Caveolin-1 Genetic Polymorphisms Interact with Fatty Acid Types to Modulate Metabolic Syndrome Risk

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Research Article

Abstract

Background: Metabolic syndrome (MetS) is related with all-cause mortality. Caveolin-1 (Cav-1) has been widely studied in dyslipidemia, and several studies have indicated that Cav-1 genetic variations may correlate with dietary intake of fatty acids. The aim of the current study was therefore to evaluate the interaction of Cav-1 rs3807992 with types of dietary fatty acid in MetS risk factor status

Methods: This cross-sectional study was carried out on 404 overweight and obese females. Dietary intake was obtained from a 147-item FFQ. The CAV-1 genotype was measured using the PCR-RFLP method. Anthropometric values and serum levels (TC, LDL, HDL, TG, FBS) were measured by standard methods.

Results: It was observed that the (AA+AG) group had significantly higher BMI, WC and DBP (P=0.02, P=0.02 and P=0.01, respectively) and lower serum LDL, HDL and TC (P < 0.05) than the GG group. It was found that A allele carriers were at higher odds of MetS (P= 0.01), abdominal obesity (P=0.06), increased TG concentration (P=0.01), elevated blood pressure (BP) (P=0.01), increased glucose concentration (P=0.45), and decreased HDL-cholesterol concentration (P=0.03). Moreover, the interaction of Cav-1 and SFA intake was significant in terms of MetS (P=0.01), LDL (P=0.03), DBP (P=0.01) and LDL/HDL (P=0.05). Additionally, the (AA+AG) group was significantly related to PUFA intake in terms of MetS (P=0.04), TG (P=0.02), glucose (P=0.02) and HOMA-IR (P= 0.01).

Conclusions: Higher PUFA consumption might attenuate the Cav-1 rs3807992 associations with MetS, and individuals with greater genetic predisposition appeared to have a higher risk of MetS, associated with higher SFA consumption To date, studies on this polymorphism have been animal studies and have not been performed on healthy and obese human society For the first time , this study provides information on the interaction of different fatty acids with the Caveolin gene, which is functionally effective in lipid metabolism

Significance

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Introduction

Metabolic syndrome (MetS) is related with metabolic abnormalities including obesity, hyperglycemia, dyslipidemia, and hypertension, and is prevalent worldwide [1]. MetS is related to all-cause mortality, myocardial infarction (MI), and stroke in patients with or without diabetes [2]. Surprisingly, the evidence demonstrates that genetic variations play a main part in the prevention and treatment of various chronic

disease, particularly in MetS [3-5]. MetS and cardiovascular diseases (CVD) also demonstrate the role of genetic and environmental factors in diet-related disorders. A genetic background of metabolic disorders has been shown to relate to death rate over the last few decades [6]. There is therefore a need to identify the genes that derive MetS and to develop new therapies. Caveolin-1 (Cav-1) is a key protein component of caveolae, and has been widely studied in dyslipidemia and CVD due to signal transduction, trafficking in cholesterol hemostasis, and triacylglycerol metabolism [7]. Mice treated with Cav-1 are resistant to high-fat diets, and they show lipodystrophy, hypertension, insulin resistance, and abnormal glucose metabolism [8]. Moreover, several studies have indicated that Cav-1 genetic variations might interact with other risk factors, including dietary intake of fatty acids, suggesting a positive association between Cav-1 and hypercholesterolemia [9]. In studies conducted among Caucasian and Hispanic cohorts, the prevalence of Cav-1 gene variant rs926198 is related with higher odds of MetS risk and low HDL [10,11]. Also, Cav-1 overexpression has been observed to relate to higher odds of atherosclerosis in experimental models [12]. The exact mechanisms are unclear, but it seems that Cav-1 is able to regulate several key enzymes in lipid metabolism, such as cholesterol ester transfer protein and phospholipid transfer protein [13]. While the association between Cav-1 polymorphisms and type 2 diabetes risk has been widely reported in various populations [14], these relationships with MetS have been inconsistent, despite several publications on the association between Cav-1 gene variants and serum lipid profiles [14-17]. To the authors' knowledge, there has been no study evaluating Cav-1 rs3807992 variant, metabolic risk factor, and the interaction of fatty acid intake levels with this SNP. Hence, the aim of the current study was to evaluate the interaction of Cav-1 genetic polymorphism with the types of dietary fatty acids, in terms of MetS risk factor status.

Material And Methods

Study Population

A total of 404 women in the range of 18-55 years old were randomly selected from among participants in a cross-sectional study performed in 2019.Participants provided written informed consent. The inclusion criteria were: obese or overweight, no alcohol consumption, and no smoking. The exclusion criteria were: CVDs, kidney failure, stroke, thyroid disease, liver disease, cancer, inflammatory illnesses, and those taking any therapeutic medications. Each participant was interviewed in order to obtain demographic data, then referred to the laboratory for blood sampling. Anthropometric measures were taken, including: height (m), weight (kg), waist circumference (WC, cm) measured at the narrowest part of the abdomen, and body mass index (BMI, kg/m^2, calculated by dividing weight by height squared). Blood pressure (BP) was measured with a sphygmomanometer (BP) after 5 minutes' rest. Triglyceride (TG) (mg/dl), high-density lipoprotein (HDL) (mg/dl), total cholesterol (mg/dl), and low-density lipoprotein (LDL) (mg/dl) were measured according to standard protocols. The study was approved by the Ethics Committee at the Tehran University of Medical Sciences (TUMS) (97-03-161-41017).

MetS Definition

MetS cases were required to meet three or more of the following criteria according to the Adult Treatment Panel III (ATP III) criteria:

1) Elevated fasting blood glucose FPG≥100 mg/dl.

2) Hypertriglyceridemia TG≥150 mg/dl

3) Elevated blood pressure (≥130/85 mmHg)

4) Low (HDL-c) <50 mg/dl in women

5) WC cut-off 80 cm [women] was considered as an indicator of abdominal obesity [18].

Genotyping

For genotyping the Cav-1 polymorphisms, DNA was extracted from whole blood via a Mini Columns kit (Type G; Genall; Exgene). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was employed to investigate Cav-1 polymorphisms (rs3807992) in gene fragments (major allele G and minor allele A). PCR was carried out using the following primers: **F**:3'AGTATTGACCTGATTTGCCATG5' **R**:5'GTCTTCTGGAAAAAGCACATGA-3'. PCR reactions were performed in a volume of 20 μl, containing 1 μl extracted DNA, 1 μl Forward primers, 1 μl Reverse primers ,7 μl distilled water and 10 μl Taq DNA Polymerase Master Mix in a DNA thermocycler. The DNA templates were denatured at 94 °C for 3 min and 40 cycles, including a min denaturation at 94 °C, a min annealing at 42-50 °C and elongation at 72 °C for 2 min. Amplified DNA was digested with Hin1II (NlaIII) restriction enzyme at 37 °C overnight, then separated by electrophoresis on an agarose gel (2%). Fragments concluding three genotypes of the Cav-1 rs3807992 variant were detected: uncut homozygous AA (213bp), cut heterozygous GA (3 bands: 118 & 95 & 213 bp) and cut homozygous GG (2 bands: 118 & 95 bp).

Statistical Analysis

Statistical analysis was performed using SPSS v.25 software (SPSS Inc., IL, USA) and significance level was considered $P < 0.05$. The Kolmogorov-Smirnov was utilized to test the normality of the data, and all data were expressed as means ± SD. The Pearson's chi-square test was used to determine the Hardy-Weinberg Equilibrium deviation among allele frequency of Cav-1 G32124A (rs3807992). Independent-sample t-test was used to evaluate the differences between the two groups, and ANCOVA test was used to evaluate for confounding effects. Binary logistic regression was used to estimate interactions between rs3807992 and high and low dietary fat intake on the Odds Ratio (OR) of the MetS component. All ORs

were adjusted for variables proven to be related to MetS components, (such as age, educational level, smoking status, physical activity and energy intake).

Dietary Assessment

The Food Frequency Questionnaire (FFQ) was a useful tool for evaluating dietary intake, and included 147 items [19]. This assessment was carried out by interviewing the occurrence of food items consumed on the basis of a predetermined list of foods. The extracted FFQ values were then changed to grams/day. For the evaluation of macro- and micronutrient content, N4 software was used; all measurements were then entered into IBM SPPS.

Results

Clinical Characteristics According to Cav-1 rs3807992 Genotypes

As shown in Table 1, 404 women with a mean age of 36.67 years were evaluated in the present study. Table 1 expresses the mean clinical characteristics of all women according to Cav-1 genotypes. It was observed that the (AA+AG) group had significantly higher BMI, WC and DBP (P=0.02, P=0.02 and P=0.01 respectively). After adjustment for confounders (age, energy intake, physical activity and DBP), BMI and DBP remained significant. Furthermore, women with (AA+AG) allele had significantly lower serum LDL, HDL and TC (P < 0.05) than the GG group. Additionally, no significant differences were detected for age, height, weight, FBG, TG and SBP.

Genotype Frequencies between MetS and Control Groups

Distributions of allele frequencies and the effect size of rs3807992 on various genetic models (codominant, dominant, recessive) had significant differences between MetS and control groups. In the codominant model, the A homozygous allele for the Cav-1 (rs3807992) gene was 52 % higher in the control group than the MetS group (OR 2.52 [1.11, 5.70], P=0.02). In the dominant model, the A homozygous allele for the Cav-1 (rs3807992) gene was 31% higher in the control group than the MetS group (OR 2.31[1.16,4.61], P=0.01) (Table 2).

Associations between Cav-1 rs3807992 and the Risk of MetS and Its Components

It was found that (rs3807992) A allele carriers were at higher odds of MetS (OR 2.31 [1.16, 4.16], P=0.01), abdominal obesity (OR 1.42[0.98,2.06], P=0.06), increased TG concentration (OR 2.12 [1.13,3.95], P=0.01), elevated blood pressure (BP) (OR 7.03 [1.43,34.44], P=0.01), increased glucose concentration (OR 0.7[0.27,1.78], P =0.45), and decreased HDL-cholesterol concentration (OR -1.4 [1.02,1.93] P=0.03) (Table 3).

Dietary Intake Relationships between Cav-1 rs3807992 Gene Polymorphisms, and their Interaction on MetS and Its Components

The results of dietary nutritional intake are described according genotype groups, which show that the (AA+AG) group had increased SFA and cholesterol consumption (g/d), compared to the GG group. No significant differences were found in other nutrient consumption values (Table 4). It was observed that the interaction of Cav-1 rs3807992 gene polymorphism and SFA intake was significant on MetS (OR 2.31 [1.16,4.61], *P*=0.01) and its components, including LDL (OR 12.95 [1.21,24.69], *P*=0.03), DBP (OR 6.52 [1.59,11.45], *P*=0.01) and LDL/HDL (OR 0.28 [-0.01,0.57], *P*=0.05) in a crude model. These values remained significant in the multi-adjusted model (adjusted for age, energy intake, BMI, smoking status, age at onset of obesity, and total PUFA intake). There was no further significant interaction between the (AA+AG) group and SFA intake on other biochemical parameters, including HDL, TG, TC and LDL/HDL, in both the crude and adjusted models (P >0.05) (Table 5). Interestingly, when Cav-1 (AA+AG) group interaction was analyzed by PUFA intake, the relationship was significant in terms of MetS (OR -0.207 [0.04, 0.95], *P*=0.04) and its components, including TG (OR -0.27 [0.05, 0.8], *P*=0.02), glucose (OR -0.06 [0.005, 0.75], *P*=0.02) and HOMA-IR (OR -0.22 [0.06, 0.78], *P*= 0.01) in the crude model. These remained significant in the adjusted model (adjusted for age, energy intake, BMI, smoking status, age at onset of obesity) (Table 6).

Discussion

According to these findings, female A-allele carriers had significantly higher BMI, WC and DBP, and had lower serum LDL, HDL and TC, compared to GG genotypes. This demonstrates that their clinical parameters are predisposed to MetS. A-allele carriers were at higher odds of MetS. To the authors' knowledge, there is little evidence describing an association between Cav-1 and metabolic syndrome. It was observed that a genetic variant of Cav-1 (rs3807992) was associated with increased MetS risk, which is consistent with previous studies that revealed a significant association between the minor allele in cav-1 variations and the odds of metabolic diseases [10,11,15,17]. Also, compared with other candidate gene studies, no studies had evaluated SNP rs3807992 and MetS risk. It is proposed that Cav-1 polymorphisms increase MetS risk through altered Cav-1 gene expression, attenuating dyslipidemia and hypertension, while impairing glucose and insulin homeostasis [12-14,20]. Cav-1 regulates signaling molecules, such as IRS1, that have a key role in appropriate insulin responses, PKA, angiotensin II receptors, active blood pressure molecules, and binding sites for calcium ions; all of these may affect various clinical traits of MetS [14,21,22]. Additionally, Cav-1 is able to effect NO, insulin, lipids, and hormone metabolisms [23]. Therefore, caveolae and its components may become useful sites for further investigation into treating MetS.

The genetic association between Cav-1 polymorphisms and MetS by dietary fat intake was reported. High dietary SFA intake (≥25gr) especially accentuated the negative effects of rs3807992 in terms of MetS risk. Furthermore, a potential gene-nutrient interaction was found between the rs3807992 Cav-1 polymorphism and PUFA intake. High PUFA intake (≥6% energy) reduced the negative effects of rs3807992 in terms of MetS risk, with the greatest protection achieved by A-allele carriers. To the authors' knowledge, this interaction has not been previously studied, and the present paper's finding support the

necessity of lower and higher consumption of SFA and PUFA, respectively, in the diets of A-allele carriers. Most previous intervention studies have shown that a higher intake of SFA was detrimental to maintaining insulin sensitivity, whereas PUFA showed beneficial effects [24]. Additionally, environmental factors, in particular dietary composition, may alter the risk of MetS. Nutrigenetic research has indicated that dietary fat background can influence genotype-phenotype relations [25].

In line with previous studies, experimental studies have reported that sphingomyelin is a key phospholipid of caveolae. SFA intake may lead to increases in sphingolipids levels in the cardiac cell membranes, thus disrupting the caveolae contents [26,27]. Moreover, Chapkin *et al.* reported that in animal models, n-3 PUFA intake may modulate the function of caveolae proteins/lipid, affecting membrane fusion and cell-cell signaling, and improving insulin signaling. Many studies have indicated that H-Ras and eNOS (endothelial nitric oxide synthase) are moved from caveolae in n-3 PUFA supplemented rats, which suppressed the Ras-dependent signaling and reduced blood pressure, thereby lowering the MetS risk [28]. Caveolae membrane fatty acids (in the internal and external leaflet) is also significantly altered by n-3 PUFA intake, and is even able to change the function of the caveolae.

Caveolae plays a unique function in the uptake of various lipid and glucose metabolites. Accordingly, caveolae is a main center for several nutrient metabolisms through the cell membrane [29]. Caveolae is able to uptake fatty acid, triacylglycerol, and cholesterol in many tissues, which leads to an elevation in caveolae density in obese rats [30,31]. However, in these animals, the number of caveolae decreases in the arterial endothelium and at the ends of smooth muscle cells, leading to dyslipidemia [32].

The mechanism observed in the present study, by which fatty acids are able to modify the genetic risk posed by Cav-1 polymorphisms, remains unknown; further studies are needed to indicate such gene-diet interventions. Several limitations can also be identified in the current study. Dietary intake was assessed by a food-frequency questionnaire (FFQ), which is self-reported and thus dependent on patient memory. Due to financial limitations, it was not possible to perform western blot analysis to determine whether rs-3807992 SNP alters the expression of Cav-1. The focus of the current study was on dietary fat composition, but other nutrient components, including carbohydrates or fiber, can also play a role in the progression of MetS. Finally, given the observational nature of the study, it is not possible to tell whether the associations which were identified in women (but not men) are of a causal nature.

Conclusion

To the authors' knowledge, this is the first study presenting the association of a genetic variant of Cav-1 rs3807992 with the risk of MetS and its components, including TG, BP, and HDL level. However, further studies are needed to determine the strength of this association in a larger population; the contribution of this study is the novel finding that rs3807992 clearly predicts MetS among obese women. Analyses of the individual components of MetS confirmed that the rs3807992 variant is related to elevated BP, dyslipidemia, low HDL cholesterol, and high TG levels. Also, Cav-1 rs3807992 genotypes are sensitive to dietary SFA and PUFA, which allows individuals to monitor and adjust SFA and PUFA consumption

accordingly. Finally, these results can be used in combination with a patient's genetic history in order to provide more applicable and tailored nutritional advice for preventing or attenuating MetS in overweight and obese women.

Declarations

Acknowledgments:

Conflict of Interest:

The authors declare no conflict of interest

List Of Abbreviations

BMI: Body mass index

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

DHA: Docosahexaenoic acid

EPA: Eicosapentaenoic acid

FBS: Fasting blood sugar

FFQ: Food frequency questionnaire

FA: Fatty acid

GWAS: Genome-wide association studies

LDL: Low-density lipoprotein

MA: Minor Allele

MetS: Metabolic syndrome

PCR: Polymerase chain reaction

RFLP: Restriction fragment length polymorphism

SNP: Single nucleotide polymorphism

TC: Total cholesterol

TG: Triglyceride

WC: Waist circumference

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Tables

Table 1. Clinical characteristics of all subjects according to Caveolin-1 rs3807992 genotypes

	means±SD		
	(GG)	(AG/AA)	*Pvalue**
Age(year)	37.56± 9.49	35.75±8.78	0.05
Height(cm)	161.30±6.08	160.96±5.58	0.58
Weight(kg)	79.71±10.91	82.12±13.23	0.07
BMI (kg/m2)	30.68±4.01	31.66±4.46	**0.02**
Physical Activity	1215.46±2033.81	1199.02±2251.97	0.95
WC(cm)	98.22±9.30	100.48±10.38	**0.02**
FBS(mg/dl)	87.98±9.62	86.95±9.75	0.36
LDL-C (mg/dl)	98.80±22.66	91.27±25.07	**0.006**
HDL-C (mg/dl)	49.7±11.16	44.04±10.16	**<0.0001**
TC (mg/dl)	186.76±33.74	182.71±37.36	0.30
TG(mg/dl)	113.11±51.20	133.31±84.14	0.13
SBP (mmHg)	109.6±15.05	112.90±14.75	0.08
DBP (mmHg)	75.87±10.77	79.31±10.06	**0.01**

SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; FBS: Fasting blood sugar; LDL: Low density lipoprotein; HDL: High density lipoprotein; TC: Total cholesterol; TG: Triglyceride; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. Values are presented as mean ± SD. Comparisons between groups were determined based on independent-samples t test. Bold values indicate statistical significance (P < 0.05).

Table 2. Investigation of the Caveolin-1 polymorphisms and a comparison of genotype

Models	SNP Rs3807992	Frequencies for the	Caveolin-1 SNP	Odds Ratio(95%CI)	P
		Control	MetS		
Codominant					
		94(55.2%)	30(45.5%)		0.06
	GG				
		31(18.4%)	13(19.7%)	2.04(0.79,5.26)	0.13
	AG				
		41(24.7%)	23(34.8%)	2.52(1.11,5.70)	**0.02**
	AA				
Dominant	GG	94(56.6%)	30(45.5%)		
		72(43.4%)	36(54.5)	2.31(1.16,4.61)	**0.01**
	AG/AA				
Recessive	AG/GG	125(75.3%)	43(65.2%)		
		41(24.7%)	23(34.8%)	2.04(0.97,4.31)	0.05
	AA				

Comparisons between groups were determined based on logistic regression analysis

Table 3. Dietary fat intakes of all subjects according to Cav-1 rs3807992genotypes

Rs3807998	Genotype (GG) means±SD	Genotype (AG/AA) means±SD	Pvalue*	Pvalue†
Energy (Kcal)	2606.84±784.51	2679.13±830.34	0.387	
Total Fat (gr)	94.38±33.95	96.11±34.59	0.625	0.47
Protein (gr)	91.09±30.68	92.63±32.57	0.637	0.54
Carbohydrate (gr)	367.59±121.64	380.70±128.47	0.312	0.32
SFA (gr)	28.84±12.27	28.12±10.80	0.544	**0.04**
Cholesterol(gr)	273.82±119.27	256.5±107.73	0.14	**0.01**
Total fiber(gr)	46.88±21.24	48.52±21.72	0.46	0.7
PUFA intake, %E	6.45±2.73	6.43±2.22	0.9	0.16
MUFA intake, %E	11.08±3.01	10.84±2.63	0.4	0.07
n-6 PUFA intake, %E	5.99±2.64	5.95±2.13	0.8	0.14
n-3 PUFA intake, %E	0.45±0.19	0.47±0.2	0.8	0.56

Values are represented as means ± SD.

Independent T test (P value*) was performed to identify significant differences between Cav-1 rs380798 genotypes in crude model

ANCOVA (P value†) was performed to adjusted potential confounding factors (age, energy intake, educational level, DBP)

Table 4. Associations between Cav-1 rs3807992 and the risk of MetS and its components

Components of MetS	(AG/ AA) vs GG OR (95%CI)	P value
MetS	2.31(1.16,4.61)	**0.01**
Abdominal obesity	1.42(0.98,2.06)	0.06
BP	7.03(1.43,34.44)	**0.01**
Glucose	0.7(0.27,1.78)	0.45
HDL-C	-1.4(1.02,1.93)	**0.03**
TG	2.12(1.13,3.95)	**0.01**

MetS: metabolic syndrome, BMI: body mass index, BP: blood pressure, HDL: high density lipoprotein, TG: triglycerides. Binary logistic adjusted: Age OR (95% CI): odds ratio (95% confidence interval)

Table 5. Interactions between the Cav-1 rs3807992 gene polymorphism and SFA intake in relation to MetS or its components

	SFA (≥25 g/d) *(AG/ AA) vs GG (95 % CI)	Pvalue
MetS	5.60(1.14,27.40)	**0.03****
DBP	6.52(1.59,11.45)	**0.01***
HDL-C	-0.87(-6.32,4.58)	0.75*
LDL	12.95(1.21,24.69)	**0.03***
LDL/HDL	0.28(-0.01,0.57)	0.05*
TG	12.64(-17.89,43.19)	0.41*
TC	1.92(-15.98,19.83)	0.83*

*Generalized linear model Adjusted (age, energy intake)

** Binary logistic Adjusted (age, energy intake, BMI, Smoking status, age at onset of obesity, total PUFA intake)

Table 6. Interactions between the Cav-1 rs3807992 gene polymorphism and PUFA intake in relation to MetS or its components

	PUFA (≥6% energy) *(AG/ AA) vs GG OR (95 % CI)	P value
MetS	-0.207(0.04,0.95)	0.04
TG ≥150 mg/dl	-0.207(0.05,0.8)	0.02**
FPG ≥100 mg/dl	-0.06(0.005,0.75)	0.02**
HOMA-IR ≥2.7	-0.22(0.06,0.78)	0.01**

** Binary logistic Adjusted (age, energy intake, BMI, smoking status, age at onset of obesity)
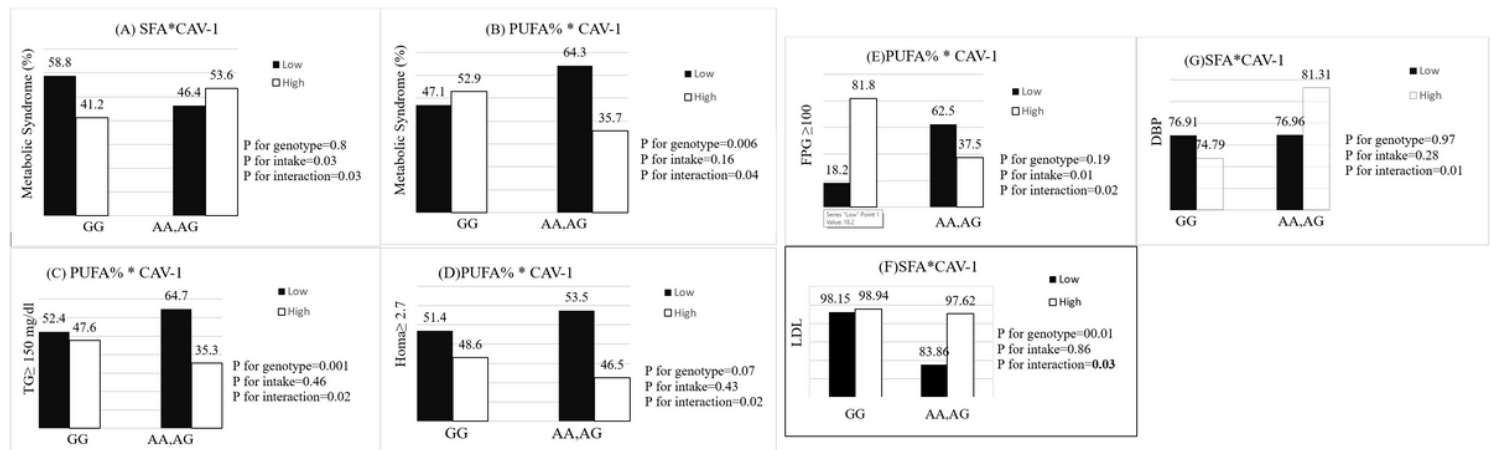
Figures

Figure 1

Percentage of MetS across rs3807992 genotypes base on low and high dietary SFA (A). Percentage of MetS across AA, AG and GG genotypes base on low and high dietary PUFA (B). Percentage of hypertriglyceridemia ≥ 150 mg/dl across AA, AG and GG genotypes base on low and high dietary PUFA(C). Percentage of HOMA-index ≥ 2.7 across AA, AG and GG genotypes base on low and high dietary PUFA (D). Percentage of hyperglycemia FPG ≥100 across AA, AG and GG genotypes base on low and high dietary PUFA (E). Mean of serum LDL and DBP across AA, AG and GG genotypes base on low and high dietary SFA (F), (G) respectively.
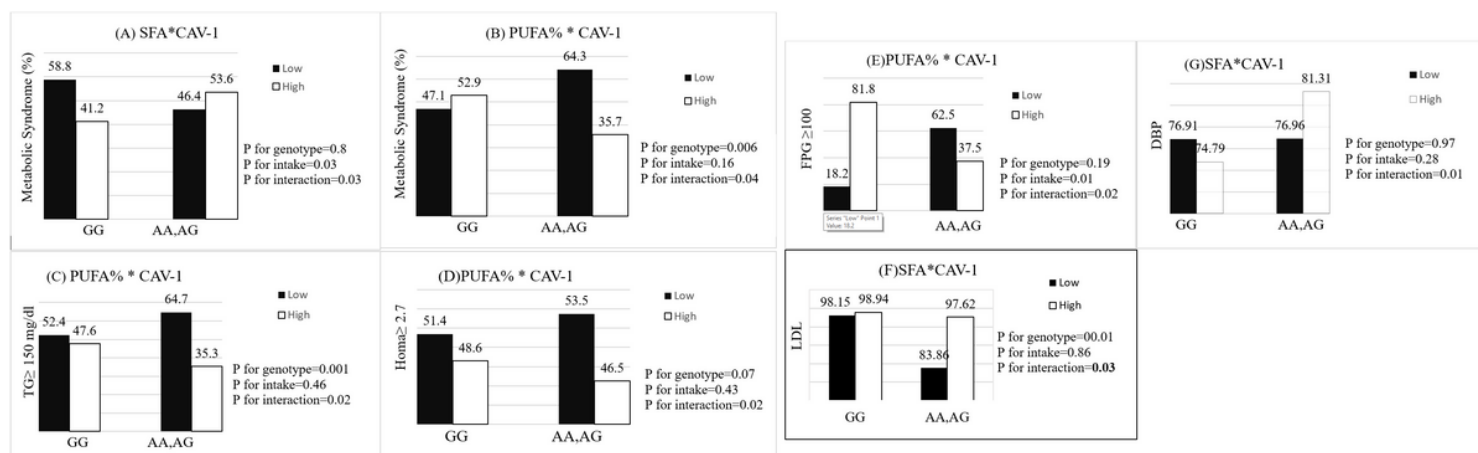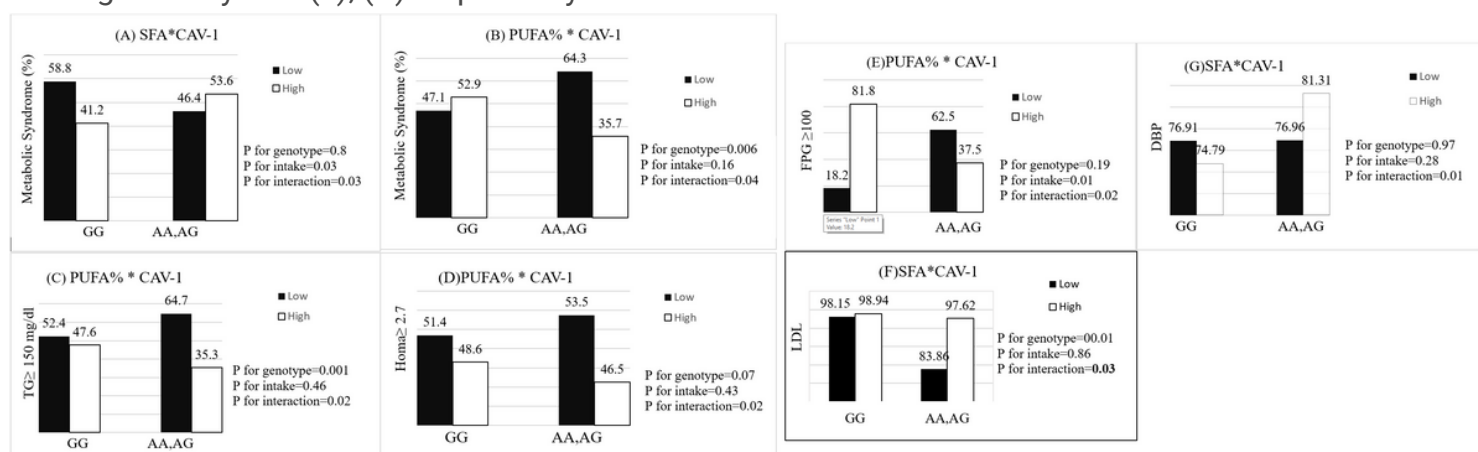
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