Genetic susceptibility, dietary cholesterol intake, and plasma cholesterol levels in a Chinese population

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Abstract Accompanied with nutrition transition, non-HDL-C levels of individuals in Asian countries has increased rapidly, which has caused the global epicenter of nonoptimal cholesterol to shift from Western countries to Asian countries. Thus, it is critical to underline major genetic and dietary determinants. In the current study of 2,330 Chinese individuals, genetic risk scores (GRSs) were calculated for total cholesterol (TC; GRS TC, 57 SNPs), LDL-C (GRS LDL-C, 45 SNPs), and HDL-C (GRS HDL-C, 65 SNPs) based on SNPs from the Global Lipid Genetics Consortium study. Cholesterol intake was estimated by a 74-item food-frequency questionnaire. Associations of dietary cholesterol intake with plasma TC and LDL-C strengthened across quartiles of the GRS TC (effect sizes: −0.29, 0.34, 2.45, and 6.47; Pinteraction = 0.002) and GRS LDL-C (effect sizes: −1.35, 0.17, 5.45, and 6.07; Pinteraction = 0.001), respectively. Similar interactions with non-HDL-C were observed between dietary cholesterol and GRS TC (Pinteraction = 0.001) and GRS LDL-C (Pinteraction = 0.004). The adverse effects of GRS TC on TC (effect sizes across dietary cholesterol quartiles: 0.51, 0.82, 1.21, and 1.51; Pinteraction = 0.023) and GRS LDL-C on LDL-C (effect sizes across dietary cholesterol quartiles: 0.66, 0.52, 1.12, and 1.56; Pinteraction = 0.020) were more profound in those having higher cholesterol intake compared with those with lower intake. Our findings suggest significant interactions between genetic susceptibility and dietary cholesterol intake on plasma cholesterol profiles in a Chinese population.

Supplementary key words epidemiology • human genetics • low-density lipoprotein • high-density lipoprotein • total cholesterol • interaction

Abnormal blood cholesterol levels, characterized by elevated total cholesterol (TC) and LDL-C and decreased HDL-C, are among the key risk factors for CVD (1), Alzheimer’s disease (2), and cancer (3) in many developed and developing countries globally. According to a recent report that pooled 102.6 million adults from 200 countries, the estimated high non-HDL-C accounted for 3.9 million global deaths in 2017, half of which were in Asian countries, where there were net increases in TC or non-HDL-C (4). Cholesterol in the human body comes from two sources: dietary intake (~30%) and de novo synthesis in the liver (~70%) (5). Numerous studies have shown that diet and lifestyle factors, genetic variation, and pharmacologic agents that modify hepatic cholesterol synthesis may individually or collectively affect plasma cholesterol levels (6, 7). Considering that most studies have not shown an appreciable relationship between dietary cholesterol intake and circulating cholesterol levels (8), despite some controversy (9), the latest Dietary Guidelines for Americans removed the restriction for dietary cholesterol (10), which was consequently adopted by other countries, including China (11). However, the responsiveness of the blood cholesterol profile to dietary cholesterol intake varied considerably between different populations and individuals (12, 13), and genetic predisposition might partially explain the heterogeneities (14).

Recent GWASs have identified many genetic loci associated with blood cholesterol levels, and many of them are involved in cholesterol biosynthesis, absorption, and efflux (15–19). Several observational and intervention studies have shown that certain genetic variants could modify the associations of dietary cholesterol intake with the plasma lipid profile (20–23). For example, individuals who carried the risk allele of rs17725246 at NPC1L1, which encoded a multipass membrane protein involving cholesterol absorption in the intestinal tract (24), had a greater plasma TC increase with the same dietary cholesterol intake than those without the risk allele in a cross-sectional study among 1,128 Caucasian subjects (20). However, most available studies only investigated the effects of individual SNPs, which exhibited rather minor influences on the response of plasma cholesterol at a given level of dietary cholesterol intake (25). Although several genes are involved in the complex regulation of maintaining cholesterol homeostasis, few studies have systematically evaluated collective effects of multiple genetic variants on the relationships between dietary cholesterol intake and plasma cholesterol. Moreover, there were some differences in allele frequencies and effect sizes for cholesterol-related SNPs between East Asians and Europeans (26), although the underlying genetic architecture of plasma lipids seems similar between...
different ethnicities (27). In addition, Chinese individuals have experienced rapid dietary transition with increased consumption of animal-source foods, and non-HDL-C levels have increased even more rapidly compared with many Western countries in the last few decades (4). It has also been observed that dietary cholesterol in Chinese individuals mainly come from egg consumption (28) rather than meat intake as in Western populations (29). Thus, by constructing genetic risk scores (GRSs) that combine multiple genetic variants, the current study aimed to examine the cumulative effects of multiple genetic variants and their interactions with dietary cholesterol intake on plasma cholesterol levels in a Chinese population.

METHODS

Study population
The study participants were from the baseline of the Nutrition and Health of Aging Population in China study, a population-based cohort study of 3,289 individuals (1,458 men and 1,831 women) aged 50 to 70 years that aimed to investigate genetic and environmental risk factors and their interaction in metabolic diseases. The study design and protocol have been described in detail previously (30). In brief, Beijing and Shanghai were selected to represent the north and south of China, respectively. A multi-stage sampling method was used to recruit the participants from two urban districts and one rural district in each city with comparable socioeconomic status. The residents were recruited if they lived at least 20 years in the areas and were free from severe psychological disorders, physical disabilities, cancer, CVD, Alzheimer’s disease or dementia, and other communicable diseases. Finally, a total of 3,289 eligible participants were recruited from March to June 2005, and all of them provided written informed consent.

Final analyses included 2,330 individuals after the exclusion of individuals with the following conditions: using lipid-lowering medications (n = 232) or self-reported hyperlipidemia (n = 262); daily energy intake of <800 or >4,000 kcal/day for men and <500 or >3,500 kcal/day for women (n = 138); and without genotype data (n = 327). The study protocol was approved by the Institute for Nutritional Sciences Institutional Review Board, and written informed consent was obtained from all participants. This study abides by the Declaration of Helsinki principles.

Data collection
Information on demographic variables, health status, health behavior, and physical activity were obtained by a face-to-face interview using a standardized questionnaire by trained staff. Educational attainment, current smoking, and current drinking were defined as previously described (30). Physical activity levels were categorized as low, moderate, or high by adapting a short format of the International Physical Activity Questionnaire (31). Dietary intake was assessed with a 74-item food-frequency questionnaire adapted from the 2002 National Nutrition and Health Survey in China (32) with minor modifications. Dietary cholesterol intake from eggs, red and processed meats, poultry, fish and shellfish, dairy products, and other foods were estimated according to the Chinese Food Composition Table (33).

All participants were invited to attend a physical examination, and anthropometric measurements were performed with a standardized protocol by trained research team members. BMI was calculated as weight/height² (kg/m²). Overnight fasting blood samples were collected and centrifuged at 4°C and then were stored at −80°C until analysis. Plasma TC, LDL-C, and HDL-C levels were measured enzymatically on a Hitachi 7080 automatic biochemistry analyzer, with reagents purchased from Wako Pure Chemical Industries. The levels of non-HDL-C were calculated by TC – HDL-C.

Genotyping and GRS calculation
Genomic DNA was extracted from peripheral plasma leukocytes, and SNPs were genotyped as described in detail previously (34). In brief, samples of the Nutrition and Health of Aging Population in China study were genotyped using an Illumina Human660W-Quad BeadChip. We excluded the SNPs with a call rate <95%, minor allele frequency (MAF) <1%, or not in Hardy-Weinberg equilibrium (P < 10⁻⁶). Imputation for the ungenotyped or missing SNPs was performed using the 1000 Genomes haplotype reference panel (phase 3) by IMPUTE version 2.1.2. We removed all imputed SNPs with an estimated call rate <99%, MAF <1%, Hardy-Weinberg equilibrium of P < 10⁻⁶, or with poor imputation quality, defined as the info measure <0.5.

A total of 117 SNPs with an MAF ≥1% and missing rate of <10% in our genetic database were selected from 141 loci that were significantly associated with plasma TC, LDL-C, or HDL-C levels in the 2013 Global Lipid Genetics Consortium (GLGC) study (16). Each SNP was recoded as 0, 1, or 2 according to the number of cholesterol-increasing alleles and weighted by its relative effect size derived from the Global Lipid Genetics Consortium data. GRSs were calculated with the following equation: GRS = (β₁ × SNP₁ + β₂ × SNP₂ + ... + βₙ × SNPₙ) × (n/sum of the β coefficients), where β is the effect size of each individual SNP on plasma cholesterol, n is the number of SNPs for each GRS, and sum of the β is the sum of effect sizes of SNPs included in GRSs (sum of the β is 2.78 for TC, 2.29 for LDL-C, and 2.86 for HDL-C). There were 35 overlapped SNPs between GRSₚₚ (57 SNPs) and GRSₚₚₐₕ (45 SNPs), 13 overlapped SNPs between GRSₚₚ and GRSₚₚₐₕ (65 SNPs), and 8 overlapped SNPs between GRSₚₚₐₕ (45 SNPs), and GRSₚₚₐₕ (65 SNPs), and 8 overlapped SNPs between GRSₚₚₐₕ and GRSₚₚₐₕ. Six SNPs were shared by the aforementioned three GRSs. Missing genotypes were replaced with the average cholesterol-increasing allele number for each SNP. The SNPs included in each GRS are summarized in supplemental Tables S1–S3.

Statistical analyses
To detect the associations of dietary cholesterol with plasma cholesterol levels, P-trends were calculated by fitting the median value of cholesterol intake in each category as a continuous variable in the linear regression model adjusted for age, sex, region, residence, educational attainment, current smoking, current drinking, physical activity, BMI, total energy intake, and dietary carbohydrate and fat intake (% energy). After further adjusting for the first four principal components, general linear regression models were used to test the associations of GRSs with plasma cholesterol levels, assuming an additive effect of the cholesterol-increasing alleles. For the interaction analysis, values of dietary cholesterol intake were naturally log-transformed before analyses because of skewed distributions, and interactions between GRSs/SNPs and dietary cholesterol intake were tested by including GRSs/SNPs × dietary cholesterol intake in a general linear regression model adjusted for the aforementioned confounding factors. All P-values were two-sided. Statistical analyses were performed in R version 3.5.1.

RESULTS

Participant characteristics
The baseline characteristics of the participants according to quartiles of dietary cholesterol intake are shown in...
Table 1. The subjects with higher cholesterol intake were younger and more likely to be male, northern and urban residents, consumers of alcohol, and with higher levels of education and a higher BMI (all \( P \leq 0.019 \)). Persons with high cholesterol consumption also had higher intakes of total energy, fat, and protein but lower carbohydrate intake (all \( P < 0.001 \)). In addition, there were no significant differences in GRSTC, GRSLDL-C, or GRSHDL-C across the extreme quartiles of dietary cholesterol intake.

**Associations of dietary cholesterol intake with plasma cholesterol levels**

As shown in Table 2, dietary cholesterol intake was positively associated with plasma concentrations of TC (\( \textit{P}_{\text{trend}} = 0.019 \)), LDL-C (\( \textit{P}_{\text{trend}} = 0.008 \)), and non-HDL-C (\( \textit{P}_{\text{trend}} = 0.021 \)) but not with plasma HDL-C concentrations (\( \textit{P}_{\text{trend}} = 0.486 \)). The mean value of plasma TC, LDL-C, and non-HDL-C in the fourth quartile was 13.1, 14.9, and 13.0 mg/dL higher than that in the first quartile, respectively.

**Associations of GRSs with plasma cholesterol levels**

All three calculated GRSs were normally distributed in terms of the number of participants across categories (Fig. 1). The median (range) of each GRS was 61.28 (46.32–73.45) for GRS TC, 42.09 (29.53–56.51) for GRS LDL-C, and 68.95 (54.24–89.17) for GRS HDL-C. As shown in Fig. 1, individuals in the highest category of GRS TC (>69) had a higher plasma TC level (169.71 vs. 111.57 mg/dL) than those in the lowest category (≤54). Average LDL-C levels increased from 131.85 to 187.41 mg/dL compared with individuals in the lowest (≤35) versus those in the highest (>50) GRS LDL-C category. Similarly, the mean HDL-C levels were 54.30 versus 45.77 mg/dL in the highest GRS HDL-C (>80) and the lowest (≤60) GRS HDL-C category. Each additional TC-increasing allele of GRS TC, LDL-C-increasing allele of GRS LDL-C, and HDL-C-increasing allele of GRS HDL-C were correspondingly associated with an increased plasma level of 0.99 mg/dL for TC (\( P = 1.01 \times 10^{-5} \)), 0.98 mg/dL for LDL-C (\( P = 3.92 \times 10^{-8} \)), and 0.47 mg/dL for HDL-C (\( P = 5.44 \times 10^{-26} \)) after multivariable adjustment. When the associations of individual SNPs with plasma TC, LDL-C, and HDL-C levels were examined, most SNPs showed expected associations with plasma lipids, although only five, six and nine SNPs were significantly associated with plasma TC, LDL-C, and HDL-C levels (\( P < 0.05 \)), respectively (supplemental Tables S1–S3).

**Interaction between dietary cholesterol intake and GRSs on plasma cholesterol levels**

As shown in Fig. 2, there were significant interactions between dietary cholesterol intake and GRSs on plasma TC and LDL-C levels. Associations of dietary cholesterol with plasma TC and LDL-C were stronger in individuals with higher GRS TC (effect sizes across GRS TC quartiles: −0.29, 0.34, 2.45, and 6.47; \( P_{\text{interaction}} = 0.002 \)) and GRS LDL-C (effect sizes across GRS LDL-C quartiles: −1.35, 0.17, 5.45, and 6.07; \( P_{\text{interaction}} = 0.001 \)) compared with those with lower scores. No significant interaction was evidenced between dietary cholesterol intake and GRS HDL-C on plasma HDL-C level (\( P_{\text{interaction}} = 0.206 \)). Moreover, the association between dietary cholesterol and non-HDL-C was also significantly modified by GRS TC (effect sizes across GRS TC

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**Table 1. Characteristics of study participants according to dietary cholesterol quartile**

| Quartiles of dietary cholesterol intake (mg/day) | N | Q1: 178.1 | Q2: 178.1–314.8 | Q3: 314.8–467.3 | Q4: >467.3 |
|---|---|---|---|---|---|
| Age (years) | 583 | 58.6 ± 6.2 | 58.3 ± 6.0 | 58.3 ± 6.0 | 583 |
| Males [%] | 59.1 ± 6.0 | 245 (41.8) | 252 (43.3) | 283 (48.5) | <0.001 |
| Northern residents [%] | 193 (33.1) | 215 (36.9) | 294 (50.5) | 368 (63.1) | <0.001 |
| Education [%] | 154 (26.4) | 231 (39.7) | 303 (52.1) | 417 (71.3) | <0.001 |
| Current smokers [%] | 143 (24.5) | 152 (26.1) | 150 (25.8) | 167 (28.6) | 0.146 |
| Current drinkers [%] | 122 (20.9) | 144 (24.7) | 153 (26.3) | 206 (35.5) | <0.001 |
| Physical activity level [%] | 389 (66.7) | 302 (51.9) | 223 (38.3) | 137 (23.5) | <0.001 |
| Low | 58 (9.9) | 54 (9.3) | 41 (7.0) | 32 (5.5) | 0.338 |
| Moderate | 205 (35.2) | 223 (38.3) | 247 (42.4) | 280 (48.0) | 0.146 |
| High | 320 (54.9) | 305 (52.4) | 294 (50.5) | 271 (46.5) | <0.001 |
| BMI (kg/m²) | 23.9 ± 5.5 | 23.9 ± 5.6 | 24.5 ± 3.7 | 24.5 ± 3.5 | <0.001 |
| Dietary intake | | | | | |
| Total energy intake (kcal/day) | 1,992 ± 608 | 2,171 ± 597 | 2,246 ± 573 | 2,491 ± 593 | <0.001 |
| Carbohydrates (% energy) | 65.2 ± 9.5 | 61.5 ± 8.5 | 58.6 ± 7.8 | 53.6 ± 8.0 | <0.001 |
| Fat (% energy) | 24.4 ± 8.3 | 27.0 ± 7.8 | 29.5 ± 7.3 | 32.4 ± 7.2 | <0.001 |
| Protein (% energy) | 10.6 ± 1.9 | 12.0 ± 2.1 | 12.9 ± 2.0 | 14.7 ± 2.6 | <0.001 |
| Cholesterol intake [mg/day (IQR)] | 116.2 (78.3, 150.9) | 236.9 (208.0, 272.3) | 406.1 (369.8, 436.4) | 552.9 (502.0, 694.8) | <0.001 |

Data are presented as means ± SDs for normally distributed continuous variables, medians (IQRs) for skewed distributed continuous variables, and counts (percentages) for categorical variables. \( P \) values are for the trend across the quartiles of dietary cholesterol intake. IQR, interquartile range.
quartiles: \(-1.70, 0.11, 1.13, \text{ and } 6.90; \ P_{\text{interaction}} = 0.001\) and \(\text{GRS}_{\text{LDL-C}}\) (effect sizes across \(\text{GRS}_{\text{LDL-C}}\) quartiles: \(-1.31, -1.08, 4.36, \text{ and } 4.53; \ P_{\text{interaction}} = 0.004\) (Fig. 2).

On the other hand, we also examined whether dietary cholesterol intake could modify the relationships between GRSs and plasma cholesterol levels. As shown in Fig. 3, compared with those with a lower cholesterol intake, individuals with a higher intake of cholesterol showed stronger genetic associations between GRSs and cholesterol levels. The increases of the plasma TC level for an increment of each TC-increasing allele were 0.51, 0.82, 1.21, and 1.31 across the first to fourth quartile of dietary cholesterol intake (\(P_{\text{interaction}} = 0.023\)), and the effect sizes of \(\text{GRS}_{\text{LDL-C}}\) on plasma LDL-C levels were 0.66, 0.52, 1.12, and 1.56 across the quartiles of dietary cholesterol intake (\(P_{\text{interaction}} = 0.020\)). The effect sizes of \(\text{GRS}_{\text{HDL-C}}\) on the plasma HDL-C level were similar across the dietary cholesterol quartiles (\(P_{\text{interaction}} = 0.627\)).

In the sensitivity analysis, dietary cholesterol intake (mg/day) was replaced by energy-scaled cholesterol intake (mg/1,000 kcal/day). As shown in supplemental Figs. S1 and S2, the associations of dietary cholesterol intake (mg/1,000 kcal/day) with plasma TC, LDL-C, or non-HDL-C levels strengthened across quartiles of \(\text{GRS}_{\text{TC}}\) and \(\text{GRS}_{\text{LDL-C}}\) (\(P_{\text{interaction}} \leq 0.005\)). The effects of \(\text{GRS}_{\text{TC}}\) on TC and \(\text{GRS}_{\text{LDL-C}}\) on LDL-C were more profound in individuals with a higher cholesterol intake (mg/1,000 kcal/day) than those with a lower intake (\(P_{\text{interaction}} = 0.019\)).

In addition, the effects of individual SNPs on the associations between dietary cholesterol intake and plasma cholesterol levels were also examined. As expected, because of the modest effect of individual SNPs, there were only 10, 10, and 2 SNPs that showed significant interactions on the relationships between dietary cholesterol and plasma TC (\(P_{\text{interaction}} \leq 0.042\)), LDL-C (\(P_{\text{interaction}} \leq 0.032\)), and HDL-C (\(P_{\text{interaction}} \leq 0.047\)), respectively (supplemental Tables S1–S3, supplemental Figure S3). Of note, significant interactions were observed for some genetic variants in the genes that are involved in cholesterol biosynthesis, absorption, and efflux such as \(\text{GPAM}, \text{MYLIP}, \text{MAFB}, \text{APOA1}\), and so on.

### DISCUSSION

In this population-based study of Chinese individuals, both GRSs and dietary cholesterol intake were significantly associated with elevated plasma concentrations of TC and LDL-C. Moreover, we also identified significant interactions between overall genetic susceptibility and dietary cholesterol intake on plasma TC, LDL-C, and non-HDL-C levels.
The finding of significant associations between dietary cholesterol and plasma concentrations of TC, LDL-C, and non-HDL-C may reflect the double shifting trends in dietary patterns from plant-based to animal-based diets, as well as in non-HDL-C changes from one of the lowest levels in the world to even surpass many Western populations in the last few decades in China, as indicated by a recent global collaboration (4). Indeed, dietary cholesterol consumption increased from 165.8 to 266.3 mg/day from 1991 to 2011 among Chinese adults (35). From 2002 to 2015, blood TC and LDL-C increased from 151.6 to 179.0 mg/dL and from 82.0 to 111.0 mg/dL, respectively, while HDL-C levels decreased from 50.3 to 48.7 mg/dL (36). Consistent with our findings, several studies in Chinese populations also observed significant associations of dietary cholesterol with circulating TC and LDL-C but not with plasma HDL-C levels (11, 37). However, the relationships of dietary cholesterol with circulating cholesterol and the risk of CVD remain controversial (9). The discrepancies might be explained by different dietary patterns, sources, and proportions of...
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macronutrients such as fat or protein, which might influence cholesterol metabolism and circulating levels somewhat differently (38), in addition to different study designs and population characteristics, including genetic background.

To our knowledge, this is the first study to show interactions between overall genetic susceptibility estimated by GRSs and dietary cholesterol intake in relation to plasma cholesterol levels. As a complex trait, circulating cholesterol levels reflect interactions between multiple genes and diet/lifestyle factors. In the current study, individuals with the highest compared with the lowest quartile of GRS TC and GRSLDL-C not only had higher plasma levels of TC and LDL-C but also showed more pronounced influences of dietary cholesterol intake on elevated plasma TC and LDL-C. Moreover, when the non-HDL-C was considered, stronger associations between dietary cholesterol and plasma non-HDL-C were also observed among individuals with higher GRS TC or GRSLDL-C compared with those with lower GRSs. Taken together, our findings show that personalized dietary guidelines might be needed for those with high genetic susceptibility for hypercholesteremia.

On the other hand, our study also suggested that dietary cholesterol intake may amplify the genetic effects on plasma TC and LDL-C levels, which further emphasizes the importance of reducing dietary cholesterol intake in the prevention of hypercholesteremia and related diseases. The effect of GRSLDL-C on plasma LDL-C was more pronounced in the participants in the third and fourth quartiles (>314.8 mg/day) of dietary cholesterol intake than those in the first two quartiles (<314.8 mg/day). To some extent, this observation raised the question of whether the previously recommended limitation of 300 mg/day for dietary cholesterol intake was appropriate. In addition, dietary cholesterol often coexisted with animal protein and saturated fat in foods such as red meat and eggs. Indeed, red and processed meat intake has been shown to increase CVD risk (39, 40). A higher intake of eggs was associated with an increased risk of CVD for individuals with diabetes, although the effect in the general population is still controversial (41–43). Therefore, maintaining low dietary cholesterol consumption should be encouraged as an important health dietary component, as recommended by the 2015–2020 Dietary Guidelines for Americans.

Although potential mechanisms underlying the aforementioned interactions need to be elucidated, it is possible that individuals with a higher genetic predisposition may have a higher biosynthesis rate and lower efflux rate and thus may be more susceptible to dietary cholesterol intake. Although we did not detect significant interactions for most SNPs, which might be due to limited sample sizes, some significant SNPs may provide new insights into potential mechanisms. For example, rs3757354 at MYLIP is associated with the expression of MYLIP, which could stimulate the ubiquitination of the LDL receptor and direct its degradation, thereby inhibiting the uptake of LDL-C from the circulation and increasing circulating LDL-C cholesterol levels (44, 45). MAFB encodes a transcription factor that upregulates the expression of ABCA1 and ABCG1, two genes involved in cholesterol efflux (46). Lipid-free APOA1 also played an important role in the process of cholesterol efflux as the primary acceptor for cholesterol efflux by ABCA1 (45). Collectively, genes involving cholesterol efflux and uptake might play an important role in the gene-diet interactions observed in the
current study. More studies are warranted to detect the underlying mechanisms.

Major strengths of this study are its well-characterized population, integrated data on dietary intake, and multiple genetic variants and plasma cholesterol phenotypes. We also controlled for possible confounding factors, including dietary carbohydrate and fat intake. Admittedly, there are several limitations. First, the cross-sectional nature of the current study cannot establish a causal inference. Second, dietary cholesterol intake was estimated by a food-frequency questionnaire, which could not avoid recall biases, although this method is commonly used in many epidemiologic studies. Third, not all of the SNPs included in GRSSs have biologic mechanisms to interact with diet on plasma cholesterol levels. Therefore, true G × E interactions could be masked or diluted in the current analysis. Fourth, some confounding factors were correlated such as BMI and total energy intake, which might reduce the precision of the estimate coefficients in the current study. Finally, our study participants were middle-aged and older Chinese adults, and our findings need to be confirmed in other populations with different ages or ethnicities.

In conclusion, individuals with higher genetic predisposition as indicated by higher GRSSs might be more sensitive to dietary cholesterol on plasma TC, LDL-C, and non-HDL-C. A higher intake of dietary cholesterol may also promote genetic predisposition to elevated plasma TC and LDL-C.

Data availability
All data can be found in the manuscript and supplemental material.

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Author contributions
X.L. and S.H. conceptualization; B.S., H.Z., and Q.J. measurements; S.H. data analysis; S.H. figure preparation; S.H writing-original draft; X.L., H.L., L.S., and G.Z. writing-review and editing; X.L. supervision. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest
The authors declare that they have no conflicts of interest with the contents of this article.

Abbreviations
GRS, genetic risk score; MAF, minor allele frequency; TC, total cholesterol.

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