questionnaire (FFQ) was used by an expert to assess the dietary intake of the subjects. Grams of foods and beverages were entered into NUTRITIONIST IV software (version 7.0; N-Squared Computing, Salem, OR)^{41,42}. According to the plant-based dietary intake, which was divided to overall plant-based diet index (PDI), healthy PDI (hPDI), and unhealthy PDI (uPDI), the intakes of the subjects were divided to 18 groups, which were: animal (Dairy, animal fat, egg, meat, fish and seafood, and miscellaneous animal-based foods), healthy (whole grains, vegetables, fruits, legumes, nuts, vegetable oils, tea, and coffee), and unhealthy plant-based foods (fruit juices, sugar-sweetened beverages, refined grains, sweets and desserts, and potatoes)^{43,44}. Foods were scored 1–10, after they were transformed to deciles. PDI, hPDI, and uPDI were assessed as scoring 10 and 1 for the highest and lowest deciles of plant food intake, healthy plant foods, and unhealthy plant foods, respectively. Conversely, unhealthy plant foods and animal food items were scored 1 to 10 for the highest and lowest deciles of animal foods and unhealthy plants foods, respectively.

Biochemical measurements. After 10–12 h night fasting, blood samples were gathered at the Nutrition and Biochemistry laboratory of the School of Nutritional Sciences and Dietetics, TUMS. Triacylglycerol kits (Pars Azmoon Inc, Tehran, Iran) were used to measure serum triglycerides (TG) by colorimetric method tests with Glycerol-3-phosphate oxidase Phenol 4-Aminoantipyrine Peroxidase (GPO-PAP). The cholesterol oxidase Phenol 4-Aminoantipyrine Peroxidase (CHOD-PAP) was used to calculate total cholesterol, and the direct method and immunoinhibition were used to measure low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Pars Azmoon (Pars Azmoon Inc., Tehran, Iran) provided all of the kits. ALT, AST, high-sensitivity C-reactive protein (hs-CRP), MCP-1, interleukin 1 beta (IL-1 β), and transforming growth factor-beta (TGF β) were measured via standard protocols. Plasminogen activator inhibitor-1 (PAI-1) (Human PAI-1*96 T ELISA kit Crystal Company) was measured in triplicate. TC was divided into HDL to discern the ratio of TC/HDL, in addition, LDL was divided by HDL to discern the ratio of LDL/HDL. Serum insulin level was also measured by radioimmune assay. More detailed about biochemical measuring are reported in our previous study⁴⁵.

DNA analysis. Based on a previous study²⁷, the Mini Columns kit (Type G; Genall; Exgene) was used for DNA extraction. The CAV-1 SNP (rs3807992) was genotyped by PCR-RFLP method, using primers, Forward: 3'AGTATTGACCTGATTTGCCATG5' Reverse: 5'GTCTTCTGGAAAAAGCACATGA-3'. The sequencing process was performed using the ABI PRISM 3730 automated sequencer (Applied Biosystems, Foster City, Calif, USA)²⁷.

Statistical analyses. The Kolmogorov–Smirnov test was used for assessing the normality of the data. The Hardy–Weinberg equilibrium and comparison of categorical variables were assessed with the χ^2 test. PDI was transformed to tertiles based on the trends. Quantitative (mean \pm SD) and qualitative variables (n (%)) were evaluated via one-way analysis of variance (ANOVA) and chi-square among PDI tertiles, respectively. Genotype groups were considered as a dominant inherent model (AA + AG) versus GG homozygous. Analysis of covariance (ANCOVA) was performed for the adjustment model (adjusting for age, physical activity and energy intake and diastolic blood pressure (DBP)). A generalized linear regression model (GLZM) was used to analyze the interactions between CAV-1 polymorphism (rs3807992) and PDI. Data were analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 25) and a P-value < 0.05 was considered as significant; but for interactions, P < 0.1 was considered significant.

Ethics approval and consent to participate. All methods were performed in accordance with the relevant guidelines and regulations. The protocol of the study was approved by the ethics committee of TUMS (Ethics number: 97-03-161-41017). All participants completed a written informed consent.

Results

Study population characteristics. The participants in this study consisted of 400 women, with a mean (SD) age of 36.67 ± 9.10 years. The majority of individuals (72.4%) were married, had a university education (47.8%), and had a history of obesity (71.2 percent). The following genotypic frequencies were found among the participants: GG (47.8%), AG (22.3%), and AA (2.3%).

The difference in means of biochemical parameters and body composition between CAV-1 rs3807992 genotypes. The comparison of variables including anthropometrics and biochemical param-

Variables	Genotypes		
	GG (n=207)	AG + AA (n=193)	P-value
Demographic variables			
Age (years)	37.56 ± 9.49	35.75 ± 8.78	0.05
Physical activity (MET-min/week)	1215.46 ± 2033.81	1199.02 ± 2251.97	0.42
Blood parameters			
FBS (mg/dl)	87.98 ± 9.62	86.95 ± 9.75	0.40
Insulin (mIU/ml)	1.21 ± 0.22	1.22 ± 0.25	0.61
HOMA-IR	3.27 ± 1.21	3.41 ± 1.36	0.40
TC (mg/dl)	186.76 ± 33.74	182.71 ± 37.36	0.37
TG (mg/dl)	113.11 ± 51.20	125.08 ± 66.66	0.11
HDL (mg/dl)	49.07 ± 11.16	44.04 ± 10.16	<0.001
LDL (mg/dl)	98.88 ± 22.66	91.27 ± 25.07	0.01
TC/HDL	3.93 ± 0.89	4.43 ± 1.91	0.008
LDL/HDL	2.07 ± 0.53	2.14 ± 0.64	0.35
Hs-CRP	4.18 ± 4.40	4.33 ± 4.76	0.79
ALT	19.04 ± 13.95	20.14 ± 14.19	0.53
AST	18.27 ± 7.44	17.95 ± 8.29	0.75
MCP-1	51.49 ± 102.26	48.42 ± 81.14	0.80
TGF-β	54.47 ± 16.18	55.34 ± 19.72	0.12
Galactin-3	4.28 ± 8.16	3.47 ± 5.56	0.60
Blood pressure			
SBP (mmHg)	110.31 ± 12.63	112.90 ± 14.75	0.12
DBP (mmHg)	75.87 ± 10.77	79.31 ± 10.06	0.007
Anthropometric parameters			
Weight (kg)	79.26 ± 10.35	80.90 ± 11.68	0.15
Height (cm)	161.30 ± 6.08	160.96 ± 5.58	0.56
BMI (kg/m ²)	30.57 ± 3.88	31.30 ± 3.93	0.07
WC (cm)	98.22 ± 9.30	99.87 ± 9.49	0.08
WHR	0.93 ± 0.05	1.41 ± 6.58	0.30
Body composition			
SMM (kg)	25.34 ± 3.27	25.63 ± 3.55	0.40
FFM (kg)	46.26 ± 5.48	46.54 ± 5.83	0.62
BFM (kg)	33.49 ± 7.96	35.64 ± 9.15	0.01
FMI	12.93 ± 3.25	13.83 ± 3.46	0.009
BF (%)	41.62 ± 5.47	42.68 ± 5.50	0.05
VFA (cm)	170.42 ± 25.32	176.65 ± 39.24	0.98

Table 1. Characteristics of the study population across rs 3807992 genotypes. Variables are presented as mean ± SD for continuous variables. *FBS* fasting blood sugar, *HOMA-IR* homeostatic model assessment for insulin resistance, *TC* total cholesterol, *TG* triglyceride, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *SMM* skeletal muscle mass, *FFM* fat free mass, *FMI* fat mass index, *BFM* body fat mass, *BFP* body fat percentage, *WHR* waist hip ratio, *WC* waist circumference, *VFA* visceral fat area, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *MCP-1* monocyte chemoattractant protein-1, *TGFβ* Transforming growth factor beta. Significant values are in bold. P-value is found by Independent T test.

eters according to two genotypes groups (GG and AG + AA) is given in Table 1. The results of this study revealed that DBP ($P=0.007$), body fat mass (BFM) ($P=0.01$), and fat mass index (FMI) ($P=0.009$) were higher in participants carrying the A allele, compared with individuals in the GG genotype. Moreover, A-allele carriers had significantly lower serum HDL ($P<0.001$) and LDL ($P=0.01$) compared to GG homozygotes; although, the TC/HDL ($P=0.008$) ratio was significantly higher. Furthermore, there was no significant association between this polymorphism and other biochemical parameters including TG, inflammatory markers (hs-CRP, MCP-1, TGFβ), and liver enzymes (ALT and AST) in both crude and adjusted models ($P>0.05$) (Table 1).

The difference in means of biochemical parameters and body composition between PDI, hPDI and uPDI. The result of comparison of biochemical parameters and body composition between PDI, hPDI and uPDI are shown in Tables 2, 3 and 4. These results displayed that women with higher PDI were older ($P=0.03$) and had higher physical activity ($P<0.001$) than those with lower PDI. Women with higher healthful

Variables	PDI groups				
	Low adherence (n = 158)	High adherence (n = 130)	P-value	P-value*	
Demographic variables					
Age (years)	35.98 ± 8.88 ¹	37.29 ± 7.93	0.19	0.21	
Physical activity (MET-min/week)	1095.89 ± 1988.02	1342.57 ± 2253.62	0.35	0.33	
Blood parameters					
FBS (mg/dl)	87.43 ± 9.62	87.59 ± 9.71	0.90	0.72	
Insulin (IU/ml)	1.21 ± 0.20	1.21 ± 0.25	0.91	0.68	
HOMA-IR	3.40 ± 1.27	3.24 ± 1.28	0.34	0.57	
TC (mg/dl)	184.33 ± 37.98	185.67 ± 33.85	0.77	0.69	
TG (mg/dl)	117.51 ± 60.55	118.54 ± 58.81	0.89	0.75	
HDL (mg/dl)	47.27 ± 11.02	46.13 ± 10.66	0.41	0.92	
LDL (mg/dl)	95.16 ± 25.06	94.51 ± 22.99	0.83	0.91	
TC/HDL	4.09 ± 1.61	4.24 ± 1.37	0.43	0.89	
LDL/HDL	2.06 ± 0.55	2.13 ± 0.62	0.34	0.78	
Blood pressure					
SBP (mmHg)	109.88 ± 12.11	113.84 ± 15.35	0.01	0.09	
DBP (mmHg)	77.09 ± 8.40	78.55 ± 10.92	0.02	0.38	
Anthropometric parameters					
Weight (kg)	79.01 ± 10.04	80.38 ± 11.24	0.28	0.74	
Height (cm)	161.17 ± 6.17	161.39 ± 5.64	0.74	0.51	
BMI (kg/m ²)	30.47 ± 3.79	30.99 ± 3.75	0.24	0.47	
WC (cm)	97.97 ± 9.07	99.21 ± 9.78	0.26	0.51	
WHR	1.50 ± 7.22	0.93 ± 0.05	0.37	0.58	
Body composition					
SMM (kg)	25.43 ± 3.06	25.97 ± 3.57	0.16	0.94	
FFM (kg)	46.34 ± 5.17	47.29 ± 6.03	0.15	0.99	
BFM (kg)	33.17 ± 8.02	35.06 ± 9.36	0.06	0.37	
BF (%)	41.27 ± 5.47	41.83 ± 5.63	0.39	0.33	
VFA (cm)	170.21 ± 36.72	166.07 ± 41.40	0.73	0.55	
RMR (kcal)	1565.22 ± 246.63	1589.23 ± 274.73	0.43	0.44	
Qualitative variables					
Marriage status	Single	36 (22.6%)	19 (14.7%)	0.11	0.12
Occupation	Unemployed	80 (51%)	92(71.3%)	0.002	0.002
Education	illiterate	2 (1.3%)	1(0.8%)	0.01	0.01
	Diploma	56 (35.2%)	70 (43.9%)		
	University	101 (63.6%)	159(55.2%)		
Weight loss history in past year	No	75 (47.5%)	58 (46.4%)	0.90	0.88

Table 2. Description of characteristics among intake of PDI. Variables are presented as mean ± SD for continuous variables and frequency for categorical variables. *PDI* plant-based diet index, *FBS* fasting blood sugar, *HOMA-IR* homeostatic model assessment for insulin resistance, *TC* total cholesterol, *TG* triglyceride, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *SMM* skeletal muscle mass, *FFM* fat free mass, *BFM* body fat mass, *BF* body fat percentage, *WHR* waist hip ratio, *WC* waist circumference, *VFA* visceral fat area, *RMR* resting metabolic rate. Significant values are in bold. P values from t test for continuous variables and chi-square test for categorical variables. *P-value as found by ANCOVA, and adjusted for (age, physical activity and energy intake and diastolic blood pressure (DBP)).

PDI had significantly lower LDL/HDL ratios in both crude ($P = 0.04$) and adjusted models ($P = 0.03$); although there was no statistically significant difference ($P > 0.05$) from the low to high unhealthy PDI.

Interactions between PDIs and *CAV-1 rs3807992* genotypes on metabolic and inflammatory markers and anthropometric measures. The interaction effects between *CAV-1* variants at *rs3807992* and PDIs (healthful and unhealthy) on metabolic and inflammatory markers, including TC, HDL, LDL, TC, TC/HDL, LDL/HDL, TG, ALT, AST, hs-CRP, MCP-1, PAI-1, and IL-1 β , are shown in Tables 5 and 6.

Interaction between PDI and *CAV-1 rs3807992* genotypes on metabolic and inflammatory markers and anthropometric measures. There is a gene-diet interaction for PDI and *CAV-1* polymorphism (*rs3807992*) on ALT (β : - 7.51, 95% CI - 14.45 to - 0.57, P : 0.03), hs-CRP (β : - 3.30, 95% CI - 5.76 to

Variables	hPDI groups				
	Low adherence (n = 158)	High adherence (n = 130)	P-value	P-value*	
Demographic variables					
Age (years)	35.57 ± 8.81 ¹	37.65 ± 7.97	0.03	0.02	
Physical activity (MET-minutes/week)	893 ± 849.77	1527.65 ± 2853.94	<0.001	<0.001	
Blood parameters					
FBS (mg/dl)	87.90 ± 9.70	87.11 ± 9.61	0.52	0.75	
Insulin (IU/ml)	1.22 ± 0.24	1.20 ± 0.21	0.35	0.89	
HOMA-IR	3.46 ± 1.37	3.20 ± 1.16	0.12	0.92	
TC (mg/dl)	181.61 ± 38.26	188.21 ± 33.77	0.15	0.66	
TG (mg/dl)	118.13 ± 63.41	117.80 ± 55.90	0.96	0.36	
HDL (mg/dl)	47.13 ± 10.55	46.41 ± 11.18	0.60	0.85	
LDL (mg/dl)	92.23 ± 25.01	97.50 ± 23.01	0.08	0.93	
TC/HDL	4.09 ± 1.81	4.23 ± 1.14	0.48	0.20	
LDL/HDL	2.16 ± 0.55	2.02 ± 0.61	0.04	0.03	
Blood pressure					
SBP (mmHg)	111.93 ± 14.31	111.35 ± 13.20	0.72	0.56	
DBP (mmHg)	77.38 ± 9.64	78.14 ± 9.62	0.51	0.50	
Anthropometric parameters					
Weight (kg)	79.77 ± 10.06	79.45 ± 11.17	0.80	0.86	
Height (cm)	161.82 ± 5.96	160.65 ± 5.85	0.09	0.76	
BMI (kg/m ²)	30.61 ± 3.85	30.79 ± 3.71	0.69		
WC (cm)	98.95 ± 9.42	98.06 ± 9.38	0.42	0.89	
WHR	1.53 ± 7.41	0.92 ± 0.05	0.33	0.34	
Body composition					
SMM (kg)	25.96 ± 3.14	25.36 ± 3.46	0.12	0.59	
FFM (kg)	47.30 ± 5.35	46.19 ± 5.80	0.09	0.51	
BFM (kg)	34.24 ± 9.29	33.78 ± 8.01	0.65	0.55	
BF (%)	41.22 ± 5.98	41.86 ± 5.01	0.32	0.23	
VFA (cm)	174.69 ± 40.52	161.41 ± 38.28	0.28	0.24	
Qualitative variables					
Marriage status	Single	34(22.5%)	21 (15.3%)	0.18	0.22
Occupation	Unemployed	94(63.1%)	78(56.9%)	0.09	0.08
Education	illiterate	2 (1.3%)	1(0.7%)	0.38	0.35
	Diploma				
	University	86 (56.9%)	73 (53.3%)		
Weight loss history in past year	No	71 (46.7%)	62 (47.3%)	0.91	0.92

Table 3. Description of characteristics among intake of hPDI. Variables are presented as mean ± SD for continuous variables and frequency for categorical variables. *hPDI* healthy plant-based diet index, *FBS* fasting blood sugar, *HOMA-IR* homeostatic model assessment for insulin resistance, *TC* total cholesterol, *TG* triglyceride, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *SMM* skeletal muscle mass, *FFM* fat free mass, *BFM* body fat mass, *BF* body fat percentage, *WHR* waist hip ratio, *WC* waist circumference, *VFA* visceral fat area, *RMR* resting metabolic rate. Significant values are in bold. P values from t test for continuous variables and chi-square test for categorical variables. *P-value as found by ANCOVA, and adjusted for (age, physical activity and energy intake and diastolic blood pressure (DBP)).

– 0.85, P: 0.008), insulin (β : – 0.14, 95% CI – 0.26 to – 0.02, P: 0.01), and MCP-1 (β : – 54.51, 95% CI – 107.72 to – 1.30, P: 0.04) in both crude and adjusted models (adjusting for age, energy intake, physical activity education, job and marriage status) (Table 5). Thus, the A-allele carriers who consumed higher PDI had lower ALT, insulin, MCP-1, and hs-CRP, compared to GG homozygotes (Fig. 1).

Interaction between healthful PDI and *CAV-1 rs3807992* genotypes on metabolic and inflammatory markers and anthropometric measures. There were significant interactions between healthful PDI and *rs3807992* on ALT (β : – 6.52, 95% CI – 13.48 to – 0.43, P: 0.04), AST (β : – 4.36, 95% CI – 8.27 to – 0.44, P: 0.02), insulin (β : – 0.18, 95% CI – 0.28 to – 0.03, P: 0.03), and TGF- β (β : – 56.05, 95% CI – 78.96 to – 3.14, P: 0.001) in both crude and adjusted adjustment model (Table 6). In particular, A-allele carriers were characterized by lower serum ALT, AST, insulin, and TGF- β , when following a healthful PDI, compared to GG homozygote. (Fig. 2).

Variables	uPDI groups				
	Low adherence (n = 157)	High adherence (n = 131)	P-value	P-value*	
Demographic variables					
Age (years)	36.87 ± 8.61	36.21 ± 8.32	0.51	0.52	
Physical activity (MET-min/week)	1300.12 ± 1992.97	1092.14 ± 2237.48	0.92	0.88	
Blood parameters					
FBS (mg/dl)	87.18 ± 8.68	87.90 ± 10.76	0.56	0.35	
Insulin (IU/ml)	1.22 ± 0.22	1.20 ± 0.23	0.47	0.34	
HOMA-IR	3.21 ± 1.17	3.47 ± 1.39	0.12	0.14	
TC (mg/dl)	185.16 ± 35.72	184.62 ± 36.85	0.90	0.99	
TG (mg/dl)	119.06 ± 61.60	116.57 ± 57.41	0.74	0.80	
HDL (mg/dl)	47.33 ± 11.04	46.07 ± 10.62	0.36	0.42	
LDL (mg/dl)	96.40 ± 23.72	92.98 ± 24.59	0.27	0.33	
TC/HDL	4.06 ± 1.06	4.28 ± 1.92	0.26	0.25	
LDL/HDL	2.09 ± 0.55	2.09 ± 0.63	0.95	0.99	
Blood pressure					
SBP (mmHg)	111.67 ± 13.52	111.64 ± 14.13	0.98	0.84	
DBP (mmHg)	77.15 ± 9.27	78.45 ± 10.01	0.26	0.20	
Anthropometric parameters					
Weight (kg)	80.46 ± 10.74	78.61 ± 10.37	0.39	0.2	
Height (cm)	161.40 ± 5.57	161.11 ± 6.35	0.10	0.84	
BMI (kg/m ²)	30.93 ± 3.83	30.43 ± 3.70	0.27	0.3	
WC (cm)	99.22 ± 9.56	97.69 ± 9.16	0.17	0.18	
WHR	0.93 ± 0.05	1.62 ± 7.95	0.28	0.34	
Body composition					
SMM (kg)	25.93 ± 3.27	25.37 ± 3.33	0.15	0.26	
FFM (kg)	47.17 ± 5.52	46.29 ± 5.64	0.18	0.32	
BFM (kg)	34.49 ± 9.04	33.44 ± 8.24	0.30	0.45	
BF (%)	41.54 ± 5.75	41.51 ± 5.30	0.96	0.99	
VFA (cm)	165.32 ± 40.19	172 ± 49.84	0.59	0.54	
RMR (kcal)	1574.26 ± 259.60	1577.93 ± 260.11	0.90	0.88	
Qualitative variables					
Marriage status	Single	26(16.5%)	29 (22.3%)	0.36	0.41
Occupation	Unemployed	97(61.8%)	77(59.7%)	0.37	0.35
Education	illiterate	1 (0.6%)	2(1.5%)	0.41	0.42
	Diploma				
	University				
Weight loss history in past year	No	67 (43.8%)	66 (50.8%)	0.28	0.33

Table 4. Description of characteristics among intake of uPDI. Variables are presented as mean ± SD for continuous variables and frequency for categorical variables. *uPDI* healthy plant-based diet index, *FBS* fasting blood sugar, *HOMA-IR* homeostatic model assessment for insulin resistance, *TC* total cholesterol, *TG* triglyceride, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *SMM* skeletal muscle mass, *FFM* fat free mass, *BFM* body fat mass, *BF* body fat percentage, *WHR* waist hip ratio, *WC* waist circumference, *VFA* visceral fat area, *RMR* resting metabolic rate. Significant values are in bold. P values from t test for continuous variables and chi-square test for categorical variables. *P-value as found by ANCOVA, and adjusted for (age, physical activity and energy intake and diastolic blood pressure (DBP)).

Interaction between unhealthful PDI and *CAV-1 rs3807992* genotypes on metabolic and inflammatory markers and anthropometric measures. Risk-allele carriers who consumed higher unhealthful PDI had higher WC (β : 0.06, 95% CI 0.001–0.12, P: 0.04), TC/HDL (β : 0.72, 95% CI 0.07–1.53, P: 0.04), MCP-1 (β : 0.37, 95% CI 0.02–0.73, P: 0.03), and galactin-3 (β : 6.60, 95% CI 0.26–12.94, P: 0.04). All data are shown in Table 6 and Fig. 3.

Discussion

To our knowledge, this is the first study to have investigated the interactions between genetic variants of the *CAV-1* gene with PDI on metabolic and inflammatory markers among Iranian women with overweight and obesity.

	β (95%CI) (AA + AG) 1(Ref) GG			P**
	Crude	P*	Adjusted	
WC (cm)	- 0.20 (- 5.35, 2.45)	0.80	- 0.13 (- 4.56, 4.30)	0.95
TC (mg/dl)	- 5.98 (- 24.3,12.33)	0.52	- 6.57 (- 24.76, 11.61)	0.47
HDL-C (mg/dl)	4.20 (- 1.24, 9.64)	0.13	4.48 (- 1.06, 10.02)	0.11
LDL-C (mg/dl)	0.79 (- 11.33,12.92)	0.89	- 0.28 (- 12.27, 11.71)	0.96
TC/HDL	- 0.49 (- 1.25,0.27)	0.20	- 0.05 (- 0.11,0.005)	0.07
ALT(IU L)	- 7.11 (- 13.81,- 0.4)	0.03	- 7.51 (- 14.45, - 0.57)	0.03
AST (IU L)	- 2.85 (- 6.65,0.95)	0.14	- 3.13 (- 7.07, 0.81)	0.12
Insulin (pmol/L)	- 0.13 (- 0.24, - 0.01)	0.03	- 0.14 (- 0.26, - 0.02)	0.01
hs-CRP (mg/L)	- 2.89 (- 5.27, - 0.51)	0.01	- 3.30 (- 5.76, - 0.85)	0.008
MCP-1(ng/ml)	- 45.75 (- 96.3,4.48)	0.07	- 54.51(- 107.72, - 1.30)	0.04
TGF β (ng/ml)	- 142.73 (- 365.94, 80.47)	0.21	- 278.06 (- 572.39, 16.26)	0.06
Galactin 3 (ng/ml)	- 0.11 (- 6.42, 6.20)	0.97	- 2.28 (- 9.57, 5.03)	0.53

Table 5. Interactions between CAV-1 rs3807992 and PDI on metabolic and inflammatory markers and anthropometric measures. Values are represented as β (95%CI). WC waist circumference, TC total cholesterol, TG triglyceride, HDL high density lipoprotein, LDL low density lipoprotein, AST aspartate aminotransferase, ALT alanine aminotransferase, hs-CRP high-sensitivity C-reactive protein, MCP-1 monocyte chemoattractant protein-1, TGF β transforming growth factor beta. A significant p-values are indicated in bold (significance considered $p < 0.05$). GLMS was performed to identify significant differences between median of PDI and CAV-1 rs3807992. P* = with unadjusted (crude) model. P** = with adjustments for potential confounding factors including (age, energy intake, physical activity education, job and marriage status). We created an interaction model by using genotype categories and dietary intake groups (PDI, hPDI and uPDI) as fixed variables and confounding markers as covariates in GLMS. GG genotype has 0 risk allele. AG genotype has one and AA genotype have two risk allele. GG genotype is considered as a reference. Low adherence of PDI is considered as a reference.

Our findings highlight a gene-diet interaction for PDI and CAV-1 polymorphism (rs3807992) on ALT, hs-CRP, insulin, and MCP-1 in both crude and adjusted models; such that the A-allele carriers who had higher PDI, had lower ALT, insulin, MCP-1, and hs-CRP compared to GG homozygotes. Based on our previous findings⁴⁶, CAV-1 (rs3807992) might be related to incremented metabolic disease risk factors in women with overweight and obesity. We also previously posited that among minor allele carriers, insulin pathways may responsible for the relationship between CAV-1 rs3807992 and metabolic factors⁴⁶.

In the present study, DBP, BFM, and FMI were higher in participants carrying the A allele compared to those in the GG genotype. There are some possible functional roles for CAV-1 may be inherited. It has been established by previous studies that CAV-1 has a major regulator function in fat distribution and genetic lipodystrophies in humans^{47,48}. Furthermore, experimental studies have reported an association between CAV-1 mRNA expression in adipose tissues in obese women compared with lean subjects^{49,50}. CAV-1-deficient mice had a smaller lean body phenotype than their wild-type counterparts^{51,52}. Lipodystrophy has been observed in CAV-1 null mice due to a variety of functions attributed to caveolae in adipocytes, including lipid droplet dysfunction, adipocyte differentiation pathway disruption, abnormalities in cholesterol and fatty acid binding, transport, and storage, and an increase in insulin signaling^{47,53}.

Moreover, A-allele carriers had significantly lower serum HDL and LDL compared to GG homozygotes. Additionally, there was no significant relationship between this polymorphism and other biochemical parameters containing TG, inflammatory markers (hs-CRP, MCP-1, PAI-1, and IL-1 β), and liver enzymes in both crude and adjusted models. Concordant with our study, Khatibi et al. also found a significant association between CAV-1 genotypes with DBP²⁶, and observed that participants with prevailing alleles had a lower risk of dyslipidemia, and that risk allele carriers, who adhered more to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, might present with lower dyslipidemia²⁶.

In our study, we also observed a significant interaction between hPDI and rs3807992 on ALT, AST, insulin, and TGF- β in both crude and adjusted models. Indeed, A-allele carriers who had higher hPDI scores, had lower serum ALT, AST, insulin, and TGF- β compared to GG homozygote. Further, risk-allele carriers who had higher uPDI scores, had higher WC, TC/HDL, MCP-1, and galactin-3. No significant interactions were observed between CAV-1 rs3807992 variants and uPDI for other metabolic-related traits. A cross-sectional study in 2021 revealed that, among people following antioxidant-rich diets, 'A' allele carriers might be more vulnerable to cardiovascular disorders; the authors also reported no significant relationship between higher adherence to dietary total antioxidant capacity (DTAC) and changes in lipid profile, HOMA-IR, and body composition components²⁷.

It is well accepted that the prevalence of obesity is directly related to dietary patterns⁵⁴. PBD alleviates body fat due to the decreased caloric intake and incremented energy expenditure because of augmented thermogenesis⁵⁵. Reduced use of saturated fats, which are usually derived from animal-based foods, might improve insulin sensitivity⁵⁵; indeed, plant-based foods are also a main source of phytochemicals⁵⁶. The consumption of phytochemicals, notably polyphenols, which exist in a variety of plant foods (e.g., berries, grapes, onions, apples,

	hPDI				P**	uPDI			
	β (95%CI) (AA + AG)			P*		β (95%CI) (AA + AG)			P**
	1(Ref) GG	Crude	Adjusted			1(Ref) GG	Crude	Adjusted	
WC (cm)	-2.67 (-7.12, 1.76)	0.23	-1.6 (-6.1, 2.72)	0.45	5.11 (0.69, 9.53)	0.02	0.06 (<0.001, 0.12)	0.04	
TC (mg/dl)	1.64 (-16.53, 19.82)	0.85	10.34 (-7.80, 28.49)	0.26	9.47(-8.82, 27.78)	0.31	10.02 (-8.54, 28.59)	0.29	
HDL-C (mg/dl)	0.6 (-4.83, 6.04)	0.82	1.61(-3.95, 7.17)	0.57	-0.96 (-6.43, 4.50)	0.72	-1.1 (-6.79, 4.59)	0.7	
LDL-C (mg/dl)	3.45 (-8.56, 15.48)	0.57	9.81 (-2.1, 21.72)	0.1	-3.39 (-15.5, 8.71)	0.58	-2.39 (-14.65, 9.85)	0.71	
TC/HDL	-0.14 (-0.9, 0.61)	0.7	-0.02 (-0.82, 0.76)	0.94	0.68 (-0.07, 1.44)	0.07	0.72 (0.07, 1.53)	0.04	
ALT(IU L)	-7.71 (-14.35, -1.06)	0.02	-6.52 (-13.48, -0.43)	0.04	-0.07 (-3.90, 3.74)	0.96	2.03 (-5.12, 9.18)	0.57	
AST (IU L)	-4.67 (-8.40, -0.94)	0.01	-4.36 (-8.27, -0.44)	0.02	0.95 (-5.79, 7.71)	0.78	-0.41 (-4.46, 3.65)	0.84	
Insulin (pmol/L)	-0.11 (-0.23, 0.003)	0.05	-0.18 (-0.28, -0.03)	0.03	0.01 (-0.1, 0.12)	0.86	0.02 (-0.09, 0.15)	0.65	
hs-CRP (mg/L)	-0.61 (-3, 1.79)	0.62	-0.67 (-3.17, 1.82)	0.59	0.04 (-2.38, 2.47)	0.97	0.17 (-2.36, 2.72)	0.89	
MCP-1(ng/ml)	-30.79 (-80.68, 19.09)	0.22	-40.58 (-93.15, 11.99)	0.13	55.69 (5.87, 105.51)	0.02	0.37 (0.02, 0.73)	0.03	
TGF β (ng/ml)	-22.59 (40.80, -3.39)	0.01	-56.05 (-78.96, -3.14)	0.001	-123.51 (-331.45, 84.42)	0.24	-192.52 (-543.98, 158.93)	0.28	
Galactin 3 (ng/ml)	2.56 (-3.37, 8.50)	0.39	2.14 (-4.24, 8.53)	0.51	6.05 (0.02, 12.09)	0.04	6.60 (0.26, 12.94)	0.04	

Table 6. Interactions between CAV-1 rs3807992 and hPDI and uPDI on metabolic and inflammatory markers and anthropometric measures. Values are represented as β (95%CI). WC waist circumference, TC total cholesterol, TG triglyceride, HDL high density lipoprotein, LDL low density lipoprotein, AST aspartate aminotransferase, ALT alanine aminotransferase, hs-CRP high-sensitivity C-reactive protein, MCP-1 monocyte chemoattractant protein-1, TGF β transforming growth factor beta. A significant p-values are indicated in bold (significance considered $p < 0.05$). GLMS was performed to identify significant differences between median of PDI and CAV-1 rs3807992. P* = with unadjusted (crude) model. P** = with adjustments for potential confounding factors including (age, energy intake, physical activity education, job and marriage status). We created an interaction model by using genotype categories and dietary intake groups (PDI, hPDI and uPDI) as fixed variables and confounding markers as covariates in GLMS. GG genotype has 0 risk allele. AG genotype has one and AA genotype have two risk allele. GG genotype is considered as a reference. Low adherence of hPDI and uPDI are considered as a reference.

cacao, green tea, soy, whole grains, etc.), is related to reduced mortality and chronic disease risk^{57–60}. The food compound of an uPDI might be associated with higher intakes of unpleasant nutrients and lower intakes of micronutrients and antioxidants, which can negatively affect metabolic syndrome and its factors. A high intake of simple carbohydrates from uPDI could also affect glucose control, lipid metabolism, and weight gain⁶¹, whilst decreased dietary fiber might impact glycemic control, insulin sensitivity, and augment inflammation. These effects could be related to reduced inflammation and oxidative stress^{62,63}. Chronic inflammation is often evident in those with poor feeding habits and a sedentary lifestyle, features which are concomitantly associated with obesity progression^{64,65}, in addition to various other pathologies, including asthma and Alzheimer disease, and different diseases related to unbalanced metabolisms such as T2DM, atherosclerosis, and cardiovascular diseases^{66–69}. Metabolic inflammation consists of a complex mechanism containing crosstalk between different tissues (like adipose tissue and liver) through the whole body. Generally, this low-grade inflammation emerges when cellular stress is distinguished by the immune system⁷⁰. Another mechanism posited to contribute to the progression of chronic inflammation involves the redundant storage of triglyceride (TG) lipids within adipose tissues. In murine models, exceeding TG storage in white adipose tissue (WAT) induces secretion of pro-inflammatory adipokines, such as IL-1, TNF- α , MCP-1, and IL-6, triggering systemic metabolic inflammation⁷¹.

Although the exact mechanism of the interaction between CAV-1 and diet has not yet been fully elucidated, some explanations have been proposed. Several studies have expressed that CAV-1 binds to endothelial nitric oxide synthase (eNOS) and HDL receptors in the caveolae and prevents their activity. Some diets, such as the PBD or anti-inflammatory diets, can dislocate CAV-1 from caveolae to the cytoplasm, leading to a reduction in the CAV-1 level, ameliorating the prohibitory effects on HDL and eNOS receptors⁷². Decreased nitric oxide (NO) generation, as a result of increased CAV-1 expression, has been thought to occur from prolonged exposure to high glucose, may play a vital role in inflammatory pathways and expansion of inflammation⁷³. Hence, it is not surprising that higher adherence to a uPDI can augment MCP-1 by changing the expression of CAV-1 and other genes.

Diet and plasma-derived nutrients may influence metabolic markers by interacting with caveolae-associated cellular signaling, according to new research³⁶. In this regard, Oberleithner et al. suggest that serum sodium and potassium can control eNOS binding to the caveolae membrane and activity⁷⁴. As a result, the beneficial benefits of a healthy PDI might be attributed to components like vegetables and fruits, which have a greater impact on potassium and sodium balance.

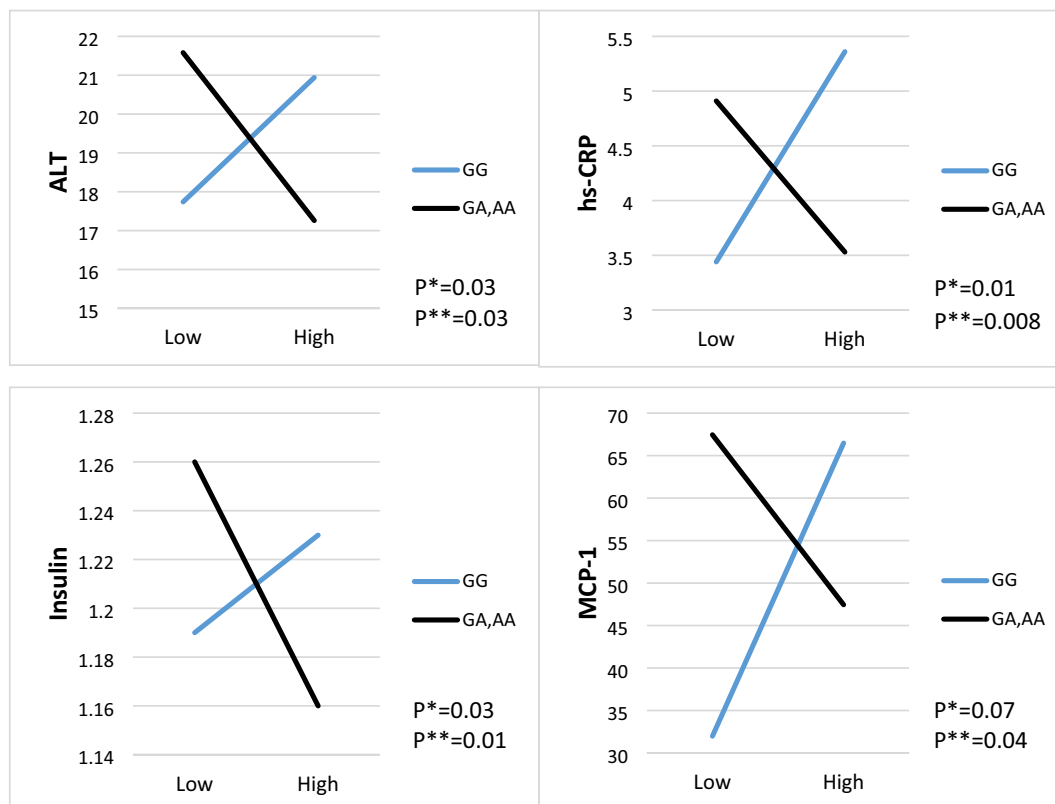


Figure 1. The interaction between CAV-1 SNP rs3807992 and plant-based diet index (PDI) on; (a) ALT, (b) hs-CRP, (c) insulin, (d) MCP-1. *P-value for curd (unadjusted) model. **P-value for the adjusted model by age, physical activity level, energy intake, education, job and marriage status. ALT alanine aminotransferase, hs-CRP high-sensitivity C-reactive protein, MCP-1 monocyte chemoattractant protein-1.

Beside, the lower liver enzyme in A-allele carriers following an hPDI in the present study can be dependent on the caffeine intake during the hPDI. In this term, we previously found a decreased AST in A-allele carriers who consumed more caffeine in a healthy dietary pattern⁴⁵. Interestingly, a candidate gene for the favorable impact of caffeine consumption is located near the CAV-1 gene⁷⁵. Therefore, we suggested a possible interaction between caffeine and CAV-1, which we hope will be confirmed in future study.

In the current study, we observed a relationship between CAV-1 with body composition, which could suggest a CAV-1 lipogenic pathway interaction. The expression of CAV-1 is found in most normal organs but notably assuming that CAV-1 is greatly expressed in adipose tissue⁷⁶ and the interplay between CAV-1 gene and lipogenic genes has been expressed⁷⁷. Visceral fat could also be associated with changes in circulating fatty acid composition⁷⁸. CAV-1 interacts with two popular receptors that augment oxidative stress: the angiotensin II receptor and mineralocorticoid receptor (MR)⁷⁹. MR blockade has been shown to reduce NADPH Oxidase 4 (NOX4) expression and lower reactive oxygen species in the kidney and heart^{80,81}.

Several studies have revealed that CAV-1 is associated with oxidative stress, as reactive species could impact the expression, degradation, post-translational changes, and trafficking of Caveolae membranes⁸². Hence, because of the impact of the CAV-1 gene with oxidative stress, it seems that adherence to hPDI could be capable of lowering the metabolic markers, and, as a result, reducing the likelihood of metabolic diseases in women with

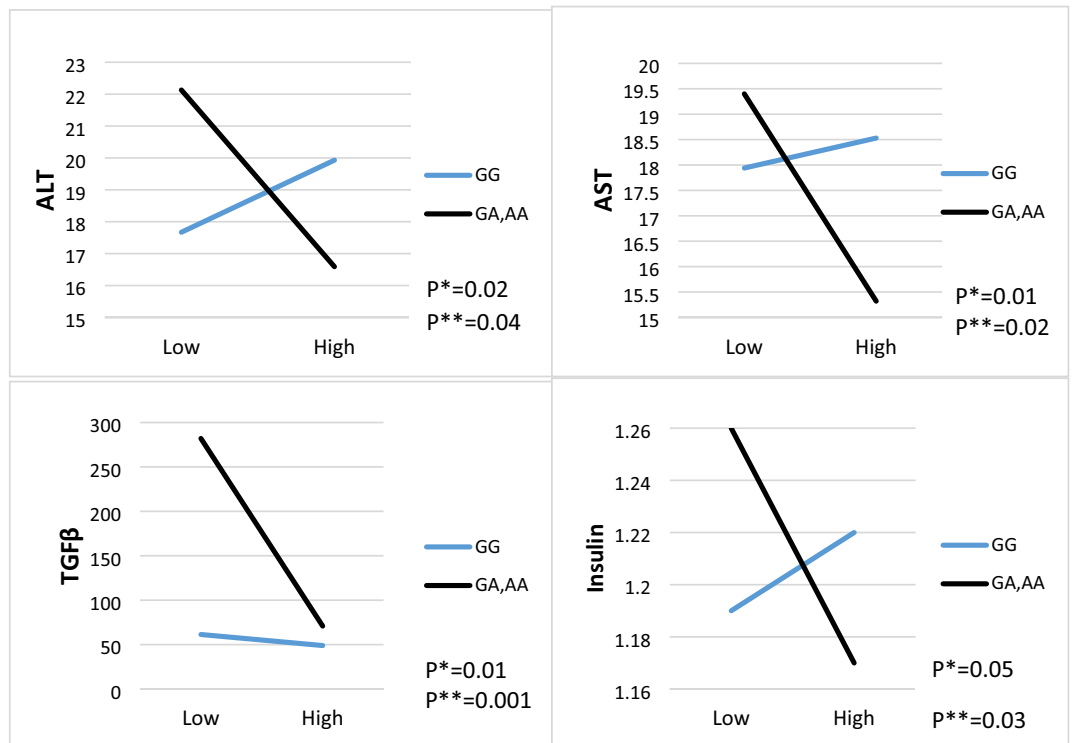


Figure 2. The interaction between CAV-1 SNP rs3807992 and healthy plant-based diet index (hPDI) on; (a) ALT, (b) AST, (c) TGF- β , (d) insulin. *P-value for curd (unadjusted) model. **P-value for the adjusted model by age, physical activity level, energy intake, education, job and marriage status. AST aspartate aminotransferase, ALT alanine aminotransferase, TGF β transforming growth factor beta.

obesity carrying a risk the allele of 'A'. Indeed, the current study provides some support for the consideration of particular dietary guidelines based on genotypes.

Although we provide novel findings of gene-diet interactions, some limitations should be considered in the interpretation of the study. First, the results of this cross-sectional study, although nationally illustrative, cannot indicate a causal relationship. Second, even though we applied a validated FFQ, measurement errors are possible. Third, our study only included women, therefore, results are not generalizable to men. Finally, although we considered potential confounders, residual confounding may still exist. We did not have any data related to family history of cancer; however, the expression of CAV-1 can be effected by this cofounding marker.

Conclusion

In conclusion, the results of the current study suggest that diet, gene variants, and their interaction, should be considered in metabolic diseases risk assessment. PDIs may provide advantages in the prohibition of chronic disease. In future studies, investigating samples from a greater geographic area with wide ranges of ages in both sexes and larger sample sizes might prove more important findings. This work clearly highlights the value of considering genotypes in dietary planning and modification. Therefore, these findings from nutrigenetic studies in future may be combine with a patient's genetic history to give more relevant and customized nutritional recommendations for women with obesity in order to avoid or reduce cardiovascular disease.

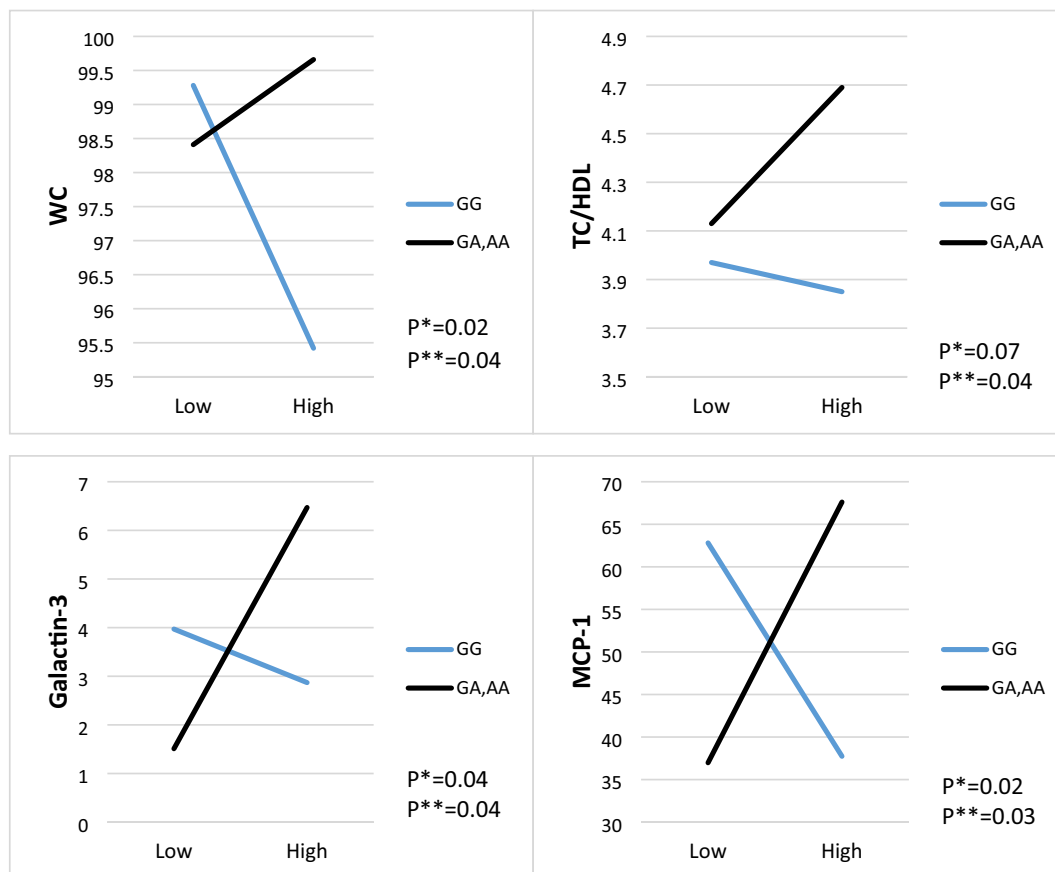


Figure 3. The interaction between CAV-1 SNP rs3807992 and Unhealthy plant-based diet index (uPDI) on; (a) WC, (b) TC/HDL, (c) Galactin-3, (d) MCP-1. *P-value for curd (unadjusted) model. **P-value for the adjusted model by age, physical activity level, energy intake, education, job and marriage status. WC waist circumference, MCP-1 monocyte chemoattractant protein-1.

Data availability

The data are not publicly available due to containing private information of participants. Data are however available from the authors upon reasonable request and with permission of Khadijeh Mirzaei.

Received: 16 February 2022; Accepted: 11 May 2022

Published online: 31 May 2022

References

- Antonopoulos, A. S. & Tousoulis, D. The molecular mechanisms of obesity paradox. *Cardiovasc. Res.* **113**(9), 1074–1086 (2017).
- Tchernof, A. & Després, J. P. Pathophysiology of human visceral obesity: An update. *Physiol. Rev.* **93**(1), 359–404 (2013).
- Chooi, Y. C., Ding, C. & Magkos, F. The epidemiology of obesity. *Metabolism* **92**, 6–10 (2019).
- Maskarinec, G. *et al.* Type II diabetes, obesity, and breast cancer risk: The multiethnic cohort. *Cancer Epidemiol. Biomarkers Prev.* **26**(6), 854–861 (2017).
- Garcia, M., Mulvagh, S. L., Merz, C. N., Buring, J. E. & Manson, J. E. Cardiovascular disease in women: Clinical perspectives. *Circ. Res.* **118**(8), 1273–1293 (2016).
- Seravalle, G. & Grassi, G. Obesity and hypertension. *Pharmacol. Res.* **122**, 1–7 (2017).
- Palmer, M. K. & Toth, P. P. Trends in lipids, obesity, metabolic syndrome, and diabetes mellitus in the United States: An NHANES analysis (2003–2004 to 2013–2014). *Obesity* **27**(2), 309–314 (2019).
- Joham, A. E., Palomba, S. & Hart, R. Polycystic ovary syndrome, obesity, and pregnancy. *Semin. Reprod. Med.* **34**(2), 93–101 (2016).
- Marchesini, G., Moscatiello, S., Di Domizio, S. & Forlani, G. Obesity-associated liver disease. *J. Clin. Endocrinol. Metab.* **93**(11), s74–s80 (2008).
- Saltiel, A. R. & Olefsky, J. M. Inflammatory mechanisms linking obesity and metabolic disease. *J. Clin. Invest.* **127**(1), 1–4 (2017).
- Weiss, R. *et al.* Obesity and the metabolic syndrome in children and adolescents. *N. Engl. J. Med.* **350**(23), 2362–2374 (2004).
- Nieuwdorp, M., Stroes, E. S., Meijers, J. C. & Büller, H. Hypercoagulability in the metabolic syndrome. *Curr. Opin. Pharmacol.* **5**(2), 155–159 (2005).
- Dandona, P., Aljada, A. & Bandyopadhyay, A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol.* **25**(1), 4–7 (2004).
- Dandona, P., Aljada, A., Chaudhuri, A., Mohanty, P. & Garg, R. Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* **111**(11), 1448–1454 (2005).
- Peeters, A. Obesity and the future of food policies that promote healthy diets. *Nat. Rev. Endocrinol.* **14**(7), 430–437 (2018).

16. Calle, M. C. & Andersen, C. J. Assessment of dietary patterns represents a potential, yet variable, measure of inflammatory status: A review and update. *Dis. Mark.* **2019**, 3102870 (2019).
17. Galland, L. Diet and inflammation. *Nutr. Clin. Pract.* **25**(6), 634–640 (2010).
18. Dias, J. A. *et al.* A high quality diet is associated with reduced systemic inflammation in middle-aged individuals. *Atherosclerosis* **238**(1), 38–44 (2015).
19. Barbaresko, J., Koch, M., Schulze, M. B. & Nöthlings, U. Dietary pattern analysis and biomarkers of low-grade inflammation: A systematic literature review. *Nutr. Rev.* **71**(8), 511–527 (2013).
20. Eichelmann, F., Schwingshackl, L., Fedirko, V. & Aleksandrova, K. Effect of plant-based diets on obesity-related inflammatory profiles: A systematic review and meta-analysis of intervention trials. *Obes. Rev.* **17**(11), 1067–1079 (2016).
21. Hu, F. B. Plant-based foods and prevention of cardiovascular disease: An overview. *Am. J. Clin. Nutr.* **78**(3 Suppl), 544s–s551 (2003).
22. Ghodoosi, N. *et al.* Associations of dietary inflammatory index, serum levels of MCP-1 and body composition in Iranian overweight and obese women: A cross-sectional study. *BMC. Res. Notes* **13**(1), 544 (2020).
23. Chun, O. K., Chung, S. J., Claycombe, K. J. & Song, W. O. Serum C-reactive protein concentrations are inversely associated with dietary flavonoid intake in US adults. *J. Nutr.* **138**(4), 753–760 (2008).
24. Oyama, J. *et al.* Green tea catechins improve human forearm vascular function and have potent anti-inflammatory and anti-apoptotic effects in smokers. *Intern. Med.* **49**(23), 2553–2559 (2010).
25. Zern, T. L. *et al.* Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. *J. Nutr.* **135**(8), 1911–1917 (2005).
26. Khatibi, N. *et al.* Interactions between caveolin 1 polymorphism and the Mediterranean and Mediterranean-DASH Intervention for Neurodegenerative Delay diet (MIND) diet on metabolic dyslipidemia in overweight and obese adult women: a cross-sectional study. *BMC Res. Notes* **14**(1), 364 (2021).
27. Mirzababaei, A. *et al.* The effect of dietary total antioxidant capacity (DTAC) and Caveolin-1 gene variant interaction on cardiovascular risk factors among overweight and obese women: A cross-sectional investigation. *Clin. Nutr. (Edinburgh, Scotland)* **40**(8), 4893–4903 (2021).
28. Razani, B., Woodman, S. E. & Lisanti, M. P. Caveolae: From cell biology to animal physiology. *Pharmacol. Rev.* **54**(3), 431–467 (2002).
29. Brown, D. A. & London, E. Functions of lipid rafts in biological membranes. *Annu. Rev. Cell Dev. Biol.* **14**, 111–136 (1998).
30. González-Muñoz, E. *et al.* Caveolin-1 loss of function accelerates glucose transporter 4 and insulin receptor degradation in 3T3-L1 adipocytes. *Endocrinology* **150**(8), 3493–3502 (2009).
31. Napolitano L. The differentiation of white adipose cells. An electron microscope study. *J Cell Biol.* **18**(3), 663–679 (1963).
32. Fan, J. Y. *et al.* Morphological changes of the 3T3-L1 fibroblast plasma membrane upon differentiation to the adipocyte form. *J. Cell Sci.* **61**(1), 219–230 (1983).
33. Li, W. *et al.* Caveolin-1 inhibits expression of antioxidant enzymes through direct interaction with nuclear erythroid 2 p45-related factor-2 (Nrf2). *J. Biol. Chem.* **287**(25), 20922–20930 (2012).
34. Zheng, Y. *et al.* Epigallocatechin-gallate stimulates NF-E2-related factor and heme oxygenase-1 via caveolin-1 displacement. *J. Nutr. Biochem.* **23**(2), 163–168 (2012).
35. Guo, Z. *et al.* Baicalein inhibits prostate cancer cell growth and metastasis via the caveolin-1/AKT/mTOR pathway. *Mol. Cell Biochem.* **406**(1–2), 111–119 (2015).
36. Majkova, Z., Toborek, M. & Hennig, B. The role of caveolae in endothelial cell dysfunction with a focus on nutrition and environmental toxicants. *J. Cell. Mol. Med.* **14**(10), 2359–2370 (2010).
37. Abaj, F., & Mirzaei, K. Caveolin-1 genetic polymorphism interacts with PUFA to modulate metabolic syndrome risk. *Br. J. Nutr.* **2021**:1–8.
38. Banna, J. C., McCrory, M. A., Fialkowski, M. K. & Boushey, C. Examining plausibility of self-reported energy intake data: Considerations for method selection. *Front. Nutr.* **4**, 45 (2017).
39. Bahrapour, N., Mirzababaei, A., Shiraseb, F., Clark, C. C. T. & Mirzaei, K. The mediatory role of inflammatory markers on the relationship between dietary energy density and body composition among obese and overweight adult women: A cross-sectional study. *Int. J. Clin. Pract.* **75**(10), e14579 (2021).
40. Hagströmer, M., Oja, P. & Sjöström, M. The International Physical Activity Questionnaire (IPAQ): A study of concurrent and construct validity. *Public Health Nutr.* **9**(6), 755–762 (2006).
41. Mirmiran, P.H.-E.F., Jessri, M., Mahan, L. K., Shiva, N. & Azizi, F. Does dietary intake by Tehranian adults align with the 2005 dietary guidelines for Americans? Observations from the Tehran lipid and glucose study. *J. Heal. Popul. Nutr.* **29**(1), 1 (2011).
42. Morgan, K. J., Zabik, M. E. & Stampely, G. L. The role of breakfast in diet adequacy of the US adult population. *J. Am. Coll. Nutr.* **5**(6), 551–63 (1986).
43. Satija, A. *et al.* Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: Results from three prospective cohort studies. *PLoS Med.* **13**(6), e1002039 (2016).
44. Pourreza, S. *et al.* Association of plant-based diet index with inflammatory markers and sleep quality in overweight and obese female adults: A cross-sectional study. *Int. J. Clin. Pract.* **75**(9), e14429 (2021).
45. Abaj, F. *et al.* Interactions between Caveolin-1 (rs3807992) polymorphism and major dietary patterns on cardio-metabolic risk factors among obese and overweight women. *BMC Endocr. Disord.* **21**(1), 138 (2021).
46. Abaj, F., Saeedy, S. A. G. & Mirzaei, K. Are caveolin-1 minor alleles more likely to be risk alleles in insulin resistance mechanisms in metabolic diseases?. *BMC. Res. Notes* **14**(1), 185 (2021).
47. Garg, A. & Agarwal, A. K. Caveolin-1: A new locus for human lipodystrophy. *J. Clin. Endocrinol. Metab.* **93**(4), 1183–1185 (2008).
48. Abaj, F., Saeedy, S. A. G. & Mirzaei, K. Mediation role of body fat distribution (FD) on the relationship between CAV1 rs3807992 polymorphism and metabolic syndrome in overweight and obese women. *BMC Med. Genomics* **14**(1), 1–8 (2021).
49. Catalán, V. *et al.* Expression of caveolin-1 in human adipose tissue is upregulated in obesity and obesity-associated type 2 diabetes mellitus and related to inflammation. *Clin. Endocrinol.* **68**(2), 213–219 (2008).
50. Fernández-Real, J. M. *et al.* Study of caveolin-1 gene expression in whole adipose tissue and its subfractions and during differentiation of human adipocytes. *Nutr. Metab. (Lond)* **7**, 20 (2010).
51. Schrauwen, I. *et al.* A frame-shift mutation in CAV1 is associated with a severe neonatal progeroid and lipodystrophy syndrome. *PLoS ONE* **10**(7), e0131797 (2015).
52. Viljanen, A. P. M. *et al.* Effects of weight loss on visceral and abdominal subcutaneous adipose tissue blood-flow and insulin-mediated glucose uptake in healthy obese subjects. *Ann. Med.* **41**(2), 152–160 (2009).
53. Razani, B. *et al.* Caveolin-1-deficient mice are lean, resistant to diet-induced obesity, and show hypertriglyceridemia with adipocyte abnormalities. *J. Biol. Chem.* **277**(10), 8635–8647 (2002).
54. Swinburn, B. A., Caterson, I., Seidell, J. C. & James, W. P. Diet, nutrition and the prevention of excess weight gain and obesity. *Public Health Nutr.* **7**(1a), 123–146 (2004).
55. Najjar, R. S. & Feresin, R. G. Plant-based diets in the reduction of body fat: Physiological effects and biochemical insights. *Nutrients* **11**(11), 1 (2019).
56. Dillard, C. J. & German, J. B. Phytochemicals: Nutraceuticals and human health. *J. Sci. Food Agric.* **80**(12), 1744–1756 (2000).
57. Rienks, J., Barbaresko, J. & Nöthlings, U. Association of polyphenol biomarkers with cardiovascular disease and mortality risk: A systematic review and meta-analysis of observational studies. *Nutrients* **9**(4), 1 (2017).

58. Nachvak, S. M. *et al.* Soy, soy isoflavones, and protein intake in relation to mortality from all causes, cancers, and cardiovascular diseases: A systematic review and dose-response meta-analysis of prospective cohort studies. *J. Acad. Nutr. Diet.* **119**(9), 1483–500. e17 (2019).
59. Kimble, R., Keane, K. M., Lodge, J. K. & Howatson, G. Dietary intake of anthocyanins and risk of cardiovascular disease: A systematic review and meta-analysis of prospective cohort studies. *Crit. Rev. Food. Sci. Nutr.* **59**(18), 3032–3043 (2019).
60. Knekt, P. *et al.* Flavonoid intake and risk of chronic diseases. *Am. J. Clin. Nutr.* **76**(3), 560–568 (2002).
61. Stanhope, K. L. Sugar consumption, metabolic disease and obesity: The state of the controversy. *Crit. Rev. Clin. Lab. Sci.* **53**(1), 52–67 (2016).
62. Najjar, R. S., Moore, C. E. & Montgomery, B. D. Consumption of a defined, plant-based diet reduces lipoprotein(a), inflammation, and other atherogenic lipoproteins and particles within 4 weeks. *Clin. Cardiol.* **41**(8), 1062–1068 (2018).
63. Romeu, M. *et al.* Diet, iron biomarkers and oxidative stress in a representative sample of Mediterranean population. *Nutr. J.* **12**, 102 (2013).
64. Rodier, F. & Campisi, J. Four faces of cellular senescence. *J. Cell Biol.* **192**(4), 547–556 (2011).
65. Cevenini, E., Monti, D. & Franceschi, C. Inflamm-aging. *Curr. Opin. Clin. Nutr. Metab. Care.* **16**(1), 14–20 (2013).
66. Weissmann, G. It's complicated: Inflammation from Metchnikoff to Meryl Streep. *Faseb J.* **24**(11), 4129–4132 (2010).
67. Murdoch, J. R. & Lloyd, C. M. Chronic inflammation and asthma. *Mutat Res.* **690**(1–2), 24–39 (2010).
68. Chambers, J. C. *et al.* C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation* **104**(2), 145–150 (2001).
69. Donath, M. Y. & Shoelson, S. E. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol.* **11**(2), 98–107 (2011).
70. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**(7121), 860–867 (2006).
71. Kanda, H. *et al.* MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J. Clin. Invest.* **116**(6), 1494–1505 (2006).
72. Matveev, S., Uittenbogaard, A., van Der Westhuyzen, D. & Smart, E. J. Caveolin-1 negatively regulates SR-BI mediated selective uptake of high-density lipoprotein-derived cholesteryl ester. *Eur. J. Biochem.* **268**(21), 5609–5616 (2001).
73. Haddad, D., Al Madhoun, A., Nizam, R. & Al-Mulla, F. Role of Caveolin-1 in diabetes and its complications. *Oxid. Med. Cell Longev.* **2020**, 9761539 (2020).
74. Oberleithner, H., Kusche-Vihrog, K. & Schillers, H. Endothelial cells as vascular salt sensors. *Kidney Int.* **77**(6), 490–494 (2010).
75. Cornelis, M. C. *et al.* Genome-wide meta-analysis identifies regions on 7p21 (AHR) and 15q24 (CYP1A2) as determinants of habitual caffeine consumption. *PLoS Genet.* **7**(4), e1002033 (2011).
76. Carver, L. A. & Schnitzer, J. E. Caveolae: Mining little caves for new cancer targets. *Nat. Rev. Cancer* **3**(8), 571–581 (2003).
77. Fernández-Real JM, Catalán V, Moreno-Navarrete JM, Gómez-Ambrosi J, Ortega FJ, Rodríguez-Hermosa JJ, *et al.* Study of caveolin-1 gene expression in whole adipose tissue and its subfractions and during differentiation of human adipocytes. *Nutr Metab (Lond)*. 2010;7:20-.
78. Otis, J. P., Shen, M. C., Quinlivan, V., Anderson, J. L. & Farber, S. A. Intestinal epithelial cell caveolin 1 regulates fatty acid and lipoprotein cholesterol plasma levels. *Dis Model Mech.* **10**(3), 283–295 (2017).
79. Baudrand, R., Pojoga, L. H., Romero, J. R. & Williams, G. H. Aldosterone's mechanism of action: Roles of lysine-specific demethylase 1, caveolin and striatin. *Curr. Opin. Nephrol. Hypertens.* **23**(1), 32–37 (2014).
80. Bayorh, M. A., Rollins-Hairston, A., Adiyiah, J., Lyn, D. & Eatman, D. Eplerenone suppresses aldosterone/ salt-induced expression of NOX-4. *J. Renin. Angiotensin. Aldosterone Syst.* **12**(3), 195–201 (2011).
81. Stas, S. *et al.* Mineralocorticoid receptor blockade attenuates chronic overexpression of the renin-angiotensin-aldosterone system stimulation of reduced nicotinamide adenine dinucleotide phosphate oxidase and cardiac remodeling. *Endocrinology* **148**(8), 3773–3780 (2007).
82. Wang, S. *et al.* Caveolin-1: An oxidative stress-related target for cancer prevention. *Oxid. Med. Cell Longev.* **2017**, 7454031 (2017).

Acknowledgements

We would like to thank all participants who gave their time to carry out this project.

Author contributions

F.A. and A.M. conceptualization; methodology; investigation; formal analysis; D.H. and N.B. writing original draft. F.A. and A.M. carried out the experiment. C.C. editing. Kh.M.: supervision; validation; project administration. All authors reviewed the manuscript.

Funding

This study was supported by a grant from Tehran University of Medical Sciences (97-03-161-41017).

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to K.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022