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The Combined Effect of Polygenic Risk from *FTO* and *ADRB2* Gene Variants, Odds of Obesity, and Post-Hipcref Diet Differences

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Keywords

Obesity · Polygenic risk scores · Hipcref diet intervention · Post-intervention differences · Malaysian adults

Abstract

Background: Computing polygenic risk scores (PRS) to predict the degree of risk for obesity may contribute to weight management programs strategically. ***Objectives:*** To investigate the combined effect of *FTO* rs9930501, rs9930506, and rs9932754 and *ADRB2* rs1042713 and rs1042714 using PRS on (1) the odds of obesity and (2) post-intervention differences in dietary, anthropometric, and cardiometabolic parameters in response to high-protein calorie-restricted, high-vitamin E, high-fiber (Hipcref) diet intervention in Malaysian adults. ***Methods:*** Both a cross-sectional study (n = 178) and a randomized controlled trial (RCT) (n = 128) were conducted to test the aforementioned objectives. PRS was computed as the weighted sum of the risk alleles possessed by each individual participant. Participants were stratified into first (PRS 0–0.64), second (PRS 0.65–3.59), and third (PRS 3.60–8.18) tertiles. ***Results:*** The third tertile of PRS was associated with significantly higher odds of obesity: 2.29 (95% CI = 1.11–4.72, adjusted p = 0.025) compared to the first tertile. Indians (3.9 ± 0.3) had significantly higher PRS compared to Chinese (2.1 ± 0.4) (p = 0.010). In the RCT, a greater reduction in high-sensitivity C-reactive protein (hsCRP) levels was found in second and third tertiles after Hipcref diet intervention compared to the control diet (p interaction = 0.048). ***Conclusion:*** Higher PRS was significantly associated with increased odds of obesity. Individuals with higher PRS had a significantly greater reduction in hsCRP levels after Hipcref diet compared to the control diet.

Introduction

Genome-wide association studies have identified a large number of genes and gene variants that are associated with the development of obesity in many populations worldwide [1]. Genes involved in energy homeostasis, adaptive thermogenesis, lipoprotein metabolism, appetite control, and insulin signaling are some of the main candidate genes that have been studied in various populations. Further, it is now an accepted fact that obesity is a polygenic disorder (rarely monogenic), with many candidate gene variants contributing to the risk of increased

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body weight and comorbidities [2]. As individual genetic variants generally confer only a moderate risk to a trait, analyzing multiple risk alleles simultaneously can be more informative and can enhance predictive power, particularly in polygenic conditions. A significant genotype effect between the number of risk alleles and the risk of abdominal obesity was identified in the LIPGENE-SU.VI.MAX study, with approximately a 2.5-fold increased risk in individuals carrying two or more risk alleles compared to individuals carrying one or no risk allele [3]. For most individuals genetic predisposition to metabolic disease has a polygenic basis [4].

Family and twin studies indicate that up to 50–90% of the variance in body mass index (BMI) is attributable to genetic factors [5]. Genetic factors also contribute to approximately 50% of the risk for type 2 diabetes mellitus (T2DM). Heritability rates of 10–30% for the metabolic syndrome (MetS) have been estimated [6, 7], indicating that these conditions are partly heritable. Nutrition and physical activity are key lifestyle factors that interact with genes and gene variants and promote the progression and pathogenesis of diet-related diseases. Excessive calorie intake and sedentary lifestyle promote the obese phenotype.

Emerging evidence from gene-diet interactions from observational studies and from randomized controlled trials (RCTs) has supported the fact that the epidemic of obesity and its comorbidities are the consequences of the interaction between multiple gene variants and lifestyle factors [8]. A recent review reported that the fat mass and obesity-related (*FTO*) and beta-2 adrenergic receptor (*ADRB2*) genes were the most investigated genes for gene-lifestyle interaction studies in intervention programs [9]. Grau et al. [10] reported that individuals carrying the TT genotype of *FTO* rs9939609 had greater reduction in homeostatic model assessment of insulin resistance and homeostatic model assessment beta after 10 weeks of low-fat diet compared to a high-fat diet in a European population. However, Matsuo et al. [11] found no significant association between *FTO* rs9939609 and weight loss outcomes after 14 weeks of calorie-restricted dietary intervention in obese Japanese women. With respect to *ADRB2* gene, Ruiz et al. [12] reported that both genotypes of *ADRB2* rs1042713 (G>A) showed a similar reduction in body weight, but that obese Spanish women carrying the risk allele (G) of *ADRB2* rs1042714 showed greater reduction in body weight compared to noncarriers (CC) after 3 months of energy-restricted diet. Low-fat dietary intervention was associated with more weight loss among overweight and obese individuals with the *IRS1* rs2943641 CC genotype compared to noncarriers (CT and TT genotypes) [13]. Overweight and obese individuals carrying the T allele of *PPM1K* rs1440581 lost more weight with a low-carbohydrate diet compared to noncarriers (C allele) [14]. The above is evidence for the fact that individuals with different genetic background may respond differently to the same intervention program [15]. Greater understanding of potential nutrient-gene interaction can aid in manipulating diet in a way that minimizes the metabolic consequences of obesity, attenuates insulin resistance, and reduces the risk of cardiometabolic diseases [16]. Early identification of at-risk individuals is of paramount importance. Considering the long asymptomatic period preceding the manifestation of T2DM and cardiovascular disease, early diagnosis of at-risk individuals could enable targeted interventions earlier in life, thus reducing morbidity and mortality [17].

Interindividual differences in phenotypes in response to dietary interventions highlight the role of nutrigenetics in the identification of nutrient-sensitive genotypes [18]. Early identification of the candidate gene variants that have the potential to influence dietary nutrients metabolically and/or at the molecular level may allow for the provision of good-quality personalized recommendations of nutrient intake to achieve effective weight loss [19].

Recent evidence suggests that the use of polygenic risk scores (PRS), including multiple gene variants that predispose an individual to obesity, may predict the degree of risk for obesity and strategically contribute to weight management programs [20]. The PRS summarizes the effect of multiple gene variants into a single score to measure the genetic susceptibility to a disease [21, 22]. It is calculated by summing all the risk alleles of the selected gene variants, each allele being weighted by the corresponding effect size [23, 24]. Single nucleotide polymorphism (SNP) analyses are often underpowered due to the small effect size of individual SNPs. Moreover, overadjustment for multiple comparisons when testing multiple independent SNPs for associations between variables may increase the likelihood of type II errors (the chance that the effective treatment is not discovered) [25]. Previous studies have reported that the inclusion of a large number of SNPs into PRS models had a larger effect size and hence greater predictive power of risk [26].

The aim of this study was to investigate the combined effect of *FTO* rs9930501, rs9930506, and rs9932754 and *ADRB2* rs1042713 and rs1042714 by PRS on (1) the odds of obesity and (2) the post-intervention differences in dietary, anthropometric, and cardiometabolic parameters in response to a 6-month high-protein calorie-restricted, high-vitamin E, high-fiber (Hipcref) diet. The details of

the dietary intervention are described in Study Design. To the best of our knowledge, this is the first study that computed PRS to investigate the effect of multiple gene variants on weight loss outcomes in the Malaysian population.

Materials and Methods

Study Design

Two different studies were conducted to test the aforementioned objective: (1) a cross-sectional study (n = 178) to assess the effect of PRS on the odds of obesity, and (2) a 6-month RCT (n = 128) to assess the effect of PRS on the post-intervention differences in dietary, anthropometric, and cardiometabolic parameters in response to a 6-month dietary intervention in overweight and obese Malaysian adults [27]. Both studies were nested in the parent study which aimed to investigate the gene-diet interaction on obesity-related phenotypes [27–29].

Participant Selection

Cross-Sectional Study. A cross-sectional study was conducted to assess the combined effect of *FTO* (rs9930501, rs9930506, and rs9932754) and *ADRB2* (rs1042713 and rs1042714) gene variants on the odds of obesity using PRS. A total of 178 Malaysian adults (Malaysian Chinese, Malays, and Indians) aged ≥18 years were recruited at random through advertisements and flyers distributed at the University of Nottingham Malaysia campus, supermarkets, and schools in the vicinity of the University of Nottingham Malaysia. A structured questionnaire was used to record information on race and ethnicity, and the questions were directed to trace back three generations to confirm ancestry. Participants completed a health and lifestyle questionnaire which included questions on past diseases, family history of past diseases, physical activity level, and substance abuse. Smoking status and alcohol consumption were reported as (1) never, (2) former, and (3) current. Individuals diagnosed with cardiovascular diseases, stroke, diabetes, renal disorders, or endocrine disorders such as hypothyroidism were excluded from the study. Exclusion criteria also included pregnant woman as well as those on cholesterol-lowering, hypoglycemic, or psychiatric medication. Interested individuals attended an initial screening to determine whether or not the participants met the specified inclusion and exclusion criteria. In total 79 obese and 99 nonobese Malaysian adults were recruited. Anthropometric parameters, physical activity levels, substance abuse, blood biochemical parameters, and genotyping for the variants of *FTO* and *ADRB2* genes were assessed in the study participants. Detailed information on the methodology undertaken for the above has been described in our earlier publications [28, 29].

RCT – Dietary Intervention. Detailed information on the study design and methodology of the Hipcref dietary intervention in overweight and obese Malaysian adults has been previously described in an earlier publication [27]. Briefly, a 6-month parallel-arm RCT (Hipcref dietary intervention) was conducted to assess the effect of the Hipcref diet on dietary, anthropometric, and cardiometabolic parameters in the study participants compared to a control diet. Participants from the Hipcref diet group received formulated diet charts with an energy deficit of 300–500 kcal/day, 30% energy from protein, 30% energy from fat, 40% energy from carbohydrate, vitamin E ≥15 mg/day, and fiber ≥25 g/day. The control diet group received generalized dietary advice on weight loss based on the Malaysian Dietary Guidelines 2010 (<1,500 kcal/day with a macronutrient composition of approximately 10–15% energy from protein, 20–30% energy from fat, and 55–70% energy from carbohydrate) [30]. The justification for this dietary strategy is based on the results that were generated from the cross-sectional study [28]. The results revealed that individuals carrying the risk allele of *FTO* rs9930506 had significantly lower high-sensitivity C-reactive protein (hsCRP) levels with high intake of protein and vitamin E compared to low intake of protein and vitamin E [28]. Dietary fiber has been reported to have a favorable effect on metabolic profile post-intervention [31]. Therefore, a Hipcref diet was formulated for all participants in the intervention arm of the study [27]. A total of 128 eligible, apparently healthy overweight and obese Malaysian adults (Malaysian Chinese, Malays, and Indians) aged ≥18 years with a BMI ≥23 were recruited to participate in the Hipcref dietary intervention study. The six waves of recruitment (cohorts) had staggered start dates between June 2015 and June 2018. Participants were randomly assigned to one of the two treatments: intervention diet (Hipcref diet, n = 65) or control diet (control diet, n = 63) using a covariate adaptive randomization technique. Eligible participants were stratified by two covariates: (1) sex (female and male) and (2) ethnicity (Malaysian Chinese, Malays, and Indians), hence a total of 6 (2 × 3) strata were constructed. All participants were blinded to the allocation of the dietary arm of the study. Of the initial 128 participants, 7 dropped out from the Hipcref diet group and 18 dropped out from the control diet group due to job relocation (n = 9), retirement (n = 5), accident (n = 2), volunteer withdrawal of consent (n = 5), and loss to follow-up (n = 4). Therefore, the study was completed with 103 participants: Hipcref diet group = 58 participants (47, females, 11 males); control diet group = 45 participants (41 females, 4 males).

Assessment on Dietary Intake, Physical Activity, Substance Abuse, Dietary Adherence, Anthropometric Parameters, Cardiometabolic Parameters, and Genotyping

At baseline and month 6 of the dietary intervention period, the following parameters were assessed, measured, and analyzed: dietary, anthropometric, physical activity levels, substance abuse, biochemical variables in blood, dietary adherence score, and genotyping for the variants of *FTO* and *ADRB2* genes. Please refer to our earlier publications for the details of the methodology undertaken for the above [27–29].

Computation of PRS

PRS were calculated as the weighted sum of the risk alleles (*FTO* and *ADRB2* genes) possessed by each individual, by computing the product of individual risk alleles and their respective natural log of odds ratio (OR) for obesity [28, 29]. The formula to evaluate PRS is as follows [23, 24, 32]:

$$PRS = \sum_{i=1}^{n} W_i X_i$$

where X_i represents the number of risk alleles, W_i represents the natural log of the OR of obesity associated with the respective risk allele of the SNP, and n represents the number of the SNPs included in PRS. All of the five SNPs (*FTO* rs9930501, rs9930506, and rs9932754 and *ADRB2* rs1042713 and rs1042714) were included in the PRS model. The risk alleles of each SNP were captured from

Table 1. Odds of obesity associated with gene variants

Gene	SNP	Risk allele	RAF	OR (95% CI)	Natural log(OR)
FTO	rs9930506 [17]	G	0.37	2.87 (1.14–7.19)	1.05
	rs9930501[a]	G	0.37	3.03 (1.23–7.49)	1.11
	rs9932754[a]	C	0.37	3.04 (1.22–7.59)	1.11
ADRB2	rs1042713 [18]	G	0.13	1.38 (0.08–23.93)	0.32
	rs1042714[a]	G	0.51	1.00 (0.40–2.23)	0

OR, odds ratio; RAF, risk allele frequency; SNP, single nucleotide polymorphism. [a] Unpublished data.

published GWAS studies: *FTO* rs9930501 (G allele), rs9930506 (G allele), and rs9932754 (C allele) and *ADRB2* rs1042713 (G allele) and rs1042714 (G allele) [33–36]. The odds of obesity for each SNP were computed in our earlier studies [28, 29]. Logistic regression was conducted to determine the risk of obesity associated with gene variants. ORs with 95% CIs were estimated for each genotype. These data were substituted in the PRS formula (Table 1). Participants were then stratified into three equal groups as the first tertile (tertile 1, PRS 0–0.64), second tertile (tertile 2, PRS 0.65–3.59), and third tertile (tertile 3, PRS 3.60–8.18) of PRS with scores increasing from the first to the third tertile.

Power and Sample Size Calculation

In the Hipcref dietary intervention study [27], the sample size was computed using the formula $n = [2SD^2(Z_{1-\alpha/2} + Z_{1-\beta})^2]/d^2$, according to Charan and Biswas [37]. The primary outcome measure was the change in body weight. Assuming an expectation of 10% reduction in body weight, an effect size (d) of 7.6 (76.0 kg – 68.4 kg = 7.6 kg) with a standard deviation of 11.2 [38] was calculated. To detect this difference with a significance level of 5% (i.e., Z_{1 – alpha/2} = 1.96) and power of 80% (i.e., Z_{1 – β} = 0.84), 34 participants were required in each group. Assuming an attrition rate of 20%, a total of 41 participants were required in each arm of the study.

Data Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22 (IBM, Chicago, IL, USA). Data were expressed as mean ± standard error or number (percentage). Log transformation was performed to transform nonnormally distributed data into normally distributed data. Participants were then stratified into three equal groups as the first tertile (tertile 1, PRS 0–0.64), second tertile (tertile 2, PRS 0.65–3.59), and third tertile (tertile 3, PRS 3.60–8.18) of PRS with scores increasing from the first to the third tertile. In the cross-sectional study, to study the effect of PRS on the odds of obesity, data were dichotomized into obese and nonobese groups (obesity was defined as a BMI ≥27.5 according to the WHO for Asian populations) [39]. The first tertile of PRS was used as the reference group. OR with 95% CI was estimated by logistic regression to determine the odds of obesity associated with PRS after adjusting for the covariates age, sex, physical activity status, smoking status, and alcohol consumption. One-way ANCOVA was performed to assess the differences in the continuous variables between the tertiles of PRS. Adjustments on the covariates age, sex, physical activity, smoking status, alcohol consumption, BMI, and total energy intake were applied where appropriate. χ^2 test was performed to compute the differences in categorical variables between the tertiles of PRS.

With respect to the RCT (Hipcref dietary intervention), the study was designed to test an approach applicable to primary care. Therefore, the analysis was conducted on an intention-to-treat basis rather than on compliance to treatment (per protocol), meaning all the participants who had been randomized into the two diet groups were included for analysis regardless of noncompleters. For the noncompleters, the last observations/measurements on the anthropometric, blood biochemical, and dietary parameters were carried forward as the post-intervention measurements for analysis. One-way ANCOVA was performed to assess the differences in the continuous variables at baseline between the tertiles of PRS after adjusting for the covariates age, sex, physical activity status, alcohol consumption, smoking status, and BMI. χ^2 test was performed to assess the differences in categorical variables at baseline between the tertiles of PRS.

The effects of PRS and dietary intervention on the post-intervention differences in anthropometric and cardiometabolic parameters at month 6 were analyzed using a general linear regression model, with adjustments for covariates and the baseline value for the respective variables. To analyze the potential interactions between PRS and dietary intervention on the post-intervention differences in anthropometric and cardiometabolic parameters, an interaction product term of PRS × dietary group was included in the models. A statistical probability level of $p < 0.05$ (two-sided) was considered significant.

Results

Association between PRS and Odds of Obesity

In the cross-sectional study, a total of 178 Malaysian adults were recruited for anthropometric measurement and genetic analysis (Chinese $n = 42$ [37 females, 5 males]; Malays $n = 86$ [78 females, 8 males); Indians $n = 50$ [39 females, 11 males]). Logistic regression was performed to examine the effect of PRS on the odds of obesity (obesity was defined as a BMI ≥27.5) [39]. Our result revealed that the third tertile of PRS (PRS 3.59–8.18) was associated with significantly higher odds of obesity (2.10 [95% CI = 1.05–4.21, $p = 0.036$] compared to the first tertile of PRS [PRS 0–0.64]) (Table 2). After adjusting for the covariates age, sex, physical activity status, alcohol consumption, and smoking status, the odds of obesity in the third tertile of PRS were increased to 2.29 (95% CI = 1.11–4.72, adjusted $p = 0.025$) compared to the first tertile of PRS. However, we found no significant association between the second tertile of PRS and the odds of obesity (2.06 [95% CI = 0.88–4.85, $p = 0.096$] compared to the first tertile of PRS).

Table 2. Association of PRS with the odds of obesity: cross-sectional study (n = 178)

PRS	Obese, BMI ≥27.5 (n = 79)	Nonobese, BMI <27.5 (n = 99)	Unadjusted OR (95% CI)	Unadjusted p value	Adjusted OR (95% CI)[a]	Adjusted p value[a]
First tertile (PRS 0–0.64)	20 (32.8%)	41 (67.2%)	1	0.082	1	0.067
Second tertile (PRS 0.65–3.58)	20 (50.0%)	20 (50.0%)	2.05 (0.94–4.65)	0.086	2.06 (0.88–4.85)	0.096
Third tertile (PRS 3.59–8.18)	40 (50.6%)	39 (49.4%)	2.10 (1.05–4.21)	0.036*	2.29 (1.11–4.72)	0.025*

Logistic regression was performed to determine the risk of obesity associated with PRS. The first tertile of PRS was used as the reference group. ORs with 95% CIs were estimated for each tertile. The average BMIs of the nonobese and obese groups were 23.0 ± 0.3 and 32.0 ± 0.5, respectively. BMI, body mass index; OR, odds ratio; PRS, polygenic risk score. [a] Adjusted for age, sex, physical activity status, smoking status, and alcohol consumption. * $p < 0.05$ was considered significant.

General Characteristics: Differences between the Tertiles of PRS at Baseline

In the RCT (Hipcref dietary intervention), statistical analyses on the comparisons of the general characteristics between the tertiles of PRS at baseline were conducted (Table 3). Our results revealed that the first tertile of PRS had significantly lower waist circumference (WC) (p = 0.023), fat mass (p = 0.049), and percent body fat (p = 0.043) compared to the second tertile of PRS. With respect to cardiometabolic parameters, the first tertile of PRS had significantly lower hsCRP levels compared to the second and third tertiles (p = 0.005). No significant difference was found between the PRS in dietary parameters ($p > 0.05$) (Table 3). No significant difference was found at baseline in other parameters listed in Table 3 between the tertiles of PRS.

Moreover, there were significant differences in the distribution of the tertiles of PRS between the ethnic groups. Results from the current study revealed that Indians (3.9 ± 0.3) had significantly higher PRS compared to Chinese (2.1 ± 0.4) (p = 0.008) after adjusting for covariates (Table 4). This finding suggests that Indians were more likely to be genetically predisposed to obesity compared to Chinese.

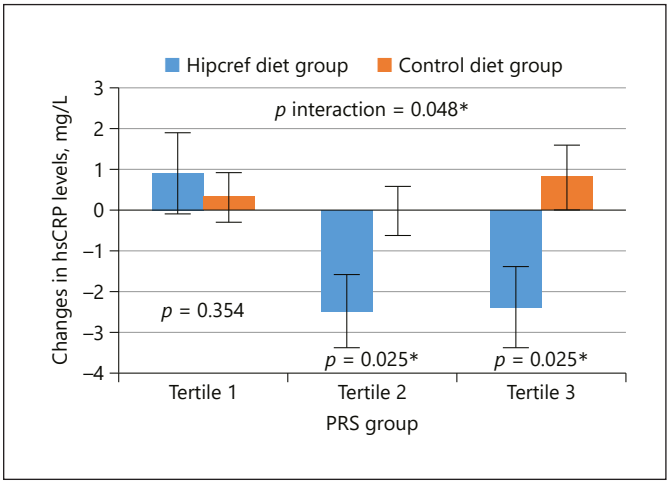

Fig. 1. Effect of the interaction between PRS and dietary group on the post-intervention difference in hsCRP levels in response to 6-month Hipcref diet versus control diet. Age, sex, physical activity, smoking status, alcohol consumption, and the baseline value for hsCRP levels were adjusted for. * $p < 0.05$ was considered significant based on a general linear regression model. Hipcref, high-protein calorie-restricted, high-vitamin E, high-fiber; hsCRP, high-sensitivity C-reactive protein; PRS, polygenic risk score.

Dietary Adherence Score: Difference between the Tertiles of PRS

No significant difference was found in the adherence score between the tertiles of PRS after adjusting for covariates (p = 0.501) (Table 5).

Effect of the Interaction between PRS and Dietary Group on the Post-Intervention Differences in Dietary Parameters

General linear regression analysis revealed no significant effect of interaction between PRS and dietary group on the post-intervention differences in dietary parameters, even after adjusting for covariates and the baseline value for respective variables ($p > 0.05$) (Table 6).

Effect of the Interaction between PRS and Dietary Group on the Post-Intervention Differences in Anthropometric and Cardiometabolic Parameters

General linear regression analysis revealed no significant effect of interaction between PRS and dietary group on the post-intervention differences in body weight and obesity-related anthropometric parameters (e.g., BMI,

Table 3. General characteristics: differences between the tertiles of PRS at baseline – dietary intervention study in overweight and obese individuals (n = 128)

Variable	Tertile 1 (n = 38)	Tertile 2 (n = 47)	Tertile 3 (n = 43)	p value
Age, years	42.7±1.7	45.3±1.7	43.7±1.6	0.716
Sex[1]				
Female	33 (86.8%)	39 (83.0%)	36 (83.7%)	0.879
Male	5 (213.2%)	8 (17.0%)	7 (16.3%)	
Ethnicity[1]				
Malays	20 (52.6%)	19 (40.4%)	18 (41.9%)	0.016*
Chinese	12 (31.6%)	7 (14.9%)	5 (11.6%)	
Indians	6 (15.8%)	21 (44.7%)	20 (46.5%)	
Physical activity status[1]				
Physically inactive	36 (94.7%)	45 (95.7%)	40 (93.0%)	0.850
Physically active	2 (5.3%)	2 (94.3%)	3 (7.0%)	
Smoking status[1]				
Never	37 (97.4%)	45 (95.8%)	43 (100%)	0.590
Current	0	1 (2.1%)	0	
Former	1 (2.6%)	1 (2.1%)	0	
Alcohol consumption[1]				
Never	37 (97.4%)	46 (97.9%)	43 (100%)	0.392
Current	0	1 (2.1%)	0	
Former	1 (2.6%)	0	0	
Anthropometric parameters				
Height[2], cm	157.6±1.2	158.7±1.1	157.5±1.1	0.494
Weight[2], kg	70.6±1.8	75.9±2.4	74.7±2.8	0.195
BMI[2]	28.5±0.7	29.9±0.7	30.0±0.8	0.233
WC[2], cm	89.4±1.6[a]	96.4±1.8[b]	94.9±2.0	0.023*
WHR[2]	0.90±0.01	0.93±0.01	0.92±0.01	0.050
Muscle mass[2], kg	23.0±07	23.8±0.8	23.4±0.8	0.861
Fat mass[2], kg	28.5±1.3[a]	32.6±1.5[b]	31.7±1.8	0.049*
Fat-free mass[2], kg	42.0±1.2	43.3±1.3	43.0±1.3	0.877
Body fat[2], %	40.1±1.1[a]	42.6±0.9[b]	42.6±0.9	0.043*
Systolic blood pressure[2], mm Hg	120.6±2.3	125.2±2.4	121.9±2.1	0.394
Diastolic blood pressure[2], mm Hg	79.5±1.6	81.1±1.4	81.9±1.7	0.556
Pulse rate[2], bpm	75.8±2.1	76.4±1.6	77.2±1.5	0.791
Blood biochemical parameters				
Fasting glucose[3], mmol/L	4.9±0.1	5.2±0.2	5.6±0.4	0.172
Fasting insulin[3], μU/mL	8.6±1.3	10.2±1.4	11.4±1.7	0.775
HOMA-IR[3]	1.9±0.3	2.6±0.6	2.9±0.5	0.549
TC[3], mmol/L	5.6±0.2	5.3±0.2	5.7±0.2	0.170
Triglyceride[3], mmol/L	1.3±0.1	1.4±0.1	1.4±0.1	0.565
HDL-C[3], mmol/L	1.7±0.1	1.5±0.04	1.5±0.1	0.050
LDL-C[3], mmol/L	3.4±0.1	3.2±0.1	3.5±0.2	0.310
TC/HDL-C[3]	3.5±0.2	3.7±0.1	4.0±0.2	0.127
hsCRP[3], mg/L	2.9±0.6[a]	6.6±1.1[b]	7.3±1.6[b]	0.005*
Dietary parameters				
TE[4], kcal	1,945±45	2,028±47	2,034±63	0.609
Protein intake[4], g	75.2±3.0	72.3±3.2	74.3±4.0	0.334
Fat intake[4], g	78.9±2.9	82.9±3.3	86.2±3.4	0.473
Carbohydrate intake[4], g	243.4±10.6	259.1±8.9	257.0±10.5	0.807
Energy from protein[3], %	15.5±0.7	14.2±0.6	14.3±0.6	0.274
Energy from fat[4], %	36.6±1.1	36.1±1.1	37.6±1.0	0.430
Energy from carbohydrate[4], %	46.7±1.3	47.6±1.4	46.9±1.2	0.981
Saturated fatty acids[4], % of TE	7.8±0.6	7.3±0.5	8.3±0.7	0.812
Monounsaturated fatty acids[4], % of TE	11.7±0.7	10.7±0.6	11.2±0.7	0.557
Polyunsaturated fatty acids[4], % of TE	6.7±0.5	6.3±0.5	6.4±0.5	0.566
Trans fatty acids[4], % of TE	0.1±0.02	0.1±0.04	0.1±0.02	0.687
Energy-adjusted fiber intake[4], g	5.8±0.4	6.0±0.6	5.8±0.5	0.915
Energy-adjusted vitamin E intake[4], mg	6.3±0.4	5.8±0.5	5.4±0.5	0.098

Data are expressed as mean ± standard error or n (%). Tertile 1: PRS 0–0.64; tertile 2: PRS 0.65–3.58; tertile 3: PRS 3.59–8.18. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PRS, polygenic risk score; TC, total cholesterol; TE, total energy intake; WC, waist circumference; WHR, waist-hip ratio. [1] p value based on χ^2 test. [2–4] p value based on ANCOVA, after adjusting for covariates in different models: [2] age, sex, physical activity, smoking status, and alcohol consumption; [3] model[2] + BMI; [4] model[2] + TE. [a, b] Figures not sharing a common letter are significantly different at $p < 0.05$. * $p < 0.05$ was considered significant.

WC, waist-hip ratio, fat mass, percent body fat, and muscle mass) at month 6 of the dietary intervention, in overweight and obese Malaysian adults ($p > 0.05$), after adjusting for covariates and the baseline value for respective variables (Table 7). However, with respect to cardiometabolic parameters our results revealed a significant effect in the interaction between PRS and dietary group on the post-intervention differences in hsCRP levels (p interaction = 0.048) after adjusting for the covariates and the baseline value for hsCRP. Participants from the second tertile of PRS had significantly greater reduction in hsCRP level with the Hipcref diet compared to the control diet (–2.5 ± 0.9 vs. –0.03 ± 0.6 mg/L, $p = 0.025$) after the intervention (Fig. 1). Similarly, participants from the third tertile of PRS had significantly greater reduction in hsCRP level with the Hipcref diet compared to the control diet (–2.4 ± 1.0 vs. –0.8 ± 0.8 mg/L, $p = 0.025$) after the intervention period (Fig. 1).

Discussion

Polygenic risk scoring accounts for the combined effect of multiple SNPs on disease outcomes and may have a larger combined effect size and hence higher power to detect association with diseases than an individual SNP [40]. Therefore, quantitative measurement of the effect of multiple gene variants is essential to detect the modulatory effect of gene variants on weight loss outcomes. In this study we aimed to compute PRS to investigate the combined effect of *FTO* rs9930501, rs9930506, and rs9932754 and *ADRB2* rs1042713 and rs1042714 gene variants on (1) the odds of obesity, dietary intake, anthropometric parameters, and cardiometabolic parameters and (2) the post-intervention differences in dietary intake, anthropometric parameters, and cardiometabolic parameters in response to a 6-month dietary intervention (Hipcref diet).

Association between PRS and the Odds of Obesity

Data from the cross-sectional study revealed that individuals from the third tertile of PRS (PRS 3.60–8.18) were associated with increased odds of obesity compared to the first tertile of PRS (PRS 0–0.64). This finding suggests that individuals carrying higher PRS were associated with increased odds of obesity compared to individuals carrying lower PRS. The current study highlights that the PRS provides a measure of genetic predisposition to obesity. Early screening of the candidate gene variants of *FTO* and *ADRB2* genes may identify individuals at risk of obesity [41].

Table 4. Differences between the ethnic groups in the mean ± standard error values of PRS

Ethnicity	PRS	p value
Chinese ($n = 24$)	2.1±0.4*	0.008*
Malays ($n = 57$)	3.0±0.4	–
Indians ($n = 47$)	3.9±0.3*	–

PRS, polygenic risk score. * $p < 0.05$ was considered significant based on ANCOVA after adjusting for the covariates age, sex, physical activity, smoking status, and alcohol consumption.

Table 5. Dietary adherence scores: differences between the tertiles of PRS

Adherence score	Tertile 1 ($n = 38$)	Tertile 2 ($n = 47$)	Tertile 3 ($n = 43$)	p value
Mean ± SE	5.8±0.8	6.6±0.9	5.5±0.7	0.501
Minimum	4.1	4.9	4.1	–
Maximum	7.4	8.4	6.8	–

Tertile 1: PRS 0–0.64; tertile 2: PRS 0.65–3.58; tertile 3: PRS 3.59–8.18. PRS, polygenic risk score; SE, standard error. $p < 0.05$ was considered significant based on ANCOVA after adjusting for the covariates age, sex, physical activity, smoking status, and alcohol consumption.

Association between PRS and Anthropometric, Cardiometabolic, and Dietary Intake Parameters at Baseline

Data from the cross-sectional study revealed no significant differences at baseline in dietary intake between the tertiles of PRS. WC, fat mass, and percent body fat were significantly higher in the second compared to the first tertile. The scores in the third tertile were higher, but did not reach statistical significance due to a smaller number of individuals categorized in the third tertile (second tertile $n = 47$; third tertile $n = 43$). With respect to cardiometabolic parameters, the second and third tertiles of PRS had significantly higher hsCRP levels compared to the first tertile. The current study shows that higher PRS were associated with increased WC, fat mass, percent body fat, and hsCRP levels compared to lower PRS.

PRS and Ethnicity

This study reports that with respect to *FTO* and *ADRB2* genes and their respective gene variants, significant differences exist between the three major Malaysian ethnic

Table 6. Effect of the interaction between PRS and dietary group on the post-intervention differences in dietary parameters in response to the 6-month Hipcref diet or the control diet

Dietary parameter	Group	Hipcref diet group (n = 65)			Control diet group (n = 63)			p interaction (PRS × intervention group)[a]
		tertile 1 (n = 20)	tertile 2 (n = 22)	tertile 3 (n = 23)	tertile 1 (n = 18)	tertile 2 (n = 25)	tertile 3 (n = 20)	
TE, kcal	baseline	2,003±72	2,017±74	2,041±96	1,904±50	2,038±62	2,025±81	0.185
	month 6	1,629±58	1,618±54	1,556±49	1,880±64	1,988±63	2,010±60	
	change	−374±66	−400±61	−485±68	−25±39	−50±25	−15±30	
Protein intake, g	baseline	80.4±6.0	70.6±4.0	76.0±5.7	76.4±4.3	73.8±5.0	72.3±5.6	0.962
	month 6	111.1±4.8	105.9±5.5	107.3±4.2	73.4±3.0	76.9±4.4	76.4±3.2	
	change	30.7±7.7	35.4±5.4	31.4±4.7	−3.0±4.6	3.1±3.4	3.0±4.3	
Fat intake, g	baseline	81.2±4.5	85.8±4.8	86.6±5.1	76.1±3.0	80.4±4.5	80.8±2.5	0.293
	month 6	58.0±3.2	59.5±3.7	55.5±2.2	70.7±4.1	75.1±3.8	79.3±4.4	
	change	−23.2±4.5	−26.3±4.8	−31.2±4.9	−5.4±3.2	−5.4±3.5	−6.3±2.9	
Carbohydrate intake, g	baseline	245.4±17.5	252.6±12.3	256.9±15.8	241.2±10.2	264.8±12.8	257.2±14.0	0.926
	month 6	177.2±8.6	176.7±8.8	171.8±7.3	258.9±8.6	271.2±11.1	265.4±10.5	
	change	−68.2±14.2	−76.0±10.7	−85.2±13.9	17.7±9.7	6.4±6.9	8.2±8.6	
Energy from protein, %	baseline	16.1±1.1	13.9±0.7	14.5±0.7	15.9±1.1	14.6±0.9	14.1±0.9	0.596
	month 6	27.5±0.9	26.6±1.3	27.6±0.6	15.4±0.3	15.5±0.7	15.0±0.4	
	change	11.4±1.4	12.7±1.4	13.0±1.1	−0.6±1.0	0.9±0.7	0.9±0.8	
Energy from fat, %	baseline	37.0±1.9	37.4±1.5	37.7±1.5	35.6±1.0	35.0±1.7	37.6±1.4	0.555
	month 6	31.4±1.0	33.1±1.4	32.3±1.0	37.7±2.0	37.7±1.8	37.3±1.8	
	change	−5.0±1.7	−4.6±1.3	−2.9±1.0	−2.0±1.1	−1.5±1.4	−2.2±1.2	
Energy from carbohydrate, %	baseline	45.8±2.1	46.0±2.1	46.7±1.7	47.1±1.2	49.0±1.8	47.2±1.8	0.496
	month 6	43.7±0.9	42.8±1.1	43.5±1.0	50.5±2.8	49.5±2.6	50.2±2.1	
	change	−2.7±1.7	−3.0±2.0	−3.0±1.7	75±1.8	4.7±1.6	5.0±1.6	
Saturated fatty acids, % of TE	baseline	7.8±0.8	8.5±0.7	8.0±0.7	8.0±0.8	6.2±0.5	8.7±1.1	0.935
	month 6	7.6±0.5	8.4±0.6	8.5±0.6	8.4±0.8	8.7±0.7	9.9±0.7	
	change	−0.2±0.8	−0.1±0.7	0.5±1.1	0.4±0.9	2.6±0.6	1.1±1.0	
Monounsaturated fatty acids, % of TE	baseline	12.2±1.0	11.8±0.9	10.3±1.0	11.0±0.7	9.8±0.8	12.4±1.0	0.683
	month 6	10.2±0.6	10.9±0.7	10.5±0.5	10.2±05	10.2±0.6	11.6±0.7	
	change	−1.9±0.8	−0.9±0.9	0.2±0.8	−0.9±0.7	0.4±0.8	−0.8±1.2	
Polyunsaturated fatty acids, % of TE	baseline	7.1±0.6	6.9±0.9	5.9±0.8	6.4±0.7	5.7±0.6	6.9±0.7	0.572
	month 6	8.3±0.5	8.2±0.6	7.7±0.5	7.4±0.9	5.9±0.6	6.4±0.4	
	change	1.2±0.7	1.3±0.7	1.8±0.8	1.0±0.8	0.2±0.6	−0.6±0.7	
Trans fatty acids, % of TE	baseline	0.2±0.03	0.1±0.03	0.1±0.03	0.1±0.03	0.1±0.01	0.1±0.02	0.726
	month 6	0.1±0.02	0.1±0.02	0.1±0.02	0.2±0.03	0.2±0.03	0.2±0.02	
	change	−0.1±0.04	−0.02±0.03	−0.01±0.03	0.1±0.04	0.03±0.1	0.04±0.03	
Energy-adjusted fiber intake, g	baseline	6.2±0.6	7.0±0.8	5.6±0.7	5.6±0.6	5.0±0.8	6.0±0.7	0.571
	month 6	13.0±0.9	13.7±0.7	13.8±0.8	9.5±0.8	8.0±0.7	9.8±0.8	
	change	6.8±0.9	6.6±1.0	8.2±0.9	3.9±0.8	3.0±0.8	3.9±0.7	
Energy-adjusted vitamin E intake, mg	baseline	5.8±0.6	6.7±0.9	4.8±0.7	6.9±0.6	5.1±0.5	6.1±0.8	0.761
	month 6	8.0±0.3	8.4±0.5	7.6±0.4	6.8±0.6	5.8±0.4	6.8±0.5	
	change	2.2±0.7	1.7±0.7	2.9±0.6	−0.9±0.6	0.7±0.5	0.5±0.4	

Tertile 1: PRS 0–0.64; tertile 2: PRS 0.65–3.58; tertile 3: PRS 3.59–8.18. Hipcref, high-protein calorie-restricted, high-vitamin E, high-fiber; PRS, polygenic risk score; TE, total energy intake. [a] A general linear regression model was used to assess the effect of the interaction between PRS and dietary group on the post-intervention differences in dietary parameters after adjusting for age, sex, physical activity, smoking status, alcohol consumption, TE, and the baseline value for the respective variable.

Table 7. Effect of the interaction between PRS and dietary group on the post-intervention differences in anthropometric and blood biochemical parameters in response to the 6-month Hipcref diet or the control diet

	Group	Intervention diet group (n = 65)			Control diet group (n = 63)			p interaction (PRS × intervention group)[a]
		tertile 1 (n = 20)	tertile 2 (n = 22)	tertile 3 (n = 23)	tertile 1 (n = 18)	tertile 2 (n = 25)	tertile 3 (n = 20)	
Anthropometric parameters								
Weight, kg	baseline	72.4±2.9	75.2±3.3	74.9±1.6	68.5±1.9	76.4±3.6	74.5±5.8	0.058
	month 6	69.9±3.0	72.1±3.4	70.3±1.9	69.5±1.9	77.6±3.6	76.3±5.7	
	change	−2.5±0.7	−3.2±0.7	−4.6±1.0	1.0±0.6	1.1±0.6	1.8±0.5	
BMI	baseline	29.3±1.2	29.6±1.1	29.8±0.6	27.6±0.7	30.2±0.9	30.1±1.6	0.125
	month 6	28.2±1.2	28.4±1.2	28.0±0.8	28.0±0.8	30.7±1.0	30.9±1.6	
	change	−1.1±0.3	−1.3±0.3	−1.8±0.4	0.4±0.9	0.5±0.3	0.8±0.2	
WC, cm	baseline	91.1±2.6	94.4±2.7	93.9±2.1	87.5±1.8	98.1±2.4	96.1±3.7	0.224
	month 6	85.9±3.0	88.4±3.0	86.7±2.5	88.6±2.1	99.3±2.5	98.2±3.5	
	change	−5.2±1.1	−6.1±1.0	−7.2±1.1	1.1±1.1	1.2±0.6	2.1±0.5	
WHR	baseline	0.89±0.02	0.92±0.01	0.92±0.01	0.90±0.01	0.94±0.02	0.93±0.01	0.369
	month 6	0.89±0.01	0.91±0.01	0.90±0.01	0.90±0.01	0.94±0.02	0.95±0.02	
	change	−0.01±0.01	−0.01±0.01	−0.02±0.01	0.01±0.01	0.01±0.01	0.01±0.01	
Muscle mass, kg	baseline	23.6±1.2	24.1±1.2	23.7±0.7	22.2±0.8	23.4±1.1	23.1±1.5	0.068
	month 6	23.5±1.1	24.0±1.2	23.0±0.6	22.3±0.8	23.3±1.1	23.4±1.5	
	change	−0.1±0.2	−0.1±0.3	−0.8±0.3	0.02±0.4	−0.1±0.2	0.3±0.2	
Fat mass, kg	baseline	29.4±2.2	31.5±2.0	31.3±1.3	27.6±1.2	33.6±2.1	32.2±3.7	0.234
	month 6	27.0±2.4	28.3±2.3	28.2±1.5	28.0±1.4	34.9±2.1	33.6±3.6	
	change	−2.4±0.8	−3.2±0.7	−3.2±0.8	0.4±0.6	1.2±0.5	1.4±0.4	
Fat-free mass, kg	baseline	43.4±1.9	43.8±2.0	43.5±1.1	40.9±1.2	42.8±1.8	42.3±2.5	0.069
	month 6	42.8±1.9	43.9±2.0	41.9±1.1	42.1±1.5	42.7±1.8	42.7±2.5	
	change	−0.3±0.3	0.1±0.6	−1.7±0.6	1.2±0.9	−0.1±0.2	0.4±0.3	
Body fat, %	baseline	40.0±1.9	41.5±1.4	41.7±1.2	40.2±1.1	43.6±1.0	42.0±1.7	0.468
	month 6	37.9±2.1	38.6±1.8	39.7±1.3	40.4±1.4	44.6±1.1	43.0±1.7	
	change	−2.1±0.8	−2.9±0.8	−2.0±0.8	0.2±0.7	1.1±0.4	1.0±0.4	
SBP, mm Hg	baseline	121.5±3.3	126.5±3.3	123.4±3.0	119.6±3.1	124.0±3.6	120.2±2.8	0.843
	month 6	116.6±3.1	121.1±3.5	118.0±2.6	117.6±3.8	122.6±2.9	116.5±3.0	
	change	−5.0±2.6	−5.4±2.3	−5.3±2.7	−2.0±3.2	−1.4±1.8	−3.7±1.9	
DBP, mm Hg	baseline	81.9±2.5	80.8±2.2	84.3±2.5	76.9±1.9	81.3±1.9	79.3±2.1	0.843
	month 6	77.3±2.9	78.1±2.4	78.7±1.9	75.3±2.0	78.9±2.0	76.7±2.5	
	change	−4.6±1.5	−2.8±1.7	−5.5±2.3	−1.6±1.8	−2.4±1.0	−2.6±2.0	
Pulse rate, bpm	baseline	76.5±3.0	77.7±2.4	77.4±1.9	75.0±3.0	75.3±2.1	76.9±2.4	0.105
	month 6	72.9±3.6	74.5±2.6	71.2±2.2	68.9±2.5	71.9±2.2	76.0±2.4	
	change	−3.5±2.7	−3.2±2.3	−6.2±2.2	−6.0±2.4	−3.4±1.9	−0.9±1.5	
Blood biochemical parameters								
Fasting glucose, mmol/L	baseline	5.0±0.3	5.3±0.4	5.1±0.2	4.6±0.1	5.1±0.2	6.2±0.9	0.381
	month 6	5.3±0.3	5.0±0.5	5.2±0.2	4.9±0.2	5.3±0.3	6.0±0.7	
	change	0.2±0.2	−0.4±0.5	0.1±0.2	0.3±0.2	0.3±0.3	−0.2±0.3	
Fasting insulin, μU/mL	baseline	11.4±2.2	11.5±2.3	12.5±3.0	5.4±0.6	9.0±1.6	10.2±1.5	0.121
	month 6	8.3±1.0	8.3±1.3	8.5±1.1	9.0±1.3	13.2±2.6	15.9±2.0	
	change	−3.2±2.1	−3.2±1.3	−4.0±2.6	3.6±1.3	4.1±1.4	5.7±1.7	
HOMA-IR	baseline	2.6±0.5	3.4±1.1	3.0±0.8	1.1±0.1	1.9±0.3	2.8±0.6	0.122
	month 6	1.9±0.3	2.1±0.5	2.0±0.3	2.0±0.3	3.3±0.7	4.4±0.8	
	change	−0.6±0.5	−1.3±0.9	−1.0±0.7	0.9±0.3	1.3±0.5	1.6±0.6	

Table 7 (continued)

	Group	Intervention diet group (n = 65)			Control diet group (n = 63)			p interaction (PRS × intervention group)[a]
		tertile 1 (n = 20)	tertile 2 (n = 22)	tertile 3 (n = 23)	tertile 1 (n = 18)	tertile 2 (n = 25)	tertile 3 (n = 20)	
TC, mmol/L	baseline	5.7±0.2	5.3±0.2	5.5±0.2	5.5±0.3	5.3±0.2	5.9±0.3	0.944
	month 6	5.5±0.2	5.4±0.2	5.1±0.2	5.4±0.3	5.4±0.2	5.4±0.2	
	change	−0.2±0.1	0.1±0.2	−0.4±0.2	−0.04±0.2	0.1±0.1	−0.5±0.2	
Triglyceride, mmol/L	baseline	1.5±0.2	1.5±0.2	1.4±0.2	1.0±0.1	1.3±0.2	1.5±0.2	0.456
	month 6	1.6±0.2	1.5±0.2	1.4±0.2	1.0±0.1	1.5±0.2	1.5±0.2	
	change	−0.1±0.1	0±0.1	0±0.3	−0.02±0.1	0.1±0.1	0.1±0.1	
HDL-C, mmol/L	baseline	1.6±0.1	1.5±0.1	1.5±0.1	1.8±0.1	1.5±0.1	1.4±0.1	0.527
	month 6	1.4±0.1	1.4±0.1	1.5±0.1	1.6±0.1	1.4±0.1	1.3±0.1	
	change	−0.1±0.1	−0.03±0.1	−0.1±0.1	−0.2±0.1	−0.02±0.03	−0.2±0.04	
LDL-C, mmol/L	baseline	3.5±0.2	3.2±0.2	3.3±0.2	3.2±0.2	3.2±0.2	3.8±0.2	0.672
	month 6	3.4±0.2	3.2±0.2	3.1±0.2	3.4±0.2	3.2±0.2	3.4±0.2	
	change	−0.1±0.1	0±0.2	−0.3±0.2	0.2±0.1	−0.01±0.1	−0.3±0.2	
TC/HDL-C	baseline	3.8±0.2	3.7±0.2	3.8±0.3	3.1±0.2	3.7±0.2	4.2±0.2	0.055
	month 6	4.1±0.3	4.2±0.2	3.7±0.2	3.5±0.2	3.9±0.2	4.4±0.2	
	change	0.3±0.1	−0.1±0.3	−0.1±0.3	0.4±0.1	0.2±0.1	0.3±0.2	
hsCRP, mg/L	baseline	3.8±1.0	6.1±1.5	8.3±2.3	1.7±0.3	7.2±1.7	6.2±2.2	0.048*
	month 6	3.8±0.9	3.4±0.9	4.9±1.4	2.1±0.6	7.6±1.3	6.6±1.8	
	change	0.9±1.0	−2.5±0.9	−2.4±1.0	0.3±0.6	−0.03±0.6	0.8±0.8	

Tertile 1: PRS 0–0.64; tertile 2: PRS 0.65–3.58; tertile 3: PRS 3.59–8.18. BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; Hipcref, high-protein calorie-restricted, high-vitamin E, high-fiber; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PRS, polygenic risk score; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference; WHR, waist-hip ratio. [a] A general linear regression model was used to assess the effect of the interaction between PRS and dietary group on the post-intervention differences in anthropometric and cardiometabolic parameters after adjusting for age, sex, physical activity, smoking status, alcohol consumption, and the baseline value for the respective variable. * $p < 0.05$ was considered significant.

groups. Malaysian Indians had significantly higher PRS compared to Malaysian Chinese. An earlier study reported that Malaysian Indians had a significantly higher frequency of the risk allele (G) of *FTO* rs9930506 compared to Malaysian Chinese and Malays [28]. This finding adds to the existing evidence that differences in allele frequencies and gene variants do exist in various ethnic groups. This fact should be accounted for when designing intervention programs in multiethnic populations.

PRS and Post-Intervention Differences in Body Weight and Body Composition

In the RCT of the current study, it was found that at month 6 of the Hipcref dietary intervention, participants in the first, second, and third tertiles of PRS lost on average 2.5, 3.2, and 4.6 kg of body weight, respectively. No weight loss was observed in the control group. In the intervention group, the difference in weight loss was not statistically significant between the PRS tertiles. However, individuals with the risk alleles responded to the weight loss program positively. Moreover, the data show a positive linear trend in the reduction of body weight (–2.5, –3.2, and –4.6 kg), BMI (–1.1, –1.3, and –1.8), WC (–5.2, –6.1, and –7.2 cm), and fat mass (–2.4, –3.2, and –3.2 kg) across the PRS tertiles (first, second, and third, respectively).

FTO. A recent meta-analysis of 9,563 participants involving 8 RCTs reported that the post-intervention differences in body weight, WC, and adiposity were not significantly different between the risk allele (A) and the non-risk allele carriers (T) of *FTO* rs9939609 [42]. However, other authors have reported contradictory findings. A meta-analysis by Xiang et al. [43] reported that individuals carrying the risk allele of *FTO* rs9939609 (TA and TT genotypes) lost more weight through diet or lifestyle intervention compared to the non-risk allele carriers (AA). The authors also reported that in a subgroup analysis, a stronger effect of *FTO* rs9939609 on weight loss was found in response to calorie-restricted diets com-

pared to other interventions. The current study is in congruence with Xiang et al. [43].

ADRB2. No significant association was found between *ADRB2* gene polymorphisms (rs1042713 and rs1042714) and weight loss after 7 weeks of lifestyle modification [44]. After 3 months of calorie-restricted diet, obese Spanish women carrying the risk allele (CG and GG genotypes) of *ADRB2* rs1042714 had greater reduction in body weight compared to the non-risk allele carriers (CC) [12]. The authors suggest that there may be a sex-specific genetic association on the changes in body weight between *ADRB2* rs1042714 and the intervention employed. Due to the smaller sample size of our male participants, data were not stratified according to sex for further analysis. This limits the power to detect differences in sex on the gene-diet interaction in the current study.

PRS and Post-Intervention Differences in Cardiometabolic Parameters

As observed in the current cross-sectional study, higher PRS was associated with increased hsCRP levels at baseline. In the RCT, significant post-intervention reduction in hsCRP levels was revealed in the second and third tertiles of PRS (–2.5 mg/L, $p = 0.025$, and –2.4 mg/L, $p = 0.025$, respectively) compared to the control diet. This finding suggests that the Hipcref diet successfully attenuated the effect of PRS on hsCRP levels and that higher-risk individuals benefited most. Obesity is a chronic low-grade inflammatory state that is associated with increased risk of MetS, diabetes, and cardiovascular disease [45]. hsCRP is a common systemic marker for investigation of inflammation and also an independent predictor of future cardiovascular events [46]. Previous studies have demonstrated the influence of proinflammatory cytokine gene variants, including tumor necrosis factor alpha (rs1800629) and interleukin 6 (rs1800795 and rs1800797), on the risk of central obesity, diabetes, and MetS [47–49]. The current study did not find any significant difference in the other (reported) cardiometabolic parameters. However, the data show a positive linear trend in the reduction of fasting insulin (–3.2, –3.2, and –4.0) and homeostatic model assessment of insulin resistance (–0.6, –1.3, and –1.0) across the PRS tertiles (first, second, and third, respectively) with dietary intervention (Table 7).

The Look AHEAD study reported that a moderate improvement in body weight and fitness after 1 year of lifestyle intervention through calorie restriction and physical activity was not able to mitigate the unfavorable cardiometabolic effects (e.g., hsCRP and triglyceride levels) associated with GCKR Leu446Pro in overweight and obese individuals with diabetes mellitus [50]. It is interesting to note that the average age (± standard deviation) of the Look AHEAD study was 59.0 ± 6.8 years and that our study participants had an average age (± standard error) of 43.7 ± 1.6 years. We opine that the advanced age in the Scottish population may have precipitated the comorbidities in the group with the risk allele. Moreover, our participants were apparently healthy overweight and obese adults without any clinical metabolic conditions.

Calorie Restriction, hsCRP, and PRS. In the RCT of the current study, the data showed a positive linear trend in the reduction of total energy intake (–374, –400, and –485 kcal/day) across the tertiles of PRS (first, second, and third, respectively). It is common knowledge that an increase in hsCRP level is associated with increased adipose tissue [51]. Therefore, a reduction in excess body fat stores can significantly reduce the inflammatory state of individuals [52]. Reduction of hsCRP levels in individuals may be due to the consequence of weight loss following a moderate reduction in calorie intake [53]. Further, reduction in total energy intake through calorie-restricted diet resulted in a significant reduction in hsCRP levels and the risk of atherosclerosis in various populations [54, 55]. The current study reveals that individuals with higher scores, i.e., at higher risk, had lower energy intake through the 6 months of the intervention trial. The mechanism underlying our findings is currently unclear. Mega et al. [56] reported that genetic risk scoring identified individuals at increased risk of both incident and recurrent coronary heart disease events. Further, individuals with the highest burden of genetic risk derived the largest relative and absolute clinical benefit from statin therapy. The authors explained that absolute risk reduction can depend on the risk profile of the population. In their study, patients with a higher burden of SNPs experienced a greater benefit with statin therapy. The authors opined that the possible explanation could be that more plaques were stabilized with the treatment. However, they cautioned that this idea merits further study to elucidate the underlying mechanism. In the current study, individuals with a higher burden of risk responded better to calorie restriction. The plausible explanation could be that those with higher burden of risk benefited through multiple phenotypes, e.g., reduction in body weight, BMI, WC, fat mass, and hsCRP levels. These positive effects may have induced a sense of well-being which then motivated the participants to adhere to

the intervention diet, followed by reduction in fat mass which resulted in significant reduction in the inflammatory marker as well.

High Protein Intake and PRS. In the RCT section of the current study, our data showed a positive linear trend in the increase of percent energy from protein (11.4, 12.7, and 13.0%) across the tertiles of PRS (first, second, and third, respectively). According to Merritt et al. [57], individuals carrying the risk allele (A) of rs1558902 of the *FTO* gene had higher BMI and WC with lower dietary protein intake compared to noncarriers (T). This effect was not found in the higher protein intake risk group, suggesting that high protein intake may be protective against the effect of *FTO* gene on BMI and WC. In the current study, high percent energy from protein (Hipcref diet intervention) may have benefited individuals with higher PRS. Huang et al. [58] reported that the risk allele carriers (A) of *FTO* rs9930609 had significant reduction in food craving and appetite with a hypocaloric high-protein weight loss diet. *FTO* is highly expressed in the arcuate nucleus of the hypothalamus. Animal and in vitro studies suggest that *FTO* plays an important role in sensing cellular amino acids [59]. The sensing of amino acid levels in the brain is known to mediate orexigenic and anorexigenic pathways to control food intake and modulate energy balance. Studies have suggested that the availability of essential amino acids may be one of the factors regulating *FTO* levels. *FTO* mRNA and protein levels were found to be dramatically downregulated by total amino acid deprivation [60]. Therefore, it is suggested that the participants with the highest PRS benefited most with high protein intake through the Hipcref diet. However, the mechanism for this effect is not clear at present. As to the *ADRB2* gene, a study by Fernandez-Twinn et al. [61] reported that rodent offspring on a "low-protein diet" demonstrated reduced beta-adrenergic responsiveness and attenuated adrenergic and insulin signaling, which increased the risk of heart failure and insulin resistance in the animals. This finding corroborates with the current findings as well.

Vitamin E, hsCRP, and PRS. In the RCT section of the current study, the data showed a positive linear trend in the intake of energy-adjusted vitamin E (2.2, 1.7, and 2.9 mg) between the first and last tertile of PRS. Vitamin E is a micronutrient with antioxidant and immune-modulating properties which can reduce oxidative stress and influence inflammatory processes [62]. A significant inverse association of vitamin E and hsCRP has been demonstrated in some studies [63, 64]. The authors reported that vitamin E may have modulated the expression of the *FTO* gene through deactivation of PKC signaling, which in turn attenuated weight gain. Moreover, Qin et al. [65] also reported that combined treatment with vitamins C and E resulted in diminished oxidative stress and prevented the loss of beta-adrenergic receptor activity due to overstimulation in rabbits with myocardial infarction.

Polyunsaturated Fatty Acids (PUFAs) and PRS. The current study reveals a positive linear trend in the intake of PUFAs (percent energy of total energy intake) (1.2, 1.3, and 1.8%), across the PRS tertiles (first, second, and third, respectively) (Table 6). Cell and animal studies have demonstrated beneficial effects of long-chain *n*-3 PUFAs on inflammation and insulin sensitivity [66–68]. The PPARγ Pro12Ala polymorphism (rs1801282) is an example of the relevance of gene-nutrient interactions in the development of obesity, MetS, and T2DM. As the ratio of total PUFAs to saturated fatty acids increased, a significant inverse relationship was shown for both fasting insulin concentrations and BMI in the Ala (G allele) carriers, suggesting that the potential protective effect of the Ala allele may be lost in the presence of a high saturated fatty acid diet [69]. More recently an inverse relationship between Ala frequency and prevalence of T2DM prevalence was observed in populations where energy from lipids exceeded 30% of the total energy intake [70]. The current study reports that study participants with risk alleles of *FTO* and *ADRB2* and possessing higher PRS benefited most from increased PUFA and vitamin E intake through the Hipcref diet intervention.

High Fiber Intake and PRS. Hosseini-Esfahani et al. [71] suggested that dietary fiber may modify the association of *FTO* SNPs (using genetic risk score) and obesity. The authors reported that in a Middle Eastern population, individuals with a high genetic risk score and high fiber intake had the lowest risk of obesity compared to those with a low genetic risk score and low fiber intake. Moreover, individuals carrying the AA genotype of *FTO* rs11076023 in the third tertile of dietary fiber intake had significantly lower WC compared to noncarriers (AT and TT genotypes) [72]. In the RCT section of the current study, the dietary data showed a positive linear trend in fiber intake (6.8, 6.6, and 8.2 g) between the first and last tertiles of PRS. Consumption of a high-fiber diet may be an effective weight management strategy for individuals carrying a higher number of risk alleles.

Limitations

It is acknowledged that the current study is exploratory and, due to the small sample size, is underpowered to

detect a large effect size. However, from the current investigation we generated several hypotheses. Moreover, our study participants were recruited from a specific geographical location (Beranang, Jalan Broga, and Bandar Kajang) and were predominantly women. These factors may have influenced the study outcome, and hence the findings of the current experiments may not be generalizable to the Malaysian population as a whole. Therefore, large-scale studies from other geographical locations are required to generalize the findings of the current study to the Malaysian population. Further, the trial duration of the dietary intervention (6 months) did not allow to investigate long-term adherence to the intervention diet and subsequent weight maintenance. This is a limitation of the intervention study.

Body composition was assessed using bioelectrical impedance analysis. This is one of the limitations of this study. Many factors such as food and fluid intake, environment, ethnicity, and phase of menstrual cycle affect bioelectrical impedance analysis estimates. We carefully controlled for confounding lifestyle factors and baseline values in the analyses. However, detailed information on other confounding factors such as individuals' mental health (e.g., stress, sleep problems, worry, depression, anxiety), sociodemographic indicators (e.g., location of residence, marital status), and socioeconomic indicators (e.g., educational attainment, social class, employment status, monthly household income, housing tenure) were not assessed. These factors may have contributed to the variations in the effect of gene-diet interactions on obesity-related phenotypes in the study participants. Due to limited resources, only the most widely reported genes *FTO* and *ADRB2* (and their gene variants) [9] were analyzed in the current study. This study is preliminary in nature, and more trials with larger sample size are warranted.

Conclusion

The data from the cross-sectional study revealed that individuals with higher PRS were associated with significantly increased odds of obesity compared to individuals with lower PRS. Malaysian Indians had significantly higher PRS compared to Chinese, suggesting that Indians were more likely to be genetically predisposed to obesity compared to Chinese. Moreover, our results revealed that higher PRS was associated with increased WC, fat mass, percent body fat, and hsCRP levels compared to lower PRS.

The RCT of the current study revealed greater reduction in hsCRP levels in the second and third tertiles of PRS after 6 months of Hipcref diet compared to the control diet. This study lays out a strategy to manage inflammation for overweight and obese individuals who are genetically predisposed to obesity. It can be suggested that the Hipcref diet delivered favorable outcomes in weight management and reduced hsCRP levels in the current study participants. However, large-scale clinical trials are needed to confirm the current findings in other population groups from other geographical locations.

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Statement of Ethics

This study was reviewed and approved by the Science and Engineering Research Ethics Committee of the University of Nottingham Malaysia. Written informed consent was requested and obtained from each individual participant. The study protocol was prepared in accordance with the ethical standards laid down by the Declaration of Helsinki, 1961 and followed the Good Clinical Practice Guidelines of the government of Malaysia (third edition October 2011, copyright Ministry of Health Malaysia).

Disclosure Statement

The authors declare no conflict of interest.

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Author Contributions

S.R. Mitra designed the study and supervised and conducted the data collection. P.Y. Tan collected and captured the data and performed statistical analysis of the data under the supervision of S.R. Mitra. P.Y. Tan and S.R. Mitra wrote the paper. Both authors read and approved the final manuscript.

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