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Original article

Interaction between genetic risk score and dietary carbohydrate intake on high-density lipoprotein cholesterol levels: Findings from the study of obesity, nutrition, genes and social factors (SONGS)

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SUMMARY

Background & aims: Cardiometabolic traits are complex interrelated traits that result from a combination of genetic and lifestyle factors. This study aimed to assess the interaction between genetic variants and dietary macronutrient intake on cardiometabolic traits [body mass index, waist circumference, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triacylglycerol, systolic blood pressure, diastolic blood pressure, fasting serum glucose, fasting serum insulin, and glycated haemoglobin].

Methods: This cross-sectional study consisted of 468 urban young adults aged 20 ± 1 years, and it was conducted as part of the Study of Obesity, Nutrition, Genes and Social factors (SONGS) project, a substudy of the Young Lives study. Thirty-nine single nucleotide polymorphisms (SNPs) known to be associated with cardiometabolic traits at a genome-wide significance level ($P < 5 \times 10^{-8}$) were used to construct a genetic risk score (GRS).

Results: There were no significant associations between the GRS and any of the cardiometabolic traits. However, a significant interaction was observed between the GRS and carbohydrate intake on HDL-C concentration ($P_{interaction} = 0.0007$). In the first tertile of carbohydrate intake (≤327 g/day), participants with a high GRS (>37 risk alleles) had a higher concentration of HDL-C than those with a low GRS (≤37 risk alleles) [Beta = 0.06 mmol/L, 95 % confidence interval (CI), 0.01–0.10; $P = 0.018$]. In the third tertile of carbohydrate intake (>452 g/day), participants with a high GRS had a lower concentration of HDL-C than those with a low GRS (Beta = −0.04 mmol/L, 95 % CI −0.01 to −0.09; $P = 0.027$). A significant interaction was also observed between the GRS and glycaemic load (GL) on the concentration of HDL-C

Abbreviations: SONGS, Study of Obesity, Nutrition, Genes and Social factors; YLS, Young Lives Study; CVDs, cardiovascular diseases; SNPs, single nucleotide polymorphisms; GRS, genetic risk score; HDL-C, high-density lipoprotein cholesterol; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TAG, triacylglycerol; TC, total cholesterol; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; BMI, body mass index; WC, waist circumference; GI, glycaemic index; GL, glycaemic load; CI, confidence interval; LACP, Latin American and Caribbean populations; HR, hazard ratio; GWA, genome-wide association; WHO, World Health Organization; FFQ, food frequency questionnaire; HWE, Hardy-Weinberg Equilibrium; SPSS, Statistical Package for the Social Sciences; SD, standard deviation; SE, standard error; TEI, total energy intake; GOLDN, Genetics of Lipid Lowering Drugs and Diet Network.

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($P_{interaction} = 0.002$). For participants with a high GRS, there were lower concentrations of HDL-C across tertiles of GL ($P_{trend} = 0.017$). There was no significant interaction between the GRS and glycaemic index on the concentration of HDL-C, and none of the other GRS*macronutrient interactions were significant.
Conclusions: Our results suggest that young adults who consume a higher carbohydrate diet and have a higher GRS have a lower HDL-C concentration, which in turn is linked to cardiovascular diseases, and indicate that personalised nutrition strategies targeting a reduction in carbohydrate intake might be beneficial for these individuals.

1. Introduction

Cardiometabolic diseases including cardiovascular diseases (CVDs) remain a threat to global public health, and in 2019, around 32 % of worldwide mortality was attributable to CVDs [1]. These diseases place a significant burden on low- and middle-income countries, where more than three-quarters of CVD deaths occur [1,2]. Obesity, a key risk factor for cardiometabolic diseases has been increasing in Latin America, affecting over 26 % of women and 21 % of men in Peru [3]. According to a study which examined mortality and disability in Peru, using data from the Global Burden of Disease, Injuries and Risk Factors (2019) study [4], high body mass index (BMI) was among the key risk factors linked to disability-adjusted life years. Similarly, a high prevalence of dyslipidaemia, in particular, low concentration of high-density lipoprotein cholesterol (HDL-C) (48 %) has been reported in Latin American and Caribbean populations (LACP) [5]. Moreover, Peru experienced a substantial increase in fatalities related to CVDs (77.8 %) between 2020 and 2022 [6].

Obesity is associated with increased risk of CVDs [7–12] which is partly driven by atherogenic dyslipidaemia [9,13]. Although the underlying mechanisms are complex, adipose tissue dysfunction results in several metabolic and cardiovascular disturbances including impaired lipid metabolism [13–15]. Obesity has been linked to alterations in the concentration and distribution of high-density lipoprotein (HDL) particles, and low levels or dysfunctional HDL contributes to the development of CVDs [9,16,17]. A meta-analysis of 97 prospective cohort studies with a total of 1·8 million participants [7] indicated that, in contrast to normal weight, overweight or obesity was linked to a higher risk of coronary heart disease and stroke, with obesity demonstrating a more substantial impact than overweight [hazard ratio (HR) and 95 % confidence interval (CI) for obesity vs normal weight: 1.69 (1.58–1.81) for coronary heart disease; 1.47 (1.36–1.59) for stroke] [7]. Numerous studies have indicated that obesity and other risk factors for cardiometabolic diseases result from multiple factors including genetic and environmental factors [18–25], and in Peru the rise in cardiometabolic risk factors has coincided with a shift in lifestyle pattern in which there is increased consumption of high-caloric foods, animal-based products and sugar-sweetened beverages [26–28] as well as a decline in physical activity [29,30].

Genome-wide association (GWA) studies have identified many genetic variants associated with cardiometabolic traits such as overweight/obesity, dyslipidaemia, high blood pressure and high fasting glucose levels, however, these variants explain a small fraction of variation in BMI [31–33] and blood lipid levels [34–36]. Moreover, the genetic susceptibility to cardiometabolic traits has been shown to be impacted by lifestyle factors such as dietary intake and physical activity level [18,19,23,37–40]. To our knowledge, no studies have examined gene–lifestyle interactions on cardiometabolic traits in the Peruvian population. Hence, we aimed to assess the interaction between a genetic risk score (GRS) and dietary macronutrient intake on cardiometabolic traits in an urban Peruvian young adult population. The GRS approach has been shown to be more effective in predicting the genetic risk of complex traits, where the effect size of single variants is often modest [19,38,40,41].

2. Methods

2.1. Study participants

This study was conducted as part of the Study of Obesity, Nutrition, Genes and Social factors (SONGS) project, a sub-study nested in the Young Lives Study (YLS) in Peru. The YLS is a multi-centre longitudinal survey established in 2002 that follows two birth cohorts (a younger cohort born in 2001–2002, and an older cohort, born in 1994–1995) of children in Peru, India (Andhra Pradesh and Telangana), Ethiopia and Vietnam. In Peru, the original sample corresponds to 2053 children aged 6–18 months in 2002. The YLS sample was selected in two stages. First, 20 clusters were randomly selected from the universe of districts in the country, excluding the wealthiest 5 %. Second, approximately 100 households were chosen at random in each cluster [42]. The sample covers the diversity of living standard conditions observed in the country [42]. Each cohort of participants was visited personally in 2002, 2006, 2009, 2013, and 2016. In 2020 and 2021, due to COVID-19 restrictions, the YLS was administered by phone survey and using an online virtual survey (2021) for collecting specific dietary data in Peru [43].

Participants for this sub-study come from 12 of the original 20 clusters and include 833 urban participants that responded to the phone survey call in 2020. The clusters were purposively chosen to capture the diversity of the country, thus districts located in the Coast, Highland and Jungle regions were selected. Participants were visited by the fieldworkers between July and October 2022 to obtain the specific data for this sub-study. From an initial sample of 833 participants, 735 participants had dietary intake data and after excluding those with missing data for genotyping (YLS participants that refused to provide a blood sample), 620 participants remained. Out of the 620 participants, 468 met the inclusion criteria and were included in the current analysis (Supplementary Figure S1). The inclusion criterion was urban young Peruvian with no diagnosis of chronic diseases. Participants were excluded if they had any chronic condition such as diabetes, thyroid disorder, or polycystic ovary syndrome ($n = 148$). Participants who were pregnant ($n = 1$) or breastfeeding ($n = 3$) were also excluded.

2.2. Anthropometric, blood pressure and biochemical measurements

Anthropometric measurements were taken by trained fieldworkers. The anthropometric variables included height, weight and waist circumference (WC) in centimetres (cm). BMI was calculated using weight (kg) divided by height in meters (m) squared. Weight

was measured using a digital platform balance (SECA 813) with 100-g precision and 200-kg capacity, while height was measured using a portable stadiometer (SECA 213) with a 1-mm precision. Finally, WC was measured using a "ergonomic circumference measuring/retractable stainless steel" tape with a 1-mm precision. The reference measurements were obtained following the standardised protocol by the World Health Organization (WHO) [44,45].

Blood pressure (BP) in mmHg and biochemical measurements were taken by trained health technicians. The BP was taken from the left hand after resting quietly in a seated position for 5 min; two consecutive BP measurements (systolic, SBP and diastolic, DBP) were taken 3 min apart using a digital upper-arm electronic device (Omron HEM-7130). After two BP measurements were taken, the mean of both SBP and DBP were calculated. Standard protocols and validation of devices have been previously reported [46]. Fasting serum lipids [total cholesterol (TC), triacylglycerol (TAG) and HDL-C], glucose and glycated haemoglobin (HbA1c) were quantified by using the RX Daytona Plus clinical chemistry analyser (Randox Laboratories Limited, Crumlin, UK) using kits supplied by Randox. Fasting serum low-density lipoprotein cholesterol (LDL-C) concentration was estimated using the Friedewald equation [47] and non-HDL-C was calculated by subtracting HDL-C from TC. Human insulin was measured using ELISA kits from Protein Simple (Bio-Techne) and the Ella automated Simple Plex instrument (Protein Simple, Bio-Techne). Briefly, plasma samples were centrifuged at 4 °C for 10 min (16,000×*g*) and the supernatant (50 μL) used for analysis, following the manufacturer's instructions (samples were diluted 1:2 prior to analysis).

2.3. Dietary assessment

Dietary intake information was assessed using an online 47-item semi-quantitative food frequency questionnaire (FFQ) previously validated in the YLS [48]. The internal consistency of the instruments demonstrated good performance, with a Cronbach's alpha of 0.82 for all food groups. For each food item, participants were asked to recall the frequency and number of portions consumed during the last month, as well as the number of portions consumed at each occasion, where portion sizes of known weight (g) were selected from a series of photographs. Field researchers input the data with usual frequency estimated within food categories, ranging from never or rarely to more than 5 times daily, which was later converted to number of times per day. To estimate the quantity consumed per day (g/day), the portion size (g) selected was multiplied by frequency per day. To estimate the macronutrient (energy, carbohydrate, protein, fat) and fibre intake, food composition data from the Instituto de Investigación Nutricional database of the Centro Nacional de Alimentación y Nutrición (Peru), and a Latin-American food composition table from the INCAP (Venezuela), was used.

The dietary glycaemic index (GI) for each participant was obtained by multiplying the published GI value of each food item by the amount consumed and the grams of available carbohydrate, then adding up the values and dividing by the total daily carbohydrate intake [49,50]. The glycaemic load (GL) was calculated by multiplying the published GI value of the food item by the amount consumed and the grams of available carbohydrate, then dividing by 100. The values were then added up to obtain the dietary GL [50,51].

2.4. SNP selection and genotyping

We selected a total of 39 SNPs which have shown an association with cardiometabolic traits at a genome-wide significance level ($P < 5 \times 10^{-8}$) (Supplementary Table S1): alpha-ketoglutarate-dependent dioxygenase (*FTO*) SNP rs1558902 [31,52–55]; transmembrane protein 18 (*TMEM18*) SNP rs13021737 [31,56–60]; melanocortin 4 receptor (*MC4R)* SNP rs6567160 [31,59,61–63]; glucosamine-6-phosphate deaminase 2 (*GNPDA2*) SNP rs10938397 [31,61,64,65]; SEC16 homolog B, endoplasmic reticulum export factor (*SEC16B*) SNP rs543874 [31,59,60,65,66]; BCDIN3 domain containing RNA methyltransferase (*BCDIN3D*) SNP rs7138803 [31,59,60,64,65]; transcription factor AP-2 beta (*TFAP2B*) SNP rs2207139 [31,58,60,64]; neuronal growth regulator 1 (*NEGR1*) SNP rs3101336 [31,56–59]; adenylate cyclase 3 (*ADCY3*) SNP rs10182181 [31,56,57,67]; ETS variant transcription factor 5 (ETV5) SNP rs1516725 [31,36,56,64]; glutaminyl-peptide cyclotransferase like (*QPCTL*) SNP rs2287019 [31,59,65,68]; G protein-coupled receptor class C group 5 member B (GPRC5B) SNP rs12446632 [31,59,64,67]; mitochondrial carrier 2 (*MTCH2*) SNP rs3817334 [56,57,66,67]; centriolar protein (*POC5*) SNP rs2112347 [31,59,61,65]; mitogen-activated protein kinase 5 (*MAP2K*) SNP rs16951275 [31,58,69]; zinc finger CCCH-type containing 4 (*ZC3H4*) SNP rs3810291 [31,61,62,65]; FPGT-TNNI3K read through (FPGT-TNNI3K) SNP rs12566985 [31,58,70]; leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2 (*LINGO2*) SNP rs10968576 [31,60,66,71]; cell adhesion molecule 1 (*CADM1*) SNP rs12286929 [31,57,59]; protein kinase D1 (*PRKD1*) SNP rs12885454 [31,65,66]; AGBL carboxypeptidase 4 (*AGBL4*) SNP rs657452 [31,57,60]; polypyrimidine tract binding protein 2 (*PTBP2*) SNP rs11165643 [31,56,60,61]; NLR family CARD domain containing 3 (*NLRC3)* SNP rs758747 [31,57]; syntaxin binding protein 6 (*STXBP6*) SNP rs10132280 [31,59,65]; Huntingtin interacting protein 1 (HIP1) SNP rs1167827 [31,66]; cell adhesion molecule 2 (*CADM2*) SNP rs13078960 [31]; far upstream element binding protein 1 (*FUBP1*) SNP rs12401738 [31,67]; olfactomedin 4 (*OLFM4*) SNP rs12429545 [56,58,65]; RAS p21 protein activator 2 (*RASA2*) SNP rs16851483 [31,58]; hypoxia inducible factor 1 subunit alpha inhibitor (*HIF1AN*) SNP rs17094222 [31,66]; hepatocyte nuclear factor 4 gamma (*HNF4G*) SNP rs17405819 [57,59,72]; toll like receptor 4 (*TLR4*) SNP rs1928295 [31,60]; neurexin 3 (*NRXN3*) SNP rs7141420 [31,64]; inflammation and lipid regulator with UBA-like and NBR1-like domains (*ILRUN* or *C6orf106*) SNP rs205262 [31]; fragile histidine triad diadenosine triphosphatase (*FHIT*) SNP rs2365389 [31,66]; neuron navigator 1 (*NAV1*) SNP rs2820292 [31]; tripartite motif containing 66 (*TRIM66*) SNP rs4256980 [31,59]; erb-b2 receptor tyrosine kinase 4 (*ERBB4*) SNP rs7599312 [31,53]; and lysine acetyltransferase 8 (*KAT8*) SNP rs9925964 [31,57].

Blood samples for genotyping (3 ml) were collected in BD Vacutainer® ethylenediamine tetraacetic acid (EDTA) tubes and transported by the World Courier Company to London, UK. The samples were collected in the fasting state through venepuncture and stored at a controlled temperature of −80 °C during transportation. Genotyping was completed by LGC Genomics, London, UK (http://www.lgcgroup.com/services/genotyping), using the competitive allele-specific PCR-KASP® assay.

2.5. Construction of genetic risk score (GRS)

An unweighted GRS was constructed by adding the number of risk alleles across all the 39 SNPs for each participant. For each SNP, a score of 0, 1 or 2 was assigned to reflect the number of risk alleles the participant carried for that SNP [0 for no risk alleles (homozygous for the non-risk allele); 1 for one risk allele (heterozygote); and 2 for two risk alleles (homozygous for the risk allele)]. The scores for the 39 SNPs were then combined to calculate the GRS. Thus, the GRS for each participant represented the total number of risk alleles the participant carried from the 39 SNPs. The risk alleles were not weighted because of insufficient information on effect sizes of the SNPs for the Peruvian population. It has been highlighted that, data on effect sizes from a GWA study conducted in

one population may not be applicable to another population because of variations in effect sizes [23,73]. Moreover, assigning weights to risk alleles has been reported to have little effect [41]. The risk alleles were defined as alleles which have shown an association with altered blood lipid levels or obesity-related traits. The risk alleles of the SNPs are shown in Supplementary Table S1. The GRS had a median of 37 risk alleles and ranged from 27 to 49 risk alleles. Participants were grouped as low risk or high risk using the median GRS as a cut-off point.

2.6. Statistical analysis

The means of continuous variables between men and women were compared using independent sample t test. The results for descriptive statistics are presented as means and standard deviation. The distribution of the data was tested using Shapiro–Wilk test and non-normally distributed variables (all the variables except fasting glucose) were log-transformed before the analysis. The frequencies of the alleles were determined by gene counting and Hardy-Weinberg Equilibrium (HWE) was calculated using the Chi-Square test. The 39 SNPs were all in HWE ($P > 0.05$) (Supplementary Table S2).

The association of the GRS with the outcome variables (BMI, WC, fasting glucose, fasting insulin, HbA1c, TC, HDL-C, LDL-C, TAG, SBP and DBP) was examined using linear regression with adjustment for sex, family history of diabetes, smoking status, physical activity level and BMI wherever appropriate. To determine interactions between the GRS and dietary macronutrient (fat, carbohydrate, protein) and fibre intake (g/day) on the outcome variables, the interaction term was added to the regression model. The analysis was adjusted for sex, BMI, family history of diabetes, smoking status, physical activity level and total energy intake. The statistically significant interaction ($P < 0.05$) was explored further by stratifying participants according to tertiles of dietary intake and examining the association of the GRS with the outcome variable in each tertile. The Bonferroni adjusted *P*-value for interaction was 0.001 (1 GRS*11 outcome variables*4 dietary factors = 44 tests; 0.05/44 = 0.001). The Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA) was used to perform the analyses.

3. Results

3.1. Characteristics of the study participants

The characteristics of the participants included in this study are summarised in Table 1. The mean age of the sample was 20 ± 1 years and men had significantly higher WC ($P = 0.008$), TAG ($P = 0.03$), SBP ($P = 1.0 \times 10^{-24}$), fasting glucose ($P = 0.001$) and HbA1c ($P = 1.92 \times 10^{-16}$) but lower fasting insulin ($P = 0.003$) than women. Men and women did not have significantly different BMI, HDL-C, LDL-C or TC. Regarding dietary intake, men had significantly higher intakes of energy ($P = 6.8 \times 10^{-12}$), total fat ($P = 0.000002$), carbohydrate ($P = 5.2 \times 10^{-14}$) and protein ($P = 1.0 \times 10^{-9}$) than women, whereas fibre intake did not vary between sexes ($P = 0.60$).

3.2. Association of the GRS with cardiometabolic traits

There were no significant associations between the GRS and any of the outcome variables after adjusting for the confounding factors, sex, family history of diabetes, smoking status, physical activity level, and BMI wherever appropriate (Supplementary Table S3). No regional effects were observed when participants were stratified according to region of residence.

3.3. Interaction of the GRS with dietary macronutrient intake on cardiometabolic traits

A significant interaction was observed between the GRS and carbohydrate intake on the concentration of HDL-C ($P_{interaction} = 0.0007$, Table 2). As shown in Fig. 1, in the first tertile of carbohydrate intake (≤327 g/day), participants with a high GRS (>37 risk alleles) had a higher concentration of HDL-C than those with a low GRS (≤37 risk alleles) [Beta = 0.06 mmol/L, 95 % confidence interval (CI) 0.01–0.10; $P = 0.02$]. In the third tertile of carbohydrate intake (>452 g/day), participants with a high GRS had a lower concentration of HDL-C than those with a low GRS (Beta = −0.04 mmol/L, 95 % CI −0.01 to −0.09; $P = 0.03$). When the effect of GL and GI were tested, a significant interaction was observed between GRS and GL on the concentration of HDL-C ($P_{interaction} = 0.002$), however no significant differences were observed when all the participants were stratified according to tertiles of GL. For participants with a high GRS, there was a lower concentration of HDL-C across tertiles of GL as shown in Fig. 2. No significant interaction was identified between GRS and GI on the concentration of HDL-C.

Although other significant interactions were observed as shown in Table 2, four of the interactions (GRS*carbohydrate on TC, GRS*fat on HDL-C, GRS*fat on glucose and GRS*protein on HDL-C) were not significant after Bonferroni correction for multiple testing. Two of the interactions (GRS*carbohydrate on serum fasting glucose and GRS*protein on serum fasting glucose) passed the Bonferroni correction, but no significant differences were found when participants were stratified according to the quantity of carbohydrate and protein intake. No regional effects were observed when participants were stratified according to region of residence. When the participants were stratified by sex, significant interactions were observed in both men and women, as shown in Table 2, but only two of the interactions (GRS*carbohydrate on the concentration of HDL-C, and GRS*fat on the concentration of HDL-C in men) met the Bonferroni threshold. However, no significant differences were found when the participants were stratified according to the quantity of carbohydrate and fat intake.

4. Discussion

Our study indicates that carbohydrate intake might modulate genetic influences on HDL-C concentration in urban Peruvian young adults. We found a significant interaction between GRS and carbohydrate intake on the concentration of HDL-C where individuals with a higher genetic risk had a lower HDL-C concentration when their intake of carbohydrate was higher (>452 g/day). Conversely, when the intake of carbohydrate was lower (≤327 g/day), the concentration of HDL-C was higher. For participants with a high GRS, there was a lower concentration of HDL-C across tertiles of GL.

4.1. Interpretation of main findings

This study builds on previous research and emphasises the potential of personalised nutrition based on a GRS for the prevention and management of lipid abnormalities in those with a high genetic risk. Given that low HDL-C concentrations have been identified as the most common lipid abnormality in LACP [5], and is related to a higher risk of CVDs [74–76], our findings have considerable public health implications. According to the dietary guidelines for Americans (2020–2025) [77], carbohydrates should make up 45–65 % of total daily calories. The WHO [78] also recommends that carbohydrates should predominantly be sourced from whole grains, vegetables, fruits and legumes. The mean carbohydrate intake as a percentage of total energy intake (TEI) in the current study was 51 %,

Table 1
Characteristics of study participants by sex.

	All ($n = 468$)		Women ($n = 210$)		Men ($n = 258$)		*P* Value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	20.4	0.5	20.4	0.5	20.5	0.5	0.88
BMI (kg/m^2)	24.3	4.1	24.4	4.2	24.2	4.2	0.60
WC (cm)	81.2	10.2	79.9	9.5	82.2	10.6	**0.008**
TAG (mmol/L)	1.1	0.7	1.0	0.6	1.1	0.7	**0.03**
HDL-C (mmol/L)	1.1	0.3	1.1	0.4	1.1	0.3	0.92
LDL-C (mmol/L)	2.0	0.6	1.9	0.6	2.0	0.6	0.22
TC (mmol/L)	3.6	0.9	3.5	1.0	3.6	0.9	0.10
SBP (mmHg)	103.5	11.0	98.5	9.1	107.5	10.7	$\mathbf{1.0 \times 10^{-24}}$
DBP (mmHg)	66.5	7.5	65.9	7.0	67.0	7.8	0.07
Fasting glucose (mmol/L)	4.4	0.8	4.3	0.8	4.5	0.7	**0.001**
Fasting insulin (pmol/L)	63.0	47.8	69.7	52.3	57.5	43.0	**0.003**
HbA1c (%)	5.4	0.3	5.3	0.3	5.5	0.3	$\mathbf{1.92 \times 10^{-16}}$
Energy (kcal/day)	3304.0	1427.7	2870.8	1116.6	3660.4	1553.4	$\mathbf{6.8 \times 10^{-12}}$
Kcal/kg of body weight	53.4	24.8	55.3	23.9	55.1	25.5	0.09
Total fat [(g/day)/% energy]	109.2 (29)	57.8 (6)	97.0 (30)	48.2 (6)	119.2 (28)	62.9 (7)	**0.000002**
Carbohydrate [(g/day)/% energy]	417.9 (51)	180.8 (8)	357.9 (50)	139.8 (8)	467.1 (52)	195.3 (8)	$\mathbf{5.2 \times 10^{-14}}$
Protein [(g/day)/% energy]	172.8 (21)	80.5 (4)	151.0 (21)	62.6 (3)	190.7 (21)	88.8 (4)	$\mathbf{1.0 \times 10^{-9}}$
Protein/kg of body weight	2.8	1.4	2.7	1.4	2.9	1.5	0.14
Fiber (g/day)	11.1	7.3	10.9	7.4	11.3	7.3	0.60
Dietary GI	57.2	4.0	56.6	4.0	58.0	3.8	**0.00003**
Dietary GL	152.9	83.5	139.8	59.4	186.3	81.9	$\mathbf{2.6 \times 10^{-14}}$

Data is presented as mean ± standard deviation. BMI, body mass index; WC, waist circumference; TAG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; GI, glycaemic index; GL, glycaemic load.
P values for the differences in means between men and women were calculated using independent sample t test.

which is within the recommended intake for Americans [77]. The mean carbohydrate intake in the first tertile was 42 % of TEI while the mean intake for the third tertile was 60 % of TEI. The mean HDL-C concentration on the other hand was 1.10 mmol/L for both men and women which is within the recommended level for men [≥40 mg/dL (1.03 mmol/L)], but lower than the recommended level for women [≥50 mg/dL (1.30 mmol/L)] [79]. A 1 mg/dL (0.03 mmol/L) increase in the concentration of HDL-C has been associated with a 2–3% lower risk of coronary heart disease [80]. However, it has been recognised that, the concentration of HDL-C does not necessarily correlate with the function of HDL [81,82].

In line with our findings, a cross-sectional study of 8314 Korean adults from the Ansan and Ansung cohort of the Korean Genome and Epidemiology Study [83] observed that, among individuals with a high GRS (third tertile of a weighted GRS using 18 SNPs), those with a high low-carbohydrate diet score, indicating a low carbohydrate content (64.6 % of TEI), had significantly lower risk of low HDL-C (odds ratio, 0.759; 95 % CI, 0.625–0.923; $P < 0.05$) than those with a low score [high carbohydrate content (78.8 % of TEI)]. However, it should be noted that the low carbohydrate diet score represented a low content of carbohydrate and a high content of protein and fat, which could have a positive effect on HDL-C depending on the type of fat [83]. Moreover, the carbohydrate intake (% of TEI) in the current study was lower than the Korean study [83]. The mean carbohydrate intake in the first tertile was 42 % of TEI while the mean intake for the third tertile was 60 % of TEI, suggesting that Peruvians might benefit from an intake of less than 60 % of TEI. Similarly, a study consisting of 920 participants from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study in the US [84] observed a significant interaction between genetic variants and carbohydrate intake on HDL-C concentration ($P_{interaction}$<0.001–0.038), in which individuals with the 'GG' genotype of potassium channel tetramerization domain containing 10 (*KCTD10*) SNP i5642G→C and metabolism of cobalamin associated B (*MMAB*) SNP 3U3527G→C; as well as those with the 'CC or TC' genotype of *KCTD10* SNP V206VT→C had lower HDL-C concentration only when they consumed diets higher in carbohydrates (≥231 g/day) ($P < 0.001$–0.011). In comparison to our study, the carbohydrate intake in this study [84] was lower (median intake of 231 g/day compared to 387 g/day in the current study). Our finding of an inverse association between GL and HDL-C concentration has also been reported in previous studies [85,86]. The first study [85] consisted of 1026 adults from the Insulin Resistance Atherosclerosis Study [85] where GL was found to be inversely associated with the concentration of HDL-C (Beta = −0.0009, $P < 0.001$). Accordingly, the second study [86] which involved 5011 participants from the third National Health and Nutrition Examination Survey found a negative association between GL and the concentration of HDL-C ($P < 0.01$). Collectively, these findings demonstrate that carbohydrate intake might modulate genetic influences on HDL-C concentration in different ethnic groups.

The mechanisms linking carbohydrate intake to HDL-C concentrations are unclear. However, it has been suggested that a lower carbohydrate diet might lead to an increase in HDL-C concentration possibly through an improvement in insulin resistance [87]. A high carbohydrate diet, consisting mainly of refined carbohydrates, was also reported to increase serum TAG concentrations by stimulating de novo lipogenesis (fatty acid production) in the liver and suppressing the activity of lipoprotein lipase through increased production of apolipoprotein CIII, especially when insulin resistance was present [88,89]. Furthermore, there is a recognised reciprocal relationship between serum TAG and HDL-C concentrations due to the exchange of neutral lipids (TAG with cholesterol esters) between TAG-rich lipoproteins and LDL and HDL, resulting in elevated atherogenic small dense LDL and reduced HDL [90,91]. Different types of carbohydrates however, can have varying effects on HDL-C concentration [92] and it has been suggested that GL serves as a measure of both the quality and quantity of dietary carbohydrates [86]. Foods with a high GL tend to induce more pronounced glycaemic and insulinemic reactions compared to those with a low GL [93]. Hence, public health strategies targeting the consumption of whole grains and fruits and vegetables might be beneficial for the Peruvian population.

Regarding the genetic risk of low HDL-C concentration in LACP and future prospects, a systematic review conducted by our team [21] indicated that, the concentration of HDL-C might be influenced

Table 2
Interaction of GRS with dietary macronutrient intake on cardiometabolic traits.

Trait		All: GRS ≤ 37 risk alleles (n = 228); GRS > 37 risk alleles (n = 240) Women: GRS ≤ 37 risk alleles (n = 107); GRS > 37 risk alleles (n = 104) Men: GRS ≤ 37 risk alleles (n = 138); GRS > 37 risk alleles (n = 119)			
		Beta Coefficient ± SE ($P_{interaction}$)			
		GRS * Carbohydrate (g/day)	GRS * Fat (g/day)	GRS * Protein (g/day)	GRS * Fiber (g/day)
HDL-C (mmol/L)	All	0.24 ± 0.07 (**0.0007**)	0.14 ± 0.06 (**0.009**)	0.17 ± 0.06 (**0.006**)	0.03 ± 0.05 (0.51)
	Women	−0.08 ± 0.11 (0.50)	0.02 ± 0.09 (0.82)	−0.05 ± 0.11 (0.63)	−0.13 ± 0.08 (0.12)
	Men	−0.38 ± 0.09 (**0.00007**)	−0.23 ± 0.07 (**0.0008**)	0.24 ± 0.08 (**0.002**)	−0.04 ± 0.06 (0.54)
LDL-C (mmol/L)	All	0.07 ± 0.08 (0.40)	0.04 ± 0.06 (0.55)	0.06 ± 0.07 (0.39)	−0.03 ± 0.05 (0.63)
	Women	−0.08 ± 0.12 (0.50)	−0.06 ± 0.10 (0.51)	−0.12 ± 0.11 (0.31)	0.00 ± 0.08 (0.98)
	Men	−0.07 ± 0.11 (0.52)	−0.02 ± 0.08 (0.78)	−0.05 ± 0.09 (0.61)	0.004 ± 0.07 (0.95)
TAG (mmol/L)	All	0.04 ± 0.11 (0.73)	−0.02 ± 0.09 (0.78)	−0.01 ± 0.10 (0.93)	−0.02 ± 0.08 (0.83)
	Women	−0.24 ± 0.17 (0.16)	−0.11 ± 0.14 (0.44)	−0.17 ± 0.17 (0.31)	−0.03 ± 0.13 (0.81)
	Men	0.03 ± 0.16 (0.86)	0.07 ± 0.12 (0.57)	0.05 ± 0.13 (0.72)	−0.01 ± 0.10 (0.90)
TC (mmol/L)	All	0.12 ± 0.06 (**0.04**)	0.06 ± 0.05 (0.18)	0.09 ± 0.05 (0.10)	−0.002 ± 0.04 (0.97)
	Women	−0.12 ± 0.10 (0.25)	−0.05 ± 0.83 (0.52)	−0.11 ± 0.10 (0.25)	−0.52 ± 0.07 (0.48)
	Men	−0.16 ± 0.08 (0.05)	−0.07 ± 0.06 (0.21)	−0.10 ± 0.07 (0.14)	0.02 ± 0.05 (0.72)
SBP (mmHg)	All	0.12 ± 0.02 (0.55)	0.004 ± 0.02 (0.78)	0.01 ± 0.02 (0.51)	0.001 ± 0.01 (0.94)
	Women	0.03 ± 0.03 (0.38)	0.00 ± 0.02 (0.90)	0.02 ± 0.03 (0.58)	0.00 ± 0.02 (0.99)
	Men	−0.03 ± 0.03 (0.25)	−0.002 ± 0.02 (0.93)	−0.02 ± 0.02 (0.44)	−0.01 ± 0.02 (0.49)
DBP (mmHg)	All	0.001 ± 0.03 (0.97)	0.003 ± 0.02 (0.86)	0.004 ± 0.02 (0.86)	0.02 ± 0.02 (0.24)
	Women	0.02 ± 0.04 (0.57)	0.02 ± 0.03 (0.53)	0.04 ± 0.04 (0.26)	−0.03 ± 0.03 (0.27)
	Men	−0.02 ± 0.04 (0.55)	−0.02 ± 0.03 (0.56)	−0.03 ± 0.03 (0.36)	−0.03 ± 0.02 (0.31)
Fasting glucose (mmol/L)	All	1.38 ± 0.39 (**0.0005**)	0.93 ± 0.31 (**0.003**)	1.19 ± 0.35 (**0.0008**)	0.41 ± 0.28 (0.15)
	Women	−1.01 ± 0.66 (0.13)	−0.58 ± 0.55 (0.29)	−1.16 ± 0.63 (0.07)	−0.99 ± 0.48 (**0.04**)
	Men	−1.51 ± 0.53 (**0.005**)	−0.98 ± 0.38 (**0.01**)	−1.07 ± 0.43 (**0.02**)	−0.20 ± 0.34 (0.57)
Fasting insulin (pmol/L)	All	0.03 ± 0.11 (0.81)	−0.09 ± 0.09 (0.35)	−0.07 ± 0.10 (0.48)	−0.01 ± 0.08 (0.94)
	Women	−0.001 ± 0.18 (0.99)	0.09 ± 0.15 (0.55)	0.13 ± 0.17 (0.45)	0.03 ± 0.13 (0.85)
	Men	−0.003 ± 0.16 (0.99)	0.13 ± 0.11 (0.26)	0.09 ± 0.13 (0.51)	−0.01 ± 0.10 (0.92)
HbA1c (%)	All	0.02 ± 0.01 (0.07)	0.01 ± 0.01 (0.52)	0.02 ± 0.01 (0.14)	0.02 ± 0.01 (**0.03**)
	Women	−0.01 ± 0.02 (0.61)	−0.00 ± 0.01 (0.73)	−0.00 ± 0.01 (0.92)	0.00 ± 0.01 (0.95)
	Men	−0.05 ± 0.02 (**0.02**)	−0.01 ± 0.02 (0.69)	−0.04 ± 0.02 (**0.04**)	−0.05 ± 0.02 (**0.002**)
BMI (kg/m^2)	All	0.05 ± 0.04 (0.17)	0.02 ± 0.03 (0.47)	0.05 ± 0.03 (0.11)	0.05 ± 0.03 (0.06)
	Women	−0.09 ± 0.06 (0.12)	−0.07 ± 0.05 (0.14)	−0.13 ± 0.05 (**0.02**)	−0.09 ± 0.04 (**0.03**)
	Men	−0.04 ± 0.05 (0.46)	0.00 ± 0.04 (0.96)	−0.02 ± 0.05 (0.65)	−0.02 ± 0.04 (0.59)
WC[a] (cm)	All	0.04 ± 0.03 (0.16)	0.02 ± 0.02 (0.47)	0.04 ± 0.03 (0.09)	0.04 ± 0.02 (0.07)
	Women	−0.05 ± 0.23 (0.84)	−0.02 ± 0.19 (0.91)	−0.19 ± 0.21 (0.39)	0.01 ± 0.16 (0.95)
	Men	−0.03 ± 0.04 (0.52)	0.00 ± 0.03 (0.92)	−0.02 ± 0.03 (0.62)	−0.02 ± 0.03 (0.42)

P values were obtained from linear regression analysis with adjustment for sex, family history of diabetes, smoking status, physical activity level, total energy intake and BMI wherever appropriate. Log-transformed variables were used for the analysis and values in bold represent significant interactions. GRS, genetic risk score; TAG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; BMI, body mass index; WC, waist circumference.
[a] 457 participants had data for waist circumference.

by interactions between genetic variants and different dietary factors, but most of the studies had not been replicated. In Brazilians, a high polyunsaturated fatty acid intake (> twice a week) was linked to higher HDL-C concentrations in individuals without the 'E4' allele of *apolipoprotein E* (*APOE*), and lower concentrations in those with the 'E4' allele [94], while in Costa Ricans, a high saturated fatty acid intake (13.5 % energy) was associated with lower HDL-C concentrations in carriers of the 'E2' allele of *APOE* [95]. To promote comparison across studies and facilitate the implementation of personalised dietary guidelines, future studies should focus on replicating previously identified gene–diet interactions. Once findings have been replicated, the evidence can further be strengthened by conducting genotype-based dietary intervention studies.

4.2. Strengths and limitations

One of the strengths of our study is the use of a GRS which reflects an individual's overall genetic predisposition to cardiometabolic traits by combining several genetic variants. Moreover, our study is the first gene–diet interaction study in Peru, capturing different regions of Peru (Coast, Highland and the Jungle), and the first to be conducted in adolescents, an unstudied non-Caucasian group which has an increasing prevalence of CVDs [96–98] and lipid abnormalities which significantly increase the risk of developing atherosclerotic CVDs later in life [99–103]. Another strength is the employment of validated methods and skilled professionals to evaluate dietary consumption, anthropometric and biochemical measurements, thereby enhancing the precision of the assessments. However, several limitations need to be acknowledged, including a small sample size which could have affected our ability to detect interactions with small effect sizes [104,105]. The cross-sectional design also prevents establishment of causality [23]. Moreover, we did not investigate types of carbohydrates which can have varying effects on cardiometabolic traits [106,107]. Additionally, using recalled FFQ rather than weighed diet diaries or biomarkers of intake can lead to underestimation of dietary intake [108,109].

4.3. Conclusions

In conclusion, our study suggests that carbohydrate intake might modulate genetic influences on HDL-C concentration in urban Peruvian young adults. The results suggest that young adults who consume a higher carbohydrate diet and have a higher GRS have a lower HDL-C concentration, which in turn is linked to CVDs. Our findings support the dietary guidelines of the WHO and indicate that personalised dietary guidelines targeting a reduction in

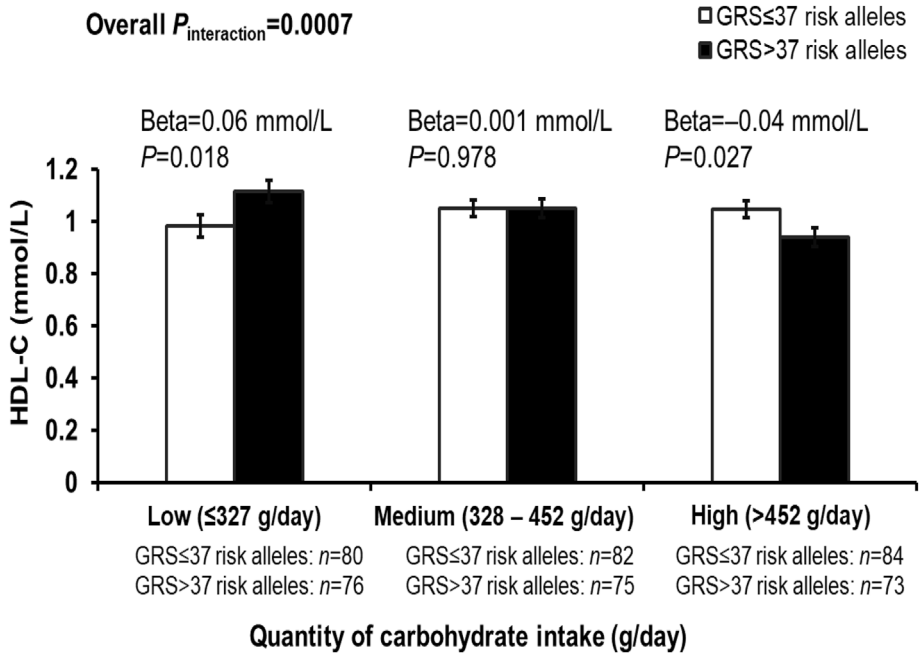

Fig. 1. Interaction of GRS and carbohydrate intake on HDL-C concentration. In the first tertile of carbohydrate intake (≤327 g/day), participants with a high GRS (>37 risk alleles) had higher HDL-C concentration than those with a low GRS (≤37 risk alleles). However, in the third tertile of carbohydrate intake (>452 g/day), participants with a high GRS had a lower HDL-C concentration than those with a low GRS. The analysis was adjusted for sex, BMI, family history of diabetes, smoking status, physical activity level and total energy intake.

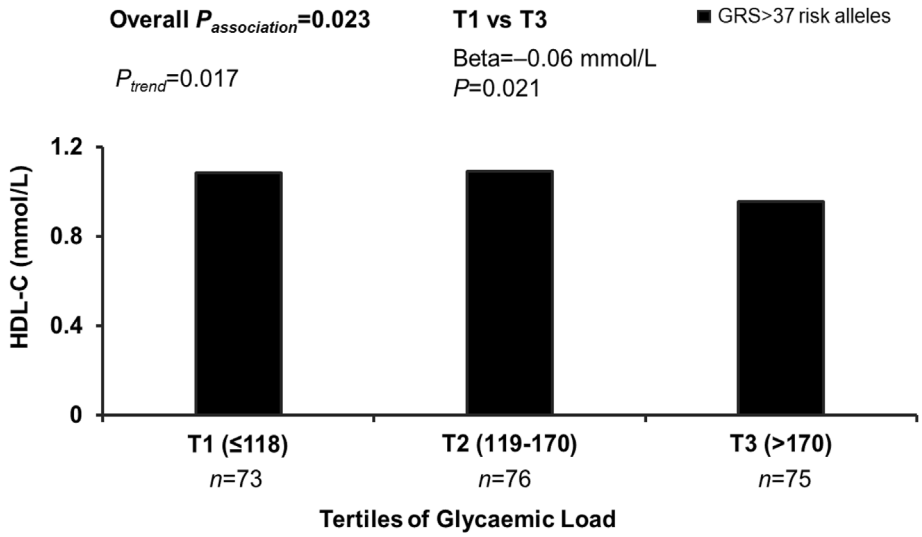

Fig. 2. Association of glycaemic load (GL) with HDL-C concentration in individuals with a high GRS. The concentration of HDL-C was lower across tertiles of GL. The analysis was adjusted for sex, BMI, family history of diabetes, smoking status, physical activity level and total energy intake.

carbohydrate intake might be beneficial for Peruvian individuals with a high genetic risk. However, randomised controlled trials and longitudinal studies with large sample sizes are required to confirm our findings.

Author contributions

K.S.V.: conceptualisation and project administration; R.W. and K.S.V.: methodology, investigation, and writing - original draft. R.W. and K.S.V.: formal analysis, software, and visualization. K.S.V., A.S. and K.C.Q.: supervision and resources. A.S., K.C.Q., D.E., M.P., M.F., A.I.A., M.A.A. and J.V.: data collection. A.S., K.S.V., K.C.Q., R.W., R.N., M.P. M.F., C.M, D.E., A.I.A., L.L, M.A.A. and J.V.: data curation and validation; K.S.V. and A.S.: funding acquisition. R.W., K.S.V., A.S., K.C.Q., J.A.L., R.N., M.P., M.F., L.M., A.I.A. and C.M.: writing - review and editing. All authors have read and agreed to the final version of the manuscript.

Compliance with ethical standards

The study was given a favourable ethical opinion for conduct by the University of Reading Ethics Committee, the Ethics Committee of the University of Oxford, UK and Nutritional Research Institute (Instituto de Investigación Nutricional in Spanish) in Lima, Peru which is accredited by the National Institute of Health. Ethical

committee approval number 180-2002/CIEI-IIN. A written informed consent was obtained from all the study participants.

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Declaration of competing interest

The authors declare that there are no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.12.027.

References

[1] World Health Organisation. Cardiovascular diseases (CVDs). Key facts; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
[2] World Health Organisation. Noncommunicable diseseases. Key facts; 2023. Available from: https://www.who.int/newsroom/factsheets/detail/noncommunicable-diseases#:∼:text=Key%20facts,%2D%20and%20middle%2Dincome%20countries.
[3] Peru Global Obesity Observatory. 2023. Available from: https://data.worldobesity.org/country/peru-171/.
[4] Rios-Blancas MJ, Pando-Robles V, Razo C, Carcamo CP, Mendoza W, Pacheco-Barrios K, et al. Estimating mortality and disability in Peru before the COVID-19 pandemic: a systematic analysis from the Global Burden of the Disease Study 2019. Front Public Health 2023;11:1189861.
[5] Carrillo-Larco RM, Benites-Moya CJ, Anza-Ramirez C, Albitres-Flores L, Sánchez-Velazco D, Pacheco-Barrios N, et al. A systematic review of population-based studies on lipid profiles in Latin America and the Caribbean. Elife 2020;9:e57980.
[6] Quezada-Pinedo HG, Ahanchi NS, Cajachagua-Torres KN, Obeso-Manrique JA, Huicho L, Gräni C, et al. A comprehensive analysis of cardiovascular mortality trends in Peru from 2017 to 2022: insights from 183,386 deaths of the national death registry. Am Heart J: Cardiol Res Pract 2023;35:100335.
[7] Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1· 8 million participants. Lancet (London, England) 2013;383(9921):970–83.
[8] Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2021;143(21):e984–1010.
[9] Stadler JT, Lackner S, Mörkl S, Trakaki A, Scharnagl H, Borenich A, et al. Obesity affects HDL metabolism, composition and subclass distribution. Biomedicines 2021;9(3).
[10] Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377(1):13–27.
[11] Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, et al. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA Cardiol 2018;3(4):280–7.
[12] Rahmani J, Haghighian Roudsari A, Bawadi H, Thompson J, Khalooei Fard R, Clark C, et al. Relationship between body mass index, risk of venous thromboembolism and pulmonary embolism: a systematic review and dose-response meta-analysis of cohort studies among four million participants. Thromb Res 2020;192:64–72.
[13] Welsh A, Hammad M, Piña IL, Kulinski J. Obesity and cardiovascular health. Euro J Prev Cardiol 2024;31(8):1026–35.
[14] Chait A, Den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Front Cardiovasc Med 2020;7:22.
[15] Rana MN, Neeland IJ. Adipose tissue inflammation and cardiovascular disease: an update. Curr Diabetes Rep 2022;22(1):27–37.
[16] Ebbert JO, Jensen MD. Fat depots, free fatty acids, and dyslipidemia. Nutrients 2013;5(2):498–508.
[17] Øhman EA, Kirchner L, Winkvist A, Bertz F, Holven KB, Ulven SM, et al. Effects of dietary and exercise treatments on HDL subclasses in lactating women with overweight and obesity: a secondary analysis of a randomised controlled trial. Br J Nutr 2022;128(11):2105–14.
[18] Vimaleswaran KS. A nutrigenetics approach to study the impact of genetic and lifestyle factors on cardiometabolic traits in various ethnic groups: findings from the GeNuIne Collaboration. Proc Nutr Soc 2020;79(2):194–204.
[19] Wuni R, Adela Nathania E, Ayyappa AK, Lakshmipriya N, Ramya K, Gayathri R, et al. Impact of lipid genetic risk score and saturated fatty acid intake on central obesity in an Asian Indian population. Nutrients 2022;14(13):2713.
[20] Wuni R, Kuhnle GGC, Wynn-Jones AA, Vimaleswaran KS. A nutrigenetic update on CETP gene-diet interactions on lipid-related outcomes. Curr Atherosclerosis Rep 2022;24(2):119–32.
[21] Wuni R, Ventura EF, Curi-Quinto K, Murray C, Nunes R, Lovegrove JA, et al. Interactions between genetic and lifestyle factors on cardiometabolic disease-related outcomes in Latin American and Caribbean populations: a systematic review. Front Nutr 2023;10:61.
[22] Wuni R, Lakshmipriya N, Abirami K, Ventura EF, Anjana RM, Sudha V, et al. Higher intake of dairy is associated with lower cardiometabolic risks and metabolic syndrome in Asian Indians. Nutrients 2022;14(18):3699.
[23] Vimaleswaran KS, Bodhini D, Lakshmipriya N, Ramya K, Anjana RM, Sudha V, et al. Interaction between FTO gene variants and lifestyle factors on metabolic traits in an Asian Indian population. Nutr Metab 2016;13:39.
[24] Vimaleswaran KS. Gene–nutrient interactions on metabolic diseases: findings from the GeNuIne Collaboration. Nutr Bull 2017;42(1):80–6.
[25] Vimaleswaran KS, Zhou A, Cavadino A, Hyppönen E. Evidence for a causal association between milk intake and cardiometabolic disease outcomes using a two-sample Mendelian Randomization analysis in up to 1,904,220 individuals. Int J Obes 2021;45(8):1751–62.
[26] Cortés Sanabria LY, Fisberg M, Guajardo V, Gómez G, Herrera-Cuenca M, Koletzko B, et al. Energy intake and food sources of eight Latin American countries: results from the Latin American Study of Nutrition and Health (ELANS). Publ Health Nutr 2018;21(14):2535–47.
[27] Santos MP, Turner B, Chaparro MP. The double burden of malnutrition in Peru: an update with a focus on social inequities. Am J Clin Nutr 2021;113(4):865–73.
[28] Aurino E, Fernandes M, Penny ME. The nutrition transition and adolescents' diets in low-and middle-income countries: a cross-cohort comparison. Publ Health Nutr 2017;20(1):72–81.
[29] Sharma B, Chavez RC, Nam EW. Prevalence and correlates of insufficient physical activity in school adolescents in Peru. Rev Saude Publica 2018;52.
[30] Loret de Mola C, Quispe R, Valle GA, Poterico JA. Nutritional transition in children under five years and women of reproductive age: a 15-years trend analysis in Peru. PLoS One 2014;9(3):e92550.
[31] Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518(7538):197–206.
[32] Brandkvist M, Bjørngaard JH, Ødegård RA, Åsvold BO, Sund ER, Vie GÅ. Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study. Br Med J 2019;366.
[33] Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in 700000 individuals of European ancestry. Hum Mol Genet 2018;27(20):3641–9.
[34] Senftleber NK, Andersen MK, Jørsboe E, Stæger FF, Nøhr AK, Garcia-Erill G, et al. GWAS of lipids in Greenlanders finds association signals shared with Europeans and reveals an independent PCSK9 association signal. Eur J Hum Genet 2024;32(2):215–23.
[35] Tada H, Won H-H, Melander O, Yang J, Peloso GM, Kathiresan S. Multiple associated variants increase the heritability explained for plasma lipids and coronary artery disease. Circulation: Cardiovasc Genet 2014;7(5):583–7.
[36] Graham SE, Clarke SL, Wu KH, Kanoni S, Zajac GJM, Ramdas S, et al. The power of genetic diversity in genome-wide association studies of lipids. Nature 2021;600(7890):675–9.
[37] Vimaleswaran KS, Cavadino A, Verweij N, Nolte IM, Leach IM, Auvinen J, et al. Interactions between uncoupling protein 2 gene polymorphisms, obesity and alcohol intake on liver function: a large meta-analysed population-based study. Eur J Endocrinol 2015;173(6):863–72.
[38] Alsulami S, Nyakotey DA, Dudek K, Bawah AM, Lovegrove JA, Annan RA, et al. Interaction between metabolic genetic risk score and dietary fatty acid intake on central obesity in a Ghanaian population. Nutrients 2020;12(7).

[39] Surendran S, Aji A, Ariyasra U, Sari S, Malik S, Tasrif N, et al. A nutrigenetic approach for investigating the relationship between vitamin B12 status and metabolic traits in Indonesian women. J Diabetes Metab Disord 2019;18(2):389–99.
[40] Alathari BE, Aji AS, Ariyasra U, Sari SR, Tasrif N, Yani FF, et al. Interaction between vitamin D-related genetic risk score and carbohydrate intake on body fat composition: a study in Southeast Asian Minangkabau women. Nutrients 2021;13(2):326.
[41] Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. Genet Med 2007;9(8):528–35.
[42] Lives Young. A guide to young Lives research: Section 5-Sampling. 2017. Available from: https://www.younglives.org.uk/sites/www.younglives.org.uk/files/GuidetoYLResearch-S5-Sampling.pdf.
[43] Curi-Quinto K, Sánchez A, Lago-Berrocal N, Penny ME, Murray C, Nunes R, et al. Role of government financial support and vulnerability characteristics associated with food insecurity during the COVID-19 pandemic among young Peruvians. Nutrients 2021;13(10).
[44] World Health Organisation. Physical status: the use of and interpretation of anthropometry, report of a WHO expert committee. 1995. Available from: https://www.who.int/publications/i/item/9241208546.
[45] World Health Organisation. Noncommunicable disease surveillance, monitoring and reporting. 2024. Available from: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/steps/manuals.
[46] Takahashi H, Yoshika M, Yokoi T. Validation of three automatic devices for the self-measurement of blood pressure according to the European Society of Hypertension International Protocol revision 2010: the Omron HEM-7130, HEM-7320F, and HEM-7500F. Blood Pres Monit 2015;20(2):92–7.
[47] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18(6):499–502.
[48] Vega-Salas MJ, Curi-Quinto K, Hidalgo-Aréstegui A, Meza-Carbajal K, Lago-Berrocal N, Arias L, et al. Development of an online food frequency questionnaire and estimation of misreporting of energy intake during the COVID-19 pandemic among young adults in Peru. Front Nutr 2022;9.
[49] Dodd H, Williams S, Brown R, Venn B. Calculating meal glycemic index by using measured and published food values compared with directly measured meal glycemic index. Am J Clin Nutr 2011;94(4):992–6.
[50] Sieri S, Agnoli C, Pala V, Grioni S, Brighenti F, Pellegrini N, et al. Dietary glycemic index, glycemic load, and cancer risk: results from the EPIC-Italy study. Sci Rep 2017;7(1):9757.
[51] Noro F, Santonastaso F, Marotta A, Bonaccio M, Orlandi S, Tirozzi A, et al. Association of nutritional glycaemic indices with global DNA methylation patterns: results from the Moli-sani cohort. Clin Epigenet 2022;14(1):189.
[52] Ligthart S, Vaez A, Hsu YH, Stolk R, Uitterlinden AG, Hofman A, et al. Bivariate genome-wide association study identifies novel pleiotropic loci for lipids and inflammation. BMC Genom 2016;17:443.
[53] Tachmazidou I, Süveges D, Min JL, Ritchie GRS, Steinberg J, Walter K, et al. Whole-genome sequencing coupled to imputation discovers genetic signals for anthropometric traits. Am J Hum Genet 2017;100(6):865–84.
[54] Wheeler E, Leong A, Liu CT, Hivert MF, Strawbridge RJ, Podmore C, et al. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. PLoS Med 2017;14(9):e1002383.
[55] Scherag A, Dina C, Hinney A, Vatin V, Scherag S, Vogel CI, et al. Two new Loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. PLoS Genet 2010;6(4):e1000916.
[56] Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, et al. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. Nat Genet 2017;49(10):1458–67.
[57] Hoffmann TJ, Choquet H, Yin J, Banda Y, Kvale MN, Glymour M, et al. A large multiethnic genome-wide association study of adult body mass index identifies novel loci. Genetics 2018;210(2):499–515.
[58] Justice AE, Winkler TW, Feitosa MF, Graff M, Fisher VA, Young K, et al. Genome-wide meta-analysis of 241,258 adults accounting for smoking behaviour identifies novel loci for obesity traits. Nat Commun 2017;8:14977.
[59] Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019;28(1):166–74.
[60] Koskeridis F, Evangelou E, Said S, Boyle JJ, Elliott P, Dehghan A, et al. Pleiotropic genetic architecture and novel loci for C-reactive protein levels. Nat Commun 2022;13(1):6939.
[61] Martin S, Cule M, Basty N, Tyrrell J, Beaumont RN, Wood AR, et al. Genetic evidence for different adiposity phenotypes and their opposing influences on ectopic fat and risk of cardiometabolic disease. Diabetes 2021;70(8):1843–56.
[62] Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet 2018;50(11):1505–13.
[63] Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet 2020;52(7):680–91.
[64] Berndt SI, Gustafsson S, Mägi R, Ganna A, Wheeler E, Feitosa MF, et al. Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. Nat Genet 2013;45(5):501–12.
[65] Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518(7538):187–96.
[66] Huang J, Huffman JE, Huang Y, Do Valle Í, Assimes TL, Raghavan S, et al. Genomics and phenomics of body mass index reveals a complex disease network. Nat Commun 2022;13(1):7973.
[67] Winkler TW, Justice AE, Graff M, Barata L, Feitosa MF, Chu S, et al. The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. PLoS Genet 2015;11(10):e1005378.
[68] Lee SB, Choi JE, Park B, Cha MY, Hong KW, Jung DH. Dyslipidaemia-genotype interactions with nutrient intake and cerebro-cardiovascular disease. Biomedicines 2022;10(7).
[69] Wood AR, Tyrrell J, Beaumont R, Jones SE, Tuke MA, Ruth KS, et al. Variants in the FTO and CDKAL1 loci have recessive effects on risk of obesity and type 2 diabetes, respectively. Diabetologia 2016;59(6):1214–21.
[70] Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesi A, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. Hum Mol Genet 2016;25(2):389–403.
[71] Liu DJ, Peloso GM, Yu H, Butterworth AS, Wang X, Mahajan A, et al. Exome-wide association study of plasma lipids in >300,000 individuals. Nat Genet 2017;49(12):1758–66.
[72] Graff M, Scott RA, Justice AE, Young KL, Feitosa MF, Barata L, et al. Genome-wide physical activity interactions in adiposity - a meta-analysis of 200,452 adults. PLoS Genet 2017;13(4):e1006528.
[73] Hüls A, Krämer U, Carlsten C, Schikowski T, Ickstadt K, Schwender H. Comparison of weighting approaches for genetic risk scores in gene-environment interaction studies. BMC Genet 2017;18(1):115.
[74] Rader DJ, Hovingh GK. HDL and cardiovascular disease. Lancet 2014;384(9943):618–25.
[75] Barter PJ, Kastelein JJP. Targeting cholesteryl ester transfer protein for the prevention and management of cardiovascular disease. J Am Coll Cardiol 2006;47(3):492–9.
[76] Pease A, Earnest A, Ranasinha S, Nanayakkara N, Liew D, Wischer N, et al. Burden of cardiovascular risk factors and disease among patients with type 1 diabetes: results of the Australian National Diabetes Audit (ANDA). Cardiovasc Diabetol 2018;17:1–12.
[77] Arnold MJ, Harding MC, Conley AT. Dietary guidelines for Americans 2020–2025: recommendations from the US Departments of Agriculture and Health and Human Services. Am Fam Physician 2021;104(5):533–6.
[78] World Health Organisation. Carbohydrate intake for adults and children. WHO guideline; 2023. Available from: https://iris.who.int/bitstream/handle/10665/370420/9789240073593-eng.pdf?sequence=1.
[79] Huxley RR, Barzi F, Lam TH, Czernichow S, Fang X, Welborn T, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. Circulation 2011;124(19):2056–64.
[80] Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79(1):8–15.
[81] Rodriguez A, Trigatti BL, Mineo C, Knaack D, Wilkins JT, Sahoo D, et al. Proceedings of the Ninth HDL (High-Density lipoprotein) workshop. Arterioscler Thromb Vasc Biol 2019;39(12):2457–67.
[82] Jung E, Kong SY, Ro YS, Ryu HH, Shin SD. Serum cholesterol levels and risk of cardiovascular death: a systematic review and a dose-response meta-analysis of prospective cohort studies. Int J Environ Res Publ Health 2022;19(14).
[83] Park S, Jang MJ, Park MY, Kim JM, Shin S. Interactive effects of the low-carbohydrate diet score and genetic risk score on Hypo-HDL-cholesterolemia among Korean adults: a cross-sectional analysis from the Ansan and Ansung Study of the Korean Genome and Epidemiology Study. Food Sci Nutr 2022;10(9):3106–16.
[84] Junyent M, Parnell LD, Lai CQ, Lee YC, Smith CE, Arnett DK, et al. Novel variants at KCTD10, MVK, and MMAB genes interact with dietary carbohydrates to modulate HDL-cholesterol concentrations in the genetics of lipid lowering Drugs and diet network study. Am J Clin Nutr 2009;90(3):686–94.
[85] Liese AD, Gilliard T, Schulz M, D'Agostino Jr RB, Wolever TMS. Carbohydrate nutrition, glycaemic load, and plasma lipids: the Insulin Resistance Atherosclerosis Study. Eur Heart J 2006;28(1):80–7.
[86] Culberson A, Kafai MR, Ganji V. Glycemic load is associated with HDL cholesterol but not with the other components and prevalence of metabolic syndrome in the third National Health and Nutrition Examination Survey, 1988–1994. Int Arch Med 2009;2:1–8.
[87] Yanai H, Tada N. Effects of energy and carbohydrate intake on serum high-density lipoprotein-cholesterol levels. J Endocrinol Metabol 2018;8(2–3):27–31.
[88] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American

College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2019;139(25):e1082–143.
[89] Merchant AT, Anand SS, Kelemen LE, Vuksan V, Jacobs R, Davis B, et al. Carbohydrate intake and HDL in a multiethnic population. Am J Clin Nutr 2007;85(1):225–30.
[90] Kannel WB, Vasan RS, Keyes MJ, Sullivan LM, Robins SJ. Usefulness of the triglyceride-high-density lipoprotein versus the cholesterol-high-density lipoprotein ratio for predicting insulin resistance and cardiometabolic risk (from the Framingham Offspring Cohort). Am J Cardiol 2008;101(4):497–501.
[91] Quispe R, Manalac RJ, Faridi KF, Blaha MJ, Toth PP, Kulkarni KR, et al. Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: the Very Large Database of Lipids-4 (VLDL-4) study. Atherosclerosis 2015;242(1):243–50.
[92] Sacks FM, Carey VJ, Anderson CA, Miller ER, Copeland T, Charleston J, et al. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. JAMA 2014;312(23):2531–41.
[93] Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76(1):5–56.
[94] de Andrade FM, Bulhões AC, Maluf SW, Schuch JB, Voigt F, Lucatelli JF, et al. The influence of nutrigenetics on the lipid profile: interaction between genes and dietary habits. Biochem Genet 2010;48(3–4):342–55.
[95] Campos H, D'Agostino M, Ordovás JM. Gene-diet interactions and plasma lipoproteins: role of apolipoprotein E and habitual saturated fat intake. Genet Epidemiol 2001;20(1):117–28.
[96] Institute for Health Metrics and Evaluation (IHME). Global burden of disease study 2019 (GBD 2019) data resources. 2019.
[97] Brown AF, Liang L-J, Vassar SD, Escarce JJ, Merkin SS, Cheng E, et al. Trends in racial/ethnic and nativity disparities in cardiovascular health among adults without prevalent cardiovascular disease in the United States, 1988 to 2014. Ann Intern Med 2018;168(8):541–9.
[98] Sniderman AD, Thanassoulis G, Williams K, Pencina M. Risk of premature cardiovascular disease vs the number of premature cardiovascular events. JAMA Cardiol 2016;1(4):492–4.
[99] Robinson JG. Lipid management beyond the guidelines. Prog Cardiovasc Dis 2019;62(5):384–9.
[100] Pletcher MJ, Bibbins-Domingo K, Liu K, Sidney S, Lin F, Vittinghoff E, et al. Nonoptimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Ann Intern Med 2010;153(3):137–46.
[101] Brunner FJ, Waldeyer C, Ojeda F, Salomaa V, Kee F, Sans S, et al. Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium. Lancet 2019;394(10215):2173–83.
[102] Koskinen JS, Kytö V, Juonala M, Viikari JSA, Nevalainen J, Kähönen M, et al. Childhood dyslipidemia and Carotid atherosclerotic Plaque in adulthood: the cardiovascular risk in young Finns study. J Am Heart Assoc 2023;12(7):e027586.
[103] Hartiala O, Magnussen CG, Kajander S, Knuuti J, Ukkonen H, Saraste A, et al. Adolescence risk factors are predictive of coronary Artery Calcification at middle age: the cardiovascular risk in young Finns study. J Am Coll Cardiol 2012;60(15):1364–70.
[104] Franks PW, Pearson E, Florez JC. Gene-environment and gene-treatment interactions in type 2 diabetes: progress, pitfalls, and prospects. Diabetes Care 2013;36(5):1413–21.
[105] Palla L, Higgins JPT, Wareham NJ, Sharp SJ. Challenges in the Use of literature-based meta-analysis to examine gene-environment interactions. Am J Epidemiol 2010;171(11):1225–32.
[106] Hollænder PL, Ross AB, Kristensen M. Whole-grain and blood lipid changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. Am J Clin Nutr 2015;102(3):556–72.
[107] Shen XL, Zhao T, Zhou Y, Shi X, Zou Y, Zhao G. Effect of oat β-glucan intake on glycaemic control and insulin sensitivity of diabetic patients: a meta-analysis of randomized controlled trials. Nutrients 2016;8(1):39.
[108] Park Y, Dodd KW, Kipnis V, Thompson FE, Potischman N, Schoeller DA, et al. Comparison of self-reported dietary intakes from the Automated Self-Administered 24-h recall, 4-d food records, and food-frequency questionnaires against recovery biomarkers 1. Am J Clin Nutr 2018;107(1):80–93.
[109] Ortega RM, Pérez-Rodrigo C, López-Sobaler AM. Dietary assessment methods: dietary records. Nutr Hosp 2015;31(Suppl 3):38–45.