

Original Article



Interactions Between Genetic Risk Score and Healthy Plant Diet Index on Cardiometabolic Risk Factors Among Obese and Overweight Women

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ABSTRACT

People with higher genetic predisposition to obesity are more susceptible to cardiovascular diseases (CVDs) and healthy plant-based foods may be associated with reduced risks of obesity and other metabolic markers. We investigated whether healthy plant-foods-rich dietary patterns might have inverse associations with cardiometabolic risk factors in participants at genetically elevated risk of obesity. For this cross-sectional study, 377 obese and overweight women were chosen from health centers in Tehran, Iran. We calculated a healthy plant-based diet index (h-PDI) in which healthy plant foods received positive scores, and unhealthy plant and animal foods received reversed scores. A genetic risk score (GRS) was developed based on 3 polymorphisms. The interaction between GRS and h-PDI on cardiometabolic traits was analyzed using a generalized linear model (GLM). We found significant interactions between GRS and h-PDI on body mass index (BMI) ($p = 0.02$), body fat mass ($p = 0.04$), and waist circumference ($p = 0.056$). There were significant gene-diet interactions for healthful plant-derived diets and BMI-GRS on high-sensitivity C-reactive protein ($p = 0.03$), aspartate aminotransferase ($p = 0.04$), alanine transaminase ($p = 0.05$), insulin ($p = 0.04$), and plasminogen activator inhibitor 1 ($p = 0.002$). Adherence to h-PDI was more strongly related to decreased levels of the aforementioned markers among participants in the second or top tertile of GRS than those with low GRS. These results highlight that following a plant-based dietary pattern considering genetics appears to be a protective factor against the risks of cardiometabolic abnormalities.

Keywords: Genetic risk score; Obesity; Healthy-plant based dietary index; Cardiometabolic risk factors

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

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INTRODUCTION

Approximately one-third of all global deaths are related to cardiovascular disease (CVD), which remains a major cause of morbidity, premature mortality, and health loss for all of the world [1,2]. The risk factors for cardiometabolic disease are high waist circumference (WC), low high-density lipoprotein (HDL) cholesterol, high triglycerides (TGs), high low-density lipoprotein (LDL) cholesterol, hypertension, and insulin resistance. Atherosclerotic CVD and diabetes mellitus can be attributed to these risk factors [3]. In 2017, CVDs were responsible for approximately 17.8 million deaths [2]. By 2030, it is predicted to rise to 23.6 million deaths from CVDs [4]. Also, the premature death rate due to CVDs is increasing in Iran, along with all regions of the world [5]. Overweight and obesity, inflammation, hypertension, hyperlipidemia, and insulin resistance are part of the risk factors for CVDs [6-9].

Several studies have demonstrated the importance of adhering to healthy dietary patterns in preventing CVD-related risk factors for their nutrients that can improve CVD risk profiles [10-12]. Several recent prospective studies in the USA have detected an association between higher intake of healthy plant-based foods and lower consumption of less healthy plant-based foods and animal foods [7,11] with a lower incidence of CVDs, coronary heart disease (CHD) and type 2 diabetes. They have developed new indices such as the healthy plant-based diet index (h-PDI) and the unhealthy plant-based diet index (uPDI), which capture the synergistic and graded intake of 3 categorical foods [13,14]. Vegan and vegetarian diets are some examples of plant-based diets that consist of more consumption of whole grains, vegetables, fruits, legumes, and nuts and less intake of uPDI or animal products. Preventing chronic diseases by following the h-PDI and less following the uPDI may contribute to improved bone health, inflammation, type 2 diabetes, and insulin resistance [15,16]. Also, it has been suggested that a plant-based diet index (PDI) can be used to predict future CVD, CHD, and type 2 diabetes events, but in a clinical setting and different populations, it is not yet clear [10].

On the other hand, genetic predisposition has also been implicated as a significant risk factor for CVDs. In this regard, a genetic risk score (GRS) could easily determine genetic factors affecting CVDs by combining accumulated genetic risk alleles for each single nucleotide polymorphism (SNP) that has a combined effect of multiple SNPs and is considered to be an effective tool for detecting cardiometabolic risk factors and predicting them [17-19]. A large variety of studies have implicated caveolin-1 (CAV-1) SNP, abundant in adipocytes [20], in the development of obesity, dyslipidemia, high blood pressure, and atherosclerosis [21-25]. In addition, previous studies have reported the association between the risk allele C for melanocortin 4 receptor (MC4R) rs17782313 and cardiovascular risk factors such as higher body mass index (BMI), insulin resistance, and high blood pressure [26-30]. Furthermore, it has been reported that cryptochromes (Cry) 1 play an important role in metabolism regulation, obesity, and insulin resistance [31-33]. Therefore, the above genetic variants have previously been reported to be individually associated with overweight, obesity, and higher BMI in some populations [34,35].

It has been reported that higher intake of healthy dietary patterns and PDI can contribute to reducing genetic risk factors of obesity, CVD, CHD, and type 2 diabetes [36-38]. However, we still know little about the potential interactions between PDI and CVD susceptibility. Additionally, there has also been no direct evidence yet as to whether genetic factors contribute to the association. Therefore, the present study has been undertaken to assess the interaction between BMI-GRS based on 3 SNPs such as MC4R (rs17782313), CAV-1

(rs3807992) and Cry-1 (rs2287161) with PDI on CVD risk factors to improve the detection of overweight and obese women at a higher risk of developing cardiometabolic risk factors and to prevent or improve CVD risk factors with dietary intervention. The present study have been addressed the issue of obesity and cardiovascular disease by considering GRS based on 3 SNPs such as MC4R (rs17782313), CAV-1 (rs3807992) and Cry-1 (rs2287161) and environmental factors such as h-PDI with a comprehensive approach.

MATERIALS AND METHODS

Study population

Three hundred and seventy-seven overweight or obese women took part in this cross-sectional study. Tehran University of Medical Sciences (TUMS) in Tehran, Iran, reviewed and approved the written informed consent of all study participants. Their ages ranged from 18 to 58 years and their BMI ranged from '25–40 kg/m²,' which refers to health centers in Tehran, Iran. The exclusion criteria were diabetes types I and II, CVD, malignancies, liver and kidney disease, thyroid disease, menopause, pregnancy, lactation, smoking, any acute and chronic diseases, getting supplementation for weight loss, dieting during the last year, and receiving lipid, glucose, and blood pressure lowering drugs. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee of the TUMS and assigned the number IR.TUMS.MEDICINE.REC.1400.1515 for ethical considerations. Written informed consent was obtained from all subjects.

Body composition analysis

Utilizing the InBody 770 scanner from InBody Co. (Seoul, Korea) and following the manufacturer's protocol, we measured body composition using a bioelectrical impedance analyzer (BIA) [39]. In accordance with the manufacturer's instructions, participants are required to remove extra clothing and metal objects, which include earrings, rings, and watches, along with shoes, coats, and sweaters. The examination takes nearly 15 seconds, and the BIA calculates weight, BMI, WC, waist to hip ratio (WHR), body fat mass (BFM), body fat (BF%), bone mineral content (BMC), and visceral fat area (VFA).

Anthropometric indices

BIA measured weight, BMI, and other anthropometric characteristics. We measured hip circumference and WC using the most prominent portion and the narrowest portion, respectively, with a precision of 0.5 cm. The height of each participant was measured and recorded with 0.5 cm precision by using a non-stretch tape measure in a standing up and unshod position.

Assessment of physical activity

We measured physical activity based on the short-form of the International Physical Activity Questionnaire (IPAQ). A validity and reliability assessment of IPAQ questionnaires was conducted across 12 countries to calculate all participants' physical activity over the past 7 days. These questionnaires had high criterion reliability, with a Spearman's ρ correlation score of 0.8 and a median validation score of 0.30, which was similar to other validation studies. Physical activity in the last week was measured using IPAQ, a validated self-report instrument [40].

Biochemical and hormonal determination

We collected venous blood between 8:00 a.m. and 10:00 a.m. after fasting overnight. We centrifuged all of the serum, aliquoted it, stored it at -80°C , and analyzed it all with a single assay technique. We measured fasting blood glucose (FBS), TG and total cholesterol (TC) by using glucose oxidase-phenol 4-aminoantipyrine peroxidase and glycerol-3-phosphate oxidase-phenol 4-aminoantipyrine peroxidase enzymatic endpoints, respectively. LDL and HDL cholesterol were measured by using a direct enzymatic clearance assay. We assessed serum inflammatory markers via an immunoturbidimetric assay (high sensitivity assay, Hitachi 902; Randox Laboratories, Crumlin, UK). Galectin, monocyte chemoattractant protein-1 (MCP-1), and high-sensitivity C-reactive protein (hs-CRP) were measured via standard protocols.

In triplicate, plasminogen activator inhibitor-1 (PAI-1) was evaluated using a Human PAI-1*96 T ELISA kit from Crystal Chem (Elk Grove Village, IL, USA). The intra coefficient of variation (CV) and inter CV were both 2.19% and 4.4%, respectively, and the minimum detectable insulin concentration was 1.76 mIU/mL. $\frac{\text{Fasting Plasma Glucose} \times \text{Fasting Serum Insulin}}{22.5}$ was used to calculate Homeostasis Model Assessment (HOMA) for Insulin Resistance [41]. We used the Hitachi 902 kit (Randox Laboratories) for all measurements and assessed all samples by standard methods at the Nutrition and Biochemistry Laboratory of the School of Nutritional and Dietetics at TUMS.

Dietary intake assessment

A dietary exposure was evaluated through the use of a validated 147-item semi-quantitative food frequency questionnaire (FFQ) that has been previously validated according to reliability and validity [42]. In the presence of a dietitian, participants recorded their consumption frequency in grams and milliliters based on their usual diet. Utilizing the NUTRITIONIST 4 (First Data Bank, San Bruno, CA, USA) food analyzer, dietary intake was analyzed for energy intake, macronutrients, and micronutrients [43].

Plant-based dietary pattern

The plant-based dietary pattern was calculated using Satija et al. [13,14]. Three indices are included: the PDI, the h-PDI, and the uPDI. Food items were classified into 18 groups based on their similarities in nutrients, including 3 categories of animal food, healthy plant food, and unhealthy plant food. Healthy or unhealthy plant foods were categorized based on existing evidence on the associations of the foods with cardiometabolic abnormalities. Healthy plant foods included whole grains, fruits, vegetables, nuts, legumes, vegetable oil, vegetarian protein alternatives, and tea/coffee. Consumption of fruit juices, sugar-sweetened beverages, refined grains, sweets and desserts, and potatoes was included in the unhealthy plant foods group. Consumption of potatoes was considered in the unhealthy plant food group to be consistent with the methods in previous studies [13,14]. Obtaining animal food items includes animal fat, dairy products, eggs, fish, seafood, meats, and other animal-based foods. These food items were then converted to quintiles of consumption, and a score of 1 to 5 was applied to each item. According to PDI, participants in the highest and lowest quintiles of plant food consumption received a score of 5 and 1, respectively. Furthermore, those participants consuming the largest amounts of animal foods were assigned a score of 1, while those consuming the least amounts of animal foods were assigned a score of 5. The h-PDI was calculated based on participants' consumption of healthy plant foods. Participants with the highest consumption and those with the lowest consumption received a score of 5 and 1, respectively. We summed the scores to obtain a total score ranging from 18 to 90 for h-PDI.

Higher total scores for h-PDI indicated higher adherence to that dietary pattern, ranging from 18 to 90 for h-PDI.

Genotyping and GRS

We extracted the total DNA using the salting out method [44]. Subsequently, a 1% agarose gel was used to assess the DNA integrity, whereas a nanodrop 8000 Spectrophotometer (Thermo Scientific, Waltham, MA, USA) was used to assess DNA concentration. SNP genotyping was carried out using the TaqMan Open Array (Life Technologies Corporation, Carlsbad, CA, USA) [45].

The forward primer for CAV-1 (rs3807992) is 3'-AGTATTGACCTGATTGCCATG-5' and the reverse primer is 5'-GTCTTCTGAAAAAGCACATGA-3'. The fragments containing three genotypes were distinguished: GG, GA, and AA. The Cry1 (rs2287161) forward primer is 5'-GGAACAGTGATTGGCTCTATCT-3' and the reverse primer is 5'-GGTCTCGGTCTCAAGAAG-3'. Then, the fragments containing three genotypes were distinguished: CC, GC, and GG. The MC4R gene primer was selected based on a previous study [46]. The MC4R (rs17782313) forward primer is 5'-AAGTTCTACCTACCATGTTCTTGG-3' and the reverse primer is 5'-TTCCCCCTGAAGCTTTTCTTGTCATTTTGAT-3'. Then, fragments containing three genotypes were distinguished: CC, CT, and TT. We created the GRS by combining three single nucleotide polymorphisms (CAV-1 [rs3807992], Cry-1 [rs2287161], and MC4R [rs17782313]) that had previously been linked to obesity-related traits in GWAS and other studies [24,34,47-49]. The risk alleles for higher BMI were assigned to each SNP by recoding them into 0, 1, or 2. Using the risk alleles of the three SNPs, the unweighted GRS was calculated. Higher scores indicate a greater genetic susceptibility to higher BMI on the GRS scale, which ranges from 0 to 6 [50].

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normal distribution of data. Pearson's χ^2 test was used for the Hardy-Weinberg equilibrium. Descriptive analysis was used to assay general characteristics of participants by the mean \pm standard deviation (SD), minimum, and maximum. Analysis of variance and analysis of covariance were performed to compare the body composition, blood pressure and metabolic and inflammatory profiles between subjects. A generalized linear model (GLM) was used in crude and adjusted models to evaluate the interactions between GRS and h-PDI concerning metabolic risk factors of the cardiovascular system. Adjustments were made for age, physical activity, energy intake, and BMI. All statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). All reported p values were 2-sided, and a p value lower than 0.05 was considered statistically significant and for interaction p value lower than 0.1 was set as statistically significant.

RESULTS

Participant characteristics

The current study was carried out on 377 women classified as overweight or obese. The means and SD of age, weight, BMI, and WC of individuals were 36.72 ± 9.17 years, 80.62 ± 11.33 kg, 31.02 ± 3.85 kg/m², and 99.18 ± 9.59 cm, respectively.

Difference in means of cardiometabolic variables across h-PDI

The main characteristics of the study population in relation to the tertile categories of the healthy plant-based diet index are presented in **Table 1**. Before adjustment for age, BMI, total energy intake, and physical activity, marginal significant differences for the HOMA index ($p = 0.06$) were found in participants with higher scores of h-PDI. After adjustment for confounding factors, there was a borderline significant difference for WHR ($p = 0.07$), although no significant differences were found for BMI. In addition, individuals in the last tertile of h-PDI were more likely to be older in both crude ($p < 0.001$) and adjusted ($p = 0.002$) models. Lower h-PDI was also related to high hs-CRP in crude ($p = 0.005$) and after adjusting ($p = 0.03$) among the study participants.

Cardiometabolic variable mean differences across GRS

Individuals in the highest tertile of GRS were characterized as having higher BMI ($p = 0.01$), BFM ($p = 0.03$), and VFA ($p = 0.05$) in the adjusted model. Also, among GRS tertiles, a significant difference was observed in the percent of BF ($p = 0.02$). Apart from a marginal significant difference for hs-CRP ($p = 0.07$), there were no significant differences for the remaining cardiometabolic parameters (**Table 2**).

Table 1. Anthropometric body composition, blood parameters and blood pressure according to tertile categories of h-PDI

Variables*	h-PDI			p value	p value [†]
	T1 (< 51)	T2 (51–57)	T3 (> 57)		
Age (yr)	34.25 ± 9.06	36.58 ± 9.35	39.50 ± 8.37	< 0.001	0.002
Body weight (kg)	82.06 ± 11.54	79.70 ± 11.19	80.10 ± 11.21	0.20	0.23
BMI (kg/m ²)	31.22 ± 4.13	30.90 ± 3.82	30.93 ± 3.59	0.76	0.46 [‡]
Body composition					
WC (cm)	100.34 ± 9.90	98.94 ± 9.50	98.22 ± 9.30	0.20	0.24 [‡]
WHR (ratio)	0.94 ± 0.05	0.93 ± 0.05	0.92 ± 0.05	0.11	0.07
BFM (kg)	35.37 ± 8.50	33.83 ± 7.87	33.59 ± 7.57	0.16	0.17
BF (%)	42.59 ± 5.73	41.86 ± 5.21	41.68 ± 5.09	0.36	0.20
BMC (g)	2.66 ± 0.32	2.63 ± 0.34	2.65 ± 0.37	0.73	0.39
VFA (cm ²)	169.94 ± 40.10	164.58 ± 36.19	162.27 ± 36.28	0.25	0.22
Blood pressure					
SBP (mmHg)	110.83 ± 12.86	110.07 ± 12.99	112.96 ± 14.69	0.32	0.43
DBP (mmHg)	77.27 ± 9.18	77.47 ± 9.70	77.86 ± 9.91	0.91	0.62
Blood sample					
FBS (mg/dL)	88.09 ± 7.94	86.73 ± 9.98	87.18 ± 10.57	0.69	0.71
Total cholesterol (g/dL)	188.44 ± 35.70	178.95 ± 35.80	184.35 ± 35.44	0.26	0.19
TG (mg/dL)	121.47 ± 65.82	113.27 ± 57.18	127.89 ± 83.06	0.39	0.53
HDL (mg/dL)	46.68 ± 9.58	46.44 ± 9.54	46.84 ± 12.35	0.96	0.97
LDL (mg/dL)	94.93 ± 25.10	91.12 ± 23.11	96.47 ± 23.35	0.32	0.59
hs-CRP (mg/L)	5.80 ± 4.71	5.32 ± 4.67	3.96 ± 4.10	0.005	0.03
HOMA index	3.60 ± 1.24	3.34 ± 1.17	3.11 ± 1.36	0.06	0.13
Insulin (mIU/mL)	1.24 ± 0.25	1.18 ± 0.20	1.21 ± 0.22	0.29	0.74
AST (IU/L)	19.09 ± 9.07	17.04 ± 5.16	17.61 ± 7.80	0.23	0.65
ALT (IU/L)	21.41 ± 15.40	17.43 ± 9.53	19.01 ± 14.01	0.18	0.55
MCP-1 (ng/mL)	45.97 ± 62.33	59.22 ± 103.66	49.47 ± 103.99	0.68	0.18
Galectin 3 (ng/mL)	6.87 ± 9.50	3.28 ± 5.85	3.65 ± 7.60	0.24	0.51
PAI-1 (ng/mL)	16.41 ± 24.10	17.73 ± 28.63	14.62 ± 34.72	0.84	0.66

Values are presented as mean ± standard deviation. Bold-style p values indicate statistical significance.

h-PDI, healthful plant-based diet index; BMI, body mass index; WC, waist circumference; WHR, waist height ratio; BFM, body fat mass; BF, body fat; BMC, bone mineral content; VAF, visceral fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HOMA, Homeostasis Model Assessment; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor 1.

*Calculated by analysis of variance. [†]Adjusted for age, BMI, physical activity, and total energy intake. [‡]BMI considered as collinear and this variable adjusted for age, physical activity, and total energy intake.

Table 2. Anthropometric body composition, blood parameters and blood pressure according to tertile categories of GRS

Variables*	GRS			p value	p value [†]
	T1 (< 3) (n = 123)	T2 (= 3) (n = 89)	T3 (> 3) (n = 124)		
Age (yr)	36.68 ± 9.57	37.20 ± 9.00	36.42 ± 8.95	0.81	0.69
Body weight (kg)	79.80 ± 10.34	80.60 ± 11.71	81.44 ± 12.01	0.48	0.58 [‡]
BMI (kg/m ²)	30.27 ± 3.62	31.21 ± 3.85	31.63 ± 3.98	0.01	0.01[‡]
Body composition					
WC (cm)	98.02 ± 9.00	99.46 ± 9.61	100.15 ± 10.08	0.17	0.16
WHR (ratio)	0.93 ± 0.05	0.93 ± 0.04	0.93 ± 0.05	0.59	0.41
BFM (kg)	32.92 ± 7.21	34.85 ± 8.08	35.21 ± 8.58	0.04	0.03
BF (%)	41.14 ± 5.10	42.68 ± 5.03	42.51 ± 5.72	0.04	0.02
BMC (g)	2.68 ± 0.33	2.63 ± 0.36	2.62 ± 0.33	0.26	0.20
VFA (cm ²)	160.25 ± 36.11	167.07 ± 38.74	170.06 ± 37.90	0.08	0.05
Blood pressure					
SBP (mmHg)	110.76 ± 11.95	111.12 ± 15.20	112.02 ± 14.31	0.80	0.82
DBP (mmHg)	77.38 ± 9.66	77.64 ± 10.09	77.68 ± 9.24	0.97	0.70
Blood sample					
FBS (mg/dL)	87.05 ± 9.04	86.03 ± 7.44	88.38 ± 11.60	0.36	0.69
Total cholesterol (g/dL)	187.07 ± 34.38	184.49 ± 39.12	178.48 ± 34.55	0.27	0.17
TG (mg/dL)	122.10 ± 67.92	109.47 ± 51.66	127.20 ± 81.90	0.33	0.34
HDL (mg/dL)	47.04 ± 9.85	48.43 ± 12.41	44.93 ± 9.98	0.14	0.22
LDL (mg/dL)	95.93 ± 22.20	96.98 ± 25.40	89.87 ± 24.08	0.13	0.09
hs-CRP (mg/L)	4.59 ± 3.97	4.62 ± 4.14	5.81 ± 5.28	0.04	0.07
HOMA index	3.36 ± 1.16	3.11 ± 1.14	3.44 ± 1.48	0.32	0.43
AST (IU/L)	17.63 ± 6.50	18.19 ± 9.31	17.72 ± 6.85	0.89	0.80
ALT (IU/L)	18.56 ± 13.36	19.59 ± 14.88	19.32 ± 11.23	0.87	0.75
Insulin (mIU/mL)	1.19 ± 0.22	1.22 ± 0.22	1.22 ± 0.23	0.70	0.55
MCP-1 (ng/mL)	48.38 ± 90.65	50.73 ± 86.85	58.19 ± 104.53	0.79	0.70
Galectin 3 (ng/mL)	3.44 ± 6.91	5.53 ± 7.90	4.12 ± 7.61	0.64	0.61
PAI-1 (ng/mL)	17.10 ± 35.99	11.55 ± 18.08	18.71 ± 29.69	0.47	0.43

Values are presented as mean ± standard deviation. Bold-style p values indicate statistical significance.

GRS, genetic risk score; BMI, body mass index; WC, waist circumference; WHR, waist height ratio; BFM, body fat mass; BF, body fat; BMC, bone mineral content; VFA, visceral fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HOMA, Homeostasis Model Assessment; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor 1.

*Calculated by analysis of variance. [†]Adjusted for age, BMI, physical activity, and total energy intake. [‡]BMI considered as collinear and this variable adjusted for age, physical activity, and total energy intake.

Participants' dietary intake based on the h-PDI

Greater h-PDI was associated with higher amounts of whole grains, fruits, nuts, and vegetable oils, as well as lower amounts of total energy intake, sugar, and saturated fatty acid (SFA) (Table 3).

Interaction between h-PDI and GRS on cardiometabolic risk factors

Using the GLM, we found significant interactions between GRS and h-PDI on BMI in a multivariate-adjusted model controlling for the covariates; higher (β , -2.51; 95% confidence interval [CI], -4.76 to -0.27; $p = 0.02$) or moderate ($p = 0.054$) h-PDI adherence was more strongly related to lower levels of BMI among individuals with higher GRS (T2 and T3) than those with lower GRS (T1). Furthermore, the genetic association with elevated BMI was stronger among participants with lower h-PDI than those with higher h-PDI (Figure 1A). There was a similar pattern of GRS-h-PDI interaction on BFM and WC; higher h-PDI was associated with lower BFM (β , -4.88; 95% CI, -9.59 to -0.17; $p = 0.04$) and WC (β , -5.54; 95% CI, -11.23 to 0.14; $p = 0.056$) among people with higher GRS, as compared with those with lower GRS. In participants with low plant-based diet intake, the genetic influence on BFM and WC was greater (Figure 1B and C). Among individuals with high GRS, moderate adherence to h-PDI (i.e., those in the T2 of h-PDI) significantly decreased WC levels (Table 4).

Table 3. Nutrient intake according to tertile categories of h-PDI

Variables*	h-PDI		
	T1 (< 51)	T2 (51–57)	T3 (> 57)
h-PDI	46.53 ± 3.96	54.52 ± 1.49	61.96 ± 3.67
Food group			
Whole grains (g/d)	96.25 ± 88.33	102.21 ± 96.54	133.99 ± 112.00
Fruits (g/d)	439.63 ± 305.16	479.97 ± 315.94	518.59 ± 351.96
Vegetables (g/d)	394.70 ± 276.14	365.96 ± 206.07	495.08 ± 279.51
Nuts (g/d)	14.15 ± 15.41	15.92 ± 22.65	16.05 ± 18.36
Legumes (g/d)	38.25 ± 25.57	44.46 ± 40.18	62.00 ± 48.59
Vegetable oils	12.51 ± 10.19	16.49 ± 14.72	18.69 ± 17.85
Tea and coffee (mL/d)	741.20 ± 675.91	614.46 ± 442.54	891.49 ± 1021.07
Fruit juices (mL/d)	24.96 ± 50.48	38.79 ± 175.30	8.06 ± 16.88
Sugar sweetened beverages (mL/d)	75.41 ± 99.82	39.09 ± 65.48	12.34 ± 18.15
Refined grains (g/d)	420.39 ± 204.50	321.83 ± 172.65	264.85 ± 142.56
Potatoes	26.86 ± 22.15	24.35 ± 26.14	19.68 ± 21.37
Sweets and desserts (g/d)	51.54 ± 32.18	39.29 ± 43.99	32.84 ± 36.79
Animal fat (g/d)	15.45 ± 16.72	14.27 ± 20.52	9.04 ± 18.34
Dairy (mL/d)	467.79 ± 284.37	330.58 ± 206.32	344.74 ± 227.46
Eggs (g/d)	28.73 ± 21.53	23.99 ± 14.73	20.48 ± 16.72
Fish and sea food (g/d)	14.85 ± 15.03	9.43 ± 10.03	8.43 ± 9.55
Meat (g/d)	84.72 ± 63.77	60.04 ± 44.48	53.15 ± 39.47
Miscellaneous animal-based food (g/d)	26.17 ± 26.87	13.92 ± 19.71	10.32 ± 13.61
Nutrient intake			
Energy (kcal/d)	2,902.16 ± 805.82	2,506.99 ± 818.91	2,468.18 ± 726.51
Protein (g/d)	103.88 ± 34.02	84.40 ± 27.90	85.73 ± 29.07
Carbohydrate (g/d)	405.08 ± 116.63	355.04 ± 134.86	355.47 ± 113.40
Total fat (g/d)	104.05 ± 35.66	91.63 ± 33.76	88.10 ± 32.65
PUFA (g/d)	20.32 ± 8.33	20.02 ± 9.90	19.41 ± 9.17
SFA (mg/d)	32.96 ± 12.47	27.34 ± 11.05	24.52 ± 9.39
Sodium (mg/d)	4,946.65 ± 1,962.36	4,231.40 ± 1,522.02	4,213.44 ± 1,467.14
Potassium (mg/d)	4,749.53 ± 1,755.38	4,162.93 ± 1,561.31	4,685.78 ± 1,837.96
Calcium (mg/d)	1,463.66 ± 572.72	1,145.56 ± 451.13	1,215.40 ± 542.17
Vitamin C (μmol/L)	185.37 ± 97.15	180.40 ± 103.80	200.75 ± 143.33
Total fiber (g/d)	50.10 ± 24.53	44.20 ± 19.75	48.50 ± 19.50

Values are presented as mean ± standard deviation.

h-PDI, healthy plant-based diet index; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

*Calculated by analysis of variance.

We then conducted analyses to examine whether there was significant evidence of GRS × h-PDI interactions on cardiometabolic markers. There is a significant gene-diet interaction for healthful plant-derived diets and GRS on hs-CRP (β , -3.42; 95% CI, -6.52 to -0.33; $p = 0.03$; **Figure 2A**), aspartate aminotransferase (AST) (β , -5.89; 95% CI, -11.54 to -0.23; $p = 0.04$; **Figure 2C**), alanine transaminase (ALT) (β , -10.14; 95% CI, -20.37 to 0.08; $p = 0.05$; **Figure 2B**), insulin (β , -0.18; 95% CI, -0.36 to -0.009; $p = 0.04$; **Figure 2D**), and PAI-1 (β , -41.73; 95% CI, -67.75 to -15.72; $p = 0.002$; **Figure 2E**) in the adjusted model (adjusting for age, energy intake, physical activity, and BMI). In particular, participants placed in the second tertile of the GRS were characterized by lower hs-CRP when they had the highest ($p = 0.03$) and moderate ($p = 0.01$) following h-PDI compared to the first tertile. Women in T2 of the h-PDI and the top tertile of GRS had significantly lower AST and insulin concentrations than those in T1 of the same pattern and genetic score, whereas individuals in the last tertile of h-PDI and GRS had lower significant levels of ALT, insulin, and PAI-1. For all the aforementioned markers, greater h-PDI adherence was observed among people with moderate or high GRS compared with those with lower GRS. Decreasing trends were observed (**Figure 2**). No significant interactions were found between GRS and healthy-PDI for other metabolic-related traits ($p > 0.05$; **Table 4**).

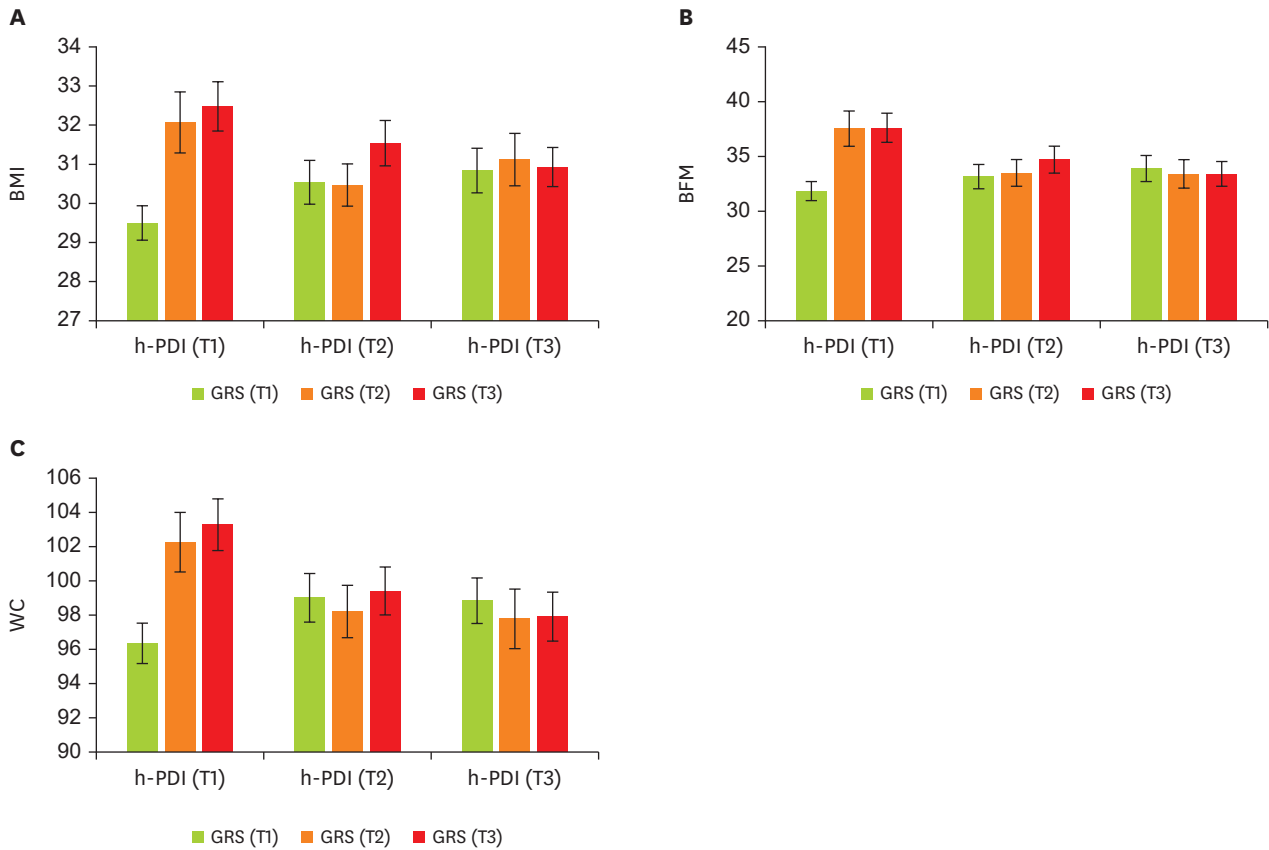


Figure 1. The interaction between tertiles of h-PDI and GRS. (A) BMI, (B) BFM, and (C) WC. Data shown are mean \pm standard error of the mean, T1 (< 51): n = 139, T2 (51–57): n = 97, and T3 (> 57): n = 141. h-PDI, healthy plant-based diet index; GRS, genetic risk score; BMI, body mass index; BFM, body fat mass; WC, waist circumference.

DISCUSSION

This cross-sectional study aimed to investigate the interaction between the healthful-PDI and BMI-GRS based on MC4R (rs17782313), CAV1 (rs38 07992), and Cry1 (rs2287161) on cardiometabolic traits in overweight and obese women. We indicated that plant-based dietary patterns evaluated by h-PDI regarding genetic susceptibility were predictive of cardiometabolic abnormalities in our population. Our findings highlight the importance that individuals at higher or moderate risk genetically may be more responsive to the benefits of plant-based dietary patterns to modify cardiometabolic risk factors.

Our findings showed a negative interaction between greater GRS with both high and moderate h-PDI on BMI and WC compared with lower GRS. Other novel significant inverse interactions were found between higher h-PDI adherence and GRS when placed in the second and last tertiles, compared with lower GRS on BFM. Our results were in line with previous studies regarding genetic effects on obesity and weight gain [36,51,52] and demonstrated that following healthy plant-based dietary patterns attenuated genetic risks of BMI [10], WC, and BFM. Similarly, the interactions between the Mediterranean diet and obesity-GRS on BMI and WC showed tendencies to decrease [53]. In comparison to other diet indices (such as Dietary Approaches to Stop Hypertension [DASH], Alternate Healthy Eating Index, and Mediterranean diet scores), h-PDI is based on several food items, including healthy

Table 4. The interaction between GRS and h-PDI on anthropometric body composition, blood parameters, and blood pressure

Variable	GRS		h-PDI										
	T1			T2 (51-57)			T3 (>57)						
	β	95% CI	p	β	95% CI	p	β	95% CI	p				
BMI (kg/m ²)	T1	Reference											
	T2	-2.64	-4.97 to -0.31	0.02	-2.41	-4.76 to -0.05	0.04	-2.29	-4.72 to 0.12	0.06	-1.94	-4.44 to 0.55	0.12
	T3	-1.99	-4.12 to 0.14	0.06	-2.15	-4.36 to 0.04	0.054	-2.93	-5.10 to -0.76	0.008	-2.51	-4.76 to -0.27	0.02
Body composition	T1	Reference											
	T2	-6.70	-12.52 to -0.89	0.02	-5.09	-11.07 to 0.87	0.09†	-6.96	-13.00 to -0.93	0.02	-4.33	-10.66 to 2.00	0.18†
	T3	-6.53	-11.86 to -1.19	0.01	-5.70	-11.29 to -0.12	0.04†	-7.86	-13.27 to -2.45	0.004	-5.54	-11.23 to 0.14	0.056†
WHR (ratio)	T1	Reference											
	T2	-0.02	-0.05 to 0.008	0.14	-0.01	-0.04 to 0.01	0.40	-0.02	-0.05 to 0.01	0.16	-0.006	-0.04 to 0.02	0.74
	T3	-0.03	-0.06 to -0.003	0.03	-0.02	-0.05 to 0.008	0.14	-0.03	-0.06 to -0.002	0.03	-0.01	-0.04 to 0.01	0.26
BFM (kg)	T1	Reference											
	T2	-5.35	-10.20 to -0.51	0.03	-4.02	-8.96 to 0.91	0.11	-6.19	-11.22 to -1.16	0.01	-5.09	-10.33 to 0.14	0.05
	T3	-4.22	-8.66 to 0.22	0.06	-3.71	-8.33 to 0.90	0.11	-6.27	-10.78 to -1.76	0.006	-4.88	-9.59 to -0.17	0.04
BF (%)	T1	Reference											
	T2	-1.97	-5.25 to 1.29	0.23	-1.02	-4.40 to 2.36	0.55	-2.31	-5.72 to 1.08	0.18	-2.10	-5.69 to 1.49	0.25
	T3	-0.50	-3.51 to 2.50	0.74	0.22	-2.94 to 3.39	0.89	-1.96	-5.01 to 1.08	0.20	-1.15	-4.37 to 2.07	0.48
BMC (g)	T1	Reference											
	T2	-0.09	-0.30 to 0.11	0.38	-0.07	-0.29 to 0.14	0.51	-0.18	-0.40 to 0.03	0.10	-0.08	-0.32 to 0.14	0.47
	T3	-0.14	-0.33 to 0.05	0.15	-0.13	-0.34 to 0.07	0.19	-0.12	-0.32 to 0.07	0.20	-0.05	-0.26 to 0.15	0.59
VFA (cm ²)	T1	Reference											
	T2	-13.18	-36.11 to 9.74	0.26	-5.51	-28.94 to 17.91	0.64	-16.05	-39.86 to 7.75	0.18	-9.54	-34.39 to 15.30	0.45
	T3	-17.06	-38.10 to 3.98	0.11	-11.86	-33.79 to 10.05	0.28	-25.40	-46.74 to -4.05	0.02	-17.09	-39.42 to 5.23	0.13
Blood pressure	T1	Reference											
	T2	2.56	-7.46 to 12.59	0.61	3.03	-7.09 to 13.16	0.55	9.02	-1.19 to 19.24	0.08	9.44	-1.22 to 20.11	0.08
	T3	-2.70	-11.92 to 6.51	0.56	-3.03	-12.52 to 6.45	0.53	0.77	-8.62 to 10.16	0.87	2.58	-7.10 to 12.26	0.60
DBP (mmHg)	T1	Reference											
	T2	-4.28	-11.35 to 2.77	0.23	-3.82	-10.86 to 3.21	0.28	4.98	-2.21 to 12.18	0.17	6.10	-1.31 to 13.51	0.10
	T3	-5.28	-11.77 to 1.21	0.11	-3.03	-9.63 to 3.56	0.36	1.29	-5.32 to 7.91	0.70	2.21	-4.51 to 8.94	0.52
Blood sample	T1	Reference											
	T2	-1.24	-9.14 to 6.66	0.75	-1.04	-8.77 to 6.68	0.79	-4.24	-12.17 to 3.68	0.29	-4.49	-12.42 to 3.43	0.26
	T3	2.29	-4.93 to 9.52	0.53	0.85	-6.26 to 7.96	0.81	-1.65	-8.89 to 5.59	0.65	-1.93	-9.14 to 5.27	0.60
Total cholesterol (g/dL)	T1	Reference											
	T2	-16.99	-45.84 to 11.85	0.24	-16.31	-45.19 to 12.57	0.26	0.81	-28.11 to 29.73	0.95	-1.51	-31.13 to 28.10	0.92
	T3	9.62	-16.73 to 35.99	0.47	13.48	-13.09 to 40.06	0.32	20.67	-5.77 to 47.11	0.12	20.83	-6.10 to 47.76	0.13
TG (mg/dL)	T1	Reference											
	T2	-1.64	-58.66 to 55.36	0.95	2.65	-57.01 to 62.31	0.93	-7.89	-65.05 to 49.25	0.78	-9.14	-70.32 to 52.03	0.77
	T3	-2.90	-55.00 to 49.19	0.91	8.96	-45.93 to 63.86	0.74	12.88	-39.37 to 65.13	0.62	10.75	-44.88 to 66.39	0.70
HDL (mg/dL)	T1	Reference											
	T2	1.02	-7.59 to 9.63	0.81	1.83	-7.00 to 10.67	0.68	6.77	-1.86 to 15.41	0.12	6.60	-2.45 to 15.67	0.15
	T3	-0.51	-8.39 to 7.35	0.89	-0.93	-9.06 to 7.19	0.82	-1.21	-9.11 to 6.67	0.76	0.14	-8.09 to 8.39	0.97

(continued to the next page)

Table 4. (Continued) The interaction between GRS and h-PDI on anthropometric body composition, blood parameters, and blood pressure

Variable	GRS			h-PDI			T3 (>57)						
	T1			T2 (51-57)			Crude						
	β	95% CI	p	β	95% CI	p	β	95% CI	p				
LDL (mg/dL)	T1	Reference					6.59	-12.73 to 25.91	0.50	4.93	-14.87 to 24.74	0.62	
	T2	6.20	-13.06 to 25.48	0.52	6.23	-13.08 to 25.55	0.52	6.59	-12.73 to 25.91	0.50	4.93	-14.87 to 24.74	0.62
	T3	11.39	-6.22 to 29.00	0.20	11.53	-6.23 to 29.31	0.20	11.04	-6.62 to 28.71	0.22	11.86	-6.15 to 29.87	0.19
hs-CRP (mg/L)	T1	Reference											
	T2	-3.08	-5.83 to -0.34	0.02	-3.49	-6.41 to -0.57	0.01	-2.89	-5.74 to -0.04	0.04	-3.42	-6.52 to -0.33	0.03
	T3	-1.98	-4.49 to 0.53	0.12	-2.16	-4.89 to 0.55	0.11	-0.90	-3.45 to 1.65	0.49	-0.34	-3.12 to 2.43	0.80
HOMA index	T1	Reference											
	T2	-0.72	-1.75 to 0.30	0.17	-0.64	-1.72 to 0.44	0.25	0.10	-0.93 to 1.13	0.84	0.50	-0.61 to 1.62	0.37
	T3	-0.37	-1.31 to 0.57	0.44	-0.36	-1.37 to 0.65	0.48	0.12	-0.82 to 1.06	0.79	0.23	-0.77 to 1.25	0.64
AST (IU/L)	T1	Reference											
	T2	-2.89	-8.88 to 3.08	0.34	-3.80	-9.94 to 2.34	0.22	0.71	-5.28 to 6.70	0.81	-1.11	-7.41 to 5.19	0.73
	T3	-4.96	-10.42 to 0.50	0.07	-5.89	-11.54 to -0.23	0.04	-3.49	-8.98 to 1.98	0.21	-4.95	-10.68 to 0.78	0.09
ALT (IU/L)	T1	Reference											
	T2	-4.73	-15.31 to 5.84	0.38	-5.94	-16.91 to 5.02	0.28	-0.79	-11.40 to 9.81	0.88	-2.83	-14.08 to 8.41	0.62
	T3	-7.18	-16.95 to 2.48	0.14	-9.64	-19.74 to 0.44	0.06	-7.75	-17.44 to 1.94	0.11	-10.14	-20.37 to 0.08	0.05
Insulin (mIU/mL)	T1	Reference											
	T2	-0.07	-0.26 to 0.10	0.40	-0.08	-0.27 to 0.10	0.37	-0.02	-0.21 to 0.15	0.76	-0.06	-0.26 to 0.13	0.51
	T3	-0.15	-0.32 to 0.01	0.07	-0.19	-0.37 to -0.02	0.02	-0.15	-0.32 to 0.01	0.08	-0.18	-0.36 to -0.009	0.04
MCP-1 (ng/mL)	T1	Reference											
	T2	6.81	-75.26 to 88.88	0.87	-2.48	-80.36 to 75.38	0.95	-44.58	-128.06 to 38.88	0.29	-44.57	-125.25 to 36.09	0.27
	T3	-31.52	-104.54 to 41.49	0.39	-33.74	-104.13 to 36.64	0.34	-24.23	-98.52 to 50.06	0.52	-27.96	-98.95 to 43.02	0.44
Galectin 3 (ng/mL)	T1	Reference											
	T2	-5.15	-15.51 to 5.20	0.32	-7.64	-18.69 to 3.39	0.17	-7.42	-19.00 to 4.16	0.20	-9.16	-21.22 to 2.90	0.13
	T3	-6.11	-15.63 to 3.41	0.20	-8.36	-18.78 to 2.05	0.11	-1.10	-11.06 to 8.85	0.82	-2.72	-13.21 to 7.76	0.61
PAI-1 (ng/mL)	T1	Reference											
	T2	-2.07	-30.13 to 25.99	0.88	-9.88	-37.08 to 17.31	0.47	-21.42	-49.43 to 6.58	0.13	-28.27	-55.25 to -1.30	0.04
	T3	-13.49	-40.73 to 13.73	0.33	-14.58	-41.05 to 11.88	0.28	-32.78	-59.58 to -5.98	0.01	-41.73	-67.75 to -15.72	0.002

Bold-style p values indicate statistical significance, $p < 0.05$ was considered significant.

GRS, genetic risk score; h-PDI, healthy plant-based diet index; T, tertile; CI, confidence interval; BMI, body mass index; WC, waist circumference; WHR, waist height ratio; BFM, body fat mass; BF, body fat; BMC, bone mineral content; VFA, visceral fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HOMA, Homeostasis Model Assessment; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor 1.

*GLM was performed to identify the interaction between GRS and h-PDI on cardiometabolic risk factors: Model 1= Adjusted for potential confounding factors including (age, energy intake, physical activity, BMI). †BMI considered as collinear and this variable adjusted for age, physical activity, and total energy intake.

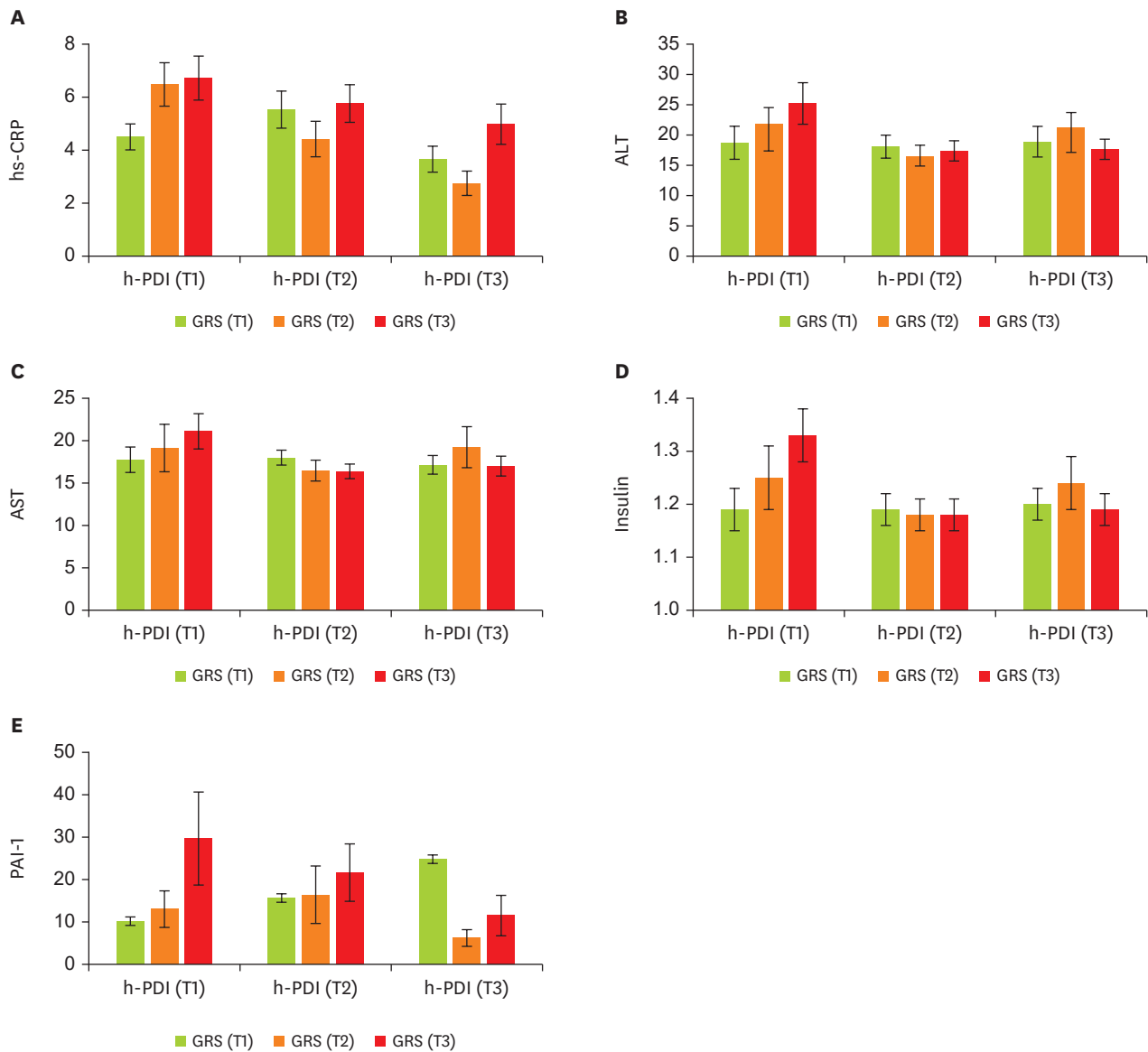


Figure 2. The interaction between tertiles of h-PDI and GRS. (A) hs-CRP, (B) ALT, (C) AST, (D) insulin, (E) PAI-1. Data shown are mean \pm standard error of the mean. h-PDI, healthy plant-based diet index; GRS, genetic risk score; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine transaminase; AST, aspartate aminotransferase; PAI-1, plasminogen activator inhibitor 1.

and less healthy plant-derived foods, to capture synergistic and graded intakes of different food items. Moreover, some components in the h-PDI, such as sugar-sweetened beverages, coffee, and saturated fat, are thought to be involved in genetic predisposition to obesity [54-59]. Therefore, the observed strong GRS-h-PDI interactions on the reduced trend of BMI and other body composition parameters, including WC and BFM, might be related to lower intakes of less healthy plant-based foods and animal foods, low energy density [60], and promoting the gut microbiota balance due to greater dietary fiber intake [61]. Furthermore, plant bioactives via regulating non-shivering thermogenesis and energy expenditure may be involved [62,63].

An earlier observational study found a significant GRS-h-PDI interaction on lipid markers [54]. Accordingly, healthier plant-based diets have been shown to be beneficial for

controlling HDL cholesterol and lowering serum TC levels [24,52,64,65], whereas the results for TGs remain controversial [64]. No significant interaction was observed in terms of lipid markers in our study, though. Concerning AST and ALT, we found that women with elevated scores of GRS with high and moderate healthy plant-based diet adherence had lower levels of AST and ALT. While, Abaj et al. have claimed that A-allele carriers of the CAV-1 polymorphism (rs3807992) who follow an unhealthy dietary pattern have a statistically significant lower AST, probably because the particular region of a candidate gene for caffeine intake is near to the CAV-1 gene [24,66]. In this vein, we have suggested a possible interaction between greater GRS and high caffeine intake in our dietary pattern with lower levels of AST. On the other hand, we also found negative significant GRS-h-PDI interactions on hs-CRP and insulin concentrations. In support of our findings, a meta-analysis underscored the effect of plant-based diets on decreasing concentrations of inflammatory biomarkers, including hs-CRP, regardless of genetic predisposition. A similar association was observed between CAV-1 variants at rs3807992 and healthy dietary intake in terms of hs-CRP concentrations [24]. Some possible biological mechanisms have been proposed that following plant-based dietary patterns potentially elicits favorable effects and improves profiles of inflammatory biomarkers (CRP and IL-6) [67-69] through energy restriction, lowering glycemic load, and reduced oxidative stress due to lower saturated fatty acids and higher polyunsaturated fatty acids [70,71]. Concordant with our results, it has been reported that people with higher dietary total antioxidant capacity have appreciably lower circulating insulin concentrations [72]. As a matter of fact, certain components of plant-based diets, such as vegetables and fruits, with the antioxidant functions of phytochemicals, increase the sensitivity of insulin [73] and might contribute to the observed strong GRS-h-PDI interactions on low insulin levels. Similar to our findings, plant-derived foods with a low glycemic index may play a potential role in reducing PAI-1 and platelet aggregation [74]. Another study showed no significant association between CAV-1 polymorphism and PAI-1 [24]. Overall, in the literature, no substantially significant interactions between GRS and h-PDI were identified for the rest of the variables.

Interestingly, it has been reported that people at higher genetic risk of obesity may obtain more benefit from lowering cardiometabolic risk factors through elevated intake of healthy plant foods, irrespective of the presence of baseline obesity [52,75]. Relatedly, based on the results of the PREDIMED trial, following a plant-food-rich dietary pattern significantly decreased the risk of CVD mortality [76]. Moreover, vegetarian diets were also associated with lower CVD mortality in the Adventist Health Study [77].

As such, these findings are believed to underlie prevention of CVD risks since early life and provide important evidence to support that greater adherence to plant-based diets among participants with higher GRS, compared with those with lower GRS, may have beneficial effects. As strength, it is important to note that we assessed individual food items to evaluate the h-PDI adherence based on different food groups. Also, our study only included overweight and obese otherwise healthy women. Thus, no known medications or illness with the possibility to affect inflammatory process and cardiometabolic diseases such as hormone therapy existed. Nonetheless, several limitations should be considered in the interpretation of this study. Due to cross-sectional design of the study, it was impossible to draw conclusive associations between GRS and h-PDI interactions with cardiometabolic risk factors. Moreover, GRS based on BMI linked genetic markers employed in this study is probably unable to estimate the true genetic impact on cardiometabolic risk factors since a

limited number of SNPs were included. Furthermore, the use of self-reported FFQ for dietary assessment is prone to measurement error. Finally, the current study with small sample size was only done among women, therefore, findings are not generalizable to men.

CONCLUSION

The involvement of h-PDI appears to be a protective factor against cardiometabolic risk factors in overweight and obese women with increased GRS. However, as a result of the limited literature conducted in this regard, large prospective studies in different populations are required to confirm these findings.

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