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The cluster of differentiation 36 (*CD36*) rs1761667 polymorphism interacts with dietary patterns to affect cardiometabolic risk factors and metabolic syndrome risk in apparently healthy individuals

Zeinab Yazdanpanah[1,2], Amin Salehi-Abargouei[1,2,5], Mehdi Mollahosseini[1,2], Mohammad Hasan Sheikhha[3,4], Masoud Mirzaei[5] and Hassan Mozaffari-Khosravi[1,2]*

[1]*Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
[2]*Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
[3]*Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
[4]*Abortion Research Center, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
[5]*Yazd Cardiovascular Research Centre, Non-communicable Research Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

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Abstract

Several studies have examined the association between *CD36* rs1761667 polymorphism with cardiometabolic risk factors and metabolic syndrome (MetS). This study aimed to investigate the interactions between rs1761667 polymorphism and dietary patterns on the cardiometabolic risk factors and the risk of MetS in apparently healthy individuals aged 20–70 years. Food consumption data were acquired using a validated semi-quantitative FFQ. Dietary patterns were identified by factor analysis. *CD36* rs1761667 was genotyped by PCR-restriction fragment length polymorphism. The gene–diet interaction was detected by the general linear model or logistic regression. Significant or marginally significant interactions were observed between healthy dietary pattern (HDP) and *CD36* rs1761667 on weight ($P = 0{\cdot}006$), BMI ($P = 0{\cdot}009$), waist circumference ($P = 0{\cdot}005$), hip circumference ($P = 0{\cdot}06$), body muscle percentage ($P = 0{\cdot}02$), body fat percentage ($P = 0{\cdot}09$), TAG-glucose index ($P = 0{\cdot}057$), atherogenic index of plasma ($P = 0{\cdot}07$), the risk of MetS ($P = 0{\cdot}02$), risk of abdominal obesity ($P = 0{\cdot}02$) and elevated blood pressure ($P = 0{\cdot}07$). Besides, a gene–diet interaction was detected between the traditional dietary pattern and rs1761667 variants on odds of hypertriglyceridaemia ($P = 0{\cdot}02$). The adherence to HDP was associated with a lower weight, BMI and higher odds of HDL-cholesterol only in A-allele carriers. In conclusion, adherence to HDP (a diet with high fibre, fish and dairy products) can be more effective on some cardiometabolic risk factors and risk of MetS components in the A-allele carrier than the GG genotype of rs1761667 polymorphism. However, future studies are required to shed light on this issue.

Key words: ***CD36* protein: SNP: rs1761667: Cardiometabolic risk factors: Metabolic syndrome risk**

CVD have a growing prevalence worldwide and are a leading cause of morbidity and mortality. These diseases can be present long before the onset of clinical symptoms[1]. In addition, metabolic syndrome (MetS) is a universal epidemic defined by a cluster of cardiometabolic abnormalities, including abdominal obesity, elevated TAG, fasting blood glucose (FBG), blood pressure and decreased HDL-cholesterol levels[2]. Cardiometabolic risk factors and components of the MetS represent a comprehensive list of existing and emerging biomarkers of diabetes mellitus, CVD and obesity-related traits[3]. Researchers have shown that increased risk for cardiometabolic disorders and MetS occur due to lifestyle factors, genetic susceptibility and the interaction between them[4,5].

Diet is a major lifestyle factor with a critical role in preventing non-communicable diseases and preserving health[6]. Since nutrients, food and food groups are consumed in combination with each other and also synergistic and interactive effects of food components, studying dietary patterns provides the opportunity to evaluate diet–disease associations[7]. Several studies have been undertaken regarding the association between cardiometabolic risk factors and dietary patterns[8]. Moreover, many genes related to cardiometabolic risk and MetS are increasingly

Abbreviations: AIP, atherogenic index of plasma; FBG, fasting blood glucose; HDP, healthy dietary pattern; MetS, metabolic syndrome; TDP, traditional dietary pattern; TyG, TAG-glucose index; WC, waist circumference; WDP, western dietary pattern.

* **Corresponding author**: Hassan Mozaffari-Khosravi, email mozaffari.kh@gmail.com

recognised, e.g., *APOE*, cyclin-dependent kinase inhibitor *2A* and cluster of differentiation 36 (*CD36*)[9–11]. *CD36* is a gene located on chromosome 7 (q11·2) and comprises fifteen alternatively spliced exons. This gene is expressed in various cell types including taste bud cells, adipocytes, skeletal, vascular endothelial cells and intestinal enterocytes[12]. *CD36* plays a decisive role in lipid metabolism, such as fat taste perception and dietary lipid intake, fatty acids utilisation by muscle and adipose tissues, lipoprotein production and transport, storage and lipolysis, and also is involved in inflammation, foam cell formation, atherosclerosis, cardiac function and insulin resistance[12,13]. Some researchers suggested that post-translational modifications of CD36 (glycosylation, acetylation, phosphorylation, ubiquitination, palmitoylation and O-GlcNAcylation) play a role in altered fatty acid uptake rates in the heart and muscle[14].

The rs1761667 is a common polymorphism in the *CD36* gene. This polymorphism is located in the intron of 5′ flanking exon 1A and is characterised by G (frequent allele) to A (minor allele) nucleotide substitution[15]. There is growing evidence showing that *CD36* rs1761667 is linked to decreased *CD36* expression, sensitivity to fat taste and high fatty food intake as a compensatory reaction[16]. The evidence has shown the association of the A allele with a higher risk of stroke and type 2 diabetes mellitus[17–19]. Moreover, a meta-analysis study demonstrated that the A allele was related to elevated total cholesterol and LDL-cholesterol and decreased HDL-cholesterol levels in Asians[20]. It was also found that the A allele was associated with higher BMI, WC, hip circumference, hypertension and coronary artery disease compared with the subjects with the GG genotype[21,22]. Indeed, the A allele seems to be a risk factor for metabolic disturbances. On the other hand, some previous studies have shown an interaction between dietary factors and *CD36* rs1761667 on cardiometabolic risk factors, for instance Lopez-Ramos *et al.*[23] indicated that the high-fat diet and high serum cholesterol levels were related to the AA genotype. Furthermore, it is demonstrated that individuals carrying the A allele have a higher fat consumption but lower BMI[24].

Although several studies have been conducted on different populations and health status, none have specifically assessed interactions between dietary patterns and rs1761667 polymorphism on cardiometabolic risk factors and the risk of MetS and its components. Therefore, the current study was undertaken to evaluate dietary patterns and rs1761667 interactions on cardiometabolic risk factors (anthropometric indices, lipid profile, blood pressure, FBG) and risk of MetS and its components in apparently healthy individuals aged 20–70 years in Yazd, Iran. We hypothesised that rs1761667 genotypes might change the association of diet with cardiometabolic risk factors and MetS and its components.

Methods

Study design and participants

For this cross-sectional study, 387 apparently healthy individuals (50·1 % females and 49·9 % males) were recruited using simple random sampling from the participants of the enrolment phase of the Yazd Health Study (YaHS) conducted from 2014 to 2015. In brief, YaHS is a comprehensive prospective study on the health and diseases in Yazd Greater Area, including 10 000 residents aged 20–70 years. Dietary intake was collected from the Yazd Nutrition Survey (a YaHS sub-study) which is locally known as the TaMYZ, which is the abbreviation of 'Taghzieh-e-Mardome Yazd' in Persian. A detailed description of the YaHS cohort study has been previously published in the literature[25]. This study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants. All procedures involving human subjects were approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (Ethnic number: 17/1/73941 and IR.SSU.SPH.REC.1398·136). After merging data from YaHS and TaMYZ studies, participants who self-reported chronic diseases (e.g. diabetes, renal or CVD, stroke, cancer, liver disease, thyroid and hypertension) or missing data were removed. Furthermore, those with malignancies, drug abuse (e.g., alcohol consumption and smoking), neurologic disorder, pregnant or lactating women, implausible energy intake (<3347·2 or > 25104 kJ/day)[26,27], or under medications affecting body composition like corticosteroids and contraceptives were removed from the study.

Dietary assessment method

The participants' dietary intakes in TaMYZ were evaluated via a 178-item semi-quantitative multiple-choice FFQ, which demonstrated acceptable validity and reliability[28]. Participants were asked to report their intake frequency (number of times per month, week or day) and the amount of food taken each time in the last 12 months. Based on a food photograph book, the portion size of foods was estimated as a unit and then converted into weight (grams per day). Food items were categorised into twenty-nine food groups for extracting dietary patterns.

Demographic and physical activity

The demographic variables of age, sex, marital status, education, job status, smoking status and past medical history of chronic disease were obtained through a validated questionnaire by trained interviewers. Information on physical activity was evaluated using a short version of the International Physical Activity Questionnaire and converted to the metabolic equivalent in minutes per week (MET-min/wk)[29]. Finally, it was classified as sedentary, moderate and active according to the median of the MET-h/wk levels.

Anthropometric and blood pressure measures

The participant's weight, body fat percentage and body muscle percentage were measured using Bioimpedance Analyzer (Omron-BF511, Japan). Height was measured using a tape measure on a straight wall. Trained interviewers performed the waist circumference (WC) and hip circumference measurements. BMI was calculated as weight (kg) divided by height in metres squared. Also, the waist-to-hip ratio was obtained by dividing WC by hip; ≥ 0·85 and 0·9 were considered abdominal obesity for women and men, respectively[30]. Systolic and diastolic blood pressure were measured after 40 min rest in a sitting position

(after completed two-thirds of the interview questions) and repeated three times with a 5-min interval between each measurement. The mean of the second and third measurements was considered the participant's blood pressure. These measurements were performed using Reichter electronic sphygmomanometers (Model N-Champion, Reister GMBH)[25].

Laboratory assessments

The levels of TAG, total cholesterol, LDL-cholesterol, HDL-cholesterol and FBG were measured using a commercial kit (Pars Azmoon) and calibrated Ciba Corning (Ciba Corp) auto-analyzers.

Index calculations

The visceral adiposity index was calculated as males: WC/(39·68 + (1·88 × BMI)) × TG/1·03 × 1·31/HDL-cholesterol or females: WC/ (39·58 + (1·89 × BMI)) × TG/0·81 × 1·52/HDL-cholesterol[31]. The logarithmic ratio of (TG to HDL-cholesterol) was used to calculate the atherogenic index of plasma (AIP)[32]. TAG-glucose index (TyG index) was calculated as ln fasting TG (mg/dl) × FBG (mg/dl)/2[33].

Diagnosis of metabolic syndrome

MetS was diagnosed according to the International Diabetes Federation. Participants who had central adiposity with two of the following four were considered as subjects with MetS: WC ≥ 94 cm for men and ≥ 80 cm for women; HDL-cholesterol < 40 mg dl for men and HDL-cholesterol < 50 mg/dl for women; serum TAG ≥ 150 mg/dl; FBG ≥ 100 mg/dl and blood pressure ≥ 130/85 mmHg[34].

DNA extraction and genotyping

Genomic DNA was extracted from 300 µl of whole blood using the FavorPrepTM DNA extraction mini kit (Favorgen Biotech Corp) based on silica technology. The *CD36* rs1761667 (G > A) was genotyped by PCR-restriction fragment length polymorphism technique using the following primers: forward 5′-CAAAA TCACAATCTATTCAAGACCA-3′; reverse 5′-TTTTGGGAGAAA TTCTGAAGAG-3′. The volume of PCR reactions was 25 µl, containing 3 µl extracted DNA, 1 µl of each primer (with concentration 10 pmol/µl), 12·5 µl Taq DNA polymerase 2× master mix red (Ampliqon, Denmark) containing 1·5 mM $MgCl_2$ and 7·5 µl distilled water. The PCR amplification was performed with denaturation at 95°C for 10 min, followed by 38 cycles at 95°C, 54°C and 72°C (each step for 30 s), and ended with a final extension at 72°C for 5 min. The PCR products (10 µl) were digested with 0·5 µl of HhaI restriction enzyme (Thermo Fisher Scientific) at 37°C for 4 h. All the mentioned methods were obtained from the study of Banerjee *et al.*[18], with minor modifications. The digested DNA fragments (10 µl) were visualised upon electrophoresis in 3·5 % agarose gel (SinaClon). Eventually, three possible genotypes of GG (52 and 138 bp), AG (52, 138 and 190 bp) and AA (190 bp) were identified. The accuracy of the PCR-restriction fragment length polymorphism results was confirmed using the sequencing process (ABI3130XL genetic analyzer, Applied Biosystems) for randomly selected samples.

Statistical analysis

The sample size was calculated by the Quanto software version 1.2.4 (Department of Preventive Medicine, University of Southern California)[35], assuming a minor allele frequency (MAF) of 0·36[21], power 0·80 ($\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}20$) and an OR of 2·75 for the *CD36* rs1761667 polymorphism based on the study of Lopez-Ramos *et al.*[23]. A sample size of *n* 301 in total was calculated based on the mentioned formula. However, considering the probability of the high rate of attrition, 387 participants who had eligibility criteria were entered into the current study. The normal distribution of variables was assessed by the Kolmogorov–Smirnov test. The genotype frequencies of this SNP were tested for Hardy–Weinberg equilibrium by Pearson's χ^2 test and non-quantitative data were analysed by χ^2 test. Principal component analysis was applied to identify dietary patterns from twenty-nine food groups. The independent Student's *t* tests and one-way ANOVA with Bonferroni post hoc test were employed for comparing continuous variables. The interaction between dietary patterns and *CD36* rs1761667 polymorphism on the quantitative and qualitative variables was evaluated using the general linear model and logistic regression, respectively, before and after adjustment for confounding variables including age, sex, energy intake, occupational, educational and marital status and physical activity. In this study, the individuals were divided into two groups, AA/AG and GG genotypes, based on previous studies[22,36]. Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corp). *P*-values ≤ 0·05 were regarded as statistically significant, and less than 0·1 was considered marginally significant for interactions[37].

Results

The main characteristics of the participants are summarised in Table 1. This cross-sectional study was conducted on 387 apparently healthy individuals (194 (50·1 %) women and 193 (49·9 %) men) aged 20–70 years. The means and SD weight and BMI among individuals were 71·72 ± 14·26 kg and 26·51 ± 4·92 kg/m^2. The frequencies of G and A alleles of rs1761667 were 52·97 % and 47·03 %, respectively, and genotype frequencies were consistent with the Hardy–Weinberg equilibrium ($P = 0{\cdot}52$). The overall prevalence of rs1761667 genotypes was 17·30 % (*n* 67), 71·30 % (*n* 276), and 11·40 % (*n* 44) for GG, AG, and AA, respectively. The study results revealed that there was no significant difference in the general characteristics, anthropometric and clinical parameters between the two genotype groups ($P > 0{\cdot}05$) (Table 1).

Association between body composition, biochemical parameters and derived dietary patterns

The principal component analysis identified three main dietary patterns: (1) western dietary pattern (WDP; high in red and processed meats, condiments, snacks, soft drinks, sweets, mayonnaise, pizza and low in grain), (2) healthy dietary pattern (HDP; rich in seafood, vegetables, fruits and dairy products) and (3) traditional dietary pattern (TDP; high in eggs, tomatoes, salt, tea, grain and low in pizza), which could explain 24·82 % of the total variance in dietary intake

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Table 1. Characteristics of the study participant across rs1761667genotypes*

Variables		Total (*n* 387)		GG (*n* 67)		AA/AG (*n* 320)		*P*-value
		n	%	*n*	%	*n*	%	
Age; *n* (%)	20–29	86	22·23	12	17·90	74	23·10	0·24
	30–39	106	27·40	25	37·30	81	25·30	
	40–49	95	24·54	12	17·90	83	25·90	
	50–59	67	17·31	11	16·40	56	17·50	
	60–69	33	8·52	7	10·40	26	8·10	
Education; *n* (%)	Elementary and lower	178	46·00	25	37·30	153	47·80	0·25
	Diploma	136	35·10	26	38·80	110	34·40	
	University educated	73	18·90	16	23·90	57	17·80	
Marriage status; *n* (%)	Single	41	10·60	8	11·90	33	10·30	0·17
	Married	339	87·60	56	83·60	283	88·40	
	Divorced or widowed	7	1·80	3	4·50	4	1·30	
Occupation; *n* (%)	Unemployed	59	15·20	7	10·50	52	16·30	0·48
	Employed	328	84·80	60	89·10	268	83·70	
Physical activity; *n* (%)	Sedentary	99	25·39	20	29·90	79	24·70	0·68
	Moderate	158	40·47	26	38·80	133	41·60	
	Active	129	34·12	21	31·30	108	33·70	
Frequency of alleles; *n* (%)			G: 52·97 %				A: 47·03 %	
		Mean	SD	Mean	SD	Mean	SD	
Height (cm)		164·65	9·94	164·80	9·53	164·62	10·04	0·89
Weight (kg)		71·72	14·26	70·96	14·96	71·88	14·13	0·63
BMI (kg/m^2)		26·51	4·92	26·18	5·41	26·58	4·83	0·55
WC (cm)		91·79	12·41	91·05	12·43	91·95	12·43	0·59
Hip circumference (cm)		101·01	11·89	101·34	11·65	100·94	11·97	0·80
WHR		0·91	0·11	0·90	0·10	0·92	0·12	0·28
Body muscle percentage (%)		30·62	6·71	31·49	7·51	30·45	6·54	0·25
Body fat percentage (%)		31·55	10·84	31·43	11·06	31·58	10·82	0·92
VAI		5·46	4·35	5·21	3·59	5·52	4·51	0·59
FBG (mg/dl)		97·09	14·79	95·52	10·15	97·43	15·58	0·34
TC (mg/dl)		191·09	39·05	194·94	40·74	190·28	38·71	0·38
HDL-cholesterol (mg/dl)		47·33	9·90	48·69	10·70	47·05	9·72	0·22
LDL-cholesterol (mg/dl)		114·67	33·53	117·42	35·17	114·10	33·21	0·46
TAG (mg/dl)		147·53	89·20	145·37	74·61	147·99	92·07	0·83
TC/HDL-cholesterol		4·17	1·07	4·14	1·04	4·18	1·09	0·77
LDL-cholesterol/HDL-cholesterol		2·49	0·81	2·49	0·84	2·50	0·81	0·96
TAG/HDL-cholesterol		3·39	2·58	3·22	2·05	3·43	2·69	0·54
AIP		0·43	0·27	0·43	0·26	0·44	0·28	0·82
TyG index		4·70	0·28	4·71	0·26	4·71	0·29	0·98
SBP (mmHg)		122·68	14·43	123·90	13·61	122·43	14·61	0·45
DBP (mmHg)		77·98	10·49	78·42	12·10	77·89	10·15	0·71

WC: waist circumference; WHR: waist-to-hip ratio; VAI: visceral adiposity index; FBG: fasting blood glucose; TC: total cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; AIP: Atherogenic index of plasma; TyG index: TAG-glucose index.
* Values are provided as mean ± standard deviation (SD), otherwise explained. Independent Student's *t* tests and chi-square analysis used for continuous and categorical variables, respectively.

(Table 2). As illustrated in Table 3, no significant relationship was observed between WDP and evaluated parameters. There was a significant association across tertiles of HDP for body muscle percentage ($P = 0{\cdot}04$) and HDL-cholesterol ($P = 0{\cdot}02$) in the crude model. However, they changed to non-significant ($P \geq 0{\cdot}05$) after adjusting in terms of age, sex, energy intake, physical activity, occupational, educational and marital status. Before adjustment for mentioned confounders, higher tertiles of TDP were associated with higher levels of total cholesterol/HDL-cholesterol ratio, TyG index and AIP (all of $P = 0{\cdot}03$). These significant differences remained after adjustment, except in the variable of total cholesterol/HDL-cholesterol ratio ($P = 0{\cdot}06$). Significant difference between tertiles of TDP and TG was observed after adjustment ($P = 0{\cdot}04$) but was not appeared before adjusting ($P = 0{\cdot}06$).

The interaction between identified dietary patterns and CD36 rs1761667 variants on cardiometabolic risk factors

The significant and marginally significant interactions between rs1761667 genotypes and dietary patterns on cardiometabolic risk factors are shown in Fig. 1. The results show significant interactions between HDP and *CD36* rs1761667 in terms of weight (P_{crude}-interaction = 0·032, $P_{adjusted}$-interaction = 0·006), BMI (P_{crude}-interaction = 0·002, $P_{adjusted}$-interaction = 0·009), WC (P_{crude}-interaction = 0·007, $P_{adjusted}$-interaction = 0·005) and body muscle percentage (P_{crude}-interaction = 0·03, $P_{adjusted}$-interaction = 0·02). Also, a marginally significant interaction was observed on the hip circumference (P_{crude}–interaction = 0·03, $P_{adjusted}$–interaction = 0·06), body fat percentage (P_{crude}–interaction = 0·02, $P_{adjusted}$–interaction = 0·09) and TyG index (P_{crude}–interaction = 0·17, $P_{adjustedc}$–interaction = 0·057).

Table 2. Factor loadings of the food groups in the three extracted dietary patterns derived from factor analysis

	Dietary patterns		
Food groups	WDP	HDP	TDP
Condiment	0·62		
Snacks	0·61		
Nuts	0·61		
Soft drinks	0·58		
Sweets and desserts	0·53		
Meats	0·45		
Mayonnaise	0·41		
Pizza	0·38		–0·34
Grain	–0·33		0·30
Hydrogenated fats			
Olive			
Fish		0·54	
Green leafy vegetables		0·52	
Fruit		0·47	
Garlic		0·47	
Yellow and orange vegetables		0·45	
Cruciferous vegetables		0·40	
Dairy product		0·37	
Pickles		0·35	
Eggs			0·61
Tomatoes			0·54
Vegetable oils			0·48
Other vegetables		0·45	0·47
Salt			0·41
Tea		–0·30	0·36
Variance explained (%)	9·80	8·39	6·62
Total variance (%): 24·82			

WDP: western dietary pattern; HDP: healthy dietary pattern; TDP: traditional dietary pattern.
Factor loadings with an absolute value < ±0·30 were omitted.

In addition, a marginally significant interaction was found between HDP and rs1761667 genotypes on the AIP in the adjusted model (*P*–interaction = 0·07); however, this result was not significant in the unadjusted model (*P*–interaction = 0·31). A significant difference was observed in weight and BMI between the three groups of HDP ($P \leq 0{\cdot}05$) in participants with A-allele. HDP was significantly associated with a lower body muscle percentage ($P = 0{\cdot}01$) and marginally significantly with a higher body fat percentage ($P = 0{\cdot}06$) in the second tertile of participants with the GG-allele. No statistically significant difference was observed in the mean WC, hip circumference, TyG index and AIP of participants with GG and A-allele genotypes in different categories of HDP. Unlike participants with the A allele, the mean of the mentioned variables in the second tertile of HDP was numerically higher in patients with the GG genotype. This difference was not statistically significant (Fig. 1). However, no relevant gene–diet (WDP, HDP and TDP) interaction was found regarding other parameters.

The interaction between identified dietary patterns and CD36 rs1761667 genotypes on MetS and its components

The interaction between *CD36* polymorphism (rs1761667) and dietary patterns (tertiles) on MetS and its components was investigated by considering the A-allele and the first tertile of the dietary pattern as reference groups.

A significant interaction was found between *CD36* gene SNP rs1761667 and HDP on the probability of MetS in the crude (*P*-interaction = 0·04) and adjusted (*P*–interaction = 0·02) models. Also, there was a gene–diet interaction between HDP and rs1761667 genotypes in association with the risk of abdominal obesity (*P*-interaction = 0·05) and elevated blood pressure (*P*-interaction = 0·099) in the crude model. This interaction remained significant in the probability of abdominal obesity (*P*-interaction = 0·02) and the odds of elevated blood pressure (*P*–interaction = 0·07). Besides, *CD36* rs1761667 polymorphism and TDP interaction were not significant in terms of TG in the crude (*P*–interaction = 0·11) but became significant after adjustment (*P*-interaction = 0·02). Although the interaction between the allele of rs1761667 and HDP was not significant regarding HDL-cholesterol levels (*P*-interaction = 0·60), higher adherence to the HDP (compared to the first quartile) was associated with higher odds of HDL-cholesterol (β (95 %CI) = 2·00 (1·04; 3·86), $P = 0{\cdot}03$) in individuals with the A-allele. Individuals with the GG genotype had a higher probability of abdominal obesity in the second tertile of HDP (β (95 %CI) = 10·79 (1·90; 61·07), $P = 0{\cdot}007$) compared with the first tertile of A-allele after adjusting potential confounders. Furthermore, lower adherence to the WDP was associated with higher odds of elevated BP among the individuals with the GG genotype as compared with A-allele (β (95 %CI) = 4·16 (1·17; 14·83), $P = 0{\cdot}02$). No significant relation was observed between *CD36* rs1761667 polymorphism and dietary patterns on other risks of MetS and its components in either crude or adjusted models (online Supplementary Table S1).

Discussion

The key findings of this cross-sectional study were the significant interaction between HDP and *CD36* rs1761667 SNP on weight, BMI, WC and body muscle percentage and marginal interaction on the hip circumference, body fat percentage, AIP and TyG index. Also, when stratified by rs1761667 genotypes, the high HDP was associated with a significantly lower weight and BMI in A-allele. Among participants who carry GG genotype, the body muscle percentage was significantly lower in the second tertile of HDP. Moreover, a statistically significant interaction was observed between the *CD36* gene rs1761667 and HDP on the odds of MetS and some of its components (hypertension and abdominal obesity). The interaction was also observed between TDP and the mentioned polymorphism on the odds of hypertriglyceridaemia. Higher intake of the HDP among the A-allele of rs1761667 was associated with higher odds of HDL-cholesterol. The probability of abdominal obesity in individuals with the GG genotype was higher in the second tertile of HDP than in the first tertile of A-allele. Furthermore, lower adherence to the WDP was associated with higher odds of elevated BP among individuals with the GG genotype. Based on these results, it appears that the presence of the A allele with high HDP is a protective factor against cardiometabolic risk factors. Thus, individuals with GG genotype may be more vulnerable to CVD despite moderate adherence to HDP which is rich in fish, vegetables and fruit.

The precise mechanism by which rs1761667 SNP interacts with dietary patterns is largely unknown. A noteworthy point about the

Table 3. Associations of body composition and biochemical markers with the tertiles of the major dietary patterns*

	1st tertile		2nd tertile		3rd tertile			
Variable	Mean	SD	Mean	SD	Mean	SD	*P*-value†	*P*-value‡
Weight (kg)								
WDP	73·11	14·75	71·68	13·68	70·27	14·28	0·20	0·30
HDP	70·52	14·60	71·33	14·91	73·31	13·14	0·27	0·16
TDP	71·95	13·58	71·26	15·89	71·95	13·22	0·76	0·70
BMI (kg/m^2)								
WDP	26·67	5·47	26·49	4·50	26·40	4·78	0·29	0·66
HDP	26·27	5·00	26·44	5·19	26·84	4·57	0·16	0·11
TDP	27·14	4·85	26·31	5·36	26·10	4·48	0·72	0·91
WC (cm)								
WDP	91·25	13·25	92·06	12·31	92·14	11·76	0·90	0·97
HDP	91·27	13·40	91·15	12·12	93·04	11·72	0·22	0·15
TDP	92·43	12·35	90·95	13·08	92·08	11·87	0·57	0·54
Hip circumference (cm)								
WDP	103·03	11·39	99·93	12·44	100·29	11·27	0·07	0·11
HDP	101·93	11·19	100·01	12·49	101·31	11·58	0·60	0·82
TDP	101·53	11·63	101·64	12·12	100·07	11·57	0·81	0·62
WHR								
WDP	0·89	0·11	0·92	0·10	0·92	0·11	0·06	0·17
HDP	0·89	0·10	0·92	0·12	0·92	0·11	0·12	0·18
TDP	0·91	0·11	0·89	.11	0·92	0·12	0·19	0·17
Body muscle percentage (%)								
WDP	31·02	6·81	30·74	6·92	30·04	6·27	0·99	0·43
HDP	30·01	6·39	30·68	6·66	31·10	6·96	**0·04**	0·14
TDP	30·04	6·76	30·62	6·74	31·14	6·51	0·70	0·55
Body fat percentage (%)								
WDP	30·75	11·24	31·61	10·84	32·35	10·29	0·99	0·97
HDP	31·72	10·72	31·45	10·76	31·55	10·98	0·22	0·46
TDP	32·91	10·97	31·56	10·69	30·24	10·62	0·37	0·97
VAI								
WDP	5·13	3·99	5·63	5·22	5·60	3·69	0·5	0·69
HDP	5·26	4·20	5·63	5·33	5·47	3·29	0·59	0·47
TDP	5·47	4·11	4·92	3·74	5·98	4·07	0·13	0·06
FBG (mg/dl)								
WDP	96·07	14·04	98·79	16·99	96·42	13·04	0·39	0·50
HDP	95·03	12·46	96·64	13·89	99·64	16·38	0·36	0·31
TDP	97·39	14·47	95·58	12·87	98·34	16·80	0·94	0·77
TC (mg/dl)								
WDP	190·69	43·35	191·26	36·14	192·16	37·29	0·78	0·48
HDP	189·98	40·04	194·54	37·50	189·57	39·38	0·47	0·47
TDP	192·18	37·25	185·37	37·03	196·60	41·83	0·21	0·12
HDL-cholesterol (mg/dl)								
WDP	47·87	10·33	47·54	10·03	46·77	9·30	0·25	0·30
HDP	48·62	10·51	48·48	10·15	45·07	8·54	**0·02**	0·09
TDP	47·86	9·69	47·47	9·78	46·85	10·22	0·23	0·37
LDL-cholesterol (mg/dl)								
WDP	114·11	36·57	114·19	31·21	116·35	32·69	0·78	0·47
HDP	113·03	3419	116·51	31·73	115·09	34·67	0·61	0·39
TDP	115·45	33·08	111·82	32·24	117·40	35·11	0·56	0·65
TAG (mg/dl)								
WDP	144·90	91·59	150·92	97·16	147·00	78·59	0·77	0·76
HDP	142·53	92·69	152·24	96·52	148·03	77·90	0·48	0·36
TDP	146·21	87·16	135·72	8591	161·02	93·46	0·06	**0·04**
SBP (mmHg)								
WDP	122·57	14·39	123·17	13·62	122·35	15·38	0·81	0·74
HDP	122·63	14·65	121·87	15·02	123·60	13·68	0·84	0·89
TDP	121·66	14·66	120·54	15·33	125·91	12·75	0·08	0·10
DBP (mmHg)								
WDP	78·55	10·81	77·93	10·61	77·50	10·17	0·60	0·34
HDP	77·12	10·38	77·20	11·23	79·66	9·75	0·17	0·29
TDP	77·17	10·61	77·22	10·64	79·59	10·18	0·22	0·36
TC/HDL-cholesterol								
WDP	4·13	1·22	4·14	1·00	4·23	1·01	0·32	0·23
HDP	4·05	1·13	4·17	1·13	4·29	0·95	0·27	0·14
TDP	4·14	1·02	4·01	0·89	4·35	1·27	**0·03**	0·06

Table 3. (*Continued*)

Variable	1st tertile		2nd tertile		3rd tertile		*P*-value†	*P*-value‡
	Mean	SD	Mean	SD	Mean	SD		
LDL-cholesterol/HDL-cholesterol								
WDP	2·47	0·93	2·46	0·70	2·56	0·78	0·37	0·27
HDP	2·40	0·82	2·50	0·80	2·60	0·80	0·15	0·11
TDP	2·49	0·81	2·41	0·71	2·59	0·90	0·14	0·37
TAG/HDL-cholesterol								
WDP	3·28	2·41	3·50	3·07	3·40	2·20	0·68	0·68
HDP	3·24	2·57	3·47	3·03	3·47	2·08	0·77	0·60
TDP	3·31	2·37	3·11	2·53	3·76	2·81	0·10	0·08
AIP								
WDP	0·42	0·27	0·43	0·28	0·44	0·27	0·41	0·33
HDP	0·41	0·28	0·43	0·29	0·46	0·24	0·43	0·26
TDP	0·43	0·27	0·40	0·26	0·48	0·28	**0·03**	**0·04**
TyG index								
WDP	4·69	0·28	4·71	0·29	4·71	0·26	0·67	0·61
HDP	4·67	0·27	4·71	0·30	4·73	0·26	0·38	0·19
TDP	4·70	0·29	4·65	0·27	4·75	0·27	**0·03**	**0·04**

WDP: western dietary pattern; HDP: healthy dietary pattern; TDP: traditional dietary pattern; WC: waist circumference; WHR: waist-to-hip ratio; VAI: visceral adiposity index; FBG: fasting blood glucose; TC: total cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; AIP: Atherogenic index of plasma; TyG index: TAG-glucose index.
Significant items with a *P*-value ≤ 0·05 are bolded.
* Data are presented as mean ± standard deviation (SD).
† Crude model (unadjusted).
‡ Adjusted for age, sex, energy intake, physical activity, occupational, educational and marital status.

HDP in this study is its high fibre content, and high-quality protein such as fish (rich in *n*-3 polyunsaturated fatty acids). According to previous studies[38–40], these compounds reduce weight and BMI and increase HDL-cholesterol. Furthermore, the consumption of dairy products (low- and high-fat) was observed in this pattern. This item appears to be associated with a lower risk of MetS components, such as low HDL-cholesterol[41]. Although some reviews have reported the benefit of fruits, vegetables, fish and dairy products on anthropometric and body composition, HDP interaction with rs1761667 genotypes may lead to increased and decreased WC and body muscle percentage, respectively, in the GG genotype. In addition, our results suggested that the GG genotype had a greater risk of hypertension in WDP. The WDP was characterised by high intakes of salty snacks, soft drinks, pizza, sweets and desserts, which reported that are associated with hypertension[42]. The present study showed that a diet with high fibre, fish and dairy products could be more effective in the A carrier than the GG genotype. The finding of gene–diet interaction may account for some of the unexplained heritability of cardiometabolic and MetS traits. On the other hand, previous studies have focussed on the interplay of rs1761667 genotypes, dietary fat taste perception or fat preference, and the association between this polymorphism and dysmetabolic conditions such as CVD, dyslipidaemia, hypertension, diabetes, MetS and obesity[18,43–46]. Scarce research has been conducted on the interaction between this polymorphism with total energy intake, macronutrients and other dietary factors[47–49], while the interplay between dietary patterns and this SNP has not been considered. Consistent with our results about cardiometabolic risk factors, a previous study demonstrated that individuals carrying the A allele have a lower BMI[24]. Furthermore, Fujii *et al.*[47] reported that participants with the AA genotype of rs1761667 had a higher intake of total fat and MUFA and a lower risk of hypertension than those with the GG genotype in Japan. In contrast with the findings, some studies have not reported any association between *CD36* rs1761667 polymorphism and cardiometabolic risk factors and MetS[45,50,51]. These discrepancies in findings might be due to the variations in the genotyping methods, ethnicity, health status, gene-environment or gene–gene interactions and interactions of rs1761667 polymorphism with other variants in the *CD36* gene. Another possible reason for these inconsistencies could be differences in the design of studies[20].

Both deficiency and abnormally up-regulated CD36 lead to dyslipidaemia, metabolic disorders, inflammation and thrombosis[14]. A genome-wide scan has provided evidence that SNP in *CD36* including rs1761667 are strongly related to *CD36* expression[52]. Melis *et al.*[16] have reported that the GG genotype of rs1761667 is characterised by the increased expression of the *CD36* receptor, which plays an important role in regulating fatty acid entry into the cell. However, it has been observed that excessive fatty acid uptake can impair *CD36* activity, induce ectopic fat deposition and reduce the activity of mitochondrial. Accordingly, it may decline lean mass and increase fat mass, especially in visceral adipose tissue[13,53]. Hence, these conditions can correspond to a trend for increased WC in GG subjects. Moreover, some documents have suggested that the A allele of this SNP is related to a decreased expression of *CD36*[52,54]. In this regard, an inverse relationship has been reported between *CD36* expression and HDL-cholesterol level[54]. One animal study indicated that hypertension is associated with increased *CD36* gene expression. Also, the overexpression of *CD36* may cause an intensified fatty acid uptake in cardiomyocytes[55]. Generally, it seems that *CD36* polymorphisms and multiple factors could change the expression of this gene, and environmental factors including diet[56,57], probably could interact with them in altering this gene expression. Due to the limited financial

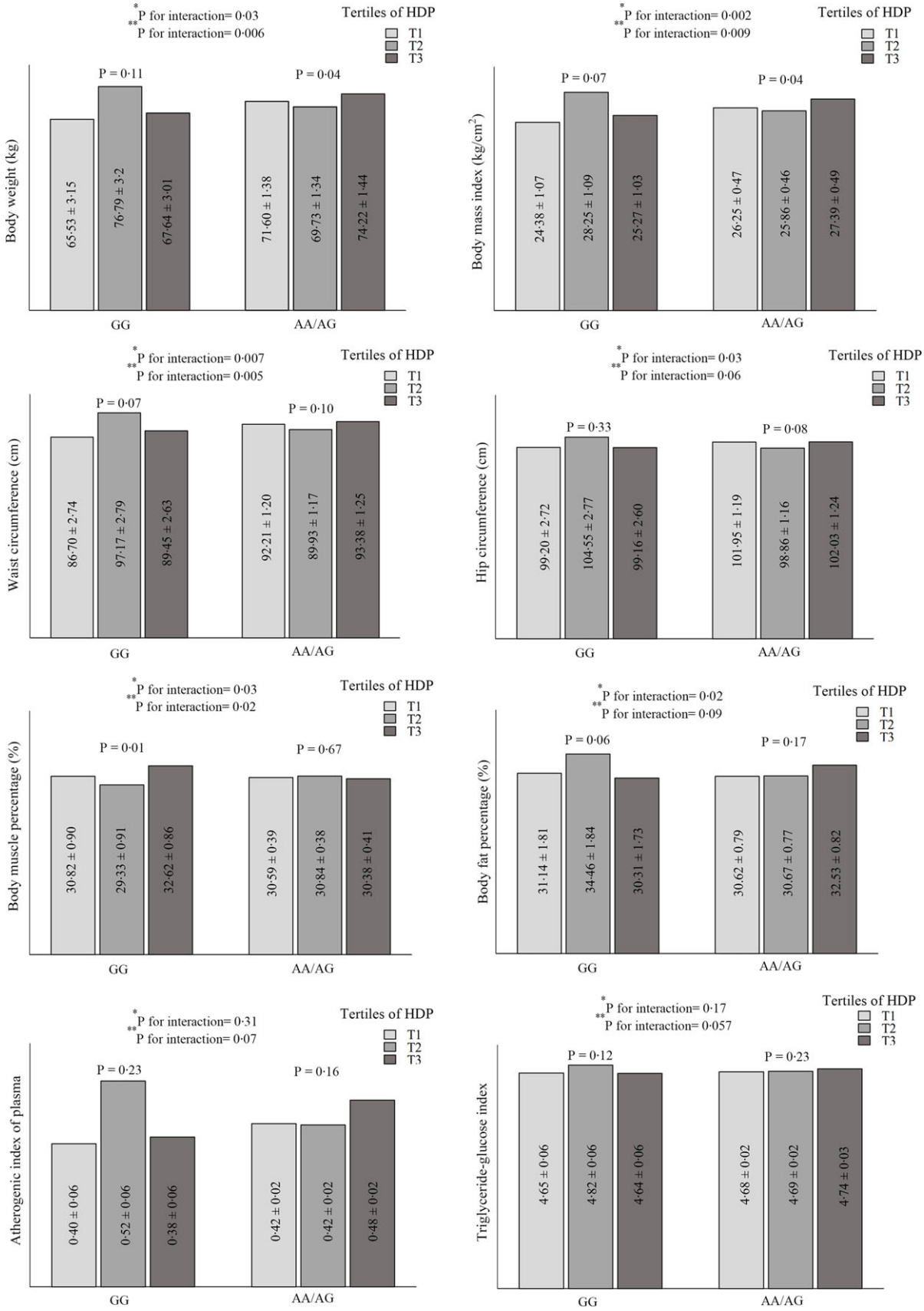

Fig. 1. Interaction between healthy dietary pattern (HDP) and CD36 rs1761667 polymorphism on cardiometabolic risk factors.
Variables are presented as mean ± standard error (SE).
*P for unadjusted interaction obtained from ANCOVA.
**P for adjusted interaction from ANCOVA. Adjusted for age, sex, energy intake, physical activity, occupational, educational, and material status.

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resources, we could not carry out quantitative PCR or western blot to realise whether rs1761667 polymorphism alters the *CD36* expression.

This cross-sectional research revealed that higher TDP adherence was associated with higher TG, AIP and TyG index. Grain (including whole- and refined-grain) and egg are among the contributors to the TDP in this study. Some studies have suggested that high refined-grains consumption is significantly related to elevated TG and FBG levels[58–60]. A systematic review and meta-analysis have reported that egg consumption had no significant effect on serum TG. Nevertheless, they observed an increasing influence on TG levels when egg interventions were compared with other foods[61].

To the best of our knowledge, the present study is the first to investigate the interaction between dietary patterns and *CD36* rs1761667 polymorphism on cardiometabolic risk factors and the risk of MetS and its components. Several potential confounders, such as age, sex, energy intake, physical activity, occupational, educational and marital status, were measured in this research. Moreover, another strength of the study is the application of a reliable and validated FFQ to collect dietary information by trained interviewers. However, some limitations need to be considered in interpreting this study. Since the design of this study was cross-sectional, causal inferences could not be drawn. The FFQ was applied for evaluating the dietary intake, which may potentially face recall bias. Dietary habits were not assessed as a confounder. Another limitation of the present study was that the health status and disease information were collected via self-reporting, which may lead to selection bias. This study was performed in a city in Iran with a unique culture and dietary intake. Therefore, the findings may not be generalisable to all Iranians or other countries and must be replicated in other populations.

Conclusions

In summary, the present study demonstrated an interaction between *CD36* rs1761667 polymorphism and HDP on weight, BMI, WC, body muscle percentage, the risk of MetS and some of its components (hypertension and abdominal obesity). Also, it showed a marginal interaction on the hip circumference, body fat percentage, AIP and TyG index. Furthermore, a significant interaction was found between this polymorphism and TDP on hypertriglyceridaemia. Based on these results, the presence of the A allele with higher adherence to the HDP is a protective factor against cardiometabolic risk factors. However, cohort studies in different populations with varied health statuses are needed to elucidate these interactions further.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114523000570

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The authors declare that there is no conflict of interest.

Ethics of human subject participation

Written informed consent was obtained from all participants. All procedures involving human subjects were approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (Ethnic number: 17/ 1/73941 and IR.SSU. SPH.REC.1398·136).

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