

ORIGINAL ARTICLE

A high carbohydrate diet induces the beneficial effect of the CC genotype of hepatic lipase C-514T polymorphism on the apoB100/apoAI ratio only in young Chinese males

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Abstract

Both diet and genetic background have profound effects on plasma lipid profiles. It was hypothesized that a high carbohydrate (high-CHO) diet could affect the ratios of serum lipids and apolipoproteins (apo) differently in subjects with different genotypes of the C-514T hepatic lipase rs1800588 polymorphism. Fifty-six healthy university students were given a stabilization diet of 54.1% carbohydrate for 7 days, followed with a high-CHO diet of 70.1% carbohydrate for 6 days. Body composition, serum lipids, apolipoproteins and the hepatic lipase C-514T rs1800588 polymorphism were analyzed. The ratios of serum lipids and apolipoproteins were calculated afterwards. At baseline, females have significantly lower waist circumference (WC) (CC genotype: $p = 0.049$; T carriers: $p = 0.015$) and waist-to-hip ratio (WHR) (CC genotype: $p = 0.019$; T carriers: $p = 0.000$) than males. When compared with those before the high-CHO diet, the body mass index (BMI) ($p = 0.043$) and WC ($p = 0.048$) were significantly decreased in the male T carriers, the TG/HDL-C ratios were significantly increased in females (CC genotype: $p = 0.047$; T carriers: $p = 0.003$). The TC/HDL-C ratios were significantly decreased in males (CC genotype: $p = 0.000$; T carriers: $p = 0.003$). And the LDL-C/HDL-C ratios were significantly decreased in all subjects (males with the CC genotype: $p = 0.001$; male T carriers: $p = 0.000$; females with the CC genotype: $p = 0.018$; female T carriers: $p = 0.006$). However, the apoB100/apoAI ratio was only significantly decreased in male CC genotype after the high-CHO diet ($p = 0.005$).

Key Words: Diet, hepatic lipase, genes, polymorphism, cardiovascular diseases, dyslipidemias, lipids, apolipoproteins, risk assessment, preventive medicine

Introduction

Cardiovascular disease (CVD) is generally recognized as a multifactorial disease, and dyslipidemia accounts for at least 50% of its risk [1]. Conventionally, it was considered that the increases in plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and/or triglyceride (TG) and the decrease in high-density lipoprotein cholesterol (HDL-C) were the major CVD causing factors. Clinical guidelines had recommended that the primary therapy was targeted to LDL-C reduction, and that the other lipid indexes were used as the secondary or supplementary targets [2]. These secondary targets include TC/HDL-C ratio of less than 4.0, non-HDL-C level of less than 3.5 mmol/L, apoB/apoAI ratio of less than 0.80, triglyceride level of less than 1.7 mmol/L and hs-CRP level of less than 2.0 mg/L [3].

A high carbohydrate (high-CHO) diet can help reduce weight gain [4] and it was found having important effects on lipid metabolism. Previous studies have demonstrated that a high-CHO diet could lead to hypertriglyceridemia, a risk factor of CVD, by increasing serum TG concentrations [5–7]. It has also been documented that a high-CHO diet could decrease the CVD risk by decreasing plasma TC and LDL-C concentrations [6].

Hepatic lipase is a 476-amino acid glycoprotein [8] that has monoglyceride, diglyceride, triglyceride hydrolase, and phospholipase AI activities [9]. Triacylglycerol and phospholipids in HDL and LDL particles are hydrolyzed by hepatic lipase, resulting in the formation of smaller and denser particles [10]. The hepatic lipase gene is located in chromosome 15q21 and consists of nine exons spanning about

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35 kb of DNA [11]. The most well studied, C-514T (rs1800588) located in the promoter region is in complete linkage disequilibrium with the SNPs A-763G (rs1077835), C-710T (rs1077834), and G-250A (rs2070895), which are associated with plasma HDL-C levels as well [12]. And other linkage studies also showed the importance of the locus on chromosome 15q22 in determining HDL-C levels [13]. It has been shown that this rs1800588 polymorphism impacted both hepatic lipase synthesis and activity [14]. The interaction of this polymorphism and dietary fat intake affecting plasma lipid concentrations has been analyzed in several studies [15–19], but data regarding the nature of this interaction and how much effect dietary fat has are controversial. Some studies have observed an effect of this polymorphism on HDL-C levels when fat intake is low [15], while others observed opposite results by investigating this in other populations with different ethnic backgrounds [16–19]. In the present study, we investigated the interaction of a high-CHO diet with the hepatic lipase C-514T (rs1800588) polymorphism on the ratios of serum lipids and apolipoproteins in a young Chinese population, which has not been reported before. This may provide new insight for further investigations for personalized dietary recommendations in a country with the largest population in the world.

Materials and methods

Subjects and diets

Healthy and young volunteers were recruited through our advertisement from West China Medical Center. The recruitment criteria included no metabolic disease history, understanding of the procedures involved, and signing written consent. Volunteers should have no cardiovascular, diabetic, endocrinological, or renal diseases. And those volunteers who took lipid-lowering drugs, hormones, consumed alcohol, smoked, or whose sleeping time or physical

activity varied widely were also excluded. Two hundred and nine university students were recruited and 60 of them who met the above criteria eventually entered the study. They were all healthy, as indicated by the medical questionnaires and physical examinations. Fifty-six students (27 males and 29 females) completed the study with good compliance. Their characteristics are shown in Table I. All volunteers were asked to maintain their normal sleep and daily activities during the entire experiment.

Previous studies have shown that serum lipids could reach a new steady state after 5 days of dietary intervention [20]. Therefore, a 13-day dietary intervention was adopted in this study, which included a 7-day stabilization diet followed by a 6-day high-CHO diet. The stabilization diet contained 54.1% carbohydrate, 15.8% protein and 30.1% fat, and the high-CHO diet contained 70.1% carbohydrate, 16.2% protein and 13.8% fat. Significant differences were found for all the ingredients, glycemic indexes and caloric intakes between the two diets ($p = 0.000$ for all) (Table II). All the meals were provided by the Department of Nutrition at West China Medical Center and prepared from foods consumed by local people daily. For each meal, all the subjects ate to their satisfaction and did not take any other food or drink except water. A dietary log was used to assess the compliance of each subject to the study design. Our protocol had been approved by Sichuan University Human Research Ethics Committee and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Blood collection and serum analysis

On the mornings of the first day starting the stabilization diet and the high-CHO diet, and the last day finishing the high-CHO diet, venous blood samples were collected between 7:00 a.m. and 8:00 a.m. Enzymatic methods were used to measure TG and TC, HDL-C was determined by precipitating apoB-containing lipoproteins with phosphotungstic-Mg²⁺,

Table I. Demographic and biochemical characteristics of the subjects.

Variables	Males (<i>n</i> = 27)	Females (<i>n</i> = 29)	All (<i>N</i> = 56)
Age (yr)	22.9 ± 1.9	22.8 ± 1.6	22.8 ± 1.8
Body mass index (kg/m ²)	21.8 ± 4.1	20.2 ± 2.5	21.0 ± 3.4
Waist circumference (cm)	74.8 ± 10.0	67.5 ± 6.2*	71.1 ± 9.0
Waist-to-hip ratio	0.89 ± 0.06	0.83 ± 0.04*	0.86 ± 0.06
Triglyceride (mmol/L)	1.00 ± 0.62	0.73 ± 0.27*	0.86 ± 0.49
Total cholesterol (mmol/L)	3.79 ± 0.54	4.00 ± 0.72	3.90 ± 0.64
HDL-C, (mmol/L)	1.44 ± 0.36	1.69 ± 0.33*	1.57 ± 0.37
LDL-C, (mmol/L)	2.09 ± 0.53	2.05 ± 0.55	2.07 ± 0.54
Apolipoprotein AI, (g/L)	1.93 ± 0.26	2.14 ± 0.16*	2.04 ± 0.23
Apolipoprotein B100, (g/L)	0.66 ± 0.23	0.69 ± 0.18	0.68 ± 0.20
Glucose (mmol/L)	0.22 ± 0.03	0.22 ± 0.03	0.22 ± 0.03
Insulin (pmol/L)	28.8 ± 22.3	32.2 ± 13.7	30.7 ± 18.2

Data are shown as mean ± SD.

* $p < 0.05$ for females vs. males (unpaired *t*-test).

Table II. Composition of the diets administered to the subjects.

Ingredients	Stabilization diet (7 days)	High-CHO diet (6 days)
Carbohydrate (% to total energy)	54.1 ± 2.4	70.1 ± 2.8*
Protein (% to total energy)	15.8 ± 1.8	16.2 ± 1.6*
Fatty acids (% to total energy)	30.1 ± 3.6	13.8 ± 1.4*
Saturated fatty acids (% to total energy)	7.5 ± 0.9	3.6 ± 0.5*
Monounsaturated fatty acids (% to total energy)	16.1 ± 1.4	7.3 ± 0.8*
Polyunsaturated fatty acids (% to total energy)	6.4 ± 1.5	2.8 ± 0.3*
Fiber (g/d)	11.6 ± 2.3	15.4 ± 3.6*
Glycemic index	76.2 ± 1.1	54.4 ± 0.7*
Caloric intake (cal/d)	2289 ± 848	2999 ± 1110*

Data are reported as means ± SD. Calories from food intake were not restricted for each meal. The volunteers ate to satiation as usual in their daily life. The diets were supplied by the Department of Nutrition at West China Medical Center.

* $p < 0.05$ for stabilization diet vs. high-CHO diet (unpaired t -test).

LDL-C was quantified by the polyvinyl sulfate precipitation method by using a semi-automated biochemistry analyzer (BT-224), and apoAI and apoB100 were measured by immunoturbidimetry assay by using a Hitachi 7070 Analyzer.

All biochemical parameters were measured three times, and the average values were used for statistical analysis.

DNA extraction and genotyping

Genomic DNA was isolated from peripheral blood leukocytes. Genotyping was performed as described by Guerra et al. [21]. PCR primers were modified. A 284-bp sequence of the hepatic lipase gene was amplified by PCR by using the primers 5'-TCTA GGATCACCTCTCAATGGGTCA-3' and 5'-GGT GGCTTCCACGTGGCTGCCTAAG-3'. DNA templates were denatured at 95°C for 3 minutes, and then 35 cycles of PCR were performed using 1 minute of denaturation at 95°C, 0.5 minute of annealing at 63°C, and 0.5 minute of extension at 72°C. The PCR products were digested with 10 U of *Nla*III and the fragments were separated by electrophoresis on a 1.5% agarose gel. The resulting fragments are 214 and 70 bp for the T allele and 284 bp for the uncut C allele.

Statistical analysis

The data of four volunteers were excluded because they did not complete the study with good compliance. All the results are expressed as mean ± standard deviation (SD). Normality of each variable was analyzed by the Shapiro-Wilk test. Unpaired t -tests were performed to calculate the differences between male and female subjects. Unpaired t -test was also used to calculate the differences of variables between subjects with different genotypes. Two-tailed paired t -tests were applied to calculate the differences of the variables before and after the high-CHO diet. Statistical significance was set at $p < 0.05$.

Results

Frequencies of genotypes and alleles of the hepatic lipase C-514T (rs1900588) polymorphism

Of the 56 subjects studied, 20 (35.7%) were wild-type homozygotes (CC), 27 (48.2%) were heterozygotes (CT), and 9 (16.1%) were mutant homozygotes (TT). The frequency of the major allele C was 60%, and the frequency of the minor allele T was 40% (Figure 1). No deviation from the Hardy-Weinberg equilibrium was found in the distribution of the genotypes ($\chi^2 = 0.002$, $p = 0.965$).

Body composition, the ratios of serum lipids and apolipoproteins in the subjects with different genotypes of the hepatic lipase C-514T (rs1900588) polymorphism at baseline

Due to the small group size of the homozygotes for the minor allele, the heterozygotes and homozygotes carrying the T allele were combined and referred to as the T carriers for statistical analysis. As shown in Table III, for body composition, females showed significantly lower waist circumference (WC) ($p = 0.049$ for the CC genotype and $p = 0.019$ for T carriers) and waist-to-hip ratio (WHR) ($p = 0.015$ for the CC genotype and $p = 0.000$ for T carriers) than their corresponding males (unpaired t -test), which was not shown in the body mass index (BMI). And no significant difference was found between different genotypes (unpaired t -test). For the ratios of serum lipids and apolipoproteins, there was no significant difference in different genotypes and genders (unpaired t -test) (Table III).

Effects of the high-CHO diet on the body composition, the ratios of serum lipids and apolipoproteins in the subjects with different genotypes of the hepatic lipase C-514T (rs1800588) polymorphism

As shown in Table IV, compared with those before the high-CHO diet, for the body composition, in all

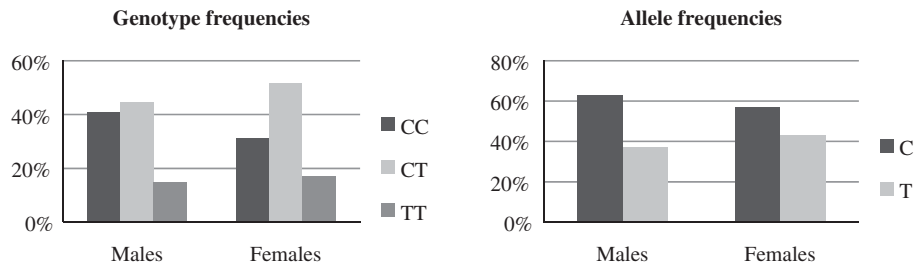


Figure 1. Genotype and allele frequencies of hepatic lipase C-514T polymorphism. No deviation was found from the Hardy-Weinberg equilibrium in the distribution of genotypes ($\chi^2 = 0.002$, $p = 0.965$).

T carriers, both BMI ($p = 0.015$) and WC ($p = 0.015$) were significantly decreased. When gender was taken into consideration, BMI and WC were significantly decreased in male T carriers ($p = 0.043$ and $p = 0.048$), while WHR did not show the change (paired t -test). Females have significantly lower WC (before the high-CHO diet: $p = 0.013$ for CC genotype and $p = 0.018$ for T carriers; after the high-CHO diet: $p = 0.024$ for CC genotype and $p = 0.013$ for T carriers) and WHR (before the high-CHO diet: $p = 0.001$ for CC genotype and $p = 0.000$ for T carriers; after the high-CHO diet: $p = 0.001$ for CC genotype and $p = 0.000$ for T carriers) than the corresponding males (unpaired t -test). Comparing different genotypes, T carriers had significantly higher WC than CC genotype in females ($p = 0.034$) only before the high-CHO diet (unpaired t -test).

For the ratios of serum lipids and apolipoproteins, in all subjects, both TC/HDL-C ($p = 0.000$ for the CC genotype and $p = 0.001$ for the T carriers) and LDL-C/HDL-C ($p = 0.000$ for the CC genotype and $p = 0.000$ for the T carriers) decreased significantly, and apoB100/apoAI decreased significantly in the CC genotype ($p = 0.032$) after the high-CHO diet (paired t -test). When gender was taken into consideration, the females had significantly higher ratios of TG/HDL-C ($p = 0.047$ for the CC genotype and $p = 0.003$ for the T carriers), and the males had significantly lower ratios of TC/HDL-C ($p = 0.000$ for the CC genotype and $p = 0.003$ for the T carriers) after the high-CHO diet (paired t -test).

LDL-C/HDL-C decreased significantly for the male subjects with the CC genotype ($p = 0.001$), the male T carriers ($p = 0.000$), the female subjects with the CC genotype ($p = 0.018$) and the female T carriers ($p = 0.006$, paired t -test). A significant reduction of apoB100/apoAI was observed in the male subjects with the CC genotype ($p = 0.005$) after the high-CHO diet intervention (paired t -test). And no significant difference was observed between different genotypes and genders for the ratios of serum lipids and apolipoproteins before and after the high-CHO diet (unpaired t -test).

Discussion

While studying the interaction of a high-CHO diet with hepatic lipase C-514T (rs1800588) polymorphism on the body composition, ratios of serum lipids and apolipoproteins in a young Chinese cohort, BMI and WC were found significantly reduced in male T carriers after the high-CHO diet. It was well-known that the high-CHO diet can help reduce weight gain [22], and it was also found that this rs1800588 polymorphism significantly associated with BMI and waist circumference only when modified by adiposity status in US diabetic men [23], our results showed that this polymorphism significantly associated with BMI and WC when modified by a high-CHO diet in healthy Chinese youth. Previous research has documented that the HL promoter with T at position -514 had approximately 30% lower

Table III. Body composition, lipid and apolipoprotein ratios of the subjects at baseline.

Variables	Males		Females		All	
	CC ($n = 11$)	T carriers ($n = 16$)	CC ($n = 9$)	T carriers ($n = 20$)	CC ($n = 20$)	T carriers ($n = 36$)
Age (yr)	22.9 \pm 2.3	23.0 \pm 1.6	22.4 \pm 1.2	23.0 \pm 1.8	22.7 \pm 1.9	23.0 \pm 1.7
Body mass index (kg/m ²)	22.1 \pm 5.0	21.7 \pm 3.6	19.1 \pm 2.5	20.8 \pm 2.5	20.8 \pm 4.3	21.2 \pm 3.0
Waist circumference (cm)	75.2 \pm 13.4	74.7 \pm 7.3	64.7 \pm 4.2 [‡]	68.7 \pm 6.6 [‡]	70.8 \pm 11.6	71.3 \pm 7.5
Waist-to-hip ratio	0.89 \pm 0.07	0.89 \pm 0.05	0.82 \pm 0.02 [‡]	0.83 \pm 0.05 [‡]	0.86 \pm 0.06	0.86 \pm 0.06
TG/HDL-C	0.80 \pm 0.79	0.80 \pm 0.73	0.45 \pm 0.26	0.47 \pm 0.26	0.63 \pm 0.61	0.62 \pm 0.54
TC/HDL-C	3.08 \pm 1.15	2.40 \pm 0.85	2.38 \pm 0.35	2.44 \pm 0.50	2.75 \pm 0.92	2.42 \pm 0.67
LDL-C/HDL-C	1.81 \pm 0.87	1.46 \pm 0.63	1.23 \pm 0.23	1.25 \pm 0.42	1.54 \pm 0.70	1.34 \pm 0.53
ApoB100/apoAI	0.37 \pm 0.15	0.32 \pm 0.12	0.32 \pm 0.07	0.32 \pm 0.08	0.35 \pm 0.12	0.32 \pm 0.10

Data are shown as mean \pm SD.

[#] $p < 0.05$ for subjects with different genotypes (unpaired t -tests). No significant difference was detected.

[‡] $p < 0.05$ for females vs. males (unpaired t -tests).

Table IV. Body composition, lipid and apolipoprotein ratios of the subjects before and after the high-CHO diet.

Variables	Males		Females		All	
	CC (n = 11)	T carriers (n = 16)	CC (n = 9)	T carriers (n = 20)	CC (N = 20)	T carriers (N = 36)
Age (yr)	22.9 ± 2.3	23.0 ± 1.6	22.4 ± 1.2	23.0 ± 1.8	22.7 ± 1.9	23.0 ± 1.7
Body mass index (kg/m ²)						
Before	21.9 ± 5.0	21.6 ± 3.6	19.1 ± 2.5	20.6 ± 2.5	20.6 ± 4.2	21.1 ± 3.0
After	21.8 ± 5.0	21.5 ± 3.5*	19.0 ± 2.4	20.5 ± 2.5	20.5 ± 4.2	21.0 ± 3.0*
Waist circumference (cm)						
Before	74.9 ± 11.9	74.5 ± 7.5	63.4 ± 4.3‡	68.7 ± 6.5##	69.7 ± 10.8	71.3 ± 7.5
After	74.4 ± 12.4	74.0 ± 7.3*	63.7 ± 4.1‡	68.2 ± 6.0‡	69.6 ± 10.9	70.8 ± 7.1*
Waist-to-hip ratio						
Before	0.90 ± 0.05	0.90 ± 0.04	0.81 ± 0.05‡	0.84 ± 0.04‡	0.86 ± 0.07	0.87 ± 0.05
After	0.90 ± 0.05	0.90 ± 0.05	0.82 ± 0.03‡	0.84 ± 0.03‡	0.86 ± 0.06	0.87 ± 0.05
TG/HDL-C						
Before	0.83 ± 0.67	0.77 ± 0.43	0.47 ± 0.21	0.53 ± 0.18	0.67 ± 0.54	0.64 ± 0.33
After	0.85 ± 0.66	0.73 ± 0.39	0.54 ± 0.24*	0.63 ± 0.24*	0.71 ± 0.53	0.67 ± 0.31
TC/HDL-C						
Before	2.96 ± 0.90	2.76 ± 0.83	2.36 ± 0.33	2.41 ± 0.38	2.69 ± 0.75	2.56 ± 0.63
After	2.32 ± 0.71*	2.30 ± 0.57*	2.19 ± 0.20	2.28 ± 0.40	2.26 ± 0.53*	2.29 ± 0.48*
LDL-C/HDL-C						
Before	1.49 ± 0.69	1.45 ± 0.65	1.24 ± 0.25	1.19 ± 0.39	1.38 ± 0.55	1.30 ± 0.53
After	1.04 ± 0.44*	1.07 ± 0.45*	0.99 ± 0.18*	1.00 ± 0.31*	1.02 ± 0.34*	1.04 ± 0.38*
ApoB100/apoAI						
Before	0.37 ± 0.19	0.35 ± 0.15	0.31 ± 0.06	0.30 ± 0.08	0.34 ± 0.14	0.32 ± 0.12
After	0.35 ± 0.18*	0.34 ± 0.15	0.30 ± 0.08	0.30 ± 0.08	0.33 ± 0.14*	0.32 ± 0.12

Data are shown as mean ± SD.

* $p < 0.05$ for after the high-CHO diet vs. after stabilization diet (paired t -tests).

$p < 0.05$ for subjects with different genotypes (unpaired t -tests).

‡ $p < 0.05$ for females vs. males (unpaired t -tests).

activity than the one with C at the same position ($p < 0.0005$) [24], after being modified by a high-CHO diet, the HL activity in T polymorphism is more favorable to BMI and WC in these Chinese males.

It was found in the study that the CC genotype of the hepatic lipase C-514T (rs1800588) polymorphism was associated with a lower apoB100/apoAI ratio in males on high-CHO diets. This ratio was significantly decreased after the high-CHO diet in the male subjects with CC genotype, but not in the female subjects with the same genotype. This discrepancy is most likely caused by the effects of estrogen which can increase plasma levels of apoAI [25], and thus will modulate HL activity [26].

As reviewed by Isaacs and colleagues [27], there is a large number of previous studies documenting the association of elevated plasma HDL-C concentration with the hepatic lipase polymorphism among general populations [14,16,21,27–29]. Other studies reported an association between this polymorphism and plasma apolipoprotein (apo) AI and HDL-TG concentrations [30]. In our study, we observed this polymorphism associated with a lower apoB100/apoAI ratio, and not significantly related to other HDL-C-related ratios.

Previous studies have also investigated the influence of dietary fat intake on the effect of the hepatic lipase C-514T (rs1800588) polymorphism on plasma lipid levels, but data are controversial [15–19]. To our knowledge, no study had investigated this influence

on the ratios of serum lipids and apolipoproteins. And our study is the first one to describe an interaction between a high-CHO diet and the hepatic lipase C-514T (rs1800588) polymorphism in a young Chinese population. We found that the hepatic lipase C-514T (rs1800588) polymorphism associated with a lower apoB100/apoAI ratio in males. Furthermore, the high-CHO diet positively associated with the TC/HDL-C and LDL-C/HDL-C ratios, and negatively associated with the TG/HDL-C ratio. It has been shown that individuals with different gene background differ widely in the response of their lipid profiles to diet [31], therefore, comparing our findings with the results of other studies is complicated, because all those studies were conducted with important ethnic differences. The Framingham study was conducted in Caucasian men and women [15], and the study by Tai and colleagues was conducted in a multiethnic Asian population composed of Chinese, Malaysian, and Asian Indian men and women [16]. Nettleton and colleagues studied a cohort of Caucasian and African American men and women from the United States [17]. Moreover, we cannot ignore that the important differences in the diets between our young and healthy Chinese population and the other investigated populations provide additional potential confusion.

Finally, it is likely that other environmental and genetic factors may also justify the different results between studies. A possible direct effect of fatty acids

on hepatic lipase expression has been suggested [10]. The effect of dietary fat on hepatic lipase activity could depend on the hepatic lipase C-514T (rs1800588) polymorphism.

It is noticeable that TG/HDL-C ratios in females were negatively influenced by the high-CHO diet. Estrogen level might be an explanation. High-CHO diets adversely increase the concentrations of TGs, which are mainly hydrolyzed by lipoprotein lipase, a key enzyme in the hydrolysis of TGs in blood. However, high levels of estrogen in females can significantly inhibit the activity of lipoprotein lipase and retard the hydrolysis of TGs [32].

In summary, the effects of the high-CHO diet were observed in a young and healthy Chinese cohort. Females might be more susceptible to hypertriglycerolemia under this diet but it has favorable effects on the TC/HDL-C and LDL-C/HDL-C ratios. However, the high-CHO diet induces the beneficial effect of the CC genotype of hepatic lipase rs1800588 polymorphism on the apoB100/apoAI ratio only in the males of this cohort. Our results provide new insight for further investigations for personalized dietary recommendations in China.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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