University of Reading

An investigation of gene-diet interactions on lipid-related traits in different ethnic groups

A thesis submitted for the fulfilment of the degree of Doctor of Philosophy

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Declaration of authorship

I confirm that this is my own work and the use of all material from other sources has been properly and fully acknowledged.

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Abstract

Cardiometabolic diseases including cardiovascular diseases (CVDs) remain a threat to global public health, placing a significant burden on low- and middle-income countries. Among the risk factors for CVDs is an altered blood lipid profile, usually characterised by a rise in the concentration of triglycerides (TG) or low-density lipoprotein cholesterol (LDL-C) and a reduction in the concentration of high-density lipoprotein cholesterol (HDL-C). Lipid-related traits such as CVDs are known to be impacted by environmental factors including dietary intake. However, evidence from genetic association studies indicates that genetic variants play a role in the development of these traits. Therefore, investigating how gene-diet interactions impact on lipid-related traits could help to improve our understanding of the underlying pathophysiology and the development of precision nutrition strategies for the prevention and management of these conditions. Gene-diet interaction studies have been extended to cover previously under-represented populations, but there is still limited research in some developing countries. The main aim of this PhD work was to investigate the association of single nucleotide polymorphisms (SNPs) as a genetic risk score (GRS) with lipid-related traits in different ethnic groups. The interaction of the GRS with dietary factors on lipid-related traits was also assessed. Additionally, the association between dairy intake, a source of saturated fat, on cardiometabolic risk factors was investigated. Finally, factors that need to be considered to facilitate the translation of nutrigenetics to personalised and precision nutrition for cardiometabolic health in diverse ethnic groups were explored. This thesis included seven studies: a review of cholesteryl ester transfer protein (*CETP*) gene-diet interactions on lipid-related outcomes; three cross-sectional cohort studies [the Obesity, Lifestyle and Diabetes in Brazil (BOLD) study, Brazilian young adults, *n*=190; the Chennai Urban Rural Epidemiological Study (CURES), Asian Indian adults, *n*=1,033; and the Study of Obesity, Nutrition, Genes and Social factors (SONGS), Peruvian young adults, *n*=468]; a case-control study (CURES, Asian Indian adults, *n*=497); a systematic review of gene-lifestyle interactions on cardiometabolic disease-related traits in Latin American and Caribbean populations; and a review focusing on the barriers in translating existing nutrigenetics insights to precision nutrition for cardiometabolic health in ethnically diverse populations. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA) and the R software version 4.3.1. Significant GRS-saturated fatty acid (SFA) intake interactions were observed in the Brazilian and Asian Indian populations, impacting on TG:HDL-C ratio ($P_{interaction}$=0.03) and waist circumference ($P_{interaction}$=0.006), respectively. A significant GRS-

total fat intake interaction on TG:HDL-C ratio was also observed in the Brazilian population ($P_{interaction}$=0.03). In the Peruvian population, a significant GRS-carbohydrate intake interaction on the concentration of HDL-C was observed ($P_{interaction}$=0.0007). Also in the Peruvian population, participants with a high GRS, had lower concentrations of HDL-C across tertiles of glycaemic load (P_{trend}=0.017). In summary, the findings of this thesis add to the field of nutrigenetics by showing the presence of genetic heterogeneity in gene-diet interactions on lipid-related traits in different ethnic groups. These findings will contribute to improved understanding of how genetic and dietary factors interact to alter the susceptibility to CVDs in different ethnic groups. Replication of the findings in large scale longitudinal and dietary intervention studies is required prior to being considered for personalised dietary guidelines.

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1. **Wuni, R.**, Kuhnle, G. G. C., Wynn-Jones, A. A. & Vimaleswaran, K. S. A Nutrigenetic Update on CETP Gene-Diet Interactions on Lipid-Related Outcomes. *Current Atherosclerosis Reports* **2022**, *24*, 119-132. https://doi.org/10.1007/s11883-022-00987-y

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7. **Wuni, R.** & Vimaleswaran, K. S. Barriers in Translating Existing Nutrigenetics Insights to Precision Nutrition for Cardiometabolic Health in Ethnically Diverse Populations. *Lifestyle Genomics* **2024**, *17*, 122-135. https://doi.org/10.1159/000541909

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Abbreviations

CURES	Chennai Urban Rural Epidemiological Study
BOLD	Obesity, Lifestyle and Diabetes in Brazil
SONGS	Study of Obesity, Nutrition, Genes and Social factors
GeNuIne	Gene-Nutrient Interactions
GWA	Genome-wide association
SNP	Single nucleotide polymorphism
GRS	Genetic risk score
HWE	Hardy-Weinberg equilibrium
LMICs	Low- and middle-income countries
LACP	Latin American and Caribbean populations
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglycerides
VLDL	Very-low density lipoprotein
IDL	Intermediate-density lipoprotein
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HbA1c	Glycated haemoglobin
FPG	Fasting plasma glucose
SFA	Saturated fatty acids
MUFA	Monounsaturated fatty acids
PUFA	Polyunsaturated fatty acids
TEI	Total energy intake
CVDs	Cardiovascular diseases
CAD	Coronary artery disease
NCDs	Non-communicable diseases
BMI	Body mass index
CHD	Coronary heart disease
CETP	Cholesteryl ester transfer protein
LPL	Lipoprotein lipase

PPARs	Peroxisome proliferator-activated receptors
T2D	Type 2 diabetes
CE	Cholesteryl esters
FFA	Free fatty acids
RCT	Randomised controlled trial
CMR	Cardiometabolic risk
MS	Metabolic syndrome
LDLR	LDL receptor
SRBI	Scavenger receptor BI
LRP	LDL receptor related protein
HL	Hepatic lipase
APOA	Apolipoprotein A
APOB	Apolipoprotein B
APOC	Apolipoprotein C
APOE	Apolipoprotein E
ABCA1	Adenosine-triphosphate-binding cassette transporter-1
LCAT	Lecithin-cholesterol acyltransferase
FFQ	Food frequency questionnaire
AA	Arachidonic acid
HOMA-IR	Homeostasis model assessment estimate of insulin resistance
HOMA-B	Homeostasis model assessment estimate of insulin secretion
QUICKI	Quantitative insulin-sensitivity check index
HR	Hazard ratio
RR	Relative risk
SD	Standard deviation
SE	Standard error
SPSS	Statistical Package for the Social Sciences
CI	Confidence interval

Chapter 1 Introduction to the thesis

1.1 Introduction

In recent decades, the rates of cardiometabolic diseases including cardiovascular diseases (CVDs) have risen dramatically, coinciding with the so-called 'obesogenic environment' which is used to describe environmental influences on nutrition and physical activity [1, 2]. One of the main risk factors for CVDs is an altered blood lipid profile, usually characterised by a reduced concentration of high-density lipoprotein cholesterol (HDL-C) and elevated levels of low-density lipoprotein cholesterol (LDL-C) or triglycerides (TG) [3, 4]. Recent advancements in genotyping technology have paved the way for research into the genetic basis of complex traits, and so far, large-scale genome-wide association (GWA) studies have discovered numerous genetic loci associated with blood lipid concentrations and the risk of CVDs [5-9]. However, only a small proportion of variability in blood lipid concentrations is explained by these genetic variants [5, 10, 11]. Moreover, diet, which is considered an environmental factor, has been shown to contribute to variations in blood lipid concentrations and the risk of CVDs [12, 13]. Therefore, dietary modification is a fundamental aspect of first line treatment of lipid-related traits [14, 15]. Nonetheless, inter-individual differences in the biological response to dietary interventions have been reported, which might be due to genetic variations [16, 17]. Therefore, it is important to examine how genetic and dietary factors interact to influence lipid-related traits.

The gene-diet interaction (nutrigenetic) approach is an innovative approach that investigates the impact of genetic variability on individual responses to diet [18]. This approach helps to determine whether the genetic risk of abnormal blood lipid concentrations and related traits is modified by dietary factors, offering the potential to design personalised dietary guidelines for preventing and managing CVDs [19, 20].

This chapter will (i) give an overview of CVDs; (ii) examine lipids as a risk factor for CVDs; (iii) discuss the influence of genetic and dietary factors on blood lipid concentrations; (iv) examine the significance of studying gene-diet interactions and the role of personalised nutrition in the prevention and management of CVDs.

1.2 An overview of cardiovascular diseases

CVDs cover a variety of conditions affecting the heart and blood vessels including ischaemic heart disease, stroke and peripheral vascular disease [21]. Most CVDs are caused by atherosclerosis, which results from the build-up of lipids and inflammation in the large arteries [22, 23]. Through narrowing of the lumen of arteries or formation of thrombi, atherosclerosis can result in reduced blood supply to the heart, brain or lower extremities, causing coronary heart disease, ischaemic stroke or peripheral vascular disease respectively [22, 23]. CVDs are a threat to global public health, accounting for over 17 million deaths in 2019, with a significant proportion (more than 75%) occurring in low- and middle-income countries (LMICs) [24]. As shown in **Figure 1.1,** a substantial majority of non-communicable disease (NCD) mortality is attributable to CVDs [25].

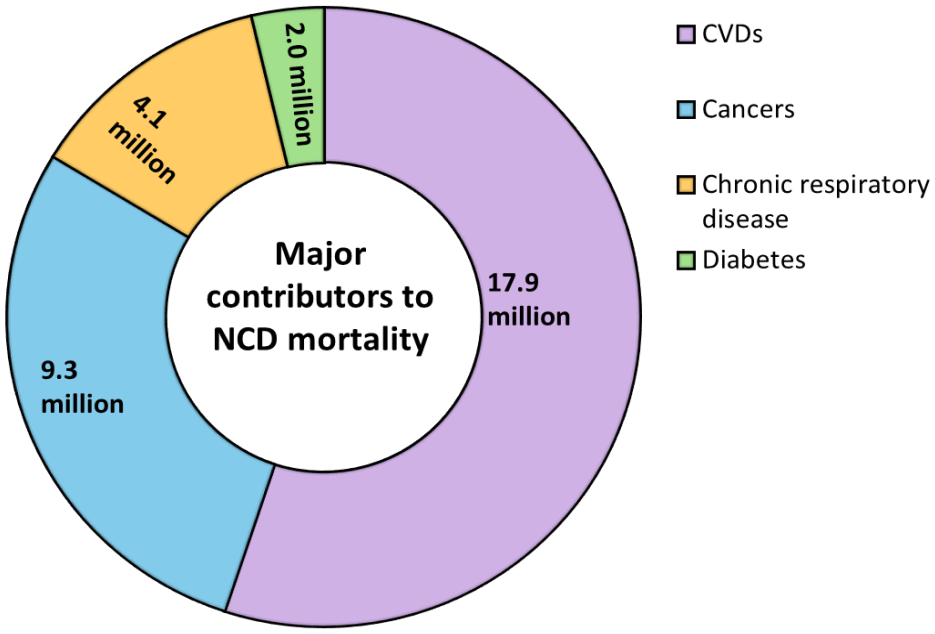


Figure 1.1 Major contributors to NCD mortality

Major contributors to non-communicable disease (NCD) mortality (80%) in people under the age of 70 [25].

Abbreviations: NCD – non-communicable disease; CVDs – cardiovascular diseases.

CVDs present severe health and economic consequences for individuals, families and communities, especially in LMICs, where individuals tend to be affected by CVDs and related conditions during their productive years, which, coupled with huge healthcare expenses and limited employment opportunities worsens the financial burden of CVDs in these countries [26, 27]. In Latin American and Caribbean populations (LACP), CVDs, in particular, ischaemic heart disease and cerebrovascular disease, are the top cause of mortality and a key contributor to disability, and this is mainly attributed to CVD risk factors [28]. Similarly, the CVD epidemic in India is marked by an early onset, greater relative risk (RR), a higher fatality rate, and an increased number of premature deaths [29], necessitating further research into the prevention and management of CVD risk factors in these regions.

1.3 Lipid as a risk factor for cardiovascular diseases

Atherosclerotic lesions are marked by the build-up of cholesterol, and low-density lipoprotein (LDL) is the primary transporter of cholesterol to the walls of arteries [30]. The main events in the onset of atherosclerotic CVD involves the retention and build-up of cholesterol-rich apolipoprotein B (ApoB)-containing lipoproteins within the arterial intima at locations prone to plaque formation [31]. The likelihood of retention of LDL particles and the risk of developing atherosclerosis are reported to be reduced when the concentration of LDL-C is around 0.5–1.0 mmol/L (20–40 mg/dL). Above this threshold, the likelihood of retention of LDL in the intima, and the subsequent initiation and progression of atherosclerotic plaque increases in a dose-dependent manner [31]. In a systematic review and meta-analysis of 14 prospective cohort studies including 1,055,309 participants [32], a positive association was found between the concentration of LDL-C and mortality from CVDs [Hazard ratio (HR), 1.21; 95% confidence interval (CI), 1.09–1.35]. In support of this, a systematic review and meta-analysis of 49 trials with a total of 312,175 participants [33] observed that, a low LDL-C concentration was associated with a lower RR of major cardiovascular events. It was identified that a 1 mmol/L (38.7 mg/dL) reduction in the concentration of LDL-C was associated with a RR of 0.77 (95% CI, 0.75–0.79, $P<0.001$). Therefore, a high concentration of LDL-C is widely considered as a key risk factor for CVDs [34], and most cardiovascular risk prediction models and prevention guidelines include LDL-C [35, 36].

As with LDL-C, a rise in the concentration of TG has been associated with increased risk of atherosclerosis and CVDs [37, 38]. Plasma TG concentration serves as a marker of TG-rich lipoproteins and their remnants such as very-low density lipoprotein (VLDL),

chylomicrons and chylomicron remnants, and the cholesterol contained within these lipoproteins is believed to contribute to the development of atherosclerosis [37, 38]. Remnant lipoproteins can enter the intima, causing low-grade inflammation, foam cell formation and atherosclerotic plaques [37, 39]. Moreover, a high concentration of TG, caused by either an increased production or decreased breakdown of TG-rich lipoproteins is reported to directly affect the composition and metabolism of both LDL and HDL, resulting in small dense LDL and HDL particles which are atherogenic [40]. A systematic review and meta-analysis of 61 prospective cohort studies [41] identified that, raised TG concentrations were associated with higher risks of CVD and total mortality in a dose-dependent manner. In comparison to the reference group (90–149 mg/dL), the combined RRs and 95% CIs for CVD mortality were 0.83 (0.75 to 0.93) for the lowest TG group (<90 mg/dL); 1.15 (1.03 to 1.29) for the borderline-high group (150–199 mg/dL); and 1.25 (1.05 to 1.50) for the high TG group (≥200 mg/dL). For total mortality, the combined RRs and 95% CIs were 0.94 (0.85 to 1.03), 1.09 (1.02 to 1.17), and 1.20 (1.04 to 1.38), respectively [41]. Similarly, alterations in TG levels were found to be predictive of major cardiovascular events in a meta-regression analysis of 40 randomised controlled trials (RCTs) (P=0.005) [42]. Taking together, these findings suggest that a raised TG concentration is a key risk factor of CVDs.

In contrast to LDL and TG-rich lipoproteins, high-density lipoprotein (HDL) is well known to have a cardioprotective effect [43-47]. Through reverse cholesterol transport, HDL facilitates the removal of excess cholesterol from peripheral tissues and promotes its excretion, thus reducing the risk of atherosclerosis and CVDs [48, 49]. However, it has been recognised that, the concentration of HDL-C does not necessarily correlate with the function of HDL [32, 50], which is exemplified by the observation that, individuals with scavenger receptor class B member 1 (*SCARB1*) gene mutations have higher CVD risk despite having high concentrations of HDL-C [50]. Nonetheless, the systematic review and meta-analysis of 14 prospective cohort studies discussed above [32] found that, increased HDL-C concentration was associated with reduced risk of mortality from CVDs [HR, 0.60, 95% CI, 0.50–0.72; P<0.01). Similarly, a meta-analysis of 23 prospective cohort and cross-sectional studies in the Asian Pacific region [51] reported that, low concentration of HDL-C [<1.03 mmol/L (<40 mg/dL) in men and <1.30 mmol/L (<50 mg/dL) in women] was associated with higher risk of coronary heart disease (CHD) in Asian participants (participants from India, China, Hong Kong, Japan, Korea, the Philippines, Singapore, South Korea, Taiwan, and Thailand) (HR, 1.67; 95% CI, 1.27–2.19). In line with these findings, a meta-analysis of 8 trials [52] reported an inverse association between the concentration of HDL-C and the risk

of cardiovascular events (HR, 0.83; 95% CI, 0.81–0.86). Altogether, these results suggest that low HDL-C concentration is a main risk factor of CVDs.

Therefore, this thesis aimed to examine factors that influence lipid-related traits. Several factors are known to contribute to the development of lipid-related traits, and these include non-modifiable factors including genetics, age and sex as well as modifiable factors such as dietary intake, physical activity level and obesity [53-55]. Managing modifiable risk factors could help to lower the risk of developing CVDs. In this thesis, genetic and dietary factors will be examined.

1.4 Lipid metabolism

Lipids are insoluble in water and as a result they have to be transported in plasma in combination with proteins, forming lipoproteins [56]. Lipoproteins consist of a central hydrophobic core containing lipids, mainly TG and cholesterol esters (CE), surrounded by a hydrophilic membrane made up of phospholipids, free cholesterol and apolipoproteins. Lipoproteins play an important role in the absorption and transport of dietary lipids by the small intestine, the movement of lipids from the liver to peripheral tissues, and the transport of lipids from peripheral tissues back to the liver and intestine, a process known as reverse cholesterol transport [57]. Lipoproteins are categorised based on their hydrated density, in ascending order as chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) [56]. These lipoproteins differ in size, lipid content, and the type of apolipoprotein they contain [58], and these characteristics are altered by the action of enzymes such as lipoprotein lipase (LPL), hepatic lipase (HL), lecithin-cholesterol acyltransferase (LCAT), and cholesteryl ester transfer protein (CETP) [56].

The metabolism of lipoproteins is dependent on apolipoproteins, which are proteins that play multiple roles such as acting as templates for the assembly of lipoprotein particles, maintaining the structure of these particles and guiding their metabolism by binding to membrane receptors as well as regulating enzyme activity [56]. The cellular uptake of lipoproteins is regulated through the binding of apolipoproteins to membrane lipoprotein receptors, and these include LDL receptors (LDLR), LDL receptor related protein (LRP) and scavenger receptor BI (SRBI). Apolipoprotein B100 (apoB100) and apolipoprotein E (apoE) both bind to LDLR, apoE also binds to LRP while apolipoprotein A (apoA) binds to SRBI [56], enabling cellular uptake of lipoproteins.

Dietary lipids, mainly TG, phospholipids and CE, are emulsified with bile salts and broken down in the intestinal lumen by various pancreatic lipases into FFA, monoglycerides and free cholesterol [59]. These products are absorbed by the intestinal enterocytes and used to resynthesise TG as well as phospholipids and CE which are assembled into chylomicrons [59]. Chylomicrons consist mainly of TG (75%) and apoB-48 as the core structural protein [60]. Upon secretion by the intestine, chylomicrons obtain apoCII from HDL and circulate through the tissues where LPL on the endothelial surface is activated by the apoCII. LPL breaks down the TG into FFA which are absorbed by the tissues (muscle and adipose) and used as energy or stored for future use [60]. When TG are removed from chylomicrons by LPL, smaller particles known as chylomicron remnants are formed. Chylomicron remnants contain apoE which enables them to bind to LRP in the liver, thereby facilitating their removal through endocytosis [57].

VLDL is synthesised in the liver and this process depends on the availability of TG [61]. The TG for VLDL assembly are produced as a preventive response to increases in FFA. The liver obtains FFA from three main sources: FFA derived from adipocytes, chylomicron remnants, and the intestine through the portal vein [61]. Nascent VLDL initially contain apoB100 as the only apolipoprotein, but they later acquire apoA (AI, AII, AIV), apoC (CI, CII, and CIII), and apoE, primarily from HDL [56]. Some of the TG in VLDL is broken down in muscle and adipose tissue by LPL, releasing FFA and forming VLDL remnants (IDL) [57]. VLDL remnants are taken up by the liver by binding to the LDL receptor via apoE. In this process, there is a further breakdown of TG by HL. The remnants also lose apoC and apoE (which are transferred to HDL), decrease in size, and transform into LDL [56], the final product of VLDL metabolism [62]. The main structural protein of VLDL, IDL and LDL is apoB-100, which is synthesised in the liver [57].

HDL on the other hand is formed from lipid-free apoAI which is secreted by the liver and the intestine [48]. ApoAI removes free cholesterol and phospholipids from peripheral tissues to form small dense HDL, by binding to the membrane adenosine-triphosphate-binding cassette transporter-1 (ABCA1), which regulates the efflux of free cholesterol from cells [56]. Some of the free cholesterol is then esterified by LCAT into cholesteryl esters (CE), converting small dense HDL to mature HDL [48]. CETP transfers CE from HDL to VLDL, IDL and LDL where they are exchanged for TG which are then transported back to HDL. HDL also transports excess cholesterol in the form of CE and free cholesterol to SRB1 cells in the liver where it is excreted in bile [63]. When CETP enriches HDL with TG, it becomes a substrate for HL, which hydrolyses the TG, causing the lipid-free apoA1 to dissociate and reducing the

size of the HDL particle, thereby forming small dense HDL [64]. The primary apolipoproteins on HDL are apoAI and apoAII, but they also contain other apolipoproteins such as apoAIV, apoCI/CII/CIII and apoE [65, 66].

1.5 Factors influencing blood lipid levels

1.5.1 Dietary factors

Diet is a known risk factor for an altered blood lipid profile, and dietary modification is considered a fundamental aspect of first line treatment of an abnormal lipid profile [14, 67]. Dietary fatty acids play a role in the metabolism of lipids and lipoproteins [68, 69], and one of the key recommendations of dietary guidelines for CVD prevention and management is to reduce the intake of total fat and saturated fatty acids (SFA) [70, 71]. A high intake of SFA has been linked to a rise in LDL-C [14, 72] and TG-rich lipoproteins [73-75]. SFA are reported to promote the activity of apoCIII, and excessive apoCIII activity leads to prolonged presence of VLDL and chylomicron remnants in circulation; while polyunsaturated fatty acids (PUFA) suppress the activity of apoCIII [76]. A systematic review and regression analysis of dietary trials indicated that replacing SFA with cis-PUFA or cis-monounsaturated fatty acid (MUFA) was associated with a significant reduction in the concentrations of total cholesterol (TC), LDL-C, HDL-C and TG; as well as in the TC to HDL-C ratio and LDL-C to HDL-C ratio [72]. Replacing SFA with carbohydrates was also associated with a significant reduction in the concentrations of TC, LDL-C and HDL-C, but with a significant increase in the concentration of TG [72]. However, a pooled analysis of 11 cohort studies [77] suggested that, replacing SFA with PUFA is more beneficial than replacing with it with MUFA or carbohydrates. In contrast, a review of direct comparison trials [67] concluded that, compared with a high MUFA intake from sources such as olive oil, a high SFA intake from sources such as butter or cream had more negative effects on blood lipids. It was also reported that, although omega-6 PUFA lowers LDL-C concentration, it can also decrease the particle size of LDL, producing a more atherogenic small dense LDL, as well as reduce the protective effect of HDL [67]. Overall, there are inconsistent results regarding the influence of dietary factors on blood lipid levels.

1.5.2 Genetic factors

1.5.2.1 Common disease common variant hypothesis

The common disease-common variant hypothesis suggests that common genetic variants contribute to the development of common diseases. Cardiometabolic diseases have a complex inheritance pattern and harmful variants with large effect sizes are mostly removed from the genome over time due to evolutionary pressure [78]. It argues that these variants occur at a high frequency but have a low 'penetrance' (the likelihood that an individual carrying the variant will develop the disease) [79]. A widely used approach for identifying alleles that increase or decrease the risk of common diseases with complex genetic components involve using markers within candidate genes or across all genes involved in a biological pathway or with similar biological functions [80].

1.5.2.2 The candidate gene approach

The candidate gene approach is a hypothesis-driven approach commonly used to examine the genetic contribution to complex diseases [81]. This approach involves examining genes that code for proteins with established roles in a disease process [82]. It is based on the idea that differences in a trait are often due to mutations in specific genes. These genes are usually genes with known biological functions that directly or indirectly modulate the processes involved in the development of the trait being examined [83]. The initial step in a candidate gene study is selecting a gene that is likely to be involved in the disease or trait being investigated. Once a candidate gene has been selected, the existing variants of the gene need to be identified to determine which alleles encode proteins with altered functions that could impact on the disease or trait being studied [84]. By genotyping common SNPs within these genes and their regulatory regions, populations of affected and unaffected individuals can be studied [82].

The effectiveness of the candidate gene approach depends on the accurate selection of genes or pathways for investigation, and as a result, a pre-existing hypothesis about the biological function is necessary which can sometimes be arbitrary [80]. Moreover, while this approach is less expensive, it is limited to genes already known or suspected to influence a particular phenotype and does not offer new insights into the biological pathways involved in the disease [82]. Additionally, associations found through candidate gene studies often fail to replicate due to various factors including low statistical power linked to insufficient sample sizes and varying causes of the disease [82, 83]. However, consistent associations have been found between SNPs of candidate genes such as *CETP* and *LPL* [85-90] and lipid-related traits.

1.5.2.3 Genetic variants and blood lipids

Genetic factors play a role in the metabolism of lipids and the risk of CVDs, and all the major blood lipid fractions, TC, LDL-C, HDL-C and TG are estimated to be 40-70% heritable [91]. The regulation of lipid and lipoprotein metabolism is a complex process involving numerous steps. A balance in lipid levels is maintained through the coordinated actions of many nuclear factors, binding proteins, apolipoproteins, enzymes and receptors, all involving multiple genes [19]. GWA studies have shown that lipid abnormalities have genetic risk factors in common, including polymorphisms in established lipid regulators and proteins such as CETP, LPL, and apoE [92, 93].

The *CETP* gene, which encodes CETP is one of the most widely studied lipid-related genes and several single nucleotide polymorphisms (SNPs) of this gene have been associated with variations in the concentration of HDL-C [94-97]. The 'B1' allele of the TaqIB SNP (rs708272) of *CETP* has been linked to higher CETP activity which leads to lower concentrations of HDL-C and higher levels of serum TG [98], and studies have shown that individuals with the 'B1B1' genotype have lower HDL-C concentrations [99-101]. Similarly, apoE functions as a ligand for both LDLR and LRP, and variations in the concentrations of TC and LDL-C have been reported in individuals with different isoforms of the *APOE* gene, the E4 isoform being associated with higher levels of TC and LDL-C compared to the E2 isoform [102, 103]. Although numerous genetic loci have been identified by GWA studies to influence blood lipid concentrations, only a small proportion of variation in blood lipid levels is explained by these variants [5, 10, 11], and there is growing evidence that an interaction between genetic variants and environmental factors such as dietary intake might be responsible for part of the missing heritability [104-108].

1.6 The nutrigenetic approach

The nutrigenetic (gene-diet interaction) approach focuses on understanding gene-diet interactions that predispose to specific diseases. Thus, a genetic variant might not always pose a higher risk of a disease as its effects might be modulated by the environmental factors that interact with it [109]. By identifying gene-diet interactions that increase the susceptibility to certain diseases, nutrigenetics offers the potential to design personalised and precise dietary guidelines for preventing and managing CVDs [19, 20].

1.6.1 Genetic variations and the role of ethnicity in cardiovascular disease risk

The Human Genome Project indicated that humans are 99.9% identical at the DNA level, and that examining the 0.1% genetic variation, especially the distribution of SNPs between affected and unaffected individuals, could offer valuable insights into the genetic factors contributing to complex traits [110]. GWA studies have identified many SNPs associated with CVDs and risk factors such as abnormal lipid levels [5, 10, 11, 111], and several studies have shown that the occurrence of SNPs varies among populations of different ancestries, resulting in disparities in disease risk [112-116]. SNPs of lipid-pathway genes such as the *APOE* gene, one of the most widely studied genes in relation to cardiometabolic diseases, have been reported to occur at different frequencies in different populations [112, 113]. The E4 isoform of the gene, which is linked to higher risk of CVDs, is reported to occur at higher frequencies in Asian and African populations compared to populations of European descent [112, 113], and this could contribute to differences in susceptibility to specific diseases among these populations. Similarly, variations in the effect size of SNPs of the *CETP* gene, an established lipid metabolism gene, have been reported among different ethnic groups [117, 118]. The effect size of the 'A' allele of *CETP* SNP rs4783961, which is associated with higher concentrations of HDL-C, was found to be larger in African American cohorts compared to European American cohorts; while another *CETP* SNP rs17231506 had larger effect sizes in European Americans and Hispanics, compared to African Americans [117]. This suggests that different ethnic groups might share the same underlying causal variant within a gene. However, due to ethnicity-specific differences in the frequencies of major and minor alleles, a SNP might have different effect sizes and varying degrees of association [117].

Moreover, variations in conventional risk factors for CVDs exist among different ethnic groups. Asian Indians are known to have distinct biochemical and physical characteristics ("the Asian Indian phenotype") which make them prone to developing cardiometabolic diseases at a lower body mass index (BMI) compared to Europeans [105]. These characteristics include central obesity, abnormal lipid levels, insulin resistance, higher amounts of visceral fat, increased overall fat, and a propensity to beta cell dysfunction [105, 119, 120]. Furthermore, ethnic groups have differences in dietary patterns, lifestyle and socioeconomic factors [121, 122] which can influence the risk of CVDs. Therefore, it is important to examine how genetic factors influence the risk of CVDs in different ethnic groups.

1.6.2 Rationale for studying gene-diet interactions

GWA studies have identified numerous SNPs associated with CVDs and risk factors such as abnormal lipid levels [5, 9-11, 123-125]. The major lipid fractions (TC, HDL-C, LDL-C and TG) in particular, are reported to have a heritability of 40-70% [91]. However, despite the discovery of a large number of genetic variants associated with lipid-related traits, only a small fraction of variability is explained by these variants [5, 10, 11], and there is growing evidence that an interaction between genetic and environment factors such as dietary intake could partly explain this so called 'missing heritability' [105, 106, 126-129]. Therefore, investigating how gene-diet interactions impact on lipid-related traits could help to improve our understanding of the underlying pathophysiology and the development of precision nutrition strategies for the prevention and management of these conditions.

1.6.3 Importance of investigating gene-diet interactions in different ethnic groups

Studies have shown that allele frequencies of SNPs vary among individuals of different ethnic backgrounds, impacting how their bodies metabolise certain nutrients [18, 106, 130-132]. With regard to circulating levels of arachidonic acid (AA) and its metabolites, which play significant roles in immune response and inflammation and have been linked to various diseases including diabetes and CVDs [133, 134], research involving individuals of European ancestry suggests that, only a small fraction of dietary linoleic acid is converted to AA in humans [135, 136]. However, it has been identified that this minimal conversion rate might not be the same for all populations due to variations in allele frequencies of SNPs which influence circulating levels of fatty acids [114-116]. Therefore, gene-diet interaction studies covering different ethnic groups are required to gain a better understanding of the genetic variations and specific nutritional requirements within these groups.

Although gene-diet interaction studies have been extended to cover previously under-represented populations [99, 137-141], a systematic review conducted as part of this thesis [106] identified that, 27 out of 33 countries in Latin America and the Caribbean had not conducted gene-diet interaction studies, indicating that there is still limited research in some areas. Given the genetic diversity and differences in dietary patterns, cultural and socioeconomic factors, gene-diet interaction studies covering populations of different ethnicities are needed to develop dietary guidelines that are tailored to each ethnic group.

1.6.4 Study designs and their roles in identifying gene-diet interactions

Study designs commonly used to investigate gene-diet interactions include observational studies such as cross-sectional, case-control and cohort studies; and interventional studies such as RCTs. A cross-sectional study design is the most common and it involves analysing data from a population at a single point in time to assess the relationship between dietary exposures and genetic variations [142]. Assessing both exposures and outcomes at the same point in time provides a 'snapshot' of the current conditions within a population, including dietary habits, nutritional status and the prevalence of disease [143]. Cross-sectional studies are also quick and relatively inexpensive, enabling the investigation of gene-diet interactions in large samples, making them useful for generating hypotheses [143]. However, causality cannot be established since it is difficult to determine if the results would change significantly if data were collected at a different time point [144]. Nonetheless, GWA studies have shown that cross-sectional studies are effective in identifying genetic variants linked to diseases, as these studies are less likely to be influenced by potential confounders and are free from reverse causation [142] (where the outcome of interest influences the exposure instead of the exposure influencing the outcome) [145].

In cohort studies, a group of individuals are followed over time to assess the development of an outcome based on different dietary exposures [146]. Cohort studies are useful in identifying exposures and risk factors prior to disease onset, thereby reducing bias in the assessment of dietary exposure [147]. They are also beneficial in investigating rare exposures and allowing the examination of multiple outcomes at the same time, although they can be time consuming and expensive due to the requirement of large sample sizes and long follow up periods [146]. Case-control studies compare individuals who have a specific health outcome (cases) with those without it (controls) to examine the impact of dietary exposure and genetic factors on the health outcome [143]. Case-control studies are usually conducted retrospectively to identify genetic and other risk factors, as well as dietary exposures that were present before the onset of the disease or trait, likely contributing to its development [148]. Case-control studies are also efficient for rare diseases, allowing for multiple exposures to be assessed [146]. As with cohort studies, case-control studies require large sample sizes to detect interactions, and there is a risk of selection bias and challenges in choosing appropriate control groups [148]. One of the main challenges in case-control studies is the potential differences between the participants in the case and control groups with regard to exposure variables and risk factors not under investigation [146]. This is

addressed by matching the participants in the case and control groups, ensuring that data collection methods are designed to be equally applicable to both groups [148]. Case-only studies which focus only on individuals with a specific health outcome are also used to investigate gene-diet interactions, and they are believed to be efficient as only cases are needed, which are generally easier to gather compared to suitable controls [147]. However, the separate or joint effects of genetic variants and dietary factors cannot be assessed [149].

One of the main challenges of observational studies is confounding. A confounder refers to a variable that is linked to both the exposure and the outcomes, without being caused by either, and can introduce bias into the relationship between a dietary exposure and the outcome, if not controlled [145]. The distribution of confounding variables may vary between populations, and it is important to identify relevant confounders and adjust for them [150]. Potential confounders in gene-diet interaction studies include age, sex and BMI [105]. Another significant issue in observational studies is accurate assessment of dietary intake, as errors in dietary assessment can reduce the power of the study, and this is particularly important for interactions with minimal effect sizes [142]. Food frequency questionnaires (FFQs) are cost effective and are commonly used in large studies to assess usual dietary intake [151], but they need to be designed and validated to account for differences in socioeconomic, cultural and ethnic backgrounds of the population being studied [152, 153]. Moreover, under estimation of dietary intake is a main limitation of FFQs, and methods such as weighed diet diaries and multiple 24-h dietary recalls are reported to provide better estimates of dietary intake than FFQs [154, 155]. However, weighed diet diaries, which can theoretically offer the most precise assessment of dietary intake, are generally not practicable for large population studies due to the significant burden they place on respondents, the high chance of poor compliance, and the expensive nature of data entry [155].

In contrast to observational studies, interventional studies (clinical trials) aim to assess the effect of a dietary intervention on the outcome of interest [156]. RCTs are considered the gold-standard due to the high level of control over dietary exposure and the ability to establish causality [157]. In an RCT, participants who meet specific inclusion and exclusion criteria are randomly placed in two distinct groups, with each group receiving a different intervention. Randomisation, if implemented properly, results in two groups that are generally comparable, considering both measured and unmeasured factors [156]. When factors that could bias the estimate of the intervention's effect on the main outcome are randomly distributed between the two groups in an RCT, it ensures that the results are free

from confounding bias [158]. Thus, in theory, any differences in the outcome between the two groups is attributed to the effect of the intervention [156]. Another important feature of an RCT which improves the validity of the results is blinding, where people involved in the study (participants, investigators or assessors) are not made aware of the assigned intervention, preventing their actions and assessments from being influenced by this knowledge [159]. RCTs however have some limitations including small sample sizes which can affect their ability to detect moderate gene-diet interactions [142]. RCTs are also costly, have high dropout rates and may not be feasible for long-term studies since altering one dietary component usually results in compensatory changes in other components, and good compliance is usually difficult to maintain [145].

An alternative to an RCT is the crossover design, where participants receive two or more interventions during different time periods, with the sequence of interventions randomised for each participant [160]. The most common is the two sequence design, where half of the participants are randomly assigned to begin with the control period and then switch to the treatment (dietary intervention) period, while the other half follows the opposite sequence [161]. This design enables the effect of an intervention to be compared within each participant, as each individual serves as their own control [160]. A challenge of the crossover trial is the potential for residual effects from the intervention to influence the outcome during the period after the intervention has ended [161]. This can be addressed by incorporating an adequate 'washout' period between the end of the first intervention and the start of the second intervention or control period. This helps to ensure that the outcomes measured during the second intervention or control period are not influenced by the effects of the first intervention [162].

1.6.5 Gene–Nutrient Interactions (GeNuIne) Collaboration

There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors [163-168]. However, most of the gene-diet interaction studies have produced inconsistent results, which might be due to genetic heterogeneity (variations in allele frequencies) and differences in dietary and lifestyle patterns across populations. Hence, the findings of gene-diet interactions conducted in one population might not be applicable to other ethnic groups due to ethnic-specific differences in gene-diet interactions [18, 130, 169]. While gene-diet interaction studies have been extended to cover previously under-represented populations, a systematic review conducted as part of this thesis [106] identified that, 27 out of 33 countries in Latin America and the Caribbean had not conducted gene-diet interaction studies, indicating that there is

still limited research in LMICs. To facilitate nutrigenetic studies in LMICs, a large-scale collaborative project, the **Ge**ne–**Nu**trient **In**t**e**ractions (**GeNuIne**) collaboration was started at the University of Reading in 2013 through funding from the British Nutrition Foundation. Specifically, the GeNuIne collaboration is aimed at investigating how genetic and lifestyle factors interact to influence chronic diseases in diverse ethnic groups, with the goal of preventing and managing chronic diseases through personalised nutrition [18, 131, 170, 171]. Through this collaboration, gene-lifestyle interaction studies have been conducted in countries such as Brazil, Peru, Ghana, India, Sri Lanka, Indonesia, Malaysia and Turkey. In addition to conducting nutrigenetic studies, the GeNuIne collaboration has initiated training and resource development in LMICs to improve the ability of professionals and policymakers to effectively apply the findings of nutrigenetics within their domains [18, 106, 131, 170, 172, 173].

1.6.6 From nutrigenetics to personalised nutrition

Evidence from epidemiological studies indicates that lipid-related traits such as CVDs result from a complex interplay between genetic and environmental factors such as dietary intake [20, 174]. Nutrients play a role not only in enzymatic reactions that drive metabolism but also in the regulation of gene expression, and might significantly influence metabolic pathways involved in diseases [175]. Therefore, dietary modification is a fundamental aspect of first line treatment of lipid-related traits [14, 15]. However, numerous studies have highlighted significant variations among individuals in terms of disease susceptibility and biological responses to diet, indicating the need for a shift away from the "one-size-fits-all" approach for optimal health and disease prevention [16, 131]. Human diversity covers a broad range of factors including genetic, phenotypic, physiological, and lifestyle factors which are not accounted for by the "one-size-fits-all" approach [17, 172]. The completion of the Human Genome Project paved the way for various large-scale genomics initiatives focused on identifying and comprehending the extent of human genetic variation [176]. The remarkable advancements in research in fields such as nutritional genetics, epigenetics, and metabolomics has generated profound insights into genotypic and phenotypic variations that affect individual responses to diet, leading to the emergence of personalised and precision nutrition [17, 176].

Personalised nutrition is based on the idea that specific foods or amounts of nutrients can alter disease susceptibility depending on genetic make-up; utilising genetic information along with biological and cultural differences such as food preferences to tailor diets according to an individual's response to nutrients [177, 178]. Precision nutrition on the hand

is a relatively new concept that refers to a broader approach focused on integrating multiple disciplines including nutrigenetics, metabolomics, epigenetics and the gut microbiome [17, 177]. The goal of precision nutrition is to incorporate knowledge from multiple disciplines to advance understanding of key concepts in nutrigenetics and nutrigenomics, enabling healthcare professionals to determine the most suitable level of care for achieving precise nutrition [178]. Thus, precision nutrition indicates personalised nutrition that is more scientifically accurate and comprehensive [177].

Dietary factors may interact with an individual's genetic characteristics and impair metabolic processes, which may contribute to the development of CVDs [20]. Therefore, understanding gene-diet interactions that predispose to altered blood lipid levels could help to design personalised dietary guidelines for the prevention and management of lipid-related traits such as CVDs [19, 20]. In a study to examine whether the incorporation of genetic information to personalise an individual's diet could enhance long-term weight management [179], it was observed that, participants who followed diets tailored to their genetic information had greater long-term reductions in BMI and improvements in fasting glucose levels.

To enhance the scientific understanding of inter-individual variability in response to dietary interventions, integrating data from nutrigenetics and nutrigenomic approaches such as metabolomics is argued to be important, although the practicality and effectiveness of this process are still being explored [180, 181]. So far, progress has been made in the mechanistic understanding of dietary interventions through the integration of omics technologies such as metabolomics and the gut microbiome [182]. Metabolomics focuses on analysing small molecules (metabolites) found in biological samples to understand changes in metabolism under various conditions [180]. Metabolites are the direct products of dietary consumption and metabolism, enabling a more accurate assessment of biological and physiological pathways as well as the related biomarkers for diet or disease [182]. The gut microbiome supports the host by interacting directly or indirectly with host cells through the production of bioactive molecules, and this interaction allows the gut microbiome to regulate various biological processes related to immunity and energy balance [183]. The application of the gut microbiome in precision nutrition involves using the gut microbiome as a biomarker to predict how specific dietary components affect host health, and the use of this information to design precision dietary interventions aimed at promoting health [183]. Epigenetics on the other hand covers the molecular processes that can alter the activity of genes without changing the DNA sequence, and these processes include DNA methylation,

histone modifications and alterations in noncoding RNAs [184]. Epigenetic changes might explain individual differences in metabolic health and responses to diet, and have the potential to identify novel biomarkers for precision nutrition and targets for precise interventions [185].

1.7 Hypothesis, aims and outline of the thesis

Genetic association studies have identified SNPs in multiple genes linked to variations in blood lipid concentrations and susceptibility to lipid-related traits such as CVDs [5, 9-11, 123-125] and there is evidence that lifestyle factors including dietary intake, might modulate the effect of these SNPs in different ethnic groups [18, 131]. Given the genetic diversity and differences in dietary patterns, lifestyle and other environmental factors, it was hypothesised that gene-diet interactions will vary across populations and ethnic groups. Therefore, this thesis aimed to:

1. Investigate the association of selected SNPs as a genetic risk score (GRS) with lipid-related traits in different ethnic groups.
2. Investigate the interaction of the GRS with dietary factors (intake of fat, carbohydrate and protein) on lipid-related traits in ethnically diverse populations.

This thesis is presented as a collection of seven published papers covering the following topics:

Chapter 2: A nutrigenetic update on *CETP* gene-diet interactions on lipid-related outcomes (Wuni et al., 2022)

An abnormal lipid profile is considered a main risk factor for CVDs and evidence suggests that SNPs of the *CETP* gene contribute to variations in lipid levels in response to dietary intake. This work aimed to identify and discuss nutrigenetic studies assessing the interactions between *CETP* SNPs and dietary factors on blood lipids.

Chapter 3: Higher intake of dairy is associated with lower cardiometabolic risks and metabolic syndrome in Asian Indians (Wuni et al., 2022)

There is conflicting evidence about the association between dairy products and cardiometabolic risk (CMR). This work aimed to assess the association of total dairy intake with CMR factors and to investigate the association of unfermented and fermented dairy intake with CMR in Asian Indians who are known to have greater susceptibility to type 2 diabetes and CVDs compared to white Europeans.

Chapter 4: Interaction between GRS and dietary fat intake on lipid-related traits in Brazilian young adults (Wuni et al., 2024)

CVDs are a top cause of mortality globally, accounting for 32% of all deaths worldwide in 2019. In Brazil, ischaemic heart disease and stroke accounted for most deaths in 2019, with a percentage increase of 18 and 14%, respectively from 2009. The occurrence of dyslipidaemia, which is an established risk factor for CVDs, has been attributed to multiple factors including genetic and environmental factors. This study utilised a GRS to assess the genetic associations and the interaction of the GRS with dietary factors on lipid-related traits in Brazilian young adults.

Chapter 5: Interactions between genetic and lifestyle factors on cardiometabolic disease-related outcomes in Latin American and Caribbean populations: A systematic review (Wuni et al., 2023)

Cardiometabolic diseases such as hypertension and type 2 diabetes are accountable for most NCD deaths and impose an economic burden in LMICs. In Latin American and Caribbean populations (LACP), the prevalence of these diseases has increased in recent years. This work was done to identify gene-lifestyle interactions that modify the risk of cardiometabolic diseases in LACP.

Chapter 6: Impact of lipid-GRS and saturated fatty acid intake on central obesity in an Asian Indian Population (Wuni et al., 2022)

Asian Indians are more prone to developing type 2 diabetes and CVDs at a lower BMI than Caucasians, due to the 'Asian Indian phenotype', which is characterised by central obesity, dyslipidaemia, and increased levels of total fat, visceral fat, insulin resistance and faster decline in beta cell function. This study used a nutrigenetic approach to establish a link between lipids and obesity in Asian Indian adults.

Chapter 7: Interaction between GRS and dietary carbohydrate intake on high-density lipoprotein cholesterol levels: Findings from the Study of Obesity, Nutrition, Genes and Social factors (SONGS) (Wuni et al., 2025)

Cardiometabolic traits are complex interrelated traits that result from a combination of genetic and lifestyle factors. In Peru, a substantial increase in fatalities related to CVDs (77.8%) between 2020 to 2022 was reported. This study aimed to assess the association

and interaction of a GRS with dietary macronutrient intake on cardiometabolic traits in an urban Peruvian young adult population.

Chapter 8: Barriers in translating existing nutrigenetics insights to precision nutrition for cardiometabolic health in ethnically diverse populations (Wuni and Vimaleswaran, 2024)

There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors. Despite the remarkable progress, several factors need to be considered before the translation of existing nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations. This work aimed to explore the potential barriers and challenges in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities.

Chapter 9: Discussion

This chapter covers a discussion of the findings of all the studies including general trends observed across the different ethnic groups, strengths, limitations, future prospects, and conclusions of this thesis.

Chapter 2 A nutrigenetic update on *CETP* gene-diet interactions on lipid-related outcomes

Published (The published version of the paper is attached as an appendix at the end of the thesis)

Wuni, R., Kuhnle, G. G. C., Wynn-Jones, A. A. & Vimaleswaran, K. S. A Nutrigenetic Update on CETP Gene-Diet Interactions on Lipid-Related Outcomes. *Current Atherosclerosis Reports* **2022**, *24*, 119-132. https://doi.org/10.1007/s11883-022-00987-y

Ramatu Wuni's contribution: For this review, I started by conducting a literature search of genome-wide association studies to identify genetic variants associated with blood lipid levels. The results showed that, the cholesteryl ester transfer protein (*CETP*) gene had the highest number of reported associations (20 out of 32 identified studies). I then conducted a literature search of nutrigenetic studies focusing on *CETP*. A total of 448 articles were identified, 227 from PubMed and 221 from Google Scholar. After applying the exclusion criteria, 49 articles were found to be eligible, of which one article was published as an abstract. I read the full-text of the 48 eligible studies in detail and extracted the results for analysis. I contacted corresponding authors to provide additional information when needed. I wrote the manuscript and revised it based on comments from the co-authors before it was submitted to the Current Atherosclerosis Reports journal. I also wrote the responses to the comments from the reviewers and revised them based on suggestions from the co-authors.

2.1 Abstract

An abnormal lipid profile is considered a main risk factor for cardiovascular diseases and evidence suggests that single nucleotide polymorphisms (SNPs) in the cholesteryl ester transfer protein (*CETP*) gene contribute to variations in lipid levels in response to dietary intake. The objective of this review was to identify and discuss nutrigenetic studies assessing the interactions between *CETP* SNPs and dietary factors on blood lipids. Relevant articles were obtained through a literature search of PubMed and Google Scholar through to July 2021. An article was included if it examined an interaction between *CETP* SNPs and dietary factors on blood lipids. From 49 eligible nutrigenetic studies, 27 studies reported significant interactions between 8 *CETP* SNPs and 17 dietary factors on blood lipids in 18 ethnicities. The discrepancies in the study findings could be attributed to genetic heterogeneity, and differences in sample size, study design, lifestyle and measurement of dietary intake. The most extensively studied ethnicities were those of Caucasian populations and majority of the studies reported an interaction with dietary fat intake. The rs708272 (TaqIB) was the most widely studied *CETP* SNP, where the 'B1' allele was associated with higher *CETP* activity, resulting in lower high-density lipoprotein cholesterol and higher serum triglycerides under the influence of high dietary fat intake. Overall, the findings suggest that *CETP* SNPs might alter blood lipid profiles by modifying responses to diet, but further large studies in multiple ethnic groups are warranted to identify individuals at risk of adverse lipid response to diet.

2.2 Introduction

The global burden of cardiovascular diseases (CVDs) is well recognised and ischaemic heart disease alone accounted for 9 million deaths in 2019, making it the top cause of death in all parts of the world [186]. An abnormal lipid profile (dyslipidaemia), indicated by low concentrations of high-density lipoprotein (HDL) cholesterol and elevated levels of low-density lipoprotein (LDL) cholesterol or triglycerides (TG), is considered a major risk factor for CVDs [107, 187]. The cardioprotective role of HDL is thought to be dependent on the function of HDL rather than the levels of HDL, which is reflected in individuals with Scavenger Receptor Class B Member 1 (*SCARB1)* gene mutations who have higher levels of HDL cholesterol but higher CVD risk [50]. There is evidence to suggest that a combination of genetic susceptibility and environmental factors including diet is responsible for CVDs [18, 105, 188]. Single nucleotide polymorphisms (SNPs) in lipid-related genes such as the cholesteryl ester transfer protein (*CETP*), lipoprotein lipase (*LPL*) and apolipoprotein E (*APOE*) genes have been found to contribute to changes in lipid profiles in response to diet [108, 126, 189]. Of these three genes, *CETP* has been shown to have more associations with blood lipids (**Supplementary Table S2.1**). CETP regulates the concentration and particle size of HDL in the plasma (**Figure 2.1**) and is considered to play an important role in reverse cholesterol transport which is a protective mechanism against atherosclerosis [48]. Increased CETP activity has been shown to result in lower HDL cholesterol levels and is linked to higher risk of CVDs [46].

Several studies have demonstrated *CETP*-diet interactions on blood lipids; however, the findings have been inconsistent [99, 100, 189-192]. The objective of this review was therefore to identify and discuss studies assessing the interactions between *CETP* SNPs and dietary factors on blood lipids and to identify the factors that can be attributed to these discrepancies.

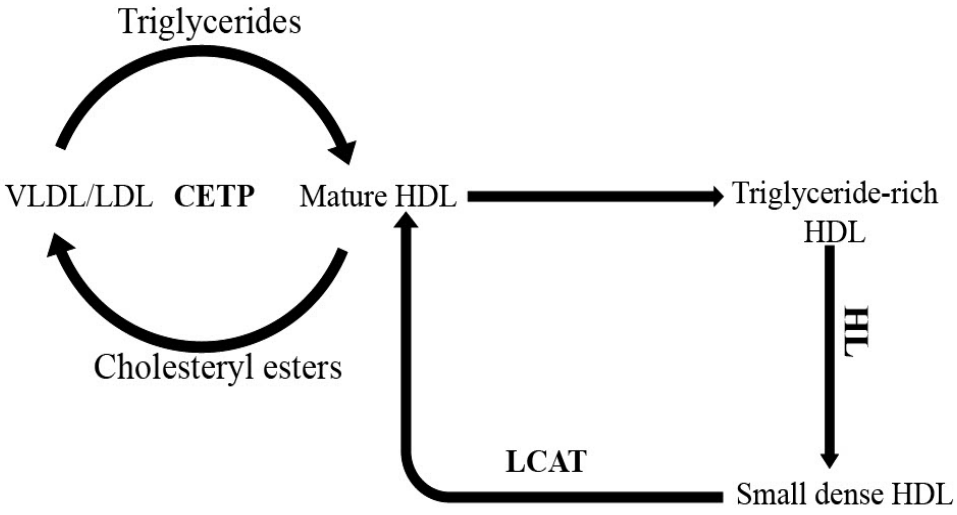


Figure 2.1 The role of cholesteryl ester transfer protein in lipid metabolism

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein which is secreted by the liver and is responsible for transporting cholesteryl esters and triglycerides between high-density lipoprotein (HDL) and Apolipoprotein B-containing lipoproteins such as very-low density lipoprotein (VLDL) and low-density lipoprotein (LDL) [64]. HDL is formed from lipid-free Apolipoprotein AI (apoAI) in a process involving the removal of free cholesterol from peripheral tissues and the subsequent esterification of some of the free cholesterol into cholesteryl esters via the actions of adenosine triphosphate binding cassette transporter A1 and Lecithin:cholesterol acyltransferase (LCAT) [48]. The enrichment of HDL with triglycerides makes it a substrate for hepatic lipase (HL) which then hydrolyses the triglycerides, resulting in dissociation of the lipid-free apoAI and a decrease in size of the HDL particle, forming small dense HDL [64].

2.3 Methods

2.3.1 Selection of the candidate gene for the review

To identify candidate genes which have been reported by genome-wide association (GWA) studies to influence blood lipid levels, a literature search was undertaken in December 2020, using the keywords: (genome-wide association study OR genome-wide association scan OR genome-wide association analysis OR GWAS OR GWA) AND (Lipids OR HDL OR LDL OR VLDL OR total cholesterol OR triglycerides OR triacylglycerol OR blood lipids). The results showed that, out of 32 identified studies (**Supplementary Table S2.1**), 20 GWA studies reported statistically significant associations between *CETP* and lipids [92,

94-97, 193-207]; while *LPL* was reported by 18 GWA studies [92, 94, 95, 97, 123, 193, 196, 197, 199, 201-209]; and *APOE* was reported by 10 GWA studies [92, 95, 97, 196-198, 200, 202-204]. *CETP* was then chosen for the review as it had the highest number of hits compared to *LPL* and *APOE*.

2.3.2 Study identification

To identify published articles, a literature search was undertaken using PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google Scholar (https://scholar.google.com/). The search covered the earliest date of indexing through to July 2021. For PubMed, the following key terms were used: (CETP OR cholesteryl ester transfer protein) AND (polymorphism OR gene OR SNP OR single nucleotide polymorphism OR genetic variation OR genetic variant OR rs3764261 OR rs1532624 OR rs1800775 OR rs9989419 OR rs4783961 OR rs708272 OR rs7499892 OR rs2303790 OR rs16965220 OR rs247616 OR rs289708 OR rs12708980 OR rs247617 OR rs173539) AND ("gene-diet interaction" OR "diet-gene interaction" OR "SNP-diet interaction" OR "diet-SNP interaction" OR "gene-nutrient interaction" OR "nutrient-gene interaction") AND (carbohydrate OR protein OR fat OR fibre OR sugar OR SFA OR MUFA OR PUFA OR Mediterranean diet OR Nordic diet OR B12 OR amino acids OR polyphenols OR egg intake OR caffeine intake OR green tea OR alcohol intake OR meat intake) AND (lipids OR HDL OR LDL OR VLDL OR total cholesterol OR triglycerides OR triacylglycerol OR blood lipids OR serum lipids). The key terms for Google Scholar were (CETP AND “gene-diet interaction” AND lipids). Only studies published in English were included.

2.3.3 Study selection

The search strategies above yielded a total of 448 articles from the two databases (227 from PubMed and 221 from Google Scholar) as shown in **Figure 2.2.** Titles of all the studies were first read to determine their relevance to the topic. Full-text of those found to be relevant were then read in detail to determine eligibility for inclusion. The criteria for inclusion in the review were: gene-diet interaction studies involving *CETP* gene polymorphisms and blood lipids. Only studies conducted in humans were included and, after applying the inclusion and exclusion criteria, 49 articles were found to be eligible, of which one article was published as an abstract. The studies excluded after reading the full-text were those focusing on interaction between *CETP* and physical activity on lipids; gene-diet interaction on lipids not including *CETP*; and gene-diet interaction review articles. Full-text of 48 eligible studies was read in detail and the results were extracted for analysis (**Supplementary Tables S2.2 and S2.3**). The results of one study [210] which was published

as an abstract were also extracted and included in the tables. The studies consisted of 28 observational studies (**Supplementary Table S2.2**) and 21 interventional studies (**Supplementary Table S2.3**).

2.3.4 Data extraction

The studies were identified by a single investigator and the following data were double-extracted independently by one reviewer: first author, publication year, location or ethnicity of participants, sample size, mean age, study design, reference SNP (rs) ID, genotype and minor allele. Corresponding authors were contacted to provide additional information where needed.

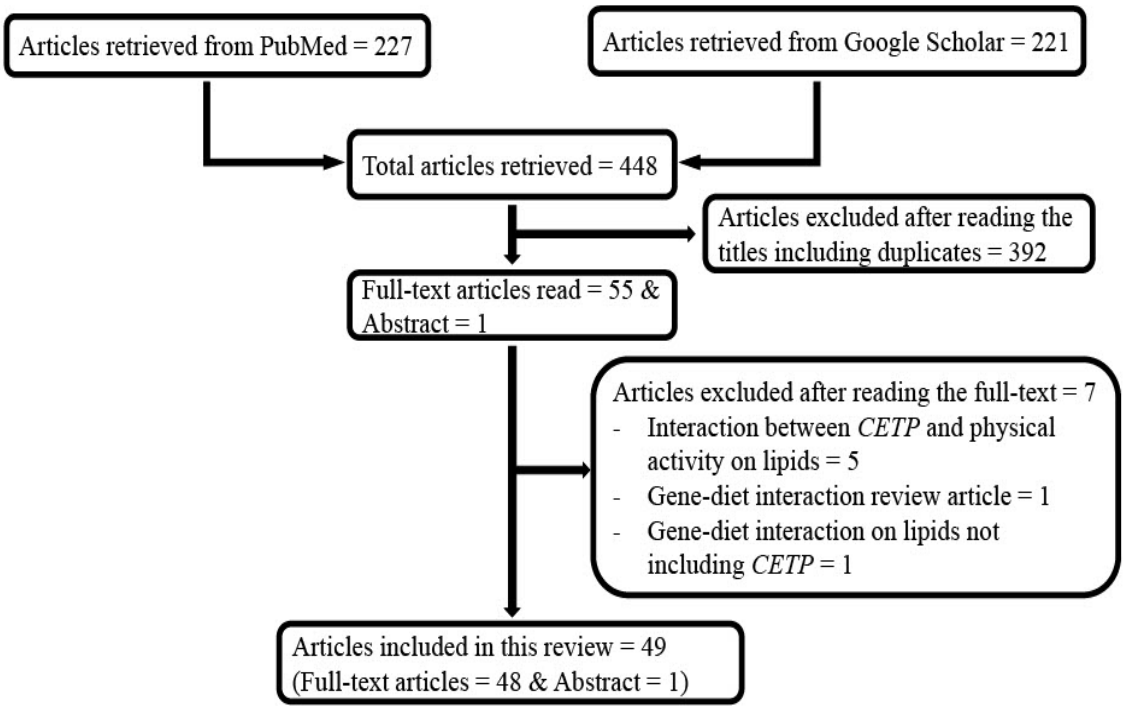


Figure 2.2 Flow chart of studies identified in the literature for *CETP*-diet interaction on lipids

2.4 Results of database search

This section reviews studies examining the interaction between dietary factors and *CETP* SNPs on blood lipids. The rs708272 (TaqIB), the most widely studied *CETP* SNP, was investigated by 31 studies. The second most studied SNP was rs5882 (I405V), accounting for 16 studies. The *CETP* SNPs rs3764261 and rs1800775 were each examined by 6 studies. All the studies were conducted in adults except for one study which was carried out in prepubertal children [211]. The ethnicities covered by the studies included British, White American, Spanish, Mexican, Chinese and Iranian as shown in **Figure 2.3**. A wide range of dietary factors were investigated by the 28 observational studies, and these included dietary carbohydrate, protein, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), coffee, sucrose, total energy intake and alcohol consumption. The 21 dietary intervention studies also focused on a variety of diets including Mediterranean diet, plant sterol ester, sesame oil, canola oil and rapeseed oil.

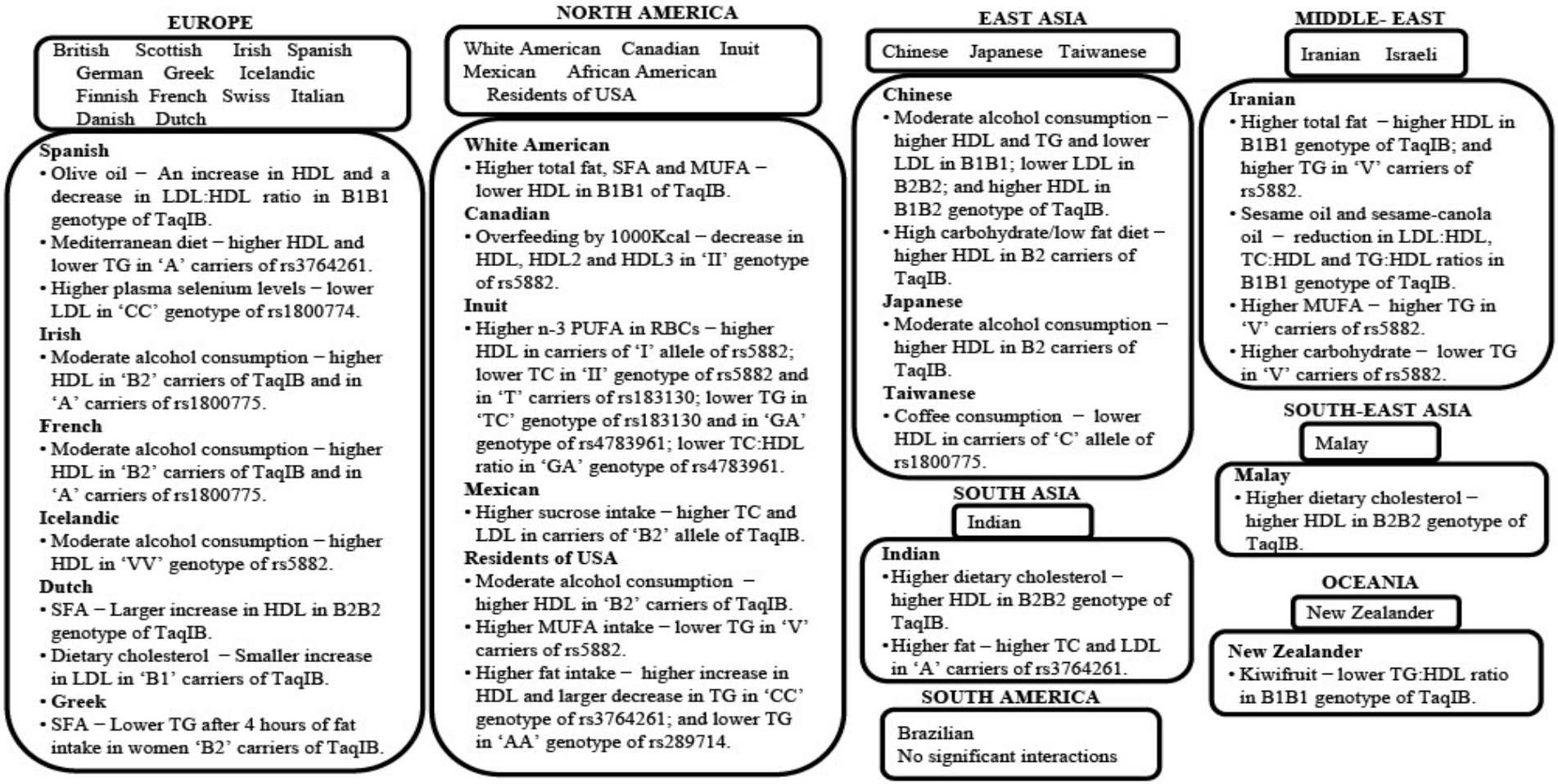


Figure 2.3 *CETP*-diet interaction studies and the interaction findings in multiple ethnicities

2.4.1 TaqIB (SNP rs708272 G > A)

The major allele ('G') is also called the 'B1' allele while the minor allele ('A') is also referred to as the 'B2' allele. Eight out of seventeen observational studies reported a significant association between TaqIB genotypes, dietary factors and blood lipids. In a cross-sectional study involving 129 Iranian patients with type 2 diabetes (T2D) without dyslipidaemia [99], a higher intake of total fat (>34.9% from total energy intake) was associated with higher HDL in participants with 'B1B1' genotype [mean HDL (mg/dL) for high total fat intake (>34.9% from total energy) vs low total fat intake (≤34.9% from total energy) = 58.6 ± 4.1 vs 36.5 ± 6.5; $P_{interaction}$=0.02]. Those with 'B2B2' genotype who had a higher intake of total fat (>34.9% from total energy) also had higher HDL [mean HDL (mg/dL) for high total fat intake (>34.9% from total energy) vs low total fat intake (≤34.9% from total energy) = 59.0 ± 4.2 vs 55.8 ± 3.3] but the interaction was more pronounced in individuals with 'B1B1' genotype, while in those with 'B1B2' genotype, the interaction was not observed. A prospective cohort study of 603 men with T2D in the United States of America (96% of whom were white) [190] on the other hand reported that, a higher intake of total fat (>33.5% from total energy intake), animal fat (>19.9% from total energy intake), SFA (>11.47% from total energy intake) and MUFA (>12.75% from total energy intake) was associated with lower HDL in participants with 'B1B1' genotype compared to those with 'B2B2' genotype [mean HDL (mg/dL) for low total fat intake (≤33.5% of energy) vs high total fat intake (>33.5% of energy): 40.0 ± 0.03 vs 36.2 ± 0.02 for 'B1B1', 41.5 ± 0.03 vs 44.9 ± 0.03 for 'B2B2', $P_{interaction}$=0.003; mean HDL (mg/dL) for low animal fat intake (≤19.9% of energy) vs high animal fat intake (>19.9% of energy): 39.7 ± 0.02 vs 36.2 ± 0.03 for 'B1B1', 42.2 ± 0.04 vs 43.5 ± 0.03 for 'B2B2', $P_{interaction}$=0.02; mean HDL (mg/dL) for low SFA intake (≤11.47% of energy) vs high SFA intake (>11.47% of energy): 39.8 ± 0.02 vs 36.2 ± 0.03 for 'B1B1', 42.2 ± 0.04 vs 43.8 ± 0.03 for 'B2B2', $P_{interaction}$=0.02; mean HDL (mg/dL) for low MUFA intake (≤12.75% of energy) vs high MUFA intake (>12.75% of energy): 39.3 ± 0.03 vs 36.5 ± 0.02 for 'B1B1', 41.9 ± 0.03 vs 44.2 ± 0.03 for 'B2B2', $P_{interaction}$=0.04]. The difference in the findings might be due to the type of fat consumed since the Iranian study only considered total fat intake while the American study investigated types of fat. Furthermore, the variation in frequency of the TaqIB SNP might also contribute to the difference in the findings. In the Iranian study [99] only 8 out of 127 normolipidemic individuals had the 'B1B1' genotype but in the American study [190] 192 out of 603 participants, had the 'B1B1' genotype. Thus, while these two studies were both conducted in patients with T2D, there is a wide variation in frequency of the 'B1B1' genotype between the two studies and this affects

the interpretation of the findings. In an animal study performed in feral adult male St. Kitts vervets monkeys (*Cercopithecus aethiops sabeus*) [212], SFA was shown to increase CETP activity, thereby reducing HDL levels which might explain the findings of the study in the American population [190]. However, in the animal study [212], the effect of SFA on CETP activity was only observed when cholesterol was added to the diet. SFA has also been shown to lower the number of LDL receptors in the liver, which slows the removal of Apopoliprotein B (ApoB)-containing lipoproteins [213], with the resulting effect of a decrease in HDL levels. It has also been demonstrated that the effect of dietary fat on *CETP* expression is not dependent solely on the composition of fat, but also on the amount of fat [214], although the mechanisms under which total fat affects *CETP* expression are still unclear [99]. A cross-sectional study of 2,858 Chinese participants, 761 Malay participants and 588 Asian Indian participants [100] demonstrated that, participants with 'B2B2' genotype had a significantly higher increase in HDL in response to a higher intake of dietary cholesterol compared to those with 'B1B1' and 'B1B2' genotypes, but the interaction was only significant in Asian Indians ($P_{interaction}$=0.0230) and Malays ($P_{interaction}$=0.0460). A cross-sectional study of 215 Mexican-Mestizos [98] also showed that, a higher sucrose intake (≥5% of total energy per day) was linked to increased levels of total cholesterol and LDL in individuals with 'B1B2'/'B2B2' genotype compared to those with 'B1B1' genotype [mean total cholesterol (mg/dL) (95% confidence interval): 200.19 (184.79–215.60) vs 165.55(142.21–188.89), $P_{interaction}$=0.0340; mean LDL (mg/dL) (95% confidence interval): 128.64 (113.59–143.69) vs 99.29 (75.52–123.05), $P_{interaction}$=0.0370]. As this study [98] was the only one which investigated sucrose intake, and considering that the sample size was 215, further studies are needed to corroborate these findings.

Several studies have investigated the interaction between alcohol intake and TaqIB genotype on HDL, LDL and TG [101, 215-217]. In a cross-sectional study of 758 healthy Chinese participants [215], individuals with 'B1B1' genotype who consumed any amount of alcohol had higher HDL (mean HDL (mmol/l): 2.09 ± 0.46 vs 1.94 ± 0.38; $P_{interaction}$<0.01), higher TG (mean TG (mmol/l): 1.42 ± 2.71 vs 0.94 ± 0.36; $P_{interaction}$<0.05) and lower LDL (mean LDL (mmol/l): 2.24 ± 0.65 vs 2.65 ± 3.01; $P_{interaction}$<0.01) compared to those with 'B1B1' genotype who did not drink alcohol. Those with 'B1B2' genotype who consumed any amount of alcohol also had higher HDL (mean HDL (mmol/l): 2.17 ± 0.55 vs 2.02 ± 0.50; $P_{interaction}$<0.05) compared to individuals with 'B1B2' genotype who did not drink alcohol; and lower TG (mean TG (mmol/l): 1.01 ± 0.86 vs 1.42 ± 2.71; $P_{interaction}$<0.05) compared to those with 'B1B1' who consumed any amount of alcohol. There were no significant

interactions between alcohol intake and TG or HDL in participants with 'B2B2' genotype. This study also observed that 'B2B2' individuals who drank any amount of alcohol had lower LDL than 'B2B2' participants who did not drink alcohol (mean LDL in mmol/l: 2.20 ± 0.52 vs 2.41 ± 0.86; $P_{interaction}$<0.0500), while there were no significant interactions between alcohol intake and LDL in those with 'B1B2' genotype. Similar findings were reported in a nested case-control study involving 505 patients with coronary heart disease (CHD) and 1,010 healthy controls from different ethnicities in the US population [101] in which it was observed that, among healthy individuals, a higher intake of alcohol (≥15g/day) was linked to higher HDL in participants carrying the 'B2' allele compared to those with 'B1B1' genotype, with 'B2B2' individuals having the highest HDL ($P_{interaction}$<0.0100). These findings are consistent with the results of a case-control study consisting of 608 Irish and French men with myocardial infarction (MI) and 742 healthy controls [217], which reported that, among individuals with a higher alcohol intake (≥75g/day), those carrying the 'B2' allele had higher mean plasma HDL (30% higher for 'B2B2' and 13% higher for 'B1B2') than those with the 'B1B1' genotype ($P_{interaction}$<0.0001). Likewise, a cross-sectional study of 1,729 Japanese participants [216] reported that, among women who consumed any amount of alcohol, those with 'B2B2' genotype had higher HDL than those with 'B1B1' or 'B1B2' genotype (mean HDL (mmol/l): 1.57 ± 0.03 for 'B1B1'; 1.57 ± 0.03 for 'B1B2'; 1.79 ± 0.06 for 'B2B2'; $P_{interaction}$=0.0220); while in men who consumed ≥2 drinks/day, those carrying the 'B2' allele had higher HDL than those with 'B1B1' genotype (mean HDL (mmol/l): 1.37 ± 0.03 for 'B1B1', 1.44 ± 0.03 for 'B1B2', 1.49 ± 0.05 for 'B2B2'; $P_{interaction}$=0.0490). These findings suggest that alcohol intake could alter lipid profiles by increasing HDL in both 'B1' and 'B2' carriers, however, the underlying mechanism is unclear and considering that alcohol intake has been linked to other health issues such as liver cirrhosis, the overall benefit needs to be carefully considered. Moreover, interaction between alcohol intake and TaqIB genotype on blood lipids has been investigated by 12 studies and eight of the studies have not found significant interactions [99, 190, 218-223].

Six out of fourteen dietary intervention studies found significant interactions between TaqIB genotype, dietary factors, and blood lipids. Three of the interactions were observed in participants carrying the 'B2' allele while the remaining three were reported in those with the 'B1B1' genotype. A six-day dietary intervention study [224], using high carbohydrate/low fat diet in 56 healthy Chinese individuals showed that, those carrying the 'B2' allele had higher HDL concentrations (mean HDL (mg/dL): 56.14 ± 10.69 after washout diet vs 59.77 ± 10.62 after high carbohydrate/low fat diet; $P_{interaction}$<0.0500) but the

interaction was not observed in individuals with 'B1B1' genotype. As the duration of this intervention was only 6 days, intervention studies with longer duration are required to confirm the effect of carbohydrate on HDL in individuals carrying the 'B2' allele. In a meta-analysis of 26 dietary interventions using SFA, trans fat, dietary cholesterol and the coffee diterpene cafestol in 405 healthy Dutch participants over a 20-year period [225], participants with 'B2B2' genotype had a larger increase in HDL in response to SFA compared to those with 'B1B1' or 'B1B2' genotypes [mean change in HDL (mmol/l): 0.08 ± 0.02 for 'B2B2', 0.03 ± 0.01 for 'B1B2', 0.04 ± 0.02 for 'B1B1' genotype; P=0.0400]; while participants carrying the 'B1' allele had a smaller increase in LDL in response to dietary cholesterol than those with the 'B2B2' genotype [mean change in LDL (mmol/l): 0.27 ± 0.14 for 'B1B1', 0.35 ± 0.08 for 'B1B2', 0.75 ± 0.15 for 'B2B2'; 'B1B1' vs 'B2B2', P=0.0300; 'B1B2' vs 'B2B2', P=0.0100]. In an oral fat tolerance test performed in 80 Greek participants who were heterozygous for familial hypercholesterolemia (HFH) and 11 control participants [226], it was demonstrated that, among participants in the HFH group who showed an abnormal postprandial TG response (TG concentration of >220 mg/dL), men with the 'B2' allele had higher levels of TG than women with the 'B2' allele after 4 hours of fat intake (279 ± 95 vs 239 ± 65 mg/dL; P=0.0300) but there were no reports of significant interactions in participants with 'B1B1' genotype.

Statistically significant interactions between carriers of the 'B1' allele and dietary factors were reported by three dietary intervention studies [211, 227, 228]. In a randomised triple-blind crossover trial performed in 95 Iranian patients with T2D and 73 healthy controls using three diets: sesame oil; canola oil; and sesame-canola oil [227], it was demonstrated that, in the T2D group, those with 'B1B1' genotype had a significant reduction in lipid ratios after consuming sesame oil and sesame-canola oil (change in LDL:HDL (mg/dL): –1.29, $P_{interaction}$=0.0270; change in TC:HDL (mg/dL), –2.82, $P_{interaction}$=0.0240; and change in TG:HDL (mg/dL), –7.00, $P_{interaction}$=0.0250) but there were no reports of significant reductions in lipid ratios in participants carrying the 'B2' allele. Another randomised controlled trial (RCT) performed in 85 New Zealander men with hypercholesterolemia, involving a 4-week healthy diet vs healthy diet plus two kiwi fruits per day [228], also showed that, among participants with 'B1B1' genotype, consumption of kiwi fruit resulted in lower TG:HDL ratio than the control diet (mean change in TG:HDL (mmol/l): –0.14 ± 0.51 for kiwifruit vs 0.09 ± 0.56 for control diet, P = 0.03; $P_{interaction}$<0.05); while in individuals carrying the 'B2' allele, the interaction was not observed. Similar results were also observed in a crossover intervention conducted in Spanish prepubertal children with mild

hypercholesterolemia, consisting of consumption of cow's skim milk vs cow's skim milk enriched with virgin olive oil for two periods of 6 weeks [211]. It was observed that, intake of olive-oil-enriched skim milk resulted in a larger increase in HDL and a decrease in LDL:HDL ratio in participants with 'B1B1' genotype compared to those carrying the 'B2' allele [mean change in HDL (mmol/l) (95% confidence interval): 0.179 (0.096 to 0.262) for 'B1B1' vs 0.089 (0.032 to 0.146) for carriers of 'B2', $P_{interaction}$<0.0010; mean change in LDL:HDL ratio (mmol/l) (95% confidence interval): –0.470 (–0.729 to 0.211) for 'B1B1' vs -0.097 (-0.275 to 0.081) for carriers of 'B2', $P_{interaction}$<0.0010]. While these studies show that individuals with the 'B1B1' genotype could benefit from consuming these diets, the interactions were reported only in those with either T2D [227] or hypercholesterolemia [211, 228] indicating that these results may not apply to healthy participants and hence, this limits the wider application of the findings.

The TaqIB, located in intron 1 of the *CETP* gene is considered to be non-functional and is believed to serve as a marker for functional SNPs in the promoter region [100, 190, 229]. The 'B1' allele differs from the 'B2' allele by the presence of a restriction site for TaqI endonuclease [100]. The 'B1' allele is believed to be associated with higher CETP activity, resulting in lower HDL and higher serum TG, and is considered a risk factor for dyslipidaemia [98]. This is supported by some of the studies as participants with the 'B1B1' genotype tended to have lower HDL [99-101, 222]. Nonetheless, the results suggest that people with this genotype can increase their HDL and modify their genetic risk by consuming sesame oil, canola oil, olive oil and kiwi fruit among others, although larger studies covering different ethnicities are warranted to tailor nutritional advice based on ethnicity and genetic profile.

2.4.2 SNP rs5882 (I405V G > A)

The SNP rs5882 (I405V) results in a substitution of Valine (V) for Isoleucine (I); hence the 'G' allele is also called the 'V' allele while the 'A' allele is also known as the 'I' allele. The frequency of the 'V' allele is 34% globally but in Africans it is 58% while in Asians it is 48% and in Europeans it is 32% [230]. Six out of eight observational studies found statistically significant interactions between this SNP and dietary factors on blood lipids. A cross-sectional analysis of 101 individuals from different ethnicities in the US population [189] showed that, a higher MUFA intake (>31g/day) was associated with lower TG in participants carrying the minor allele ('V') ($P_{interaction}$=0.0060) but there were no reports of significant interactions in individuals with 'II' genotype. A longitudinal study of 4,700 Iranian participants over 3.6 years [231] reported that, a higher MUFA intake was linked to increased levels of TG in participants carrying the 'V' allele (mean changes in TG (mg/dL)

across quartiles of MUFA intake: –3.03, 1.73, 8.06, 8.85; $P_{interaction}$=0.0010); but the interaction was not observed in those with 'II' genotype. This study also observed that, a higher intake of total fat correlated with increased levels of TG in those carrying the 'V' allele (mean changes in TG (mg/dL) across quartiles of total fat intake: –1.90, 2.6, 6.06, 8.88; $P_{interaction}$=0.0010) but the interaction was not significant in those with 'II' genotype. A higher carbohydrate intake was also found to be associated with decreased levels of TG in 'V' allele carriers (mean changes in TG (mg/dL) across quartiles of carbohydrate intake: 6.65, 7.29, 4.42, –3.28; $P_{interaction}$=0.0100) but the interaction was not significant in individuals with 'II' genotype [231]. Interactions with MUFA were also reported in a nested case-control of 441 Iranian participants with metabolic syndrome and 844 healthy controls [232] wherein carriers of the 'V' allele had a reduced risk of low HDL with a low intake of MUFA (<8.4% of energy) and an increased risk of low HDL with a higher intake of MUFA (9.6–11% of total energy intake) compared to those with 'II' genotype (odds ratio for low HDL across quartiles of MUFA intake: 0.49, 0.66, 0.88, 0.66 for carriers of 'V' allele vs 1, 0.61, 0.62, 0.68 for 'II' genotype; $P_{interaction}$=0.0200). The findings of these studies suggest that the SNP rs5882 (I405V) may modify the link between fat intake and blood lipids. A higher intake of MUFA and total fat appears to be unfavourable in Iranian participants carrying the 'V' allele by leading to an increase in TG levels and the risk of low HDL while carbohydrate intake seems to be beneficial in reducing TG levels in these 'V' allele carriers [231, 232]. Conversely, the study in the US population [189] implies MUFA is beneficial in individuals carrying the 'V' allele. As this study [189] was performed in participants from different ethnicities, it is difficult to confirm ethnicity as a reason for the differential response to MUFA. Moreover, the study was performed in participants with overweight and obesity which could influence the findings since obesity is known to alter the interaction between diet and genotype on lipids [189]. Nonetheless, the Iranian case-control study [232] also involved participants with metabolic syndrome as well as healthy controls; but the study did not report the findings for healthy controls. It has been demonstrated that, *CETP* transgenic mice fed with MUFA had improved LDL receptor activity with a corresponding increase in the uptake of ApoB-containing lipoproteins by the liver [233], which could explain the reduction in TG levels associated with a high MUFA diet. The lipid-lowering effect of MUFA has also been linked to a decrease in expression of the transcription factor liver X receptor α (LXRα) which is involved in CETP activation [234]. Moreover, it has been argued that animal-based sources of MUFA also contain substantial amounts of SFA which could mask the effects of MUFA

[235], implying that the source of MUFA needs to be taken into account when assessing the impact of MUFA on lipid-related outcomes.

In a cross-sectional study of Icelandic participants (152 men and 166 women) [236], alcohol intake was found to be associated with higher HDL in men with 'VV' genotype (13.7% higher HDL than 'II' genotype) compared to men with 'II' or 'IV' genotypes ($P_{interaction}$<0.0200) but the interaction was not statistically significant in women. Interactions with HDL were also observed in a cross-sectional study of 553 Inuit participants [237] in which higher levels of omega 3 polyunsaturated fatty acids (n-3 PUFA) in red blood cells (RBCs) was associated with higher HDL in participants carrying the major allele ('I') compared to those with 'VV' genotype [β (mmol/l) = 0.0263 ± 0.0115 for 'IV' genotype, β (mmol/l) = 0.0017 ± 0.0131 for 'II' genotype; $P_{interaction}$=0.0271]. The study also found that n-3 PUFA in RBCs had a negative correlation with total cholesterol in participants with 'II' genotype compared to those with 'VV' or 'IV' genotype [β (mmol/l) = −0.0290 ± 0.0307; $P_{interaction}$=0.0334]. In another cross-sectional study of 553 Inuit participants [192], individuals with 'II' genotype had a greater increase in total cholesterol with a higher intake of total fat than those with 'VV' or 'IV' genotype (β (mmol/l) = 0·0024 ± 0·0026; $P_{interaction}$=0.0460). These findings imply that while n-3 PUFA intake was beneficial for Inuit participants carrying the 'I' allele [237], higher total fat intake was not favourable for these participants [192]. PUFA is believed to promote the synthesis of LDL receptors which has the effect of increasing hepatic uptake of ApoB-containing lipoproteins [238], thereby raising the levels of HDL. To understand how PUFA affects regulation of the *CETP* gene, a study [239] was conducted in *CETP* transgenic mice which demonstrated that n-3 PUFA resulted in elevated *CETP* messenger RNA (mRNA) and protein levels, possibly by being a ligand for peroxisome proliferator-activated receptors α (PPARα), which is involved in the regulation of lipid-related genes [239]. However, increased *CETP* activity is known to have an inverse effect on HDL levels and does not explain the beneficial effect on HDL observed in the Inuit study. This raises the question of whether particular *CETP* SNPs dictate the response of the CETP protein to n-3 PUFA.

Only one of the six dietary intervention studies reported significant interactions between the I405V SNP and dietary factors on blood lipids. In this study [240], Canadian monozygotic twins (12 pairs) who were overfed by 1000Kcal per day for a period of 100 days showed a significant decrease in HDL, HDL_2 and HDL_3 in those with 'II' genotype compared to individuals with 'VV' genotype [mean change in HDL (mmol/l): −0.12 ± 0.04 vs 0.02 ± 0.04, *P*=0.02; mean change in HDL_2 (mmol/l): −0.08 ± 0.03 vs 0.03 ± 0.03, *P*=0.04; mean change in HDL_3 (mmol/l): −0.04 ± 0.02 vs -0.004 ± 0.02, *P*=0.0020], but there were no

reports of significant interactions in individuals with 'IV' genotype. The 'II' genotype of SNP rs5882 is believed to affect the ability of the CETP protein to mediate the exchange of cholesteryl esters for TG, resulting in increased TG concentrations [232], although this SNP has not been reported by any of the 32 GWA studies to impact on lipids.

It has also been shown that the 'VV' genotype of the SNP rs5882 is associated with lower plasma CETP levels and increased HDL concentration [241] however, baseline HDL data for participants with the 'VV' genotype was not available for all the studies because, there were not enough participants with the 'VV' genotype in the two Iranian studies [231, 232]. Also, in the two Inuit studies [192, 237], baseline HDL data was not recorded separately for 'VV', 'IV' or 'II' genotypes. However, in the Icelandic study [236], those with the 'VV' genotype had higher baseline HDL levels. Overall, the findings indicate that the SNP rs5882 may modify dietary response to lipids, but further studies are needed to clarify the differences in the results of some of the studies.

2.4.3 SNP rs3764261 (C > A)

Significant interactions between dietary factors and SNP rs3764261 on blood lipids were observed in two out of four observational studies. In a longitudinal study of 4,700 Iranian participants over 3.6 years [231], it was reported that, a higher fish intake was associated with a larger decrease in total cholesterol (TC) in participants carrying the minor allele ('A') (mean changes in TC (mg/dL) with quartiles of fish intake: 8.02, 6.93, 6.54, 5.58) compared to those carrying two copies of the major allele ('C') (mean changes in TC (mg/dL) with quartiles of fish intake: 3.65, 6.62, 4.57, 8.93) ($P_{interaction}$=0.02). Interactions with fat intake were also observed in a cross-sectional study of 3,342 Indian participants [242] in which a high dietary fat intake (≥76.98g/day) was associated with increased levels of TC (β(mmol/l) = 0.097 ± 0.041; $P_{interaction}$=0.018) and LDL (β(mmol/l) = 0.085 ± 0.041; $P_{interaction}$=0.0420) in participants carrying the 'A' allele but there were no reports of interactions in those with 'CC' genotype. A high fat diet has been demonstrated to increase CETP activity in transgenic mice [243] which has the effect of increasing TC and LDL and could account for the findings reported. Moreover, the SNP rs3764261 (C > A) is located in the 5^1 region of the *CETP* gene and has been shown to regulate expression of the gene, the 'C' allele being associated with increased *CETP* expression and reduced HDL levels [244].

Two dietary intervention studies reported statistically significant interactions between the SNP rs3764261 and dietary factors on blood lipids. In a prospective, randomized, single-blind controlled dietary intervention trial carried out in 424 Spanish patients who had acute coronary syndrome (ACS) or CHD and also had metabolic syndrome

[191], wherein participants consumed either a Mediterranean diet or a low-fat diet, it was observed that, after 1 year, consumption of Mediterranean diet was associated with higher HDL and lower TG in participants carrying the 'A' allele compared to those with 'CC' genotype (mean HDL (mg/dL): 41 vs 38, $P_{interaction}$=0.0060; mean TG (mg/dL): 130 vs 146, $P_{interaction}$=0.0400). This finding indicates that Mediterranean diet might be beneficial in increasing HDL in Spanish participants with ACS or CHD who carry the 'A' allele [191]; however, this finding might not be applicable to healthy individuals. In another study which was performed on participants from different ethnicities and involved a 2-year randomised weight-loss trial, consisting of low-fat diet (20% fat) vs high-fat diet (40% fat); and a 2-year RCT consisting of low-fat diet (30% fat) vs low carbohydrate (high fat) diet [214], the combined results of the two interventions showed that, among participants with 'CC' genotype, those in the high-fat diet group had a higher increase in HDL (11.7 vs 4.5%; $P_{interaction}$=0.01) and a larger decrease in TG (–25.1 vs. –11.7%; $P_{interaction}$=0.0007) than those in the low-fat diet group, but there were no significant interactions in participants with 'CA' or 'AA' genotype. These results suggest that a high-fat diet (40% fat) in individuals from different ethnicities who have the 'CC' genotype might contribute to increased HDL and reduced TG levels [214] although the findings are not in agreement with the study performed in *CETP* transgenic mice [243] in which a high fat diet resulted in increased CETP activity which lowered HDL levels. Considering that this was a weight loss intervention, it is unclear whether the changes in lipid levels were due to the high-fat diet or the loss of weight or both since physical activity has been shown to interact with genetic risk score and impact on waist-hip ratio [245]. Moreover, the 'C' allele of the SNP rs3764261 is regarded as a significant risk factor for low HDL [244, 246] although it has been demonstrated that this risk can be overcome by weight gain prevention [244]. The SNP rs3764261 has also been shown by GWA studies to influence HDL levels in Asian Indians [94, 199], Japanese [96, 201], African-American [97], Chinese [193], Lebanese [194] and Finnish [205] but the evidence indicates that this SNP has not been extensively studied by gene-diet interaction studies. Therefore, further studies in different ethnicities are required to confirm the effect of the SNP in modifying dietary response to lipids.

2.4.4 C-629A (SNP rs1800775 C > A)

The SNP rs1800775 has been shown to be associated with HDL in seven of the nineteen GWA studies [92, 94, 95, 196, 201, 204, 205]. Two out of five observational studies reported significant interactions between dietary factors and the SNP rs1800775 (C-629A) on blood lipids. In a cross-sectional study of 9,075 Taiwanese participants [247], consumption of coffee was found to be associated with lower HDL in women carrying the minor allele ('C') compared to women with 'AA' genotype [β (mg/dL) = −1.8095 for 'AC' genotype, β (mg/dL) = −2.8151 for 'CC' genotype; $P_{interaction}$<0.0001]; and in men carrying the 'C' allele compared to men with the 'AA' genotype [β (mg/dL) = −1.9623 for 'AC' genotype, β (mg/dL) = −2.7154 for 'CC' genotype; $P_{interaction}$<0.0001]. A case-control study consisting of 568 Irish and French men with MI and 668 healthy controls [248] showed that, among individuals carrying the major allele ('A'), alcohol consumption was associated with higher HDL in healthy participants ($P_{interaction}$<0.0020) and in patients who were not treated with lipid-lowering medication ($P_{interaction}$<0.0010) while in individuals with 'CC' genotype, there was no association between alcohol intake and HDL. The results suggest that dietary factors other than fat intake may also play a role in modulating lipid levels, but these interactions need to be explored further to allow for comparison of results across multiple ethnic groups. The SNP rs1800775 (C-629A) is located in the promoter region of the *CETP* gene and the 'A' allele is associated with reduced *CETP* expression and higher HDL levels [100]. The 'A' allele of SNP rs1800775 (C-629A) is in a high degree of linkage disequilibrium with the 'B2' allele of SNP TaqIB and it is believed that this association is responsible for the protective effect of the 'B2' allele [100]. However, some are of the view that there might be other functional SNPs that are in linkage disequilibrium with TaqIB apart from SNP rs1800775 (C-629A) but it is unclear what these SNPs are [190, 229]. Moreover, despite the SNP rs1800775 (C-629A) being reported by several GWA studies to be associated with blood lipids, this SNP has not been extensively studied in gene-diet interaction studies. To date, only one dietary intervention study [249] investigated the SNP rs1800775 (C-629A) which also failed to demonstrate any significant SNP-diet interactions on lipids. This study was an RCT performed in 490 participants from different ethnicities in the UK population and involved a reference diet [~18% SFA, 12% MUFA, 38% total fat, 45% carbohydrate (CHO)] for 4 weeks, followed by 1 of three diets: a MUFA diet (~10% SFA, 20% MUFA, 38% total fat, 45% CHO); a low fat diet (~10% SFA, 11% MUFA, 28% total fat, 55% CHO); or the reference diet for 24 weeks. The findings overall indicate that further large studies are needed to confirm the effect of the SNP rs1800775 in altering lipid profiles in response to diet.

2.4.5 Other SNPs

Other *CETP* SNPs which have been reported to interact with dietary factors and influence blood lipids are SNPs rs183130 (C-4502T), rs4783961 (G-971A), rs289714 (C > T), and rs1800774 (C > A). In the cross-sectional study of 553 Inuit participants [250], higher levels of n-3 PUFA in RBCs was linked to lower TC levels in participants carrying the minor allele ('T') of the SNP rs183130 (C-4502T) compared to those with 'CC' genotype (β (mmol/l) = –0.0632 ± 0.0241 for 'CT' genotype, β (mmol/l) = –0.0421 ± 0.0343 for 'TT' genotype; $P_{interaction}$=0.0326); and lower TG levels in those with the 'TC' genotype of the SNP rs183130 (C-4502T) compared to individuals with 'TT' genotype (β (mmol/l) = –0.0095 ± 0.0051 vs β (mmol/l) = 0.0073 ± 0.0073; $P_{interaction}$=0.0300) while there were no reports of significant interactions between n-3 PUFA in RBCs and TG in participants with 'CC' genotype. This study also reported that individuals with the 'GA' genotype of the SNP rs4783961 (G-971A) who had higher levels of n-3 PUFA in RBCs had lower TG levels (β (mmol/l) = –0.0106 ± 0.0057; $P_{interaction}$=0.0032) and lower TC:HDL ratio (β (mmol/l) = –0.0055 ± 0.0033; $P_{interaction}$=0.0483) compared to participants with 2 copies of the minor allele ('A') of the SNP rs4783961 (G-971A). These findings point to a beneficial role of PUFA in Inuit participants carrying the 'T' allele of the SNP rs183130(C-4502T) and the 'G' allele of the SNP rs4783961 (G-971A). PUFA is believed to improve the breakdown of ApoB-containing particles thereby reducing TG concentrations [232], which is consistent with this finding. However, in a cross-sectional study of 821 participants who were normal glucose tolerant and 861 participants with T2D, involving the Transcription Factor 7-Like 2 (*TCF7L2*) gene [251], higher PUFA intake (mean PUFA intake of 29g/day) was linked to 1.64 mg/dL lower HDL while lower PUFA intake (mean PUFA intake of 9g/day) was associated with 1.96 mg/dL higher HDL in Asian Indian participants carrying the 'T' allele of the *TCF7L2* SNP rs12255372 compared to those with the 'GG' genotype ($P_{interaction}$<0.0001). In another cross-sectional study involving 101 participants of different ethnicities in the US population [189], it was reported that, among participants with two copies of the major allele ('A') of the SNP rs289714, those who consumed >92 grams of total fat per day, had lower TG levels (103 ± 63 mg/dL) than those who consumed <31 grams of total fat per day (135 ± 15 mg/dL) ($P_{interaction}$=0.0010). The interaction was significant for both the dominant and recessive modes of inheritance ($P_{interaction}$=0.0010 and $P_{interaction}$=0.0230 respectively), but there were no reports of significant interactions in individuals with 'GG' genotype. In another cross-sectional study of 1,315 Spanish participants [252], higher plasma selenium levels were found to be associated with elevated LDL levels in all the three genotypes of the SNP rs1800774 but participants

with two copies of the major allele ('C') had lower LDL compared to those with 'CT' and 'TT' genotypes [odds ratio per an interquintile range increase in plasma selenium (95% confidence interval): 0.97 (0.74 to 1.27) for 'CC', 1.76 (1.38 to 2.25) for 'CT', 3.20 (1.93 to 5.28) for 'TT' genotype; $P_{interaction}$=0.0002]. Selenium was also reported to be associated with lipid levels in a systematic review and meta-analysis [253], but it was shown to be linked to significant improvement in the levels of TC and TG and had no significant effect on LDL levels**.** A systematic review published in 2017, in which the results of 23 gene-diet interaction studies involving *CETP* were analysed [254], concluded that, SNPs in the *CETP* gene may influence the effect of dietary factors on metabolic traits but that the findings from these studies were inconsistent and suggest that multiple factors might be involved.

2.5 Conclusion

In summary, this review has identified statistically significant interactions between 17 dietary factors and 8 SNPs in the *CETP* gene on blood lipids in the following populations: Mexican, Iranian, Spanish, White American, Chinese, Malay, Indian, Irish, French, Japanese, New Zealander, Dutch, Greek, Icelandic, Inuit, Canadian, Taiwanese and residents of the USA. The SNPs showing significant interactions with dietary factors (such as total fat intake, MUFA, n-3 PUFA, Mediterranean diet, olive oil and sesame-canola oil) were TaqIB (rs708272 G > A); rs5882 (I405V); rs3764261 (C > A); rs1800775 (C-629A); rs183130(C-4502T); rs4783961 (G-971A); rs289714 (C > T); and rs1800774 (C > A). The macronutrient investigated by majority of the studies was dietary fat, comprising of total fat, SFA, MUFA and PUFA. Total fat intake accounted for majority of the interactions across different SNPs, being associated with unfavourable lipid outcomes in some individuals but not others.

Studies reporting significant interactions in individuals with the B1B1 genotype of the SNP TaqIB (rs708272) have been performed in participants with either T2D or hypercholesterolemia. Similarly, those reporting significant interactions in individuals carrying the 'V' allele of the SNP rs5882 have been conducted in participants with overweight and obesity or metabolic syndrome. Moreover, some of the significant interactions involving the SNP rs3764261 have also been reported in patients with ACS or CHD, suggesting that some of the findings of these studies may not apply to healthy participants. Overall, the findings suggest that *CETP* SNPs might alter blood lipid profiles by modifying responses to diet, but further large studies in multiple ethnic groups are warranted to identify individuals at risk of adverse lipid response to diet which is essential in developing dietary guidelines that are tailored to specific groups of people. Information

on the underlying genetic factors for dyslipidaemia will also contribute to improved understanding of the mechanisms involved, which is central to the development of effective preventative strategies as well as identifying areas for further research.

Chapter 3 Higher intake of dairy is associated with lower cardiometabolic risks and metabolic syndrome in Asian Indians

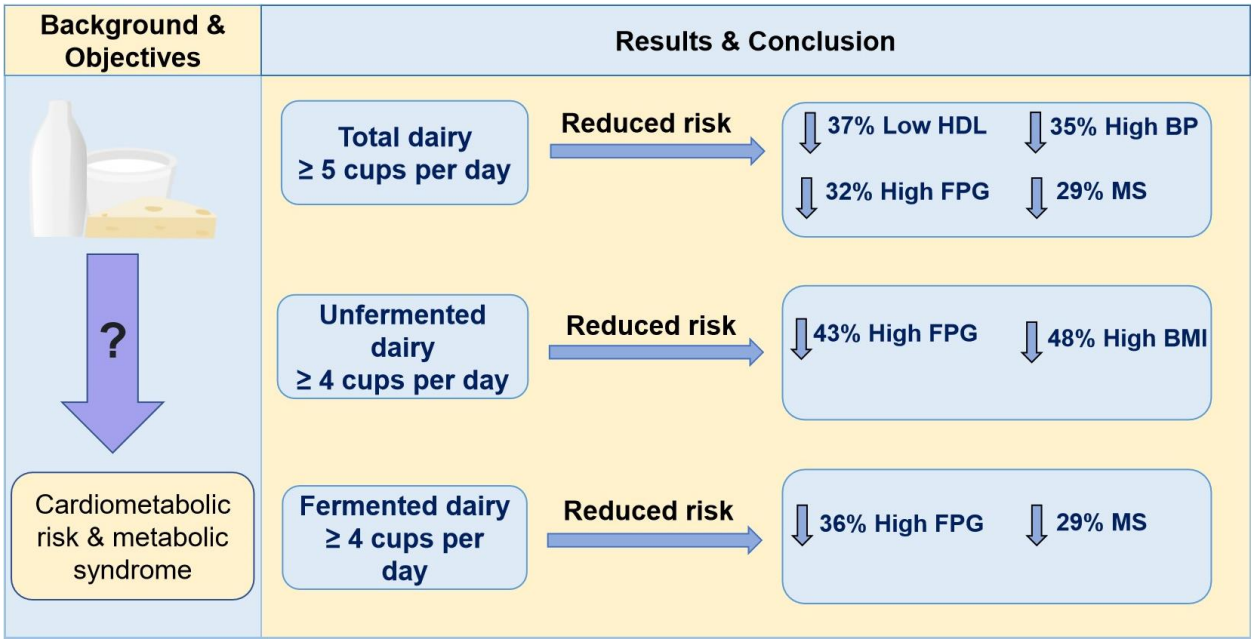
Published (The published version of the paper is attached as an appendix at the end of the thesis)

Wuni, R., Lakshmipriya, N., Abirami, K., Ventura, E. F., Anjana, R. M., Sudha, V., Shobana, S., Unnikrishnan, R.,Krishnaswamy, K., Vimaleswaran, K. S. & Mohan, V. Higher Intake of Dairy Is Associated with Lower Cardiometabolic Risks and Metabolic Syndrome in Asian Indians. *Nutrients* **2022**, *14*. https://doi.org/10.3390/nu14183699

Ramatu Wuni's contribution: For this study, I wrote the data analysis plan and interpreted the results of the analysis, carried out a literature search and wrote the manuscript. I revised the manuscript based on comments and suggestions from the co-authors. I formatted the manuscript according to the guidelines of *Nutrients* before it was submitted for publication. I prepared a graphical abstract as required by the journal. I also wrote the responses to the comments from the reviewers and revised them based on suggestions from the co-authors.

3.1 Abstract

There is conflicting evidence about the association between dairy products and cardiometabolic risk (CMR). We aimed to assess the association of total dairy intake with CMR factors and to investigate the association of unfermented and fermented dairy intake with CMR in Asian Indians who are known to have greater susceptibility to type 2 diabetes and cardiovascular diseases compared to white Europeans. The study comprised 1033 Asian Indian adults with normal glucose tolerance chosen from the Chennai Urban Rural Epidemiological Study (CURES). Dietary intake was assessed using a validated open-ended semi-quantitative food frequency questionnaire. Metabolic syndrome (MS) was diagnosed based on the new harmonising criteria using central obesity, dyslipidaemia [low high-density lipoprotein cholesterol (HDL) and increased serum triglycerides (TG)], hypertension and glucose intolerance. Increased consumption of dairy (≥5 cups per day of total, ≥4 cups per day of unfermented or ≥2 cups per day of fermented dairy) was associated with a lower risk of high fasting plasma glucose (FPG) [hazard ratio (HR), 95% confidence interval (CI): 0.68, 0.48–0.96 for total dairy; 0.57, 0.34–0.94 for unfermented dairy; and 0.64, 0.46–0.90 for fermented dairy; P<0.05 for all] compared to a low dairy intake (≤1.4 cups per day of total dairy; ≤1 cup per day of unfermented dairy; and ≤0.1 cup per day of fermented dairy). A total dairy intake of ≥5 cups per day was also protective against high blood pressure (BP) (HR: 0.65, 95% CI: 0.43–0.99, P<0.05), low HDL (HR: 0.63, 95% CI: 0.43–0.92, P<0.05) and MS (HR: 0.71, 95% CI: 0.51–0.98, P<0.05) compared to an intake of ≤1.4 cups per day. A high unfermented dairy intake (≥4 cups per day) was also associated with a lower risk of high body mass index (BMI) (HR: 0.52, 95% CI: 0.31–0.88, P<0.05) compared to a low intake (≤1 cup per day), while a reduced risk of MS was observed with a fermented dairy intake of ≥2 cups per day (HR: 0.71, 95% CI: 0.51–0.98, P<0.05) compared to an intake of ≤0.1 cup per day. In summary, increased consumption of dairy was associated with a lower risk of MS and components of CMR.



Graphical abstract

3.2 Introduction

Asian Indians have been shown to have distinct biochemical and clinical characteristics that put them at risk of type 2 diabetes (T2D) and cardiovascular diseases (CVDs) [105, 119, 120, 255]. The distinct features include central obesity, dyslipidaemia, insulin resistance, increased levels of visceral fat, total fat, and propensity to beta cell dysfunction [105, 119, 120, 255]. The components of the 'Asian Indian Phenotype' are included in the metabolic syndrome (MS), which refers to a group of interconnected risk factors that make an individual susceptible to CVDs and T2D [256]. According to a systematic review and meta-analysis involving 133,926 participants from 111 studies [257], MS affects 1 in 3 adults in India, and the prevalence is higher among people in urban areas (32%) than those living in rural areas (22%). MS is associated with increased CVDs and all-cause mortality [258, 259] warranting studies in Asian Indians who are known to have a predisposition to MS.

The existence of an entity called MS is surrounded by controversies, partly due to variations in the definition of MS [260-263]. However, it is generally agreed that the risk factors of central obesity, high blood pressure (BP), elevated levels of triglycerides (TG), low concentration of high-density lipoprotein cholesterol (HDL) and elevated fasting plasma glucose (FPG) tend to co-exist and are important indicators of an individual's risk of CVDs and T2D [260-264]. The increasing prevalence of these risk factors has been linked to genetic and environmental factors [18, 105, 126, 128, 265], and there is growing interest in the role of different types of food in the development of MS [105, 128, 256, 265]. Several studies have reported a protective effect of dairy consumption on the risk of MS [256, 266-269]. Consumption of at least two servings of dairy per day compared to no dairy intake, has been linked to a lower prevalence of MS [256]. Increased consumption of dairy (>7 times per week) was also found to be associated with a reduced risk of MS and central obesity compared to no dairy intake [269]. However, one study [270] reported that participants who did not consume milk had a lower risk of insulin resistance and MS compared to those who drank milk, making the findings inconsistent. Moreover, it has been suggested that fermented dairy might confer greater anti-inflammatory and cardiometabolic benefits than unfermented dairy [271, 272]. Possible mechanisms for the proposed benefits of fermented dairy include the action of microbial cultures on gut microbiota, changes in lipid and glyceride profiles and the release of more bioactive compounds involved in regulating several metabolic and immune pathway genes [271-273].

Furthermore, consumption of dairy is high among Asian Indians [274-276] who also have a high prevalence of MS [257, 277, 278]. An examination of the dietary profile of 2042 Asian Indian participants [274] showed that, dairy intake was within the national recommendation of 300 g/day [279]. However, despite dairy consumption being linked to lower risk of MS [256, 266-268], few studies have examined the impact of dairy intake on the risk of MS in Asian Indians. Hence, the present study sought to investigate the association of total dairy consumption with MS and components of cardiometabolic risk (CMR) in Asian Indians. We also aimed to determine the association of fermented and unfermented dairy products with MS and components of CMR.

3.3 Methods

3.3.1 Study population

The current study consisted of 1033 adults with normal glucose tolerance chosen from the Chennai Urban Rural Epidemiological Study (CURES), and details of the study design have been given in previous publications [105, 126, 251, 280, 281]. In brief, a total of 26,001 adults were recruited between 2001 to 2003 from the urban part of Chennai in Southern India through systematic random sampling, and the follow-up study was conducted between 2012 and 2013 and consisted of 2410 participants. The sample for the current study was chosen from the follow-up cohort as shown in **Supplementary Figure S3.1**. Approval was obtained from the Institutional Ethics Committee, and written informed consent obtained from all the study participants.

3.3.2 Data collection

Demographic (including medical history and physical activity), anthropometric, biochemical and dietary data were collected both at baseline (2001–2003) and after 10 years (2012–2013) using a structured, pretested, and validated interviewer-administered questionnaire [282]. Family history of diabetes was considered as positive if either parents or sibling/s had diabetes. Smokers were defined as those who were currently smoking, and alcohol use was defined as current alcohol consumption.

Height, weight, waist circumference (WC) and BP were measured using standardised techniques [280], and body-mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Biochemical analyses, including fasting plasma glucose (FPG) and lipids, were performed in all individuals; in addition, plasma glucose estimation 2 h after a 75 g oral glucose load was performed in individuals without diabetes

[280]. Biochemical analyses were performed in a laboratory certified by the National Accreditation Board for Testing and Calibration Laboratories and the College of American Pathologists on a Hitachi 912 autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Basel, Switzerland) for estimation of plasma glucose (GOD-POD method).

3.3.2.1 Outcome ascertainment

General obesity

General obesity was defined as BMI ≥ 25 kg/m^2 and overweight as BMI ≥ 22.9 kg/m^2 in accordance with the Asia Pacific guidelines [283].

Metabolic syndrome

MS was diagnosed based on the new harmonising criteria [284]. Individuals with any three of the following abnormalities viz. high WC (Asia Pacific cut-off ≥80 cm for female, ≥90 cm for male), hypertriglyceridemia [serum TG ≥1.70 mmol/L (≥150 mg/dL)], low HDL [male participants ≤ 1.04 mmol/L (≤40 mg/dL); female participants ≤1.30 mmol/L (≤50 mg/dL)], abnormal glucose metabolism [defined as FPG ≥5.6 mmol/L (≥100 mg/dL)] and elevated BP [systolic BP (SBP) ≥130 mmHg or diastolic BP (DBP) ≥85 mmHg] were considered to have MS.

The term "cardiometabolic risk" was first employed by the American Diabetes Association as an umbrella term to include all the risk factors for diabetes and CVD [285]. The components of CMR given in the present analysis are central and general obesity; elevated levels of triglycerides, total cholesterol and LDL and reduced HDL concentration; hyperglycaemia; hypertension; and insulin resistance.

3.3.2.2 Dietary assessment

Dietary intake was assessed by trained dietitians using a validated open-ended semi-quantitative 222-item food frequency questionnaire (FFQ) both at baseline and follow-up. The FFQ was designed to estimate the usual dietary intake of participants, the development and validation of which have been described elsewhere [282]. The FFQ included both the frequency as well as the servings of food items consumed by the individuals which was then converted to standardised portion sizes. However, any new food item reported (new market foods over 10-year period) during the follow-up period was updated in the in-house Nutritional Epidemiology ('EpiNu') software. Dairy intake was estimated from the FFQ using the 'EpiNu' software. Total dairy intake consists of unfermented plain milk and milk included in tea and coffee; Indian milk sweets and desserts; and fermented milk, which consists of Indian yoghurt (curd) and buttermilk. The 'EpiNu' software which contains information on

the nutritional composition of food that is mainly consumed in the Chennai area was developed for the local population using recipes from a wide range of sources, including fast-food and home-made. Details of the development of the 'EpiNu' software are available in a previous publication [282].

3.3.3 Statistical analyses

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and the data analysis plan is attached as an appendix (**Appendix A**). All food groups and nutrients were energy adjusted by the residual method [286]. As nutrients and food groups were not normally distributed, estimates were expressed in median and interquartile range (IQR). The Mann-Kruskal Wallis test was used to compare differences between the medians of continuous variables, and the chi-squared test was used to test differences in proportions. The lowest, medium and highest intakes of total dairy, unfermented and fermented dairy were derived by stratifying the data into deciles and regrouping as lowest (quartile 1(Q1)–quartile 4 (Q4)), medium (Q5–Q8) and highest intake (Q9–Q10) to test the association with CMR using the regression model. The hazard ratio (HR) for incidence of CMR and MS in each group of dairy intake (lowest intake, medium intake and highest intake) and its subdivision (fermented and unfermented) was calculated using Cox proportional hazards analysis. Potential confounders were identified by the univariate analysis and entered simultaneously into the multiple Poisson regression model with p-value <0.2. The model was adjusted for age, sex, BMI, income, smoking, alcohol, major cooking oil, total polyunsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level (PAL), total energy (kcal) and tea and coffee intake. The linear trend across the lowest, medium and highest dairy intake and incidence of CMR and MS were tested with the regression model [287]. Difference between the dairy product and its subdivisions was assessed using the Kruskal-Wallis test for all the continuous variables. The *P* values were tested for statistical significance at <0.05 level.

3.4 Results

3.4.1 Characteristics of the study participants

The median age of the study participants was 36 (IQR: 15) years. As shown in **Table 3.1**, smoking and alcohol consumption were reported by 16% and 23% of participants, respectively. Nearly half of the participants (44%) had a family history of diabetes. The median SBP (113 mmHg), DBP (72 mmHg), FPG (84 mg/dL) and postprandial glucose (106

mg/dL) were within the normal ranges. Consumption of tea and coffee was the main source of dairy (80%) as shown in **Figure 3.1** and **Table 3.2**. The medians of the lowest, medium, and the highest total dairy intake were 208, 411 and 755 g/day (1.4, 3 and 5 cups per day), respectively.

Table 3.1 Baseline characteristics of the study population (*n*=1033)

Variables	**Overall Median (Interquartile Range)/*n* (%)**
Age (years)	36 (15)
Gender n (%)	
Men *n* (%)	433 (42)
Women *n* (%)	600 (58)
Smoking (yes) *n* (%)	160 (15)
Alcohol (yes) *n* (%)	242 (23)
Income per month n (%)	
INR. <2000	24 (2)
INR. 2000–5000	197 (19)
INR. 5000–10,000	415 (40)
INR. >10,000	397 (39)
Family history of diabetes (yes) *n* (%)	449 (43)
Weight (kg)	58 (17)
BMI (kg/m^2)	23.2 (6.2)
Waist circumference (cm)	84 (16)
Systolic BP (mmHg)	113 (19)
Diastolic BP (mmHg)	72 (13)
Fasting blood glucose (mg/dL)	84 (12)
Postprandial blood glucose (mg/dL)	106 (33)
Total Cholesterol (mg/dL)	175 (47)
Triglyceride (mg/dL)	96 (65)
High density lipoprotein (mg/dL)	42 (13)
Low density lipoprotein (mg/dL)	109 (39)

Data presented as median (interquartile range) for continuous variables; and as number (*n*) (%) for categorical variables. INR – Indian rupees; BMI – body mass index; BP – blood pressure.

Table 3.2 Consumption of dairy and its products (g/day)

	Median (Interquartile Range)		
Dairy and its products (g/day)	***Lowest Intake*** **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**
Total dairy products	208 (116)	411 (144)	755 (228)
Fermented dairy products (curd and buttermilk)	32 (66)	75 (119)	167 (215)
Milk	10 (39)	37 (94)	74 (148)
Tea and coffee (contribution by milk)	118 (118)	235 (176)	471 (353)
Milk sweets and desserts (milk sweets, ice cream, milk shake and other milk beverages)	2 (8)	3 (10)	5 (22)

3.4.2 Association of total dairy consumption and components of cardiometabolic risk

A total dairy intake of ≥5 cups compared to ≤1.4 cups per day was associated with a decreased risk of three of the components of CMR [high BP, FPG and low HDL] and MS as shown in **Table 3.3** and **Figure 3.2**, respectively. A decreased incidence of two of the components of CMR (high FPG and low HDL) was also observed among individuals in the medium total dairy intake group (≥3 cups per day) compared to those in the low total dairy intake group (≤1.4 cups per day) (**Table 3.3**). There was no association between total dairy intake and insulin resistance as shown in **Supplementary Figure S3.2**.

Table 3.3 Total dairy consumption and its association with components of cardiometabolic risk

	Hazard Ratio (95% Confidence Interval)		
	Lowest Intake **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**
Total dairy products (g/day)	***208* (*116*)** **1.4 cups**	***411* (*144*)** **3 cups**	***755* (*228*)** **5 cups**
Blood pressure (mmHg) ≥140/90	1 (ref)	0.82(0.63–1.08)	0.65(0.43–0.99) *
BMI (kg/m^2) ≥22.9	1 (ref)	0.84(0.66–1.08)	0.78(0.53–1.15)
Waist circumference (cm) (>80: F; >90: M)	1 (ref)	0.87(0.7–1.09)	0.87(0.62–1.24)
Total cholesterol (>200 mg/dL)	1 (ref)	0.72(0.51–1.01)	0.70(0.42–1.18)
Triglyceride (>150 mg/dL)	1 (ref)	1.05(0.76–1.44)	0.74(0.45–1.22)
High-density lipoprotein (mg/dL) (≤40: F; ≤50: M)	1 (ref)	0.74(0.59–0.93) *	0.63(0.43–0.92) *
Low-density lipoprotein (>100 mg/dL)	1 (ref)	0.95(0.77–1.17)	0.83(0.61–1.12)
Fasting plasma glucose (>100 mg/dL)	1 (ref)	0.75(0.6–0.95) *	0.68(0.48–0.96) *

Data presented as median (interquartile range). * *P*-value<0.05 considered as significant. Adjusted variables are age, sex, BMI, income, smoking, alcohol, major cooking oil, total poly unsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level, total energy (kcal) and tea and coffee intake (g/day).

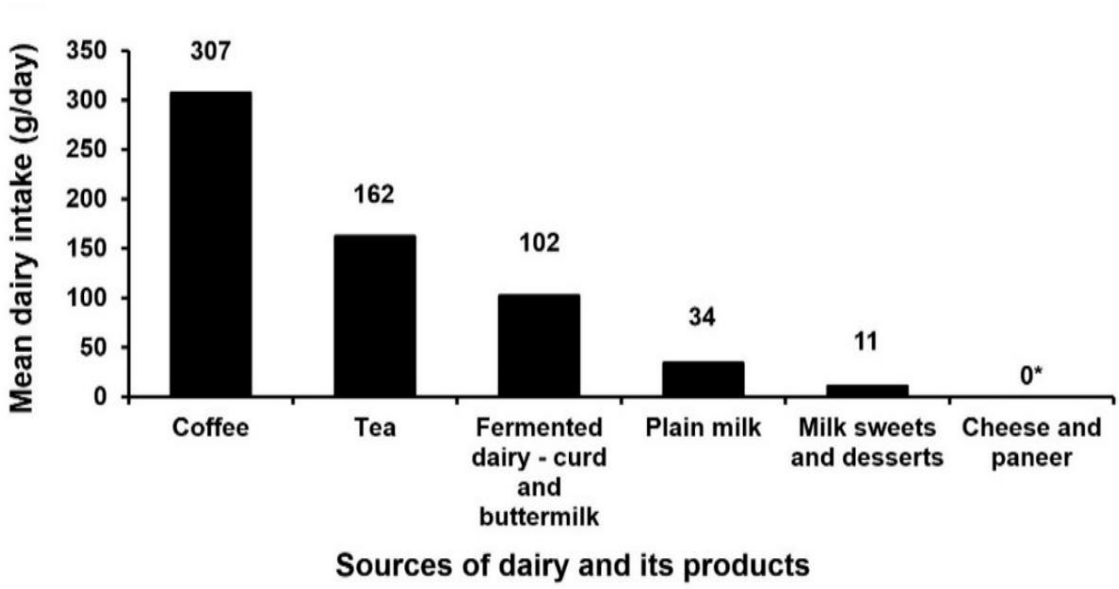


Figure 3.1 The sources of dairy and its products among the Chennai urban adults

Milk sweets and desserts include Indian milk sweets, ice cream, milk shakes and other milk beverages. * Cheese and paneer intake was reported by only three individuals in the sample, and this resulted in a median value of 0.

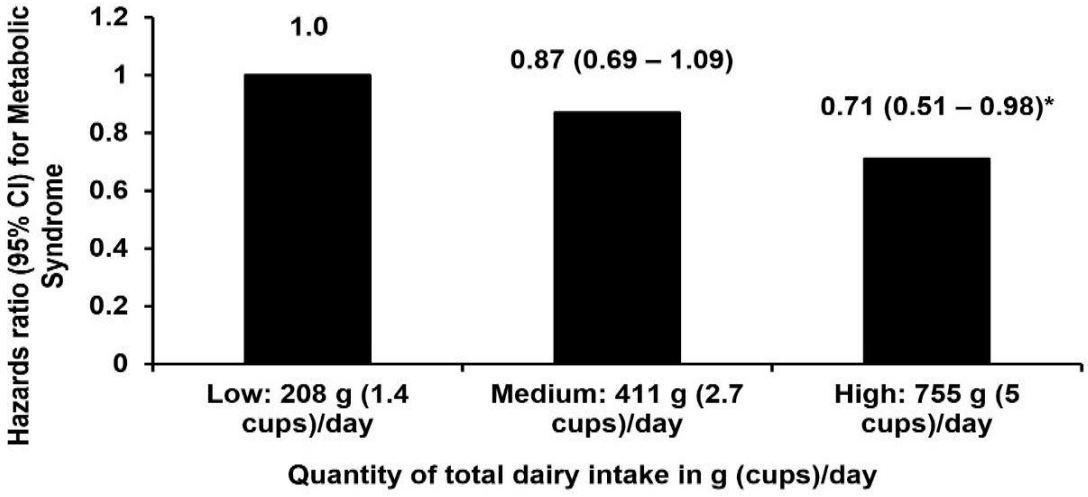


Figure 3.2 Total dairy consumption and its association with metabolic syndrome

Data presented as median. * *P*-value<0.05 considered as significant. Adjusted variables are age (years), sex, BMI, income, smoking, alcohol, major cooking oil, total polyunsaturated fatty acids (PUFA) (g), added sugar (g), total energy (kcal) and tea and coffee intake.

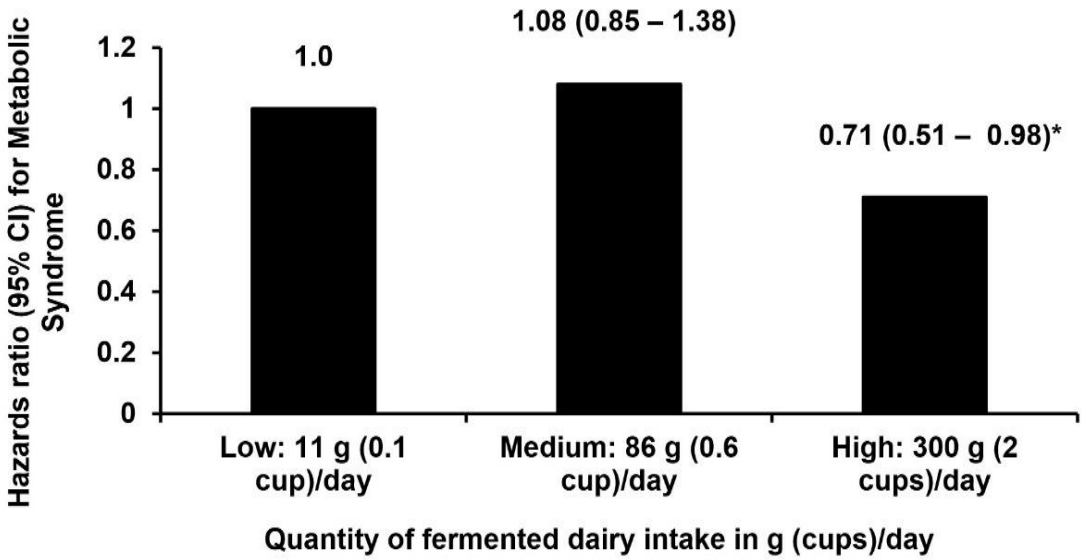


Figure 3.3 Fermented dairy consumption and its association with metabolic syndrome

Data presented as median. * *P*-value<0.05 considered as significant. Adjusted variables are age (years), sex, BMI, income, smoking, alcohol, major cooking oil, PUFA (g), added sugar (g), physical activity level, total energy (kcal) and tea and coffee intake.

3.4.3 Association of fermented dairy consumption and components of cardiometabolic risk

Consumption of 2 cups per day or more of fermented dairy was associated with a lower incidence of high FPG (**Table 3.4**) compared to an intake of ≤0.1 cups per day. A high fermented dairy intake (≥2 cups per day) was also associated with a lower risk of MS compared to a low fermented dairy intake (≤0.1 cups per day) [hazard ratio (HR): 0.71, 95% confidence interval (CI): 0.51–0.98, *P*<0.05] as shown in **Figure 3.3**.

Table 3.4 Fermented and unfermented dairy consumption and its association with components of cardiometabolic risk

	Hazard Ratio (95% Confidence Interval)					
	Unfermented Dairy Products (g/day)			**Fermented Dairy Products (g/day)**		
	Lowest Intake **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**	***Lowest Intake*** **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**
Dairy product **(*g/day*)**	***138* (*86*)** **1 cup**	***290* (*103*)** **2 cups**	***581* (*175*)** **4 cups**	***11* (*23*)** **0.1 cup**	***86* (*54*)** **0.6 cup**	***300* (*116*)** **2 cups**
Blood pressure (mmHg) ≥140/90	1 (ref)	1.01 (0.73–1.41)	0.75 (0.45–1.27)	1 (ref)	0.83 (0.63–1.10)	0.71 (0.49–1.03)
BMI (kg/m^2) ≥22.9	1 (ref)	0.70 (0.50–0.99)	0.52 (0.31–0.88) *	1 (ref)	0.83 (0.63–1.10)	0.71 (0.49–1.03)
WC (cm) (>80: F; >90: M)	1 (ref)	0.91 (0.71–1.15)	0.89 (0.62–1.26)	1 (ref)	1.12 (0.92–1.37)	1.03 (0.81–1.34)
Total cholesterol (>200 mg/dL)	1 (ref)	0.78 (0.5–1.22)	0.59 (0.3–1.16)	1 (ref)	10 (0.72–1.39)	0.83 (0.54–1.28)
Triglyceride (>150 mg/dL)	1 (ref)	0.83 (0.57–1.2)	0.68 (0.38–1.22)	1 (ref)	1.14 (0.84–1.53)	0.98 (0.69–1.4)
HDL (mg/dL) (≤40: F; ≤50: M)	1 (ref)	1.02 (0.77–1.34)	0.93 (0.63–1.37)	1 (ref)	0.86 (0.69–1.06)	0.76 (0.57–1.01)
LDL (>100 mg/dL)	1 (ref)	0.92 (0.71–1.19)	0.77 (0.53–1.13)	1 (ref)	1.09 (0.9–1.33)	0.88 (0.69–1.13)
Fasting plasma glucose (>100 mg/dL)	1 (ref)	0.62 (0.44–0.88)	0.57 (0.34–0.94) *	1 (ref)	0.96 (0.74–1.24)	0.64 (0.46–0.90) *

Data presented as median (interquartile range). * *P*-value<0.05 considered as significant. Adjusted variables are age, sex, BMI, income, smoking, alcohol, major cooking oil, total polyunsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level (PAL), total energy (kcal) and tea and coffee intake. HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; BMI – body mass index; WC – waist circumference.

3.5 Discussion

The present study has found evidence of a protective effect of dairy consumption against CMR factors in Asian Indians. We found a reduced risk with an increased intake of dairy products, where consumption of ≥5 cups per day of total, ≥4 cups per day of unfermented or ≥2 cups per day of fermented dairy was associated with a reduced risk of high FPG. A total dairy intake of ≥5 cups per was also associated with a lower risk of high BP, low HDL and MS. Consumption of ≥4 cups per day of unfermented dairy was also associated with a decreased incidence of high BMI; while an intake of ≥2 cups per day of fermented dairy was also associated with a lower risk of MS. Given that Asian Indians have high prevalence of CVDs and T2D [105, 119, 255, 274], these findings are of public health importance. India is the largest producer of milk and it is commonly consumed by all classes of income groups, providing value for money and nutrients [275]. The results indicate that increasing the consumption of dairy products might help to reduce the risk of MS and its individual components in Asian Indians.

At baseline, the most widely consumed dairy products were reported to be tea and coffee with milk [274], and the same trend continued in the follow-up period after 10 years. In the Chennai area, a large quantity of milk is typically used in the preparation of tea and coffee, hence milk added to tea and coffee is a main source of dairy in the study population. Given that tea and coffee intake may independently influence the risk of CVDs (**Supplementary Table S3.1**), we adjusted for tea and coffee intake in our analysis. Our findings are consistent with previous studies in which dairy consumption showed a protective effect against MS [256, 266-269]. In the Prospective Urban Rural Epidemiology (PURE) study [256], a large, multinational cohort study involving 112,922 individuals from 21 countries with a median follow-up of 9.1 years, a higher total dairy intake (≥2 servings per day) compared with no intake, was associated with a decreased prevalence of MS [odds ratio (OR), 0.76; 95% CI, 0.71–0.80; P_{trend}<0.0001]. Similarly, the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), which involved 9835 participants [266], observed that total dairy intake was inversely associated with metabolic risk score (Beta=−0.04 ± 0.01, *P*=0.009). The French Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) [268], a cohort study of 3435 participants also observed a negative association between consumption of dairy products, except cheese, and incidence of MS (OR, 0.88; 95% CI, 0.79–0.97; *P*=0.01) and impaired fasting glycaemia/T2D (OR, 0.85; 95% CI 0.76–0.94; *P*=0.001). A prospective study of 7240 Koreans [269] also reported that, a high consumption of dairy (≥7 times a week) was associated with a decreased risk of MS (HR,

0.72; 95% CI, 0.62–0.84; P_{trend}<0.001) compared to no consumption of dairy. Overall, these findings indicate that consumption of dairy might be beneficial in reducing the risk of MS in different ethnic groups, but large dietary intervention studies will help to corroborate the findings.

The inverse association between dairy consumption and the risk of individual components of CMR observed in our study is also consistent with previous studies. In the PURE study [256], a higher total dairy intake (≥2 servings per day) compared to no intake, was associated with a decreased incidence of hypertension (HR, 0.89; 95% CI, 0.82–0.97; P_{trend}=0.02) and T2D (HR 0.88; 95% CI, 0.76–1.02, P_{trend}=0.01). The Caerphilly Prospective Study of 2512 men [288] also reported that participants in the highest milk consumption group had a 10.4 mmHg lower SBP (P_{trend}=0.023) than those who did not consume milk after a 22.8 year follow-up. This study [288] also observed lower levels of glucose (P_{trend}=0.032) with increasing intake of milk and dairy products. Furthermore, a cross-sectional study of 205 Indian participants with MS [289] showed that, consumption of milk and milk products (>4 servings/day) was associated with a lower risk of hypertension (OR, 0.54 95% CI, 0.18–1.67). A study involving 133 Indian women with gestational diabetes [290] also found an inverse association between consumption of dairy products and adverse neonatal outcomes (OR, 0.14, 95% CI, 0.02–0.8; *P*=0.03). Moreover, a systematic review of randomised controlled trials [291] reported that dairy intake had a beneficial effect on body weight. All in all, the findings call for large, randomised trials to confirm the effect of dairy products on BP, BMI and blood glucose levels.

Our finding of a positive association between dairy intake and high HDL is also supported by a cohort study of 11,377 Norwegian participants (The Tromsø Study) [292] where consumption of cheese was positively associated with HDL concentration (Beta=0.02 mmol/L, 95% CI, 0.01–0.03). However, this association was only observed for total dairy intake in our study. The study [292] also reported that, a high intake of fermented dairy (250 g/day) was associated with lower TG concentration (Beta=−1.11, 95% CI, −1.96 to −0.24; *P*=0.01) than a low intake, but this was not observed in our study. One possible explanation is that, cheese was a main part of fermented dairy in the Norwegian study [292] while in our study, the median intake of cheese was zero. On the whole, the findings indicate a need for large scale randomised trials to confirm the association of dairy products with blood lipids.

The average intake of SFA (% of energy) for this study population, Chennai urban area was 9% of total energy intake (TEI), which is within the recommended daily allowance of <10% of TEI [71]. Dairy is known to contain high amounts of SFA which is linked to

elevated LDL concentration and high risk of CVDs leading to concerns about the health benefits of dairy, with some people resorting to low-fat dairy alternatives [265, 293]. However, it has been noted that, SFAs are a large group of fatty acids, and their effects may vary depending on the type of food [265]. Moreover, a large multinational cohort study of 136,384 individuals from 21 countries (PURE) [265] observed no significant association between higher intake of SFA from dairy sources and total mortality or major CVD. Furthermore, odd chain fatty acids are the major SFAs in milk and they have been associated with better CVD outcomes with regards to lipids [294, 295]. The association of dairy intake with favourable lipid levels has also been linked to the presence of oleic acid, a monounsaturated fatty acid (MUFA) in dairy products [292] which is known to increase the concentration of HDL and lower the levels of LDL and TG [296-298]. Fatty acids derived from milk have also been associated with a decrease in the number of small dense LDL particles, which is linked to a favourable lipid profile since small dense LDL is negatively associated with HDL and positively associated with TG and fasting insulin levels [299]. Milk is a rich source of different nutrients [265, 293], and it has been suggested that the protective effect of dairy consumption on the risk of MS is dependent on the individual as well as joint effect of the different nutrients [300, 301]. Milk protein is believed to suppress angiotensin I-converting enzyme, which is involved in BP regulation [302]. Milk is also a rich source of potassium, which helps in regulating BP [303]. Whey protein derived from milk has also been reported to influence glucose levels through its involvement in the regulation of gastrointestinal hormones [301]. Fermented dairy is believed to confer greater anti-inflammatory and cardiometabolic benefits than unfermented dairy [271, 272], but intake of fermented dairy was relatively low in this study, and this could have influenced our findings of fewer associations between fermented dairy and CMR. It has also been suggested that, the associations of dairy with blood lipids may be impacted by dairy matrix and fat content [292]. Moreover, findings from a large mendelian randomisation analysis of 1,904,220 individuals from three population-based studies [304] indicate that, genetic variants linked to milk consumption, might also influence BMI and lipid levels, suggesting that multiple factors are involved in the association of dairy intake with reduced risk of MS.

The strength of our study is the large sample size and the use of validated instruments in a well-characterised population. This study is one of few studies which have examined the association of total, unfermented and fermented dairy with the risk of MS in Asian Indians. Our study has some limitations. Comparing the benefits of fermented and unfermented dairy intake was not possible due to the relatively low intake of fermented dairy compared to

unfermented dairy. Additionally, we did not investigate the effect of individual dairy products on the risk of MS. Furthermore, the fat content of the dairy products was not analysed in our study. Coffee and tea might also influence CVD risk independently as shown in **Supplementary Table S3.1**, but data on intake of caffeine and phenolic compounds was not available. However, we adjusted for coffee and tea intake in the regression model. Moreover, evidence from nutrigenetic studies shows that genetic variants might be involved in modifying responses to diet, which is outside the scope of this study. Nonetheless, our findings support previous work and add to the evidence linking dairy consumption to lower risk of MS and components of CMR.

3.6 Conclusion

We found that increased consumption of dairy (≥5 cups per day of total, ≥4 cups per day of unfermented or ≥2 cups per day of fermented dairy) was associated with a lower risk of high FPG. A total dairy intake of ≥5 cups per day was also protective against high BP, low HDL and MS. A high unfermented dairy intake (≥4 cups per day) was also as-sociated with a lower risk of high BMI, while a reduced risk of MS was observed with a fermented dairy intake of ≥2 cups per day. The findings indicate that increasing the consumption of dairy might help to reduce CMR factors (high BP, BMI, FPG and low HDL) and MS in Asian Indians. Larger studies are needed to confirm our findings. Once our findings are confirmed, dietary guidelines focusing on increasing the consumption of dairy might be effective in reducing the risk of MS and components of CMR in Asian Indians.

Chapter 4 Interaction between genetic risk score and dietary fat intake on lipid-related traits in Brazilian young adults

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Ramatu Wuni's contribution: For this study, I started by writing up a data analysis plan which was approved by my primary supervisor. I then cleaned the dataset, evaluating the variables and ensuring non-normally distributed variables were log-transformed prior to the analysis. I performed all the statistical analyses using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA) and the R software version 4.3.1. I interpreted the results, carried out a literature search and wrote the manuscript. I revised the manuscript based on comments and suggestions from the co-authors. I also formatted the manuscript according to the guidelines of the British Journal of Nutrition before it was submitted for publication. I also wrote the responses to the reviewers' comments and revised them based on suggestions from my primary supervisor.

4.1 Abstract

The occurrence of dyslipidaemia, which is an established risk factor for cardiovascular diseases, has been attributed to multiple factors including genetic and environmental factors. We used a genetic risk score (GRS) to assess the interactions between genetic variants and dietary factors on lipid-related traits in a cross-sectional study of 190 Brazilians (mean age: 21 ± 2 years). Dietary intake was assessed by a trained nutritionist using three 24-hour dietary recalls. The high GRS was significantly associated with increased concentration of triglycerides (TG) [Beta=0.10 mg/dL, 95% confidence interval (CI) 0.05–0.16; P<0.001], low-density lipoprotein cholesterol (Beta=0.07 mg/dL, 95% CI 0.04–0.11; P<0.0001), total cholesterol (Beta=0.05 mg/dL, 95% CI: 0.03–0.07; P<0.0001) and the ratio of TG to high-density lipoprotein cholesterol (HDL-C) (Beta=0.09 mg/dL, 95% CI: 0.03–0.15; P=0.002). Significant interactions were found between the high GRS and total fat intake on TG:HDL-C ratio ($P_{interaction}$=0.03) and between the high GRS and saturated fatty acids (SFA) intake on TG:HDL-C ratio ($P_{interaction}$=0.03). A high intake of total fat (>31.5% of energy) and SFA (>8.6% of energy) was associated with higher TG:HDL-C ratio in individuals with the high GRS (Beta=0.14, 95% CI: 0.06–0.23; P<0.001 for total fat intake; Beta=0.13, 95% CI: 0.05–0.22; P=0.003 for SFA intake). Our study provides evidence that the genetic risk of high TG:HDL-C ratio might be modulated by dietary fat intake in Brazilians and these individuals might benefit from limiting their intake of total fat and SFA.

4.2 Introduction

Cardiovascular diseases (CVDs) are a top cause of mortality globally, accounting for 32% of all deaths worldwide in 2019 [305]. Over three-quarters of mortality from CVDs has been reported to occur in low- and middle-income countries [305], highlighting the enormous impact of CVDs in these countries. In Brazil, ischaemic heart disease and stroke accounted for most deaths in 2019, with a percentage increase of 18 and 14%, respectively from 2009 [306]. An analysis of the factors contributing to death in Brazil using data from the Global Burden of Disease 2019 study [307] indicated that, more than 80% of deaths from CVDs is attributable to cardiovascular risk factors. Among the risk factors for CVDs is an altered blood lipid profile (dyslipidaemia), which is evidenced by a rise in the concentration of triglycerides (TG) or low-density lipoprotein cholesterol (LDL-C) and a reduction in the concentration of high-density lipoprotein cholesterol (HDL-C) [3, 107].

The occurrence of dyslipidaemia has been attributed to multiple factors including genetic and environmental factors [18, 104, 130, 251, 308, 309]. Dietary fatty acids are involved in modulating the metabolism of lipids and lipoproteins [68, 69], and dietary recommendations to reduce CVD risk advocate for a reduction in saturated fatty acids (SFA) and total fat intake [71]. A high SFA intake has been associated with a rise in TG-rich lipoproteins which is associated with increased risk of myocardial infarction (MI), ischaemic stroke, and other CVDs [73-75]. Consumption of SFA has also been linked to a rise in circulating levels of inflammatory biomarkers [310, 311] which contributes to the development of cardiometabolic diseases, including CVDs [312-314]. A meta-analysis involving a total of 49 prospective studies [315] identified that, higher concentration of circulating SFA was associated with a 50% increased risk of CVDs, 63% increased risk of coronary heart disease (CHD) and 38% increased risk of stroke. In a cross-sectional study of 282 Brazilian adults [316], consumption of SFA was found to be higher than the recommended intake in 79.7% of the participants. The fat content of processed foods in Brazil was also found to be composed of high amounts of SFA, ranging from 9.3 to 12 grams per 100 grams of food products [317].

Evidence from genome-wide association (GWA) studies has implicated several genetic loci for the development of dyslipidaemia [95, 124, 201, 204, 318], but these variants account for a small proportion of variability in blood lipid concentrations, and there is growing evidence that an interaction between genetic variants and environmental factors is responsible for part of the missing heritability [105, 106, 126-129]. Single variants often have small effect sizes and an effective approach to assessing the genetic contribution to complex

traits is the use of a genetic risk score (GRS), which allows the combined effect of multiple variants to be analysed [245, 319]. Single nucleotide polymorphisms (SNPs) of lipid-pathway genes have been reported to contribute to variations in blood lipid concentrations [130, 228, 320, 321]; and the proteins encoded by these genes include cholesteryl ester transfer protein (CETP), which regulates HDL-C concentration and particle size by promoting the transfer of cholesteryl esters and TG between lipoproteins [48]; apolipoprotein AI (apoAI) which is the main component of HDL-C and is involved in the maturation of HDL-C [322]; glucokinase regulatory protein, which regulates the activity of glucokinase [323, 324]; sortilin, which regulates plasma LDL-C by facilitating hepatic uptake of ApoB100-containing lipoproteins [325]; and hepatic lipase (LIPC) and endothelial lipase (LIPG) which hydrolyse lipoproteins to release free fatty acids [125, 326]. Only a few studies have utilised a GRS to assess the interactions between dietary intake and genetic variants on CVD traits in Brazilians [139, 319, 327], with even fewer studies focusing on young adults. Two of the studies [319, 327] used data from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) cross-sectional study and involved 187 and 200 participants aged 19–24 years, respectively. Significant GRS-diet interactions were found in relation to vitamin D and glycaemic traits, respectively. The third study [139], which was also a cross-sectional study, consisted of 228 adults (19–60 years) and significant GRS-diet interactions on dyslipidaemia were reported. Hence, the aim of this study was to assess the genetic associations and the interaction of the GRS with dietary factors on lipid-related traits in Brazilian young adults.

4.3 Methods

4.3.1 Study participants

The study consisted of 190 young adults aged 19-24 years from the BOLD cross-sectional study [128, 319]. Participants were recruited between March and June 2019 from the Federal University of Goiás. The study was performed as part of the gene-nutrient interactions (GeNuIne) collaboration which is aimed at investigating how genetic and lifestyle factors interact to influence chronic diseases in diverse ethnic groups, with the goal of preventing and managing chronic diseases through personalised nutrition [18, 131, 170, 171]. Details of the study design are published elsewhere [319, 327]. In brief, a total of 416 individuals expressed interest in the study but 207 individuals were found to be eligible. Participants were excluded if they were using lipid-lowering medication, vitamins, or mineral supplements; had undergone dietary interventions in the past six months; or

undertaking vigorous physical activity; or had a diagnosis of any chronic disease such as type 2 diabetes, dyslipidaemia, or hypertension. Out of the 207 eligible participants, 200 completed the study, however, 190 participants were included in the present analysis after excluding participants with missing data for genetic and phenotypic measurements. The selection of the participants is shown in **Supplementary Figure S4.1.**

The study was approved by the Ethics Committee of the Federal University of Goiás (protocol number 3.007.456, 08/11/2018) and written informed consent was obtained from all the study participants. The study was performed in accordance with the ethical principles in the Declaration of Helsinki.

4.3.2 Anthropometric and biochemical measurements

Measurement of anthropometric parameters was done by trained staff from the Nutritional Genomics research group of The Federal University of Goiás, Brazil. A Tanita® (Tanita Corporation, Itabashi, Tokyo, Japan) portable electronic scale, which has a maximum capacity of 150 kg, was used to weigh participants. For height, a stadiometer with a movable rod was used and the volunteers were asked to keep upright with heels, calves, shoulder blades and shoulders pressed against the wall, knees straight, feet together and arms extended along the body; the head raised (making a 90º angle with the ground), with the eyes looking at a horizontal plane ahead, in accordance with the Frankfurt plane. Weight and height were used to calculate the body mass index (BMI) using the formula: weight (kg)/the square of the height (m^2). Waist circumference was measured using an inelastic measuring tape at the midpoint between the lowest rib margin and the iliac crest [328].

Blood pressure was measured when the patient was seated, positioning the arm at heart level. Three measurements were taken, with five-minute intervals between them. At the end, the average of the three measurements was considered, as proposed by the American Heart Association [329] and approved by the VI Brazilian Guideline on Hypertension [328].

Approximately 10mL of venous blood was collected from the medial cubital vein following a 12-hour fasting period. The blood collection procedure was performed by a trained healthcare professional using single-use materials. Participants were instructed to abstain from consuming alcohol for 72 hours and avoid engaging in strenuous physical activity for 24 hours prior to the blood collection. The samples were processed immediately after collection at the Romulo Rocha Laboratory (Goiânia, Brazil). The levels of TG, total cholesterol (TC) and HDL-C were assessed using direct enzymatic colorimetry. LDL-C levels were calculated using the Friedewald, Levy, and Fredrickson equation (1972) [330].

4.3.3 Dietary assessment

Dietary intake was assessed by a trained nutritionist using three 24-hour dietary recalls consisting of non-consecutive days, including one weekend [331]. The nutritionist conducted the first interview in person according to multiple-pass method [332], and the following two interviews were conducted via phone calls. To assist in estimating portion sizes of various foods, participants were provided with measuring equipment such as measuring cups and spoons. Intake of nutrients and energy was determined from the dietary recalls using the Avanutri Online® diet calculation software (Avanutri Informática Ltda, Rio de Janeiro, Brazil) with three Brazilian food composition databases, Brazilian Institute of Geography and Statistics, 2011 [333], food composition table-support for nutritional decision making (2016) [334] and food studies and research centre-Brazilian food composition table (2011) [335]. For processed or ultra-processed foods that were not in the databases, the information in the label was manually added.

4.3.4 SNP selection and genotyping

A total of seven SNPs representing seven loci were selected for this study based on their association with lipid-related traits at a genome-wide significance level ($P<5 \times 10^{-8}$): cholesteryl ester transfer protein (*CETP*) SNP rs3764261 [94, 96, 97, 124, 205, 336], glucokinase regulator (*GCKR*) SNP rs1260326 [124, 195, 205, 321, 337-339], endothelial lipase (*LIPG*) SNP rs7241918 [124, 340-342], sortilin 1 (*SORT1*) SNP rs629301 [124, 340, 341], hepatic lipase (*LIPC*) SNP rs1532085 [124, 203, 205, 339], apolipoprotein A1 (*APOA1*) SNP rs964184 [95, 124, 195, 197, 200, 202, 207, 343] and ATPase plasma membrane Ca2+ transporting 1 (*ATP2B1*) SNP rs2681472 [344-347]. **Table 4.1** shows the SNPs, effect sizes, *P*-values and the GWA studies. A review by our team [130] indicated that the *CETP* gene had the highest number of reported associations with lipid traits, and it was concluded that SNPs of the *CETP* gene could potentially alter blood lipid profiles by interacting with diet. The *GCKR* gene was chosen as it has been reported to influence alterations in blood lipid profiles [348-353]. The *LIPG* gene, another key lipid metabolism gene has been reported to play a role in inflammation and could influence the risk of CVDs [326, 354, 355]. Furthermore, the *SORT1* gene is considered the strongest genome-wide LDL-C associated locus [95, 123, 336, 356-358] and the *LIPC* gene is also a main lipid-pathway gene which has been associated with abnormal lipid profiles [124, 203, 205, 341, 359]. Additionally, the *APOA1* gene has been widely studied and has been linked with variations in blood lipid levels [124, 197, 202, 318, 360] and the risk of CVDs [361-364]. Similarly, the *ATP2B1* gene has been reported to influence the risk of developing CVDs [344, 345, 347, 363, 365]. Six of the SNPs included in

our GRS (rs3764261, rs1260326, rs7241918, rs629301, rs1532085, rs964184) had previously been included in a GRS by a genetic association study involving 6,358 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) Classic cohort [366] which observed significant associations between the GRS and lipid traits. The genotyping procedure has been previously published [327]. Briefly, blood samples (3ml each) for genotyping were collected in BD Vacutainer® ethylenediamine tetraacetic acid (EDTA) tubes and kept at a controlled temperature of –80ºC during transportation by the World Courier Company. Genotyping was performed by LGC Genomics, London, UK (http://www.lgcgroup.com/services/genotyping), using the competitive allele-specific PCR-KASP® assay.

Table 4.1 SNPs used to construct the GRS and the reported traits by genome-wide association studies

Gene & SNP	Effect Allele	Lipid Trait & Effect size in mg/dL (*P*-value)				Population & Sample Size	GWA Study
		HDL-C	LDL-C	TG	TC		
CETP rs3764261	A	+0.24 (1×10^{-769})	−0.05 (2×10^{-34})	−0.04 (2×10^{-25})	+0.05 (4×10^{-31})	European ancestry (UK, Finland, Sweden, US, Italy, Greece, Germany, Estonia, Norway): n=94,595	Willer et al. 2013 [341]
	A	+3.39 (7×10^{-380})		−2.88 (1×10^{-12})	+1.67 (7×10^{-14})	European ancestry (Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) n=99,900 for HDL n=96,598 for TG n=100,184 for TC	Teslovich et al. 2010 [124]
	A	+3.48 (7×10^{-29})				Northern Finnish Founder: n=4,763	Sabatti et al. 2009 [205]
	A	+0.20* (9×10^{-18})				African American: n=7,813	Lettre et al. 2011 [97]
	A	+3.18* (7×10^{-43})				Indian n=1036	Khushdeep et al. 2019 [94]

Table 4.1 continued

CETP rs3764261	A	+6.20 (3×10^{-12})		Japanese n=900	Hiura et al. 2009 [96]
LIPG rs7241918	G	−1.31 (3×10^{-49})		European ancestry (Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) n=99,900	Teslovich et al. (2010) [124]
	A		−1.94 (2×10^{-19})	European ancestry (Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark): n=100,184	Teslovich et al. (2010) [124]
	G	−0.09* (1×10^{-44})	−0.06* (4×10^{-18})	European ancestry (UK, Finland, Sweden, US, Italy, Greece, Germany, Estonia, Norway): n=94,595	Willer et al. (2013) [341]

Table 4.1 continued

LIPG rs7241918	G	−0.08* (4×10^{-55})	−0.02* (1×10^{-8})			European ancestry n=115,082	Richardson et al. (2022) [367]
	A	+0.02* (3×10^{-27})				Multi-ancestry (African: n=23761; Asian: n=13,171; European: n=90272; Hispanic or Latin American: n=6620)	Bentley et al. 2019 [340]
GCKR rs1260326	T			+8.76 (6×10^{-133})	+1.91 (7×10^{-27})	European ancestry (Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) n=96,598 for TG n=100,184 for TC	Teslovich et al. (2010) [124]
	T			+0.12 (2×10^{-239})	+0.05* (3×10^{-42})	European ancestry (UK, Finland, Sweden, US, Italy, Greece, Germany, Estonia, Norway): n=94,595	Willer et al. (2013) [341]

Table 4.1 continued

GCKR rs1260326	T		+0.12* (2×10^{-31})		European (UK, Finland, Sweden, US, Italy, France) n=19,840	Kathiresan et al. (2009) [318]
	T		+0.12* (5×10^{-88})	+0.05* (3×10^{-13})	European (UK, Finland, Sweden, Iceland, Netherlands, Germany, Estonia): n=62,166	Surakka et al. (2015) [360]
	T	+0.03* (6×10^{-60})			European ancestry: n=440,546	Richardson et al. (2020) [342]
	T		1.41† (2×10^{-13})		Mexican: *n*=2240	Weissglas-Volkov et al. (2013) [321]
	T	+0.03* (7×10^{-10})			Multi-ancestry (European: n=76,627; Hispanic: n=7,795; East Asian: n=6,855; African American: n=2,958; South Asian: n=439)	Hoffman et al. 2018 [9]

Table 4.1 continued

SORT1 rs629301	G	–5.65 (1×10^{-170})	–5.41 (6×10^{-131})	European ancestry (UK, Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, Croatia, Switzerland, Austria, France, Denmark) n=100,184 for TC *N*=95,454 for LDL-C	Teslovich et al. (2010) [124]
	G	–0.17* (5×10^{-241})	–0.13* (2×10^{-170})	European ancestry (UK, Finland, Sweden, US, Italy, Greece, Germany, Estonia, Norway) n=94,595	Willer et al. (2013) [341]
	G	+0.04* (4×10^{-15})	–0.14* (7×10^{-135})	Multi-ancestry (European: n=76,627; Hispanic: n=7,795; East Asian: n=6,855; African American: n=2,958; South Asian: n=439)	Hoffman et al. 2018 [9]
	T	+4.46* (1×10^{-128})		Multi-ancestry (African: n=23,761; Asian: n=13,171; European: n=90,272; Hispanic or Latin American: n=6,620)	Bentley et al. 2019 [340]

Table 4.1 continued

SORT1 rs629301	G	−6.03* (2×10^{-72})	−5.80* (2×10^{-57})	European n=29,902	Kulminski et al. (2020) [368]
	T	+0.11* (2×10^{-31})		Japanese n=72,866	Sakaue et al. (2021) [347]
LIPC rs1532085	A	+0.11* (1×10^{-188})	+0.05* (7×10^{-47})	European ancestry (UK, Finland, Sweden, US, Italy, Greece, Germany, Estonia, Norway) n=94,595	Willer et al. (2013) [341]
	A	+0.11* (1×10^{-213})		Multi-ancestry European: n=187,167 East Asian (China, Japan, Republic of Korea, Philippines, Singapore, Taiwan): n=34,930	Spracklen et al. (2017) [359]

Table 4.1 continued

LIPC rs1532085	G	−0.13* (1×10^{-35})		European ancestry (UK, Finland, Sweden, Australia, Italy, Netherlands, Germany, Croatia, Norway, Denmark) n=21,412	Aulchenko et al. 2009 [203]
	G		+2.99 (2×10^{-13})	European ancestry (Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) n=96,598	Teslovich et al. (2010) [124]
	A	+1.90 (2×10^{-10})		Northern Finnish Founder: n=4,763	Sabatti et al. 2009 [205]
APOA1 rs964184	G	+2.85 (1×10^{-26})	+16.95 (7×10^{-240})	European ancestry (UK, Finland, Sweden, US, Australia, Iceland, Italy, Netherlands, Germany, Croatia, Switzerland, Austria, France, Denmark) n=96,598 for TG; n=95,454 for LDL-C	Teslovich et al. (2010) [124]

Table 4.1 continued

APOA1 rs964184	G		+0.24* (2×10^{-157})	European (UK, Finland, Sweden, Iceland, Netherlands, Germany, Estonia) n=62,166	Surakka et al. (2015) [360]
	G	−0.03* (2×10^{-11})		European (UK, Finland, Italy, Switzerland) n=17,723	Waterworth et al. 2010 [197]
	G	−0.05* (3×10^{-12})	+0.16* (4×10^{-33})	African American: n=7,601, Hispanic: n=3,335 for TG; African American: *n*=7,917, Hispanic: *n*=3,506 for HDL-C	Coram et al. 2013 [202]
	G	−0.17 (1×10^{-12})	+0.30* (4×10^{-62})	European ancestry (UK, Finland, Sweden, US, Italy, France) n=19,840	Kathiresan et al. (2009) [318]
		CAD	**MI**		
ATP2B1 rs2681472	G	1.07† (8×10^{-11})		European n=63731	Nelson et al. 2017 [345]

Table 4.1 continued

ATP2B1 rs2681472	G	+0.07* (1×10^{-11})	European (UK, Finland): n=461,823; Japanese: n=161,206	Sakaue et al. (2021) [347]
	G	1.08† (6×10^{-9})	European: n=126630, Hispanic or Latin American (US): *n*=3615, Middle Eastern, North African or Persian: n=754, African American or Afro-Caribbean (US): n=2908, South Asian (India, UK, Pakistan): n=23,156; East Asian (Republic of Korea, China): n=9396	Nikpay et al. (2015) [344]
	G	1.07† (1×10^{-12})	European N=∼472,000	Hartiala et al. (2021) [365]

SNP – single nucleotide polymorphism; GRS – genetic risk score; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; GWA – genome-wide association.

* Effect sizes are in units of standard deviation

† Odds ratio

4.3.5 Construction of GRS

To construct the GRS, each SNP was first tested for independent association with the lipid-related traits using linear regression analysis, adjusted for age, sex and BMI. An unweighted GRS was then constructed by summing the number of risk alleles across all the seven SNPs (*CETP* rs3764261, *GCKR* rs1260326, *LIPG* rs7241918, *SORT1* rs629301, *LIPC* rs1532085, *APOA1* rs964184 and *ATP2B1* rs2681472) for each participant. For each SNP, a score of 0, 1 or 2 was assigned depending on whether the participant carried no risk alleles (homozygous for the non-risk allele), one risk allele (heterozygote) or two risk alleles (homozygous for the risk allele). The scores for the seven SNPs were then added up to create the GRS. The effect sizes of the SNPs were not considered and the GRS for each participant represented the total number of risk alleles they carried from the seven SNPs. An unweighted GRS was used because although we selected SNPs which have shown associations with lipid-related traits, the studies were not conducted in the Brazilian population, and it has been reported that effect sizes may vary across populations and data from a GWA study conducted in one population may not apply to another population [105, 369]. Moreover, assigning weights to risk alleles has been shown to have minimal effect [370]. The risk alleles were defined as alleles previously reported to be associated with increased concentration of TG, LDL-C or TC; or reduced concentration of HDL-C; or increased risk of coronary artery disease (CAD) or MI. The GRS ranged from 1 to 10, and the median GRS (6 risk alleles) was used as a cut-off point for grouping participants as low risk (GRS<6 risk alleles) or high risk (GRS≥6 risk alleles).

4.3.6 Statistical analyses

An independent sample t test was used to compare the means of continuous variables between men and women. The results for descriptive statistics are presented as means and standard deviation (SD). To test for normality, the Shapiro–Wilk test was used and all the biochemical, anthropometric and dietary variables, except total fat, carbohydrate, and monounsaturated fatty acids (MUFA) intake [percentages of total energy intake (TEI)], were log-transformed prior to the analysis. Allele frequencies were determined by gene counting and Hardy-Weinberg equilibrium (HWE) was calculated using the Chi-square test. All the seven SNPs were in HWE (P>0.05) (**Supplementary Table S4.1**), and the alleles had a frequency >5%.

Linear regression was used to test the association of the GRS with lipid levels and blood pressure, with adjustment for age, sex and BMI. To determine interactions between

the GRS and dietary factors on the outcome variables [TG, TG:HDL-C ratio, HDL-C, LDL-C, TC, systolic blood pressure (SBP), and diastolic blood pressure (DBP)], the interaction term was included in the regression model. The dietary factors examined were the intakes of fat, carbohydrate, and protein. Statistically significant GRS-diet interactions (P<0.05) were investigated further by stratifying participants according to the quantity of dietary intake. A significant interaction between the GRS and total fat intake was explored further by analysing the effects of subtypes of fat [SFA, MUFA and polyunsaturated fatty acids (PUFA)]. The median intake of total fat, SFA, MUFA and PUFA was used as a cut-off point to place participants into groups: 'low' (for participants with an intake lower than or equal to the median) and 'high' (for those with an intake higher than the median); and the effect of the GRS on the outcome was examined for participants in each group. The Bonferroni adjusted P-value for association was 0.007 (1GRS*7 outcome variables = 7 tests; 0.05/7=0.007), and for interaction, it was 0.002 (1GRS*7 outcome variables*3 dietary factors = 21 tests; 0.05/21=0.002). The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA). Additionally, the GRS was scaled by converting the scores to units of standard deviation from the mean [371] and the association of the GRS as a continuous variable with the lipid-related traits was tested by linear regression using the R software version 4.3.1 [372]. The data analysis plan is attached as an appendix (**Appendix B**).

4.3.7 Power and sample size calculation

Power calculation was performed using the QUANTO software, version 1.2.4 (May 2009) [373] in the form of minimum detectable effect at 80% power and a significance level of 5%. For a SNP with a minor allele frequency (MAF) of 5%, the minimum detectable effect at 80% power was 6.6 mg/dL for TC, LDL-C and TG. For a SNP with a MAF of 50%, the minimum detectable effect at 80% power was 2.9 mg/dL for TC, LDL-C and TG.

4.4 Results

4.4.1 Characteristics of the study participants

The demographic and clinical characteristics of the participants in this study are summarised in **Table 4.2.** The mean age of the sample was 21 ± 2 years and men had higher BMI and WC than women (P=0.01 and P<0.001, respectively). Women, however, had higher concentrations of HDL-C (P<0.0001) and TC (P=0.01) but lower TG:HDL-C ratio (P=0.006), SBP (P<0.0001), and DBP (P<0.001) than men. Intakes of total energy and protein were

higher in men than in women (P=0.003 and P=0.04, respectively), but consumption of total fat, SFA, MUFA, PUFA and carbohydrate did not differ significantly between men and women. **Table 4.3** shows the characteristics of the study participants according to GRS. Participants with a high GRS had a significantly lower intake of energy (P=0.02) than those with a low GRS. No other significant differences were observed between participants in the two groups. The distribution of the GRS across deciles of TC, LDL-C, TG and TG:HDL ratio is presented in **Supplementary Figure S4.2**.

Table 4.2 Characteristics of study participants by sex

	All (*n*=190)		**Women (*n*=141)**		**Men (*n*=49)**		***P* value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age (years)	21	2	21	2	22	2	0.17
BMI (kg/m^2)	23	1	23	1	24	1	**0.01**
WC (cm)	72	1	69	1	83	1	**<0.001**
TG (mg/dL)	76	2	76	2	75	2	0.81
TG:HDL ratio	2	2	1	2	2	2	**0.01**
HDL-C (mg/dL)	55	1	59	1	46	1	**<0.0001**
LDL-C (mg/dL)	99	1	100	1	99	1	0.80
TC (mg/dL)	174	1	178	1	163	1	**0.01**
SBP (mmHg)	107	1	105	1	114	1	**<0.0001**
DBP (mmHg)	64	1	63	1	67	1	**<0.001**
Energy (kcal/day)	1735	1	1668	1	1944	1	**0.003**
Total fat (% of energy)	32	6	32	6	31	6	0.14
SFA (% of energy)	9	1	9	1	9	1	0.84
MUFA (% of energy)	8	3	8	3	8	3	0.07
PUFA (% of energy)	5	2	5	2	5	2	0.08
Carbohydrate (% of energy)	51	7	51	7	51	8	0.88

Protein (% of energy)	17	1	16	1	18	1	**0.04**	

SD – standard deviation; BMI – body mass index; WC – waist circumference; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; SFA – saturated fatty acids; MUFA – monounsaturated fatty acids; PUFA – polyunsaturated fatty acids.

P values for the differences in means between men and women were calculated using independent sample t test.

Table 4.3 Association of GRS with blood lipids and blood pressure and the characteristics of the participants stratified by GRS

Trait	**GRS<6 (*n*=92)**		**GRS≥6 (*n*=98)**		*P* value
	Mean	**SE**	**Mean**	**SE**	
TG (mg/dL)	67.3	1.0	84.9	1.0	**<0.001**
TG:HDL-C ratio	1.2	1.0	1.5	1.0	**0.002**
HDL-C (mg/dL)	54.5	1.0	55.5	1.0	0.56
LDL-C (mg/dL)	91.4	1.0	107.6	1.0	**<0.0001**
TC (mg/dL)	164.1	1.0	183.7	1.0	**<0.0001**
SBP (mmHg)	106.9	1.0	107.2	1.0	0.69
DBP (mmHg)	63.2	1.0	64.1	1.0	0.48
Characteristic	**GRS<6 (*n*=92)**		**GRS≥6 (*n*=98)**		*P* value*
	Mean	**SD**	**Mean**	**SD**	
Age (years)	21	2	21	2	0.28
Sex (W/M)	67/27	–	78/26	–	0.56
BMI (kg/m^2)	23	1	23	1	0.97
WC (cm)	73	1	72	1	0.59
Energy (kcal/day)	1827	1	1648	1	**0.02**
Total fat (% of energy)	32	6	32	6	0.99
SFA (% of energy)	9	1	9	1	0.45
MUFA (% of energy)	8	2	8	3	0.27

PUFA (% of energy)	5	1	4	2	0.12
Carbohydrate (% of energy)	51	7	50	7	0.68
Protein (% of energy)	17	1	17	1	0.84

GRS – genetic risk score; SE – standard error; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; SD – standard deviation; W – women; M – men. *P* values were obtained from linear regression analysis with adjustment for age, sex and body mass index. Log-transformed variables were used for the analysis and values in bold represent significant associations.

* *P* values for the differences in means between participants with low GRS and those with high GRS were obtained using independent sample t test. The distribution of sex in the two groups was compared using the Chi-Squared test.

4.4.2 Association of the GRS with blood lipids

Four significant associations were identified between the GRS and lipid traits where individuals carrying six or more risk alleles had significantly higher TG, LDL-C, and TC concentrations, as well as higher TG:HDL-C ratio compared to participants with less than six risk alleles (**Table 4.3**). When the GRS was tested as a continuous variable, each standard deviation increase in the GRS was associated with a 1.05 mg/dL increase (95% CI 1.02 – 1.07) in the concentration of TC (P=0.002); 1.07 mg/dL increase (95% CI 1.03 – 1.12) in the concentration of LDL-C (P<0.001); 1.14 mg/dL increase (95% CI 1.07 to 1.21) in the concentration of TG (P<0.0001); and a 1.16 mg/dL increase (95% CI 1.09 – 1.24) in TG:HDL-C ratio (P<0.0001). All the associations remained significant after Bonferroni correction for multiple testing. The distribution of the lipid-related traits across deciles of the GRS is presented in **Figure 4.1**. As the decile of the GRS increased, the concentration of TC, TG, LDL-C and TG:HDL also increased.

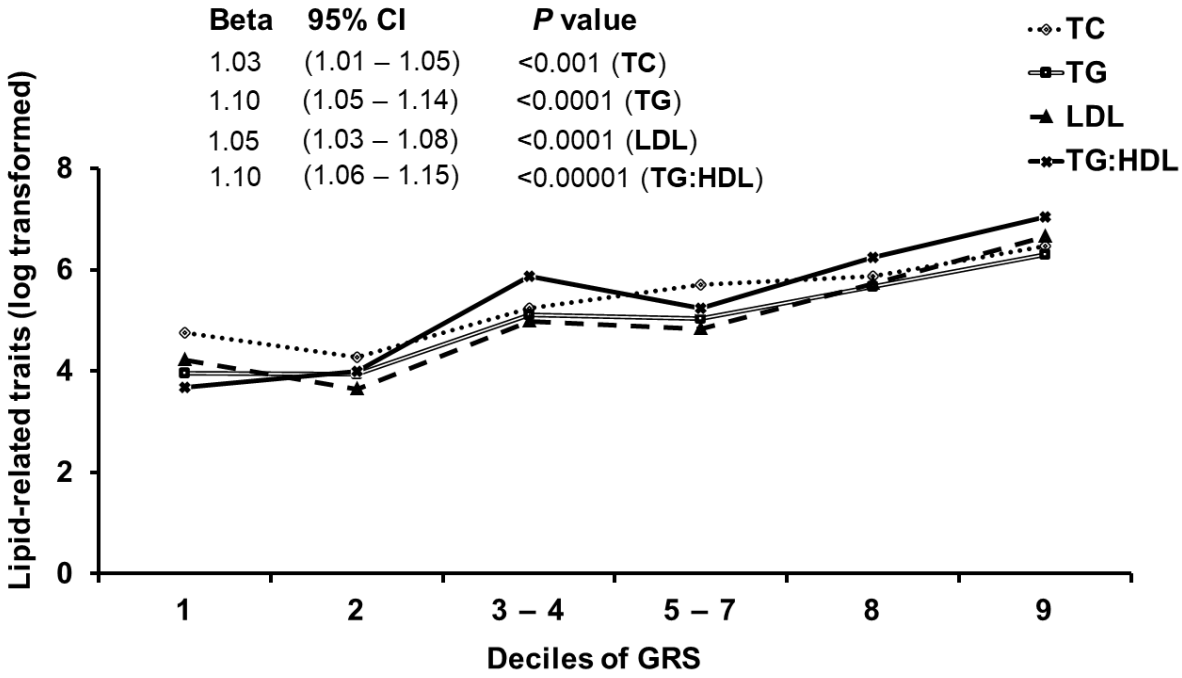

Figure 4.1 Distribution of lipid-related traits across deciles of GRS (genetic risk score)

TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TG:HDL-C – ratio of triglycerides to high-density lipoprotein cholesterol.

4.4.3 Interaction between GRS and dietary factors on blood lipids

There was a significant interaction between GRS and total fat intake on TG:HDL-C ratio ($P_{interaction}$=0.03) as shown in **Table 4.4**. In the high total fat intake group (>31.5% of TEI), participants carrying six or more risk alleles had a higher TG:HDL-C ratio compared to those carrying less than six risk alleles (Beta=0.14, 95% CI: 0.06–0.23; P<0.001) (**Figure 4.2**). No significant difference in TG:HDL-C ratio was found between participants with a high GRS (≥6 risk alleles) and those with a low GRS (<6 risk alleles) in the low total fat intake group (≤31.5% of TEI). When subtypes of fat were investigated, a significant interaction was found between GRS and SFA intake on TG:HDL-C ratio ($P_{interaction}$=0.03) (**Figure 4.3**), where a high SFA intake (>8.6% of TEI) was associated with a higher TG:HDL-C ratio in participants with a high GRS compared to those with a low GRS (Beta=0.13, 95% CI: 0.05–0.22; P=0.003); but there was no significant difference in TG:HDL-C ratio when SFA intake was low (<8.6% of TEI). A significant interaction was also observed between GRS and total fat intake on HDL-C concentration ($P_{interaction}$=0.007). However, when individuals were stratified according to quantity of total fat intake, there was no significant association between the GRS and HDL-C concentration. The interactions did not pass the Bonferroni threshold.

Table 4.4. Interaction between GRS and dietary factors on blood lipids and blood pressure

Trait	GRS * Protein (% of energy)			GRS * Fat (% of energy)			GRS * Carbohydrate (% of energy)		
	Beta Coefficient	**SE**	$P_{interaction}$	**Beta Coefficient**	**SE**	$P_{interaction}$	**Beta Coefficient**	**SE**	$P_{interaction}$
TG (mg/dL)	0.33	0.30	0.27	0.01	0.01	0.26	-0.004	0.004	0.30
TG:HDL-C ratio	0.28	0.32	0.39	0.01	0.01	**0.03**	-0.01	0.004	0.06
HDL-C (mg/dL)	0.06	0.14	0.70	-0.01	0.002	**0.007**	0.004	0.002	0.05
LDL-C (mg/dL)	0.29	0.18	0.12	-0.001	0.003	0.75	0.001	0.002	0.69
TC (mg/dL)	0.22	0.13	0.10	-0.002	0.002	0.35	0.001	0.002	0.46
SBP (mmHg)	0.002	0.05	0.96	-0.0002	0.001	0.83	-0.001	0.001	0.17
DBP (mmHg)	-0.03	0.08	0.71	0.00004	0.001	0.98	-0.001	0.001	0.31

GRS – genetic risk score; SE – standard error; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure.

P values were obtained from linear regression analysis with adjustment for age, sex and body mass index. Log-transformed variables were used for the analysis and values in bold represent significant interactions.

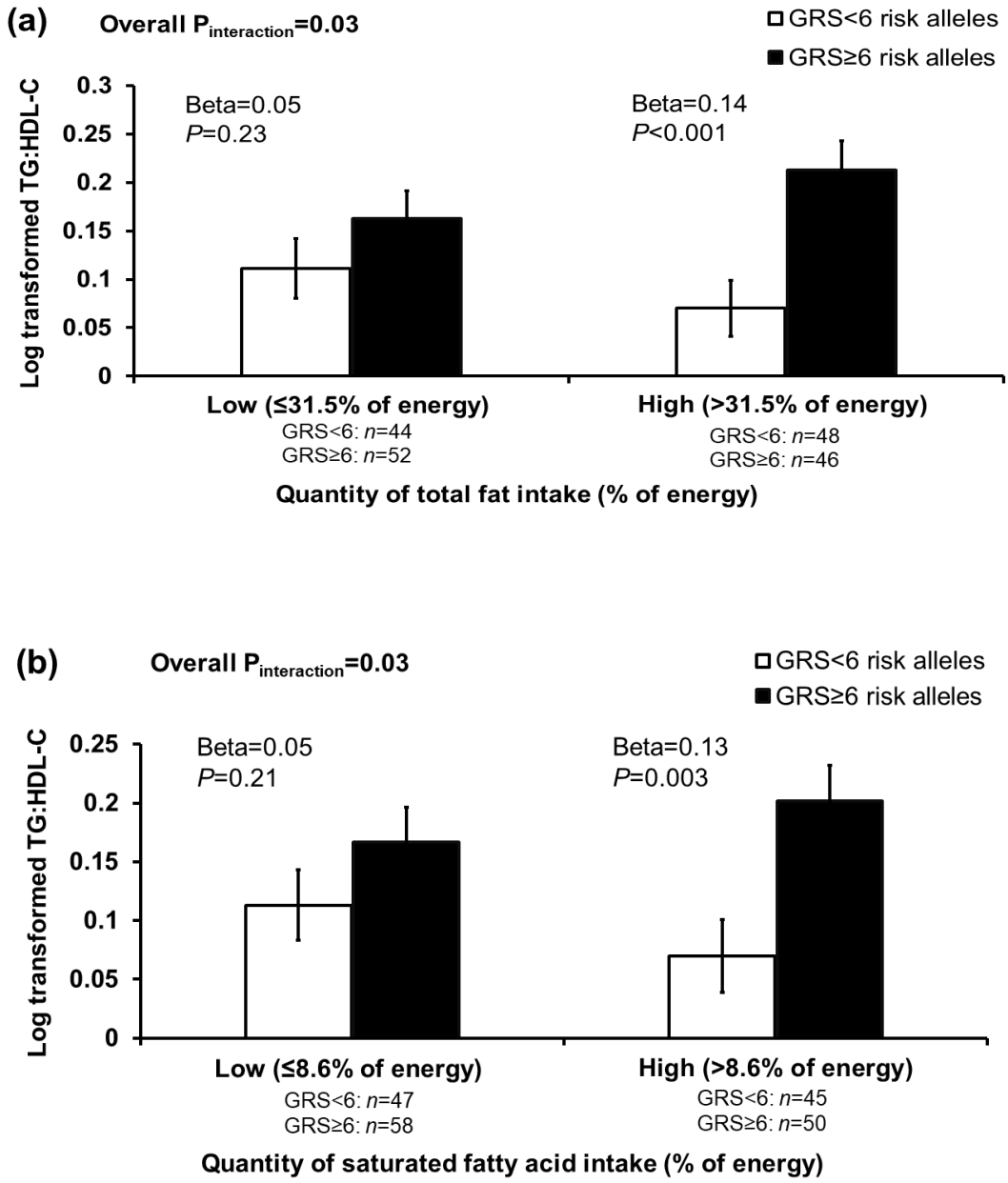

Figure 4.2 Interaction between GRS (genetic risk score) and dietary fat intake on TG:HDL-C (triglycerides to high-density lipoprotein cholesterol) ratio.

(a) Interaction between GRS and total fat intake on TG:HDL-C ratio. Low refers to total fat intake lower or equal to the median and high refers to total fat intake above the median. In the high total fat intake group, participants with a high GRS (≥6 risk alleles) had higher TG:HDL-C ratio than those with a low GRS (<6 risk alleles). There was no significant difference in TG:HDL-C ratio in the low total fat intake group.

(b) Interaction between GRS and SFA (saturated fatty acids) intake on TG:HDL-C ratio. Low refers to SFA intake lower or equal to the median and high refers to SFA intake above the median. A high intake of SFA was associated with higher TG:HDL-C in participants with a high GRS compared to those with a low GRS, but no significant difference in TG:HDL-C was observed when SFA intake was low.

4.5 Discussion

Our findings provide evidence that the genetic risk for disturbances in blood lipids concentration might be modulated by dietary fat intake. Significant interactions were found between the GRS and total fat intake on TG:HDL-C ratio; and between the GRS and SFA intake on TG:HDL-C ratio. Increased consumption of total fat (>31.5% of energy) and SFA (>8.6% of energy) was associated with higher TG:HDL-C ratio in participants carrying ≥6 risk alleles compared to those with <6 risk alleles. The results suggest that the TG:HDL ratio in Brazilian young adults with a high genetic risk for disturbances in lipid-related traits maybe responsive to dietary fat intake; hence, interventions targeting a reduction in total fat and SFA intake could potentially benefit these individuals. Although the interactions did not pass the Bonferroni threshold, three of the SNPs included in our GRS (*CETP* rs3764261, *APOA1* rs964184 and *GCKR* rs1260326) have previously been reported to interact with dietary fat intake and influence lipid-related traits. In a study involving two trials [a 2-year randomised weight loss trial (POUNDS LOST) consisting of 732 overweight/obese adults and a replication in 171 overweight/obese adults from an independent 2-year randomised weight loss trial (DIRECT)] [214], significant interactions were observed between the *CETP* SNP rs3764261 and dietary fat intake on changes in the concentration of HDL-C and TG (pooled $P_{interaction}$<0.01). Similarly, a prospective, randomised, single-blind controlled dietary intervention trial [Coronary Diet Intervention With Olive Oil and Cardiovascular Prevention (CORDIOPREV)] involving 424 Spanish individuals with metabolic syndrome [191], found significant interactions between the *CETP* SNP rs3764261 and Mediterranean diet on the concentration of HDL-C ($P_{interaction}$=0.006) and TG ($P_{interaction}$=0.04). In another study consisting of 734 overweight/obese adults from the POUNDS LOST trial [374], the *APOA1* SNP rs964184 was also found to interact with dietary fat intake in relation to changes in the concentration of HDL-C, LDL-C and total cholesterol ($P_{interaction}$=0.006, 0.02 and 0.007, respectively). Additionally, a cross-sectional study of 3,342 individuals (1,671 sib pairs) in India [242] found a significant interaction between the *APOA1* SNP rs964184 and dietary fat intake on the concentration of TG (P=0.04). This study [242] also observed significant

interactions between the *CETP* SNP rs3764261 and dietary fat intake on the concentrations of total cholesterol (P=0.02) and LDL-C (P=0.04). Furthermore, an interaction between the *GCKR* SNP rs1260326 and MUFA intake on HDL-C concentration was reported in a cross-sectional study of 101 participants of different ethnicities in the US population ($P_{interaction}$=0.02) [189]. Therefore, the interactions in our study cannot be ruled out completely; hence a replication is warranted.

The ratio of TG:HDL-C has been identified as an independent predictor of CHD, mortality from CVDs and insulin resistance [74, 75, 375, 376]. Hence, our findings have significant public health implications in terms of prevention and management of dyslipidaemia in individuals with a high genetic risk. Our data support the recommendations of the WHO [71] to reduce the intake of total fat and SFA to less than 30% and 10% of energy intake, respectively to help prevent cardiometabolic diseases. Our findings are also in agreement with the dietary guidelines for Brazilians which recommend decreasing the intake of food rich in solid fat and added sugar and limiting the daily energy intake from total fat to less than 30% [377, 378].

In the current study, the GRS was positively associated with the concentration of TG, LDL-C and TC; and the ratio of TG:HDL-C. Our findings are consistent with those of a study involving 8,526 participants from two Danish cohorts [379] [a randomised nonpharmacological intervention study (Inter99), n=5,961; and a population-based epidemiological study (Health2006), n=2,565], in which a positive association was identified between lipid-GRS and the concentration of TG (Beta=1.4% mmol/L, P<0.0001); LDL-C (Beta=0.024 mmol/L, P<0.0001); and TC (Beta= 0.027 mmol/L, P<0.0001). Similarly, a prospective study of 3,495 Swedish participants [380], reported significant associations between lipid-GRS and changes in the concentration of TC and TG after a 10-year follow up [Beta=0.02 mmol/L per effect allele, P<0.0001 for TC; Beta=0.02 mmol/L per effect allele, P<0.0001 for TG]. The European Prospective Investigation of Cancer (EPIC)-Norfolk cohort study, consisting of 20,074 participants [381], also found a positive association between a lipid-GRS and the concentration of TG [Beta=0.25 mmol/L, 95% CI 0.22–0.27 per allele change; P<0.001], indicating the role of genetic polymorphisms in predicting variability in blood lipid concentration.

A systematic review and meta-analysis of six prospective studies including 10,222 participants [74] reported that, in patients with CHD, those with elevated TG:HDL-C ratio had increased risk of all-cause mortality [Hazard ratio (HR)=2.92, 95% CI 1.75–4.86; P<0.05] and major adverse cardiovascular events (HR=1.56, 95% CI 1.11–2.18; P<0.05) compared to

those with lower TG:HDL-C ratio. In line with our findings, a study conducted in 228 Brazilian adults [139] reported a significant interaction between a GRS based on lipid metabolism genes and intake of solid fat, alcoholic beverages and added sugar on the risk of dyslipidaemia ($P_{interaction}$<0.001), where participants with a high GRS had a lower risk of dyslipidaemia when their intake of solid fat, alcoholic beverages and added sugar was below the median. Similarly, a prospective randomised controlled trial involving 523 Spanish patients with CAD from the CORDIOPREV study [382] reported that, carriers of the risk allele ('G' allele) of *APOA1* SNP rs964184 who consumed a low-fat diet (containing <30% of total fat) had reduced post-prandial TG concentrations after 3 years, while 'G' allele carriers on a Mediterranean diet (containing a minimum of 35% of total fat) continued to have higher post-prandial TG concentrations. Along these lines, a fat response genetic score based on SNPs showing a positive interaction with dietary fat in relation to LDL-C, was found to predict a 1-year change in LDL-C in a sample of 422 Black and Hispanic participants from the Women's Health Initiative cohort [383]. A significant interaction was identified between the dietary modification trial arm and fat response genetic score for LDL-C concentration (P=0.002), where participants in the control arm showed a trend towards minimal reductions in LDL-C concentrations at higher fat response genetic scores, while the opposite trend was observed in participants following a low-fat diet [383]. Taking together, these findings suggest that the genetic susceptibility to dyslipidaemia could be modulated by dietary fat intake in different populations.

A nationwide dietary survey involving 32,749 Brazilian individuals (≥10 years old) [384] highlighted a change in dietary pattern in Brazil which is characterised by increased consumption of processed foods rich in fat and simple sugars. An increase in the consumption of ultra-processed food among Brazilians aged ≥10 years was also reported in a study using food consumption data from 2008–2009 (n=34,003) and 2017–2018 (n=46,164) Household Budget Surveys [385]. Similarly, an assessment of the diet quality of Brazilians using data from the national survey [377] showed that, in 60% of the population, the mean SFA intake was 10.7% of TEI, which exceeds the WHO's recommendation of <10% of TEI [71]. The study [377] also reported that solid fat and added sugar contributed more than 45% of TEI. In the present study, the median intake of total fat was 31.5% of TEI which is more than the recommended intake of <30% [71]; however, the median intake of SFA (8.6% TEI) was within the recommended level [71]. This suggests that individuals who have a genetic predisposition to dyslipidaemia may find greater benefit from adhering to dietary recommendations.

The mechanisms through which dietary fat intake affects blood lipid concentration have been examined by several studies [68, 238, 386-388]. Dietary fatty acids affect lipid metabolism through the activation of several transcription factors and nuclear receptors including peroxisome proliferator-activated receptors (PPARs) and liver X receptors [238, 388]. PPARs regulate the expression of different genes involved in lipid and lipoprotein metabolism and the activation of PPARs is positively correlated with the chain length and degree of unsaturation of fatty acids [68, 238, 388]. SFA are also believed to decrease LDL-C receptor activity which slows the clearance of TG-rich lipoproteins [238], and this could explain the increased TG:HDL-C ratio observed among participants in the high SFA intake group. Consumption of SFA has also been shown to suppress the expression of genes involved in fatty acid oxidation and synthesis of TG [68], and promote the expression of inflammatory genes [389]. However, SFA of different chain lengths and from different food sources have been reported to exert different effects on cardiometabolic traits [390, 391].

The main strength of our study is the use of a GRS based on established lipid metabolism genes. Our study is one of few studies which have utilised this approach to explore CVD traits in Brazilian young adults, considering the increased prevalence of CVDs in young people aged 15–49 years in Brazil in 2019 [392]. The GRS approach is more effective in assessing the genetic contribution to complex traits such as blood lipid concentration since single variants often have moderate effect sizes and hence less likely to accurately predict the genetic risk of multifactorial traits [104, 129, 281]. Another strength is the use of validated techniques and trained personnel to assess biochemical, anthropometric, and dietary variables, which enhances the accuracy of the assessments. However, our study has some limitations. The small sample size could have influenced our findings since large sample sizes improve the power to detect interactions with small effects [393, 394]. Additionally, we were not able to replicate our findings due to a lack of access to similar Brazilian cohorts with data on both genetics and dietary information. Nonetheless, we were able to replicate previously reported associations and interactions. Another limitation is the use of self-reported dietary recalls which can introduce bias through overestimation and underestimation of dietary intake [152, 395]. Moreover, we did not investigate types or food sources of SFA which have been reported to have different effects on CVD traits [294, 390]. Additionally, the cross-sectional design means that causality between dietary fat intake and TG:HDL-C ratio cannot be established [105].

4.6 Conclusion

In conclusion, our study provides evidence that the genetic risk of increased TG:HDL-C ratio might be modulated by dietary fat intake. The findings indicate that Brazilian young adults with a high genetic risk for dyslipidaemia might benefit from limiting their intake of total fat and SFA. Our results support the dietary guidelines of the WHO which recommend reducing total fat and SFA to help prevent cardiometabolic diseases. The findings suggest that personalised nutrition strategies based on GRS might be effective for the prevention and management of dyslipidaemia but confirmation in dietary intervention studies with large sample sizes is required.

Chapter 5 Interactions between genetic and lifestyle factors on cardiometabolic disease-related outcomes in Latin American and Caribbean populations: A systematic review

Published (The published version of the paper is attached as an appendix at the end of the thesis)

Wuni, R., Ventura, E. F., Curi-Quinto, K., Murray, C., Nunes, R., Lovegrove, J. A., Penny, M., Favara, M., Sanchez, A. & Vimaleswaran, K. S. Interactions between genetic and lifestyle factors on cardiometabolic disease-related outcomes in Latin American and Caribbean populations: A systematic review. *Frontiers in Nutrition* **2023**, *10*, 61. https://doi.org/10.3389/fnut.2023.1067033

Ramatu Wuni's contribution: For this systematic review, I conducted a literature search using different databases including PubMed and Google Scholar to identify studies that examine the interactions between genetic variants and lifestyle factors on cardiometabolic disease-related traits in Latin American and Caribbean populations. A total of 26,171 publications were identified and screened for title and abstract and 101 potential studies were evaluated for eligibility. After full-text screening and risk of bias assessment, 74 studies were selected for inclusion in the review. I read the full-text of the 74 studies in detail and extracted the results for analysis. I contacted corresponding authors to provide additional information when needed. I wrote the manuscript and revised it based on comments and suggestions from the co-authors. I formatted the manuscript according to the guidelines of Frontiers in Nutrition before it was submitted for publication. I also wrote the responses to the comments from the reviewers and revised them based on suggestions from the co-authors.

5.1 Abstract

The prevalence of cardiometabolic diseases has increased in Latin American and the Caribbean populations (LACP). To identify gene-lifestyle interactions that modify the risk of cardiometabolic diseases in LACP, a systematic search using 11 search engines was conducted up to May 2022. Eligible studies were observational and interventional studies in either English, Spanish, or Portuguese. A total of 26,171 publications were screened for title and abstract; of these, 101 potential studies were evaluated for eligibility, and 74 articles were included in this study following full-text screening and risk of bias assessment. The Appraisal tool for Cross-Sectional Studies (AXIS) and the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) assessment tool were used to assess the methodological quality and risk of bias of the included studies. We identified 122 significant interactions between genetic and lifestyle factors on cardiometabolic traits and the vast majority of studies come from Brazil (29), Mexico (15) and Costa Rica (12) with *FTO*, *APOE*, and *TCF7L2* being the most studied genes. The results of the gene-lifestyle interactions suggest effects which are population-, gender-, and ethnic-specific. Most of the gene-lifestyle interactions were conducted once, necessitating replication to reinforce these results. The findings of this review indicate that 27 out of 33 LACP have not conducted gene-lifestyle interaction studies and only five studies have been undertaken in low-socioeconomic settings. Most of the studies were cross-sectional, indicating a need for longitudinal/prospective studies. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and the built environment. The protocol has been registered on PROSPERO, number CRD42022308488.

5.2 Introduction

Cardiometabolic diseases such as hypertension and type 2 diabetes (T2D) are accountable for most non-communicable disease (NCD) deaths and impose an economic burden on low- and middle-income countries [396]. In Latin American and the Caribbean populations (LACP), the prevalence of hypertension, T2D and obesity is 47, 22, and above 20%, respectively [397, 398]. The aetiology of cardiometabolic diseases is multifactorial where studies have demonstrated an interaction between the environment, genetic, behavioural, physiological, and socioeconomic factors [18, 170, 171, 281, 399, 400]. These intertwined mechanisms interact, modifying the risk of developing cardiometabolic diseases. Genetic variations or single nucleotide polymorphisms (SNPs) may modify the susceptibility to cardiometabolic diseases conditioned by the exposure to lifestyle factors [18, 170]. Genome-wide association studies have identified several genetic loci associated with cardiometabolic traits but most of these studies have been performed in Caucasian populations [95, 197, 198, 203, 339, 401]. Similarly, majority of nutrigenetic studies have been performed in Western countries and the findings might not be applicable to low-income countries due to variations in allele frequencies, dietary pattern and environmental factors [18, 130].

Factors such as changes in patterns of food consumption, the process of urbanization, increased health and socioeconomic disparities, underfinanced healthcare systems, lower levels of income and productivity, and the rise in sedentary lifestyle have led to an increase in NCDs [402-406]. Moreover, studies have shown that metabolic responses to lifestyle factors such as diet and physical activity vary between ethnicities due to genetic heterogeneity [18, 105, 128, 170], and hence we sought to determine which lifestyle factors are interacting with genetic variants in different LACP with regard to cardiometabolic disease traits. The discovery of gene-lifestyle interactions in LACP will help to identify population subgroups that will respond to lifestyle interventions.

The influence of gene-lifestyle interactions on obesity, T2D and cardiovascular diseases (CVDs) has been broadly studied, and there is evidence that the genetic risk of cardiometabolic traits can be modified [18, 170, 407-410]. However, to our knowledge, no previous systematic reviews have been conducted regarding the interactions of genetic and lifestyle factors on cardiometabolic disease traits in LACP. Thus, the objective of this systematic review was to identify studies examining the interactions between genetic variants and lifestyle factors such as diet, nutrient intake, nutritional status, physical activity,

socioeconomic factors, and the built environment on obesity, cardiovascular diseases, and T2D-related traits in LACP.

5.3 Methods

5.3.1 Inclusion and exclusion criteria

Eligible for inclusion were articles that explored the interaction between genetic variations and lifestyle factors on cardiometabolic disease traits in LACP. All cardiometabolic diseases and traits were considered including CVDs, cerebrovascular diseases such as stroke, blood lipid levels, obesity-related traits such as body mass index (BMI) and T2D-related traits such as fasting glucose. The eligible articles included observational and dietary intervention studies and were in either English, Spanish, or Portuguese. Articles that did not explore gene-lifestyle interactions or were not based on LACP were excluded.

5.3.2 Information sources and search strategy

A literature search was conducted in MEDLINE (via PubMed and EBSCO Host), Web of Science, ScienceDirect, SciELO, SCOPUS, Taylor & Francis Online, Cochrane library, LILACS (Latin American and Caribbean Health Sciences Literature), IBECS, Google Scholar, and ERIC (Education Resources Information Center via EBSCO Host) search engines until the 25th of May 2022. To reach literature saturation, the researchers conducted independent search strings (**Supplementary Section 1, Table S5.1**), and the included publications were searched through to identify potential articles in reference lists. We followed the Peer Review of Electronic Search Strategies (PRESS) guideline [411] and the literature search was limited to human participants and had no dates of publication restrictions. The protocol was registered on PROSPERO, number CRD42022308488.

5.3.3 Study selection, synthesis methods, effect measures, and data collection process

Duplicate articles were removed using Rayyan software [412], titles and abstracts were blindly screened to assess against the pre-established inclusion criteria, followed by full-text screening and discussion until consensus between E.F.V. and R.W. All the data required to assess the eligibility of the studies was available, hence study investigators were not contacted to obtain or confirm the data. The reviewers ensured consistency across the data that needed to be extracted, and a narrative synthesis was conducted to collate the data, including populations, lifestyle factors, study designs, genetic variations, cardiometabolic

disease traits, and *P*-values for gene-lifestyle interactions on obesity, diabetes and CVD traits. *P*-values for gene-lifestyle interactions were used as indicators of the relationship between the exposure (genetic and lifestyle factors) and the outcome (cardiometabolic traits). *P*-values<0.05 were considered statistically significant. $P_{interaction}$ refers to the *P*-value for the interaction between the genetic variant and dietary/lifestyle factors on cardiometabolic traits. To synthesize the findings, we categorised the outcomes into four categories: obesity, diabetes, CVD, and overall cardiometabolic risk. We then coded the exposures considering major themes; proteins, carbohydrates, fats, and fibre as well as plasma fatty acids, polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), breastfeeding, smoking, alcohol, coffee, and lifestyle (if the exposure was multiple, including factors embracing diet, physical activity, smoking, and/or socioeconomic status, education), macronutrients (when the exposures included at least proteins, carbohydrates, fats and fibre), and micronutrients (when the exposure referred to minerals or vitamins). The final graphical representation of the interaction between the genetic variations, and the coded lifestyle factors on the clustered outcomes was a heat map, where the intensity of the colour corresponds to the *P*-values of the gene-lifestyle interactions (**Figures 5.1–5.4**). All heat maps were produced using the ggplot2 package [413] in R software with RStudio environment [414]. A meta-analysis could not be conducted due to the wide range of dietary factors, genetic variants and cardiometabolic traits investigated by the included studies, in addition to heterogeneity in the methods used.

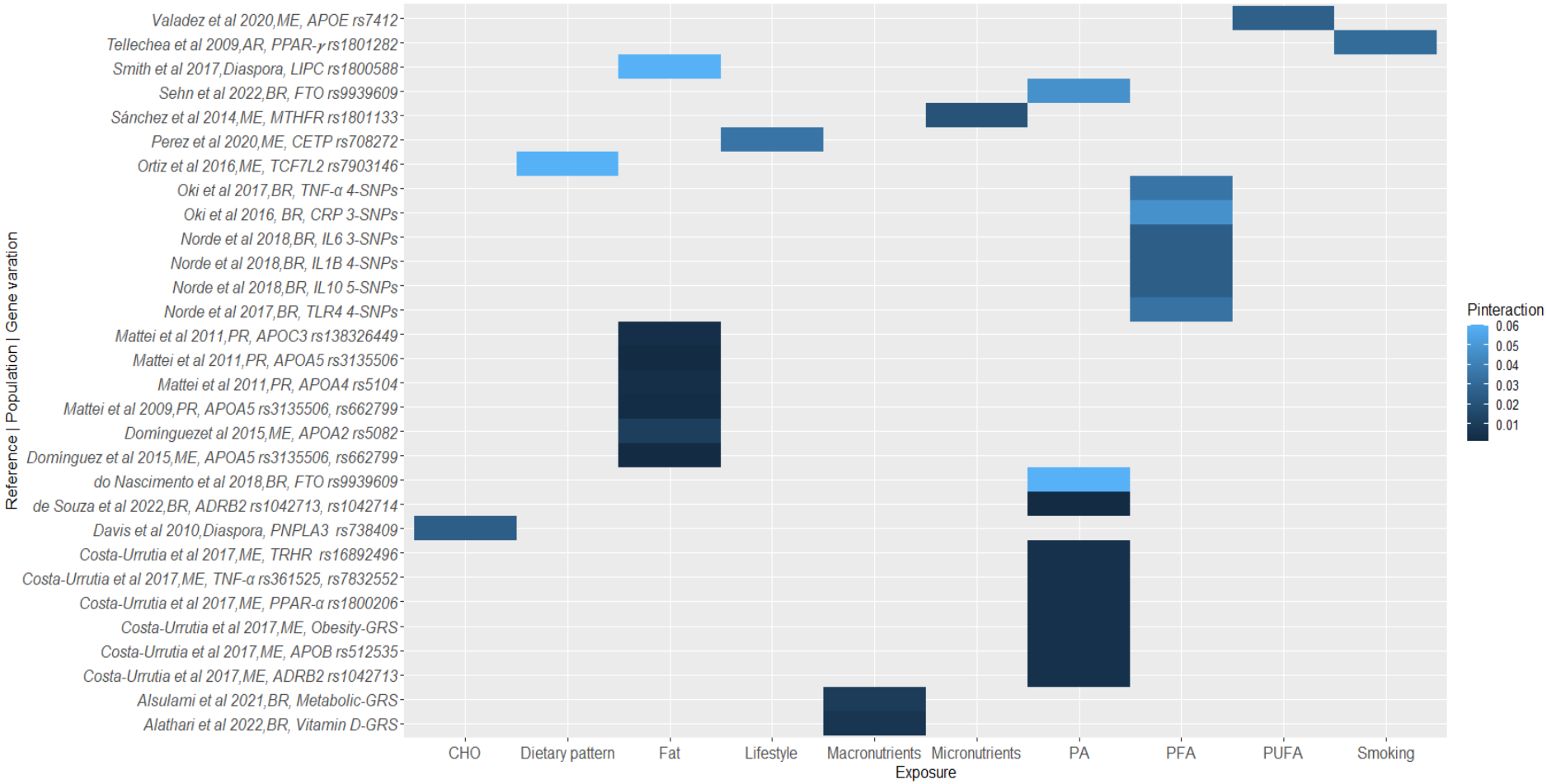

Figure 5.1 A heat map showing the findings for gene-lifestyle interactions on overall cardiometabolic disease risk

Alsulami et al. [327], Metabolic-GRS = *TCF7L2 (rs12255372, rs7903146); MC4R (rs17782313, rs2229616); PPAR-γ (rs1801282); FTO (rs8050136); CDKN2A/2B (rs10811661); KCNQ1 (rs2237892); CAPN10 (rs5030952);* Alathari et al. [319], Vitamin D-GRS = *VDR (rs2228570, rs7975232), DHCR7 (rs12785878), CYP2R1(rs12794714), CYP24A1(rs6013897), GC (rs2282679), FTO (rs8050136, rs10163409), TCF7L2 (rs12255372, rs7903146),*

MC4R (rs17782313), KCNQ1 (rs2237895, rs2237892), CDKN2A (rs10811661), PPAR-γ (rs1801282), CAPN10 (rs5030952); Costa-Urrutia et al. [415], Obesity-GRS = *ABCA1 (rs2230806, rs9282541); ADIPOQ (rs2241766); ADRB2 (rs1042713); AGT (rs699); APOA4 (rs675); APOB (rs512535); APOE (rs405509); CAPN10 (rs2975760, rs2975762, rs3792267); FTO (rs1121980, rs9939609); HNF4 (rs745975); LIPC (rs1800588); LPL (rs320); PPAR-α (rs1800206); PPAR-γ (rs1801282); SCARB1 (rs1084674); TCF7L2 (rs7903146); TNF (rs361525); TRHR (rs1689249, rs7832552*); Norde et al. [416], 5-SNPs = *IL10 rs1554286, rs1800871, rs1800872, rs1800890, rs3024490*; Oki et al. [417], 4-SNPs = *TNF-α rs1799724, rs1800629, rs361525, rs1799964;* Norde et al. [418], 4-SNPs = *TLR4 rs11536889, rs4986790, rs4986791, rs5030728;* Oki et al. [419], 3-SNPs = *CRP rs1205, rs1417938, rs2808630;* Norde et al. [416], 4-SNPs = *IL1B rs16944, rs1143623, rs1143627, rs1143643; 3-SNPs = rs1800795, rs1800796, rs1800797;* BR, Brazilian; ME, Mexican; PR, Puerto Rican; AR, Argentinian.

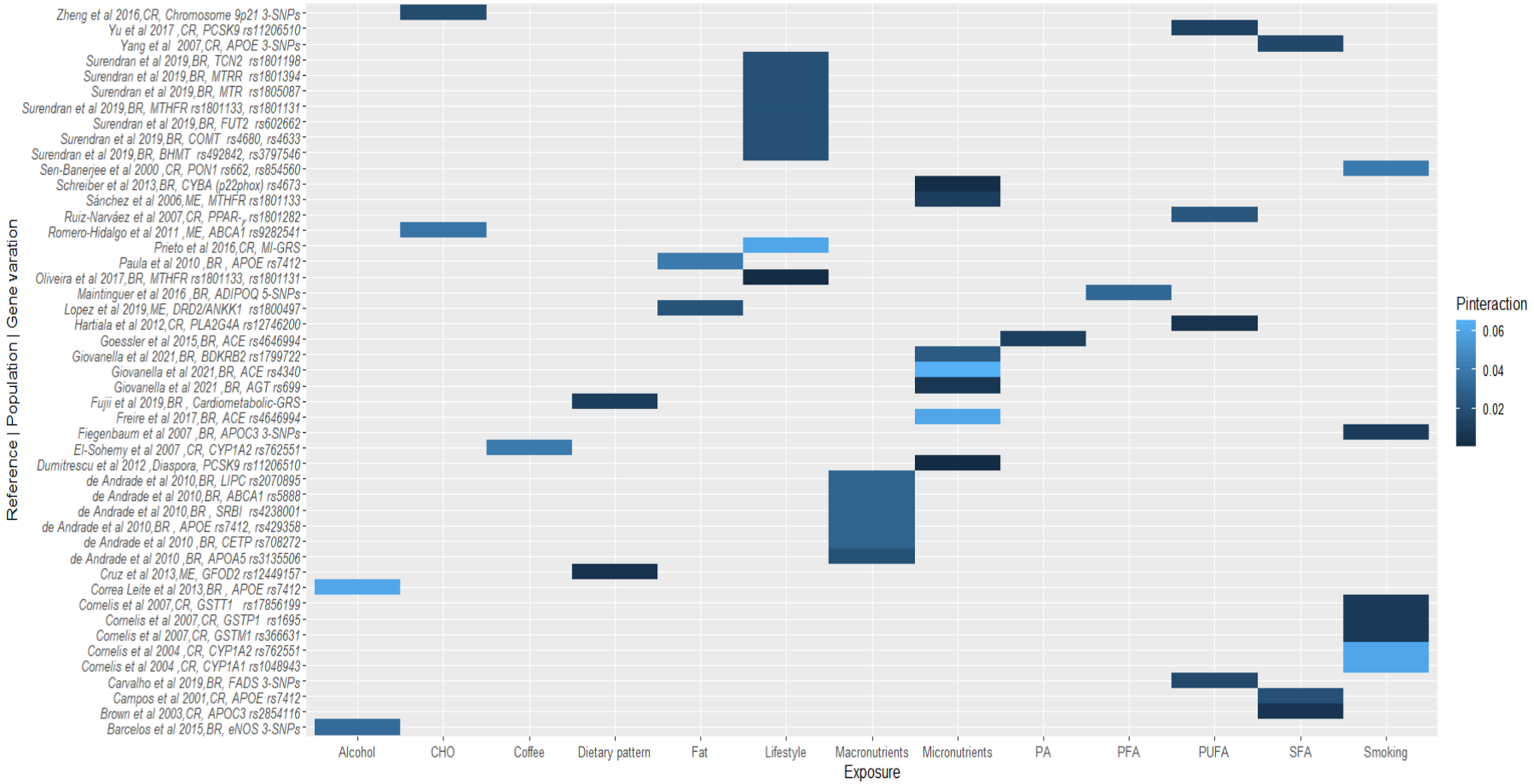

Figure 5.2 A heat map showing the findings for gene-lifestyle interactions on cardiovascular disease traits

Sotos-Prieto et al. [420], MI-GRS = *CDKN2A/2B (rs4977574, rs10757274, rs2383206, rs1333049); CELSR2-PSRC1-SORT1 (rs646776, rs599839); CXCL12(rs501120, rs1746048); HNF1A, C12orf43 (rs2259816); MRAS (rs9818870); SLC22A3 (rs2048327); LPAL2 (rs3127599); LPA (rs7767084, rs10755578);* Fujii et al. [139], Cardiometabolic-GRS = *APOA5 (rs662799); APOB (rs693, rs1367117); LDLR (rs688, rs5925); LIPC (rs2070895, rs1800588);* Yang et al. [421], 3-SNPs = *APOE rs7412, rs449647, rs429358*; Fiegenbaum et al. [422], 3-SNPs = APOC3 rs2854116, rs2854117,

rs5128; Maintinguer Norde et al. [423], 5-SNPs = ADIPOQ rs2241766, rs16861209, rs17300539, rs266729, rs1501299; Carvalho et al. [424], 3-SNPs = FADS rs174575, rs174561, rs3834458; Barcelos et al. [425], 3-SNPs = eNOS rs2070744, rs1799983, rs61722009; Zheng et al. [426], 3-SNPs = Chromosome 9p21 rs4977574, rs2383206, rs1333049. BR, Brazilian; CR, Costa Rican.

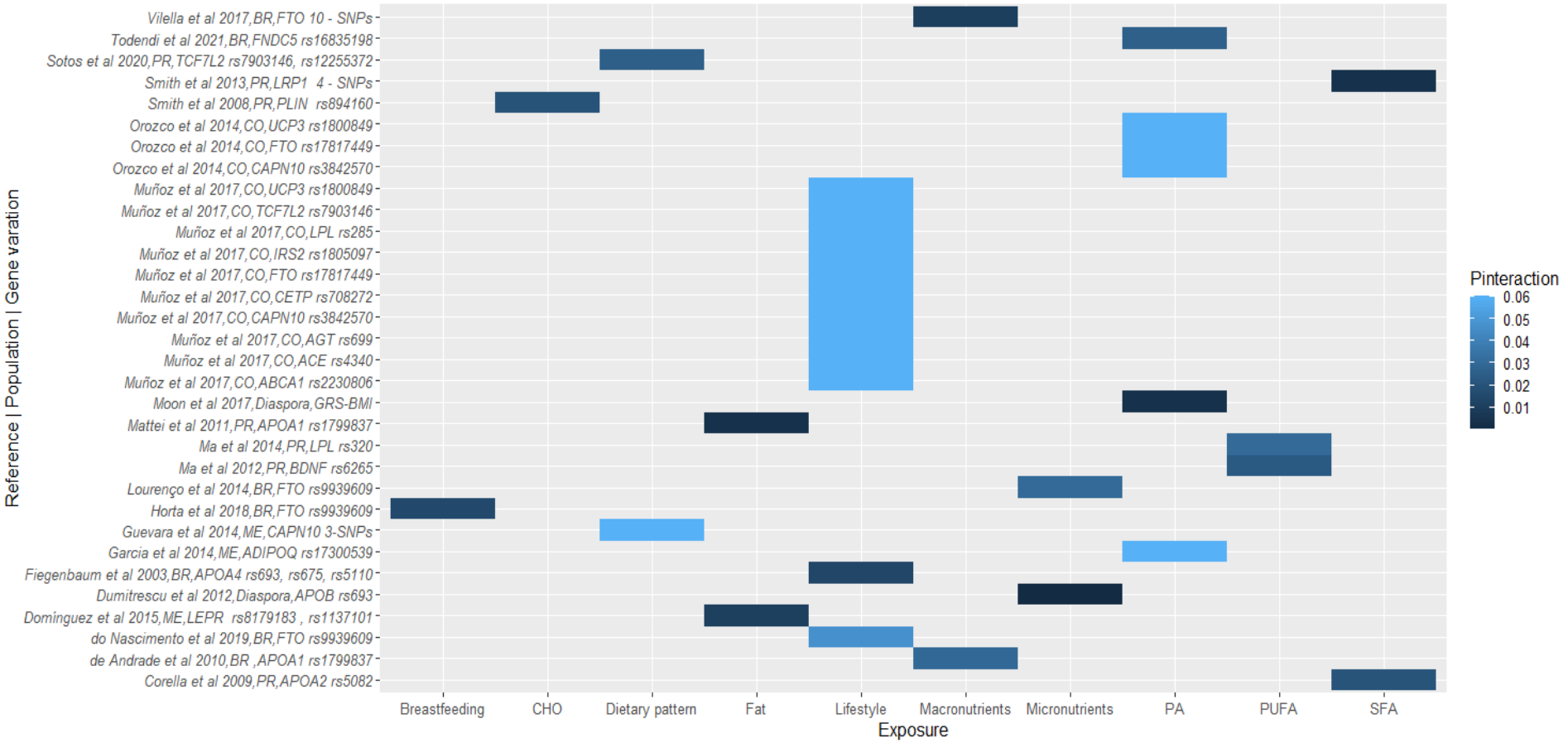

Figure 5.3 A heat map showing the findings for gene-lifestyle interactions on obesity traits

Vilella et al. [427], 10-SNPs = *FTO rs79149291, rs62048379, rs115530394, rs75066479, rs2003583, rs115662052, rs114019148, rs62034079, rs1123817, rs16952663;* Smith et al. [428], 4-SNPs = *LRP1 rs1799986, rs1799986, rs1800191, rs715948*; Guevara-Cruz et al. [429], 3-SNPs = *CAPN10 rs5030952, rs3792267, rs2975762*. BR, Brazilian; PR, Puerto Rican; ME, Mexican; CO, Colombian.

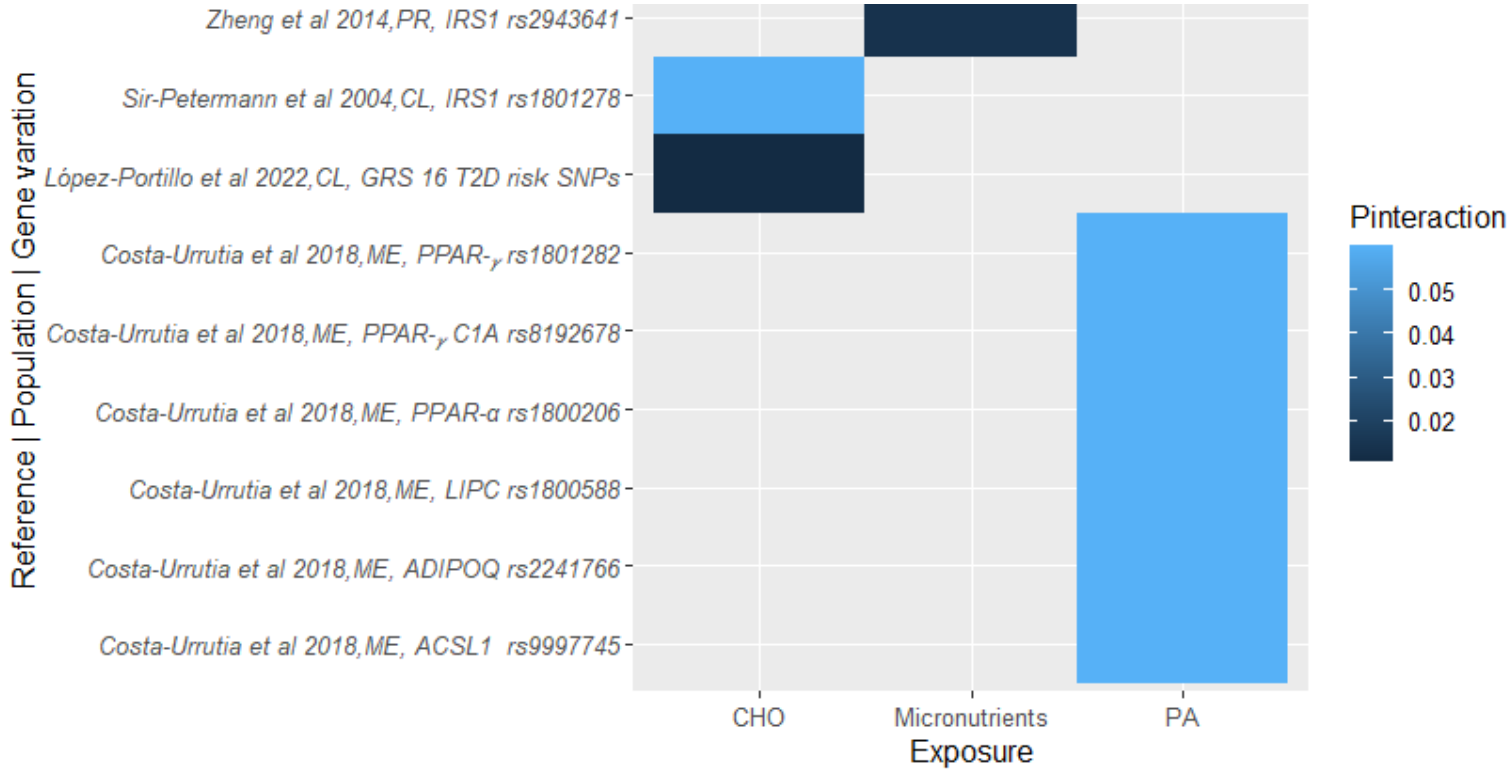

Figure 5.4 A heat map showing the findings for gene-lifestyle interactions on diabetes traits

López-Portillo et al. [430], GRS-16 Type 2 Diabetes (T2D) risk SNPs = *MTNR1B (rs10830963); TCF7L2 (rs7903146); CDKAL1 (rs7756992); ADCY5 (rs11717195); ANK1 (rs516946); BCAR1 (rs7202877); CDC123 (rs11257655); DUSP9 (rs5945326); GRB14 (rs3923113); RASGRP1 (rs7403531); TLE4 (rs17791513); TLE1 (rs2796441); ZBED3 (rs6878122)*.

5.3.4 Data items

Data was extracted in **Table 5.1** and the main outcomes were diabetes, obesity, CVD, and their related traits including lipid levels, blood pressure and anthropometric measurements.

Table 5.1 Summary table of gene-lifestyle interactions and study characteristics

Gene & SNP	Population & Sample Size	Study Design	Dietary/Lifestyle Factor	Outcome	$P_{interaction}$*	Reference
FTO						
rs9939609	Brazilian *n*=1088	LS	Plasma vitamin D	BMI	0.02 – 0.04	Lourenço et al. 2014 [431]
rs9939609	Brazilian *n*=1215	C-S	Screen time	Cardiometabolic risk score	0.047	Sehn et al. 2022 [432]
rs9939609	Brazilian *n*=432	C-C	Physical activity intervention	TC, HDL, LDL, TG, glucose, insulin, HOMA-IR, QUICKI	NS	do Nascimento et al. 2018 [433]
rs9939609	Brazilian *n*=3701	P-C	Breastfeeding	BMI, overweight, fat mass, lean mass, WC, visceral and subcutaneous abdominal fat thickness	0.01 – 0.02	Horta et al. 2018 [434]
rs9939609	Brazilian *n*=434	C-C	hypocaloric diet, physical exercise program	BMI, WC, AC	0.047	do Nascimento et al. 2019 [435]
rs17817449	Colombian *n*=212/212	C-C	Physical activity	BMI	NS	Orozco et al. 2014 [436]
rs17817449	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
rs79149291, rs62048379, rs115530394, rs75066479, rs2003583, rs115662052, rs114019148, rs62034079, rs1123817, rs16952663	Brazilian *n*=1191	C-S	Carbohydrate, protein, total fat, MUFA, PUFA:SFA intake	Overweight/obesity	0.01	Vilella et al. 2017 [427]

Table 5.1 Continued

APOE						
rs7412, rs429358	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
rs7412	Brazilian *n*=252	C-S	Total fat, PUFA:SFA	LDL, TG, VLDL	<0.05	Paula et al. 2010 [439]
rs7412	Brazilian *n*=851	P-C	Alcohol intake	SBP, DBP	NS	Correa Leite et al. 2013 [440]
rs7412	Mexican *n*=224	C-S	MUFA intake, n-3:n-6	TC, Non-HDL, LDL, HbA1c	0.016 – 0.035	Torres-Valadez et al. 2020 [441]
rs7412	Costa Rican *n*=420	C-S	SFA	TG, TC, VLDL, LDL, HDL, Apo A1, Apo B, LDL particle size	0.02 – 0.03	Campos et al. 2001 [442]
rs7412, , rs429358, rs449647	Costa Rican *n*=1927/1927	C-C	SFA	TC, HDL, LDL, TG, MI	0.0157	Yang et al. 2007 [421]
APOA5						
rs3135506	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
rs3135506, rs662799	Mexican *n*=100/100	C-C	SFA, total fat	TC, TG, LDL, HDL, obesity	0.001 – 0.02	Domínguez-Reyes et al. 2015 [443]
rs3135506, rs662799	Puerto Rican *n*=802	LS	Total fat	WC, serum glucose, SBP, DBP, HDL, IDL, TC, VLDL	0.002 – 0.032	Mattei et al. 2009 [444]

Table 5.1 Continued

APOA5						
rs3135506	Puerto Rican *n*=821	LS	Total fat	WC, SBP, DBP	0.001 – 0.005	Mattei et al 2011 [445]
MTHFR						
rs1801133, rs1801131	Brazilian *n*=3803	C-S	Physical activity, alcohol intake, and blood folate	Homocysteine	<0.001-0.002	Oliveira et al. 2017 [446]
rs1801133, rs1801131	Brazilian *n*=113	C-S	Fat, protein, carbohydrate intake, physical activity	Vitamin B12, homocysteine, folic acid, HDL, LDL, TG, oxidized LDL	0.005 – 0.034	Surendran et al. 2019 [309]
rs1801133	Mexican *n*=996 (women); 231 (new-borns)	P-C	Folate and Vitamin B12	Weight, length and BMI of new-born	0.02	Torres-Sánchez et al. 2014 [447]
rs1801133	Mexican *n*=130	C-S	Vitamin B12, alcohol intake	Plasma Folate, total homocysteine	0.01	Torres-Sánchez et al. 2006 [448]
ACE						
rs4340	Brazilian *n*=335	C-S	Sodium, potassium, calcium, magnesium	SBP, DBP	0.004 – 0.009	Giovanella et al. 2021 [449]
rs4340	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
rs4646994	Brazilian *n*=234	C-C	Sodium	Hypertension	NS	Freire et al. 2017 [450]

Table 5.1 Continued

ACE						
rs4646994	Brazilian *n*=34	RCT	Physical activity	SBP, DBP	0.02 –0.002	Goessler et al. 2015 [451]
TCF7L2						
rs7903146	Mexican *n*=137	P-LS	Two diets: Nopal tortilla and whole grain bread	Weight, BMI, WC, HC, WHR, glucose, HbA1c, TG, TC, HDL, LDL, insulin, HOMA-B, HOMA-IR, GLP-1	NS	López-Ortiz et al. 2016 [452]
rs7903146	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
rs7903146, rs12255372, rs7903146, rs12255372	Puerto Rican *n*=1120	C-S	Mediterranean diet score	BMI, WC, weight	0.014 – 0.036	Sotos-Prieto et al. 2020 [453]
ABCA1						
rs5888	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
rs9282541	Mexican *n*=3591	C-S	Carbohydrate	HDL	0.037	Romero-Hidalgo et al. 2011 [454]
rs2230806	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]

Table 5.1 Continued

LIPC						
rs2070895	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
rs1800588	Mexican *n*=167/398	C-C	Maximal oxygen consumption (VO2 max), muscle endurance (ME)	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. 2018 [455]
rs1800588	Dominican/Puerto Rican, other Caribbean Hispanics *n*=41	RCT	High fat diet	HDL, LDL, TC, TG, glucose	NS	Smith et al. 2017 [456]
APOC3						
rs2854116, rs2854117, rs5128	Brazilian *n*=673	C-S	Smoking	TG	0.009	Fiegenbaum et al. 2007 [422]
rs2854116, T-625del	Costa Rican *n*=336	C-S	SFA	TG, TC, LDL, HDL, Apo B, LDL diameter	0.0004 –0.01	Brown et al. 2003 [457]
rs138326449	Puerto Rican *n*=821	LS	Total fat	WC, SBP, DBP	0.001 – 0.005	Mattei et al 2011 [445]
CETP						
rs708272	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
rs708272	Mexican *n*=215	C-S	Sucrose intake, physical activity	TC, LDL,TG, HDL, TG:HDL, BMI, WC	0.033 – 0.037	Campos-Perez et al 2020 [98]

Table 5.1 Continued

CETP						
rs708272	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
ADIPOQ						
rs2241766, rs16861209, rs17300539, rs266729, rs1501299	Brazilian *n*=262	C-S	Plasma fatty acids (14:0, 16:0, 16:1 n-7, 18:0, 18:1, 18:2 n-6, 18:3 n-3, 20:3 n-6, AA, EPA, DPA, DHA, SFA, MUFA, n-6, n-3, PUFA, n-3 HUFA, SCD-16, SCD-18, D5D, D6D)	Systemic Inflammation	0.019 – 0.044	Maintinguer Norde et al. 2016 [423]
rs17300539	Mexican *n*=394	C-S	MUFA, physical activity	adiponectin level	NS	Garcia-Garcia et al. 2014 [458]
rs2241766	Mexican *n*=167/398	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. 2018 [455]
PPAR-γ						
rs1801282	Mexican *n*=167/398	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. 2018 [455]
rs1801282	Costa Rican *n*=1805/1805	C-C	PUFA intake	MI, PUFA in adipose tissue	0.016 –0.03	Ruiz-Narváez et al. 2007 [459]

Table 5.1 Continued

PPAR-γ						
rs1801282	Argentina *n*=572	C-S	Smoking status	MetS, fasting plasma glucose, SBP, DBP, WC, HDL, TG, fasting insulin, loginsulin, HOMA-IR, LogHOMA-IR, QUICKI	0.031	Tellechea et al. 2009 [460]
PPAR-γ C1A						
rs8192678	Mexican *n*=167/398	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. 2018 [455]
PPAR-α						
rs1800206	Mexican *n*=167/398	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. 2018 [455]
rs1800206	Mexican *n*=608	C-C	VO2 max, ME	BMI, WC, fat mass, pre-DM	0.001 – 0.007	Costa-Urrutia et al. 2017 [415]
APOA4						
rs693, rs675, rs5110	Brazilian *n*=391	C-S	Smoking, alcohol intake, physical activity	BMI, WC	0.007 – 0.02	Fiegenbaum et al. 2003 [461]
rs5104	Puerto Rican *n*=821	LS	Total fat	WC, SBP, DBP	0.001 – 0.005	Mattei et al 2011 [445]

Table 5.1 Continued

IRS1						
rs2943641	Puerto Rican *n*=1144	LS	25(OH)D	HOMA-IR	0.004 – 0.023	Zheng et al. 2014 [462]
rs1801278	Chile *n*=243	NRCT	3-day unrestricted diet containing 300 g/d of carbohydrate, an overnight fast of 10h and 75 g glucose	Fasting glucose, fasting insulin, fasting HOMA-IR, insulinogenic index, insulin sensitivity index composite	NS	Sir-Petermann et al. 2004 [463]
IRS2						
rs1805097	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
PON1						
rs662	Mexican *n*=206	C-S	Urinary 1-hydroxypyrene	Serum asymmetric dimethylarginine (ADMA)	0.02	Ochoa-Martínez et al. 2017 [464]
rs662	Mexican *n*=185	C-S	Urinary arsenic levels	ADMA, fatty acid-binding protein 4, micro-RNAs	<0.001 – <0.010	Ochoa-Martínez et al. 2021 [465]
rs662, rs854560	Costa Rican *n*=492/518	C-C	Smoking status	MI	0.04	Sen-Banerjee et al. 2000 [466]

Table 5.1 Continued

AGT						
rs699	Brazilian *n*=335	C-S	Sodium, potassium, calcium, magnesium	SBP, DBP	0.004 – 0.009	Giovanella et al. 2021 [449]
rs699	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
ADRB2						
rs1042713, rs1042714	Brazilian *n*=197	P-C	Physical exercise intervention	Body fat, AC, BMI, DBP, SBP, TC, HDL, LDL, TG, glucose, insulin, HOMA-IR, QUICK, TG-glucose index	0.001	de Souza et al. 2022 [467]
rs1042713	Mexican *n*=608	C-C	VO2 max, ME	BMI, WC, fat mass, pre-DM	0.001 – 0.007	Costa-Urrutia et al. 2017 [415]
TNF-α						
rs1799724, rs1800629, rs361525, rs1799964	Brazilian *n*=281	C-S	Plasma fatty acids (C14:0, C16:0, C18:0, C16:1, C18:1, n-6, C18:2, C20:3, C20:4, n-3, C18:3, C20:5, C22:5, C22:6, n-3 HUFA, SCD-16, SCD-18, D5D, D6D, n-6:n-3, SFA, MUFA, PUFA)	Systemic inflammation	0.026 –0.044	Oki et al. 2017 [417]

Table 5.1 Continued

TNF-α						
rs361525, rs7832552	Mexican *n*=608	C-C	VO2 max, ME	BMI, WC, fat mass, pre-diabetes	0.001 – 0.007	Costa-Urrutia et al. 2017 [415]
CAPN10						
rs5030952, rs3792267, rs2975762	Mexican *n*=31	P-C	Low SFA diet, soy protein, soluble fiber	TC, TG, HDL, LDL	NS	Guevara-Cruz et al. 2014 [429]
rs3842570	Colombian *n*=212/212	C-C	Physical activity	BMI	NS	Orozco et al. 2014 [436]
rs3842570	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
PCSK9						
rs11206510	Costa Rican *n*=1932/2055	C-C	LC n-3 PUFA, EPA, DPA, DHA	MI	0.012	Yu et al. 2017 [468]
rs11206510	Mexican American *n*=1734	C-S	Serum Vitamin A	LDL	7.65×10^{-5}	Dumitrescu et al. 2012 [469]
CYP1A2						
rs762551	Costa Rican *n*=2014/2014	C-C	Coffee intake	MI	0.04	El-Sohemy et al. 2007 [470]
rs762551	Costa Rican *n*=873/932	C-C	Smoking	MI	NS	Cornelis et al. 2004 [471]
CYP1A1						
rs1048943	Costa Rican *n*=873/932	C-C	Smoking	MI	NS	Cornelis et al. 2004 [471]

Table 5.1 Continued

APOA2						
rs5082	Mexican *n*=100/100	C-C	SFA, total fat	TC, TG, LDL, HDL, obesity	0.001 – 0.02	Domínguez-Reyes et al. 2015 [443]
rs5082	Puerto Rican *n*=930	C-S	SFA	BMI	0.02	Corella et al. 2009 [137]
APOA1						
rs1799837	Puerto Rican *n*=821	LS	Total fat	WC, SBP, DBP	0.001 – 0.005	Mattei et al 2011 [445]
rs1799837	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
APOB						
rs512535	Mexican *n*=608	C-C	VO2 max, ME	BMI, WC, fat mass, pre-DM	0.001 – 0.007	Costa-Urrutia et al. 2017 [415]
rs693	Mexican American *n*=1734	C-S	Serum Vitamin E	LDL	8.94×10^{-7}	Dumitrescu et al. 2012 [469]
LPL						
rs320	Puerto Rican *n*=1171	LS	Low PUFA, n-3 PUFA, n-6 PUFA intake	BMI, WC	0.02 – 0.04	Ma et al. 2014 [472]
rs285	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]

Table 5.1 Continued

UCP3						
rs1800849	Colombian *n*=212/212	C-C	Physical activity	BMI	NS	Orozco et al. 2014 [436]
rs1800849	Colombian *n*=1081	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. 2017 [437]
TLR4 *rs11536889, rs4986790, rs4986791, rs5030728*	Brazilian *n*=262	C-S	Systemic Inflammation	0.034	Norde et al. 2017 [418]	Systemic Inflammation
BDKRB2 *rs1799722*	Brazilian *n*=335	C-S	Sodium, potassium, calcium, magnesium	SBP, DBP	0.004 – 0.009	Giovanella et al. 2021 [449]
FADS *rs174575, rs174561, rs3834458*	Brazilian *n*=250	C-S	α-linolenic acid, linoleic:α-linolenic acid ratio.	Plasma concentration of PUFA	0.004 – 0.028	Carvalho et al. 2019 [424]
CYBA (p22phox) *rs4673*	Brazilian *n*=1298	C-S	Urinary sodium	SBP, DBP, hypertension	<0.001 – 0.004	Schreiber et al. 2013 [473]
eNOS *rs2070744, rs1799983, rs61722009*	Brazilian *n*=113	C-S	Alcohol intake	SBP, DBP, nitrite levels in plasma	0.033	Barcelos et al. 2015 [425]
FNDC5 *rs16835198*	Brazilian *n*=1701	C-S	Cardiorespiratory fitness, lower limb strength	WC, BMI	0.007 – 0.044	Todendi et al. 2021 [474]
LEPR rs8179183 , rs1137101	Mexican *n*=100/100	C-C	SFA, total fat intake	TC, TG, LDL, HDL, obesity	0.001 – 0.02	Domínguez-Reyes et al. 2015 [443]

Table 5.1 Continued

ACSL1 rs9997745	Mexican *n*=167/398	C-C	VO2 max, ME	pre-diabetes	NS	Costa-Urrutia et al. 2018 [455]
TRHR rs16892496	Mexican *n*=608	C-C	VO2 max, ME	BMI, WC, fat mass, pre-diabetes	0.001 – 0.007	Costa-Urrutia et al. 2017 [415]
DRD2/ANKK1 rs1800497	Mexican *n*=175	C-S	Maltose, total fat, MUFA, dietary cholesterol	TG	0.001 –0.041	Ramos-Lopez et al. 2019 [475]
GFOD2 rs12449157	Mexican *n*=41	P-C	Low SFA diet, soy protein and soluble fiber	TC, LDL, HDL, TG	0.002 – 0.006	Guevara-Cruz et al. 2013 [476]
PLA2G4A *rs12746200*	Costa Rican *n*=1936/2035	C-C	n-6 PUFA intake	MI	0.005	Hartiala et al 2012 [477]
CRP *rs1205, rs1417938 , rs2808630*	Brazilian *n*=262	C-S	Plasma fatty acids (Myristic acid, Palmitic acid, Stearic acid, C16:1, C18:1, n-6, C18:2, C20:3, C20:4, n-3, C18:3, C20:5, C22:5, C22:6, n-3 HUFA, SFA, MUFA, PUFA, SCD-16, SCD-18, D5D, D6D, n-6/n-3)	Systemic Inflammation	0.047	Oki et al. 2016 [419]
GSTM1 *rs366631* ***GSTP1*** *rs1695* ***GSTT1*** *rs17856199*	Costa Rican *n*=2042/2042	C-C	Cruciferous vegetables, smoking	MI	0.008	Cornelis et al. 2007 [478]

Table 5.1 Continued

IL1B *rs16944, rs1143623, rs1143627, rs1143643* ***IL6*** *rs1800795, rs1800796, rs1800797* ***IL10*** *rs1554286, rs1800871, rs1800872, rs1800890, rs3024490*	Brazilian *n*=301	C-S	Plasma fatty acid (C14:0, C16:0, C16:1 n-9, C18:0, C18:1 n-9, C18:2 n-6, C18:3 n-3, AA, EPA, DHA, n-6, n-3); desaturates activity (SCD-16, SCD-18, D6D, D5D)	MetS	0.007 – 0.043	Norde et al. 2018 [416]
MTR *rs1805087* ***MTRR*** *rs1801394* ***TCN2*** *rs1801198* ***COMT*** *rs4680, rs4633* ***BHMT*** *rs492842, rs3797546* ***FUT2*** *rs602662*	Brazilian *n*=113	C-S	Fat, protein, carbohydrate intake, physical activity	Vitamin B12, homocysteine, folic acid, HDL, LDL, triglycerides, oxidized LDL	0.005 – 0.034	Surendran et al. 2019 [309]
GSTM1 *rs366631* ***GSTP1*** *rs1695* ***GSTT1*** *rs17856199*	Costa Rican *n*=2042/2042	C-C	Cruciferous vegetables, smoking	MI	0.008	Cornelis et al. 2007 [478]
LRP1 *rs1799986, rs1799986, rs1800191, rs715948*	Puerto Rican *n*=676	P-C	SFA, palmitic acid (C16:0), stearic acid (C18:0), butyric acid (C4:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0)	BMI, WC, HC	0.002 – 0.004	Smith et al. 2013 [428]
PLIN *rs894160*	Puerto Rican *n*=920	LS	Complex carbohydrate, total carbohydrate, simple sugars	WC, HC, BMI	0.004 – 0.035	Smith et al. 2008 [479]

Table 5.1 Continued

Chromosome 9p21 *rs4977574, rs4977574, rs2383206, rs1333049*	Costa Rican *n*=1560/1751	C-C	Sugar sweetened beverages, fruit juice	MI	0.005 –0.03	Zheng et al. 2016 [426]
BDNF *rs6265*	Puerto Rican *n*=1340	LS	PUFA, n-3 : n-6, food intake	BMI, WC, HC	0.002 – 0.043	Ma et al. 2012 [480]
PNPLA3 *rs738409*	Hispanic ancestry *n*=153	C-S	Carbohydrate, sugar	Hepatic fat	0.01 – 0.04	Davis et al. 2010 [481]
SRBI *rs4238001*	Brazilian *n*=567	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fibre	LDL, TG, TC	0.018 – 0.04	de Andrade et al. 2010 [438]
GRS*:TCF7L2 (rs12255372, rs7903146); MC4R (rs17782313, rs2229616); PPAR-γ (rs1801282); FTO (rs8050136); CDKN2A/2B (rs10811661); KCNQ1 (rs2237892); CAPN10 (rs5030952)*	Brazilian *n*=200	C-S	Total fat, SFA, PUFA, MUFA, carbohydrate, protein	HbA1c, HOMA-IR, HOMA-B, fasting glucose, fasting insulin, insulin:glucose, body fat mass, BMI, WC	0.002 –0.017	Alsulami et al. 2021 [327]
GRS: *VDR (rs2228570, rs7975232), DHCR7 (rs12785878), CYP2R1(rs12794714), CYP24A1(rs6013897), GC (rs2282679), FTO (rs8050136, rs10163409), TCF7L2 (rs12255372, rs7903146), MC4R (rs17782313), KCNQ1 (rs2237895, rs2237892), CDKN2A (rs10811661), PPAR-γ (rs1801282), CAPN10 (rs5030952)*	Brazilian *n*=187	C-S	Carbohydrate, protein, fat and fibre	BMI, WC, body fat, glucose, HbA1c, fasting insulin	0.006	Alathari et al. 2022 [319]

Table 5.1 Continued

***GRS**: ABCA1 (rs2230806, rs9282541); ADIPOQ (rs2241766); ADRB2 (rs1042713); AGT (rs699); APOA4 (rs675); APOB (rs512535); APOE (rs405509); CAPN10 (rs2975760, rs2975762 , rs3792267); FTO (rs1121980, rs9939609); HNF4 (rs745975); LIPC (rs1800588); LPL (rs320); PPAR-α (rs1800206); PPAR-γ (rs1801282); SCARB1 (rs1084674); TCF7L2 (rs7903146); TNF (rs361525); TRHR (rs1689249, rs7832552)*	Mexican *n*=608	C-C	VO2 max, ME	BMI, WC, fat mass, pre-diabetes	0.001 – 0.007	Costa-Urrutia et al. 2017 [415]
***GRS:** CDKN2A/2B (rs4977574, rs10757274, rs2383206, rs1333049); CELSR2-PSRC1-SORT1 (rs646776, rs599839); CXCL12(rs501120, rs1746048); HNF1A, C12orf43 (rs2259816); MRAS (rs9818870); SLC22A3 (rs2048327); LPAL2 (rs3127599); LPA (rs7767084, rs10755578)*	Costa Rican *n*=1534/1534	C-C	Lifestyle cardiovascular risk score (unhealthy diet, physical inactivity, smoking, elevated waist:hip ratio, high alcohol intake, low socioeconomic status.)	MI	NS	Sotos-Prieto et al. 2016 [420]
GRS based on 97 BMI associated SNPs	Puerto Rican, Mexicans, Dominicans, Cuban, Central American, South American *n*=9645	P-C	Total physical activity, physical activity at a moderate to vigorous intensity, sedentary behaviour	BMI, fat mass, fat mass index, fat percentage, WC Fat-free mass	0.001 –0.005	Moon et al 2017 [482]

Table 5.1 Continued

GRS: *MTNR1B* (*rs10830963*); *TCF7L2* (*rs7903146*); *CDKAL1* (*rs7756992*); *ADCY5* (*rs11717195*); *ANK1* (*rs516946*); *BCAR1* (*rs7202877*); *CDC123* (*rs11257655*); *DUSP9 (rs5945326*); *GRB14* (*rs3923113*); *RASGRP1* (*rs7403531*); *TLE4* (*rs17791513*); *TLE1* (*rs2796441*); *ZBED3* (*rs6878122*)	Chile *n*=2828	P-C	Sugar sweetened beverages intake	Fasting glucose	0.001 –0.02	López-Portillo et al. 2022 [430]
GRS: *APOA5 (rs662799); APOB (rs693, rs1367117); LDLR (rs688, rs5925); LIPC (rs2070895, rs1800588)*	Brazilian *n*=228	C-S	Brazilian Healthy Eating Index Revised	Dyslipidaemia	0.001 –0.019	Fujii et al. 2019 [139]

APOE – Apolipoprotein E; *APOA* – apolipoprotein A; *ApoB* – apolipoprotein B; *SRBI* – scavenger receptor class B member 1; *ABCA1* – ATP binding cassette subfamily A member 1; *CETP* – cholesteryl ester transfer protein; *APOC3* – Apolipoprotein C; *ADIPOQ* – adiponectin; *TLR4* – toll like receptor 4; *FTO* – alpha-ketoglutarate dependent dioxygenase; *CRP* – C-reactive protein; GRS – genetic risk score; *MTHFR* – methylenetetrahydrofolate reductase; *FADS* – fatty acid desaturase; *TNF* – tumour necrosis factor; *ADRB* – adrenoceptor beta; *ACE* – angiotensin I converting enzyme; *AGT* – angiotensinogen; *BDKRB* – bradykinin receptor; *eNOS* – endothelial nitric oxide synthase; *CYBA* – cytochrome B-245 alpha chain; *IL* – interleukin; *FNDC5* – fibronectin type III domain containing 5; *VDR* – vitamin D receptor; *DHCR7* – 7-Dehydrocholesterol Reductase; *CYP2R1* – cytochrome P450 family 2 subfamily R member 1; *CYP24A1* – cytochrome P450 family 24 subfamily A member 1; *GC* – group-specific component; *TCF7L2* – transcription factor 7 like 2; *MC4R* – melanocortin-4-receptor; *KCNQ1* – potassium voltage-gated channel subfamily Q member 1; *CDKN* – cyclin dependent kinase inhibitor; *PPAR* – peroxisome proliferator activated receptor; *CAPN* – Calpain; *MTR* – methionine synthase; *MTRR* – 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; *TCN2* – transcobalamin 2; *COMT* – catechol-O-methyltransferase; *BHMT* – betaine-homocysteine S-methyltransferase; *FUT2* – fucosyltransferase 2; *LEPR* – leptin receptor; *TRHR* – thyrotropin

releasing hormone receptor; *LIPC* – hepatic lipase; *ACSL* – acyl-CoA synthetase long chain family member 1; *GFOD2* – Glucose-Fructose Oxidoreductase Domain Containing 2; *PCSK9* – proprotein convertase subtilisin/kexin type 9; *PON1* – Paraoxonase 1; *CYP1A2* – cytochrome P450 family 1 subfamily A member 2; *PLA2G4A* – phospholipase A2 group IVA; *GSTM1* – glutathione S-transferase Mu 1; *GSTP1* – glutathione S-transferase Pi 1; *GSTT1* – glutathione S-transferase theta 1; *CYP1A1* – cytochrome P450 family 1 subfamily A member 1; *CELSR2* – Cadherin EGF LAG seven-pass G-type receptor 2; *PSRC1* – proline and serine rich coiled-coil 1; *SORT1* – sortilin 1; *CXCL12* – C-X-C motif chemokine ligand 12; *HNF1A* – hepatocyte nuclear factor 1; *MRAS* – muscle RAS oncogene homolog; *SLC22A3* – solute carrier family 22 member 3; *LPAL2* – lipoprotein(A) like 2, pseudogene; *LPA* – lipoprotein(A); *IRS* – insulin receptor substrate; *MTNR1B* – melatonin receptor 1B; *CDKAL1* – CDK5 regulatory subunit-associated protein 1-like 1; *ADCY5* – adenylyl cyclase type V; *ANK1* – ankyrin-1. *BCAR1* – breast cancer anti-estrogen resistance protein 1; *CDC123* – cell division cycle 123; *DUSP9* – dual specificity phosphatase 9; *GRB14* – growth factor receptor bound protein 14; *RASGRP1* – RAS guanyl-releasing protein 1; *TLE* – transducin-like enhancer protein; *ZBED3* – zinc finger BED-Type containing 3; *UCP3* – uncoupling protein 3; *LPL* – lipoprotein lipase; MetS – metabolic syndrome; SBP – systolic blood pressure; DBP – diastolic blood pressure; WC – waist circumference; BMI – body mass index; TG – triglycerides. HDL – high-density lipoprotein cholesterol; HOMA-IR – homeostasis model assessment estimate of insulin resistance; QUICKI – quantitative insulin-sensitivity check index; AUC – area under the curve TC – total cholesterol; VLDL – very-low density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; MI – myocardial infarction; PUFA – polyunsaturated fatty acid; MUFA – monounsaturated fatty acid; SFA – saturated fatty acid; n-3 – omega-3; LC – long-chain; EPA – eicosapentaenoic acid; DPA – docosapentaenoic acid; DHA – docosahexaenoic acid; C-S, – cross-sectional; RCT – randomised controlled trial; NRCT – non-randomised controlled trial; P-C – prospective cohort; LS – longitudinal study; C-C – case-control; NS – not significant. *Only significant $P_{interaction}$ values are given.

5.3.5 Risk of bias and certainty of assessment

To evaluate the methodological quality and risk of bias (RoB) of cross-sectional studies we used the Appraisal tool for Cross-Sectional Studies (AXIS) [483] (**Supplementary Section 2, Tables S5.2 and S5.3**). Cohort studies, case-control studies, and non-randomized trials were assessed by using the RoB in Non-randomized Studies – of Interventions (ROBINS-I) assessment tool [483, 484] (**Supplementary Section 2, Table S5.4**). Risk of bias due to missing results was assessed using the AXIS RoB (questions 12 to 14) and the ROBINS-I assessment [part 5 (questions 5.1 to 5.4)]. The current article adheres to the recommendations of the Synthesis without Meta-analysis (SWiM) in Systematic Reviews: Reporting Guideline [485].

5.4 Results

5.4.1 Study selection and characteristics

The search string results had an output of 29,092 articles and from these, 101 articles were identified as potential studies. After the full-text screening, 27 articles were excluded for the following reasons: six studies were not based on LACP [486-491], five studies aimed to identify the effect of genomic ancestry [492-496], six studies focused only on genetic associations [497-502], eight studies did not include cardiometabolic diseases [503-510], and two studies investigated gene-phenotype interactions [511, 512] as shown in **Figure 5.5.** Finally, after excluding the irrelevant articles based on the exclusion criteria, 74 studies were included in this systematic review as shown in **Table 5.1**.

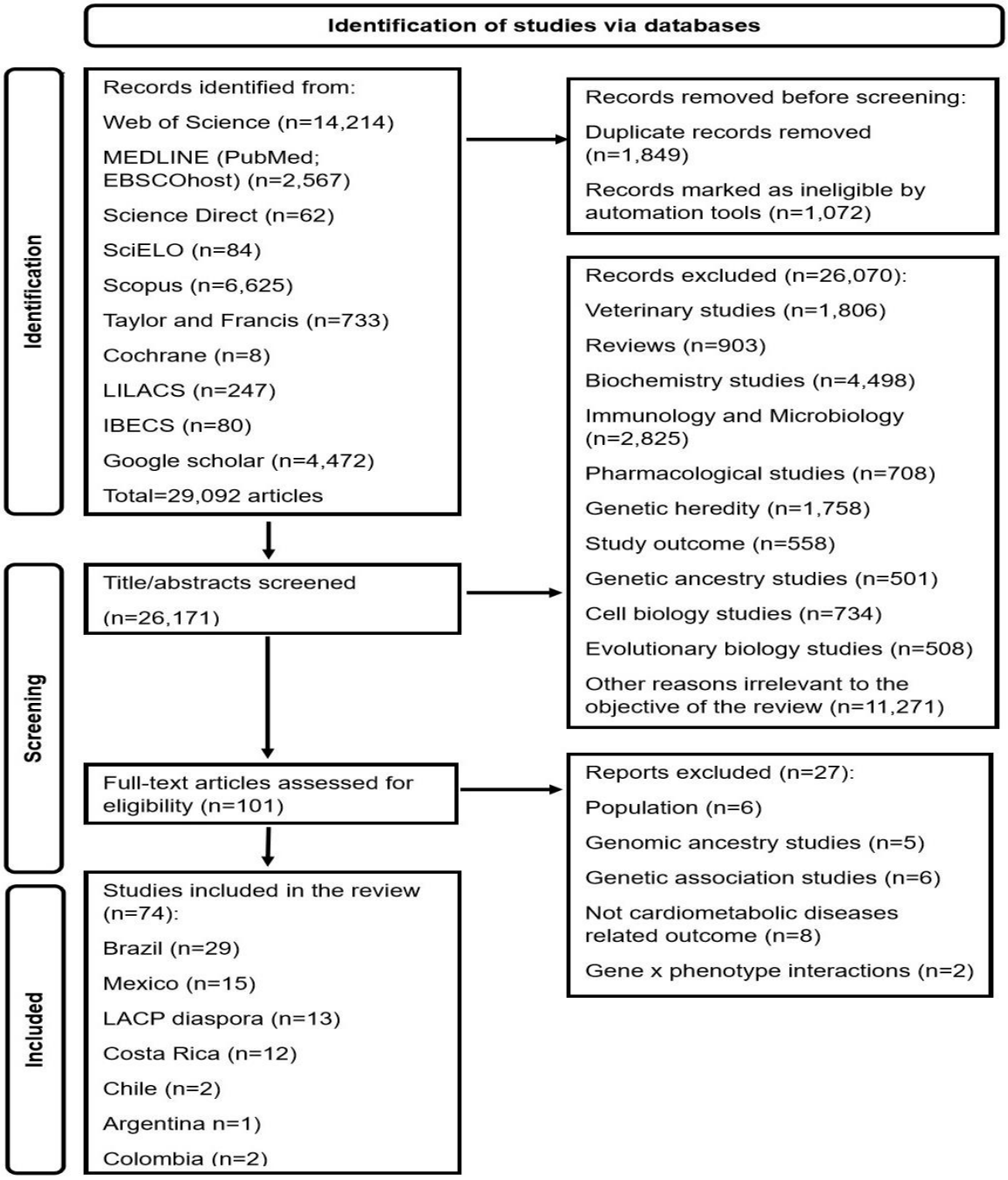

Figure 5.5 A flow chart showing the exclusion criteria and selection of studies

Literature search was conducted in MEDLINE (via PubMed and EBSCO Host), Web of Science, ScienceDirect, SciELO, SCOPUS, Taylor & Francis Online, Cochrane library, LILACS (Latin American and Caribbean Health Sciences Literature), IBECS, Google Scholar, and ERIC (Education Resources Information Center via EBSCO Host) search engines until the 25th of May 2022.

5.4.2 Gene-lifestyle interactions in LACP

The 74 studies conducted in LACP encompass ethnicities from Argentina, Colombia, Chile, Costa Rica, Mexico, Brazil, and LACP diaspora, including Dominicans, Puerto Ricans, Mexicans, and other Hispanic ethnicities residing in the United States of America (USA). Most of the studies are focused on four countries: Brazil (29), Mexico (15), Costa Rica (12) and Puerto Ricans in Boston (10). The studies have identified 122 significant gene-lifestyle interactions on cardiometabolic traits (P<0.05), as shown in **Table 5.1**. The results are stratified by country to enable identification of ethnic-specific gene-lifestyle interactions and to present a structured mapping of the research gaps for a multidisciplinary audience.

5.4.3 Gene-lifestyle interactions in Brazilians

5.4.3.1 Interaction between dietary fat intake and genetic variants on CVD traits

Interaction between dietary fat intake and genetic variants on CVD-related traits was examined by five Brazilian studies [139, 309, 424, 438, 439]. In a cross-sectional study of 567 participants [438], a significant interaction was reported between olive oil intake and Apolipoprotein E (*APOE*) genotype on low-density lipoprotein cholesterol (LDL) ($P_{interaction}$=0.028), where a high intake of olive oil (≥ once a week) was associated with lower LDL levels in men carrying the 'E2' allele but had no effect in men without the 'E2' allele. In this study [438], a high polyunsaturated fatty acid (PUFA) intake (> twice a week) was associated with increased LDL levels in carriers of the 'E4' allele, but this was not observed in participants without the 'E4' allele ($P_{interaction}$=0.04). A reduction in triglyceride levels in response to a high PUFA intake was also observed in carriers of the 'E2' allele but not in participants without the 'E2' allele ($P_{interaction}$=0.04). A high PUFA intake was also associated with increased high-density lipoprotein cholesterol (HDL) concentration in participants without the 'E4' allele and reduced HDL levels in carriers of the 'E4' allele ($P_{interaction}$=0.018) [438]. In contrast, a cross-sectional study of 252 Brazilian women [439] observed increased triglyceride and very-low density lipoprotein cholesterol (VLDL) in response to a low PUFA or a high fat diet intake in carriers of the 'E4' allele of *APOE*, but not in non-carriers ($P_{interaction}$<0.05 for both). The findings of the first study [438] indicate that, PUFA intake might be beneficial in increasing HDL levels in individuals without the 'E4' allele, while in those with the 'E4' allele, PUFA intake might contribute to a rise in triglyceride and LDL levels which is associated with higher risk of CVDs [513]. Nonetheless, the findings of the second study [439] suggest a detrimental effect of low PUFA intake in carriers of the 'E4' allele. The differences in the findings could be attributed to the small sample sizes and the fact that, the

second study [439] was conducted in women unlike the first study [438]. PUFA is a ligand for peroxisome proliferator-activated receptors (PPARs) which are involved in regulating several lipid-pathway genes and it has been suggested that, increased consumption of PUFA might promote the expression of APOE and hepatic uptake of 'E4'-containing VLDL particles [514, 515].

Furthermore, a cross-sectional study of 228 Brazilian participants from the Health Survey of São Paulo (HS-SP) [139] observed significant interactions between a GRS based on seven SNPs (**Table 5.1**) and the Brazilian Healthy Eating Index Revised (BHEI-R) on the risk of dyslipidaemia. Participants with a higher GRS (5 to 8) had a lower odds ratio for dyslipidaemia with an intake of BHEI-R oil component above the median ($P_{interaction}$=0.019); while those with a GRS >9 had a lower odds ratio for dyslipidaemia with an intake of BHEI-R solid fats, alcoholic beverages and added sugars (SoFAAS) component below the median ($P_{interaction}$<0.001). Similarly, a cross-sectional study involving 250 pregnant women [424] observed significant interactions between fatty acid desaturase (*FADS*) SNPs (rs174561 and rs3834458) and dietary α-linolenic acid (ALA) and linoleic/α-linolenic acid ratio (LA/ALA) on plasma concentrations of omega-3 (n−3) PUFAs. It was reported that, in women with high ALA intake, plasma ALA concentrations were higher in homozygotes for the minor allele (P<0.05), compared to carriers of the major allele (MM and Mm) of rs174561 and rs3834458. However, the *P* values given in the study (P=0.004 for rs174561 and P=0.028 for rs3834458) seem to represent associations stratified by genotype, instead of interactions. FADS are involved in the synthesis of PUFA and their activation is linked to inflammation and coronary artery disease [516, 517], and these findings suggest that SNPs which alter the activation of FADS might affect plasma concentration of PUFA. In another cross-sectional study of 113 adolescents from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) study [309], no significant interactions were reported between seven genes involved in the one-carbon metabolism pathway (**Table 5.1**) and fat intake on lipid-related traits.

5.4.3.2 Interaction between dietary fat intake and genetic variants on glycaemic traits

Interaction between dietary fat intake and genetic variants on glycaemic traits was investigated by two cross-sectional studies [319, 327] using data from the BOLD study. In the first study which consisted of 200 participants [327], a high total fat intake (37.98% of total energy intake (TEI)/day) was shown to interact with a 10-SNP metabolic-GRS (**Table 5.1**), where individuals with 5 or more risk alleles had increased homeostasis model assessment estimate of insulin secretion (HOMA-B) ($P_{interaction}$=0.016), fasting insulin

($P_{interaction}$=0.017), body fat mass ($P_{interaction}$=0.009), and decreased insulin:glucose ratio ($P_{interaction}$=0.01), but the interaction did not influence homeostasis model assessment estimate of insulin resistance (HOMA-IR), glycated haemoglobin (HbA1c), or waist circumference (WC). Similarly, the second BOLD study [319] which also examined the interaction between dietary fat intake and a 10-SNP metabolic-GRS did not find significant interactions between the GRS and dietary fat intake on fasting glucose, fasting insulin or HbA1c (**Table 5.1**). The mechanisms through which dietary fat intake influence glycaemic traits are unclear, although a sustained increase in blood glucose levels following a high fat meal has been reported [518].

5.4.3.3 Interaction between plasma fatty acid profile and genetic variants on systemic inflammation

Five Brazilian cross-sectional studies [416-419, 423] investigated the interaction between plasma fatty acids and genetic variants on systemic inflammation, using data from the HS-SP. The first study [423] consisted of 262 adults, and significant interactions were identified between plasma n-3 and adiponectin (*ADIPOQ*) SNP rs2241766 ($P_{interaction}$=0.019); arachidonic acid and *ADIPOQ* rs16861209 ($P_{interaction}$=0.044); docosapentaenoic acid and *ADIPOQ* rs16861209 ($P_{interaction}$=0.037); and SFA and *ADIPOQ* rs17300539 ($P_{interaction}$=0.019) on the risk of systemic inflammation. Carriers of the 'G' allele of rs2241766 had a reduced odds ratio of having inflammatory biomarkers when plasma n-3 levels were above the median, while participants with the 'CC' genotype of rs16861209 had a lower odds ratio of having inflammatory biomarkers in the 50th percentile of plasma arachidonic acid and docosapentaenoic acid. Moreover, carriers of the 'A' allele of rs17300539 had a higher odds ratio of having inflammatory biomarkers in the upper 50th percentile of plasma SFA compared to those with the 'GG' genotype [423]. In the second study [418], which consisted of 262 participants, an interaction was also observed between plasma arachidonic acid/eicosapentaenoic acid ratio and toll-like receptor 4 (*TLR4*) SNP rs11536889, in which individuals with the 'C' allele had an increased odds ratio of having inflammatory biomarkers at the higher percentile of arachidonic acid/eicosapentaenoic acid ratio ($P_{interaction}$=0.034). Similarly, the third study consisting of 262 participants [419] identified a significant interaction between plasma palmitoleic acid and C-reactive protein (*CRP*) SNP rs1417938, where individuals with the 'AA' genotype had a higher odds ratio of having inflammatory biomarkers with a plasma palmitoleic acid above the median ($P_{interaction}$=0.047).

In line with these findings, an increasing risk of having inflammatory biomarkers in response to increasing plasma SFA was observed in carriers of the 'A' allele of tumor necrosis

factor-α (*TNF*-α) SNP rs180062 (-308G/A) ($P_{interaction}$=0.041); while a decreasing risk with increasing plasma stearic acid was found in participants with the 'GG' genotype ($P_{interaction}$=0.046), in a sample of 281 participants from the HS-SP [417]. Furthermore, a decreasing risk of metabolic syndrome (MetS) was observed in response to increasing plasma stearic acid levels in 'A' allele carriers of interleukin 1 beta (*IL1B*) SNP rs16944 ($P_{interaction}$=0.043), and in response to increasing plasma arachidonic acid levels in those with the 'GG' genotype of interleukin 10 (*IL10*) SNP rs1800896 ($P_{interaction}$=0.007), in a sample of 301 participants from the HS-SP [416]. However, no significant interactions were identified between total SFA, myristic acid, palmitic acid, stearic acid and *ADIPOQ* SNPs rs1501299 and rs266729; *TLR4* SNPs rs11536889 and rs5030728; and *CRP* SNP rs1205 on inflammatory biomarkers in three of the studies [416, 417, 423]. Plasma fatty acid profile is considered an indicator of dietary fatty acid intake [423] and these findings suggest that plasma fatty acid profile can interact with SNPs of several genes and modify the risk of systemic inflammation which is linked to cardiometabolic diseases such as type 2 diabetes and CVDs [423].

5.4.3.4 Interaction between carbohydrate intake and genetic variants on cardiometabolic traits

Three Brazilian cross-sectional studies [309, 319, 327] investigated the interactions between carbohydrate intake and genetic variants on cardiometabolic traits, using data from the BOLD study. In the first study which consisted of 113 participants [309], a total carbohydrate intake of 47.7% TEI was associated with a significantly increased homocysteine concentration ($P_{interaction}$=0.031) in carriers of the *`AA´* genotype of fucosyltransferase 2 (*FUT2*) SNP rs602662. Carbohydrate intake also interacted with Catechol-O-Methyltransferase (*COMT*) SNP rs4680, increasing oxidised-LDL more in carriers of `AA´than `GG´genotype ($P_{interaction}$=0.005) [309]. Notwithstanding, after applying Bonferroni correction for multiple testing, none of the interactions were considered significant [309]. Moreover, the other two studies [327] which consisted of 200 participants and [319] which consisted of 187 participants, from the BOLD study, did not identify significant interactions between carbohydrate intake and a metabolic-GRS based on 10 SNPs (**Table 5.1**) on cardiometabolic traits.

5.4.3.5 Interaction between protein intake and genetic variants on cardiometabolic traits

Three studies [309, 319, 427] investigated the interaction between protein intake and genetic variants on cardiometabolic traits, two of which [309, 319] used data from the BOLD study. A cross-sectional study of 1191 overweight and normal weight children [427]

observed a significantly increased BMI(P=0.01) among participants carrying the '*T*' allele of *FTO* SNP rs79149291 with a protein intake above 12.7% TEI/day [427]. Similarly, in the BOLD study discussed above [309], those with a protein intake of 16.99% TEI who were carriers of the *`AA´* genotype of *FUT2* SNP rs602662 ($P_{interaction}$=0.007) had increased homocysteine levels [309]. However, in the other BOLD study [319], there were no interactions between protein intake and a GRS based on 10 SNPs (**Table 5.1**) on obesity or diabetes traits.

5.4.3.6 Interactions between micronutrients and genetic variants on cardiometabolic traits

The interaction between micronutrients and genetic variants on cardiometabolic traits was examined by *five* Brazilian studies [431, 446, 449, 450, 473]. A cross-sectional study of 335 healthy young adults [449], observed a pronounced increase in systolic blood pressure (SBP) ($P_{interaction}$=0.016) among carriers of the *`G´* allele of Angiotensinogen (*AGT*) SNP rs699 with a higher plasma magnesium (209.3 mg). Similarly, among those with a high calcium intake (573.3 mg), carriers of the *`T´* allele of Bradykinin Receptor B2 (*BDKRB2*) SNP rs1799722 had significantly higher SBP ($P_{interaction}$=0.015) and diastolic BP (DBP) ($P_{interaction}$=0.014) than carriers of the *`CC´* genotype [449]. In line with these findings, a case-control study of 234 elderly people [450] reported an interaction between sodium intake and angiotensin-converting enzyme (*ACE*) SNP rs4646994 on the risk of hypertension, where carriers of the *`I/I´* genotype with a high sodium intake (>2 g/day) had an increased risk of hypertension ($P_{interaction}$=0.007). Furthermore, in a cross-sectional study of 1298 healthy adults [473], those carrying the *`T´* allele of Cytochrome B-245 Alpha Chain (*CYBA*) (*p22phox*) with more than 86.5 mEq sodium per 12 h of urine collection, had increased SBP ($P_{interaction}$<0.001) and DBP ($P_{interaction}$=0.011). Sodium is known to increase BP by reducing vasodilation [519], while dietary calcium is believed to stabilize intracellular calcium in smooth muscles, thereby reducing vasoconstriction and BP [520]. Additionally, the '*A*' allele of *AGT* SNP rs699 is thought to be a risk factor for elevated SBP, possibly due to its association with a rise in plasma AGT levels [449, 511], and the findings of the study discussed above [449] indicate that, the protective effect of the '*G*' allele might be lost in the presence of higher plasma magnesium.

Similarly, in a longitudinal study of 1088 children with a follow up of 4.6 years [431], those with a deficit of plasma vitamin D (<75 nmol/L) and carriers of the risk allele (*`A´*) of *FTO* SNP rs9939609 had increased BMI ($P_{interaction}$=0.033). However, a cross-sectional study

examining folate intake in 5914 healthy adults [446] did not identify interactions between folate intake and *MTHFR* SNP rs1801133 on homocysteine concentrations.

5.4.3.7 Interactions between alcohol intake and genetic variants on cardiometabolic traits

Three Brazilian studies [425, 440, 446] examined the interaction between alcohol intake and genetic variants on cardiometabolic traits. In a cross-sectional study of 113 participants [425], a significant interaction was observed between alcohol intake and endothelial nitric oxide synthase (*eNOS*) SNP rs2070744 (-786 T/C) on plasma nitrite levels. Individuals carrying the 'C' allele who consumed alcohol had lower plasma nitrite levels ($P_{interaction}$=0.033). However, there were no significant interactions between alcohol intake and rs2070744 on BP [425]. Similarly, in a cross-sectional study of 3,803 participants from the Pelotas Birth Cohort [446], an interaction was identified between alcohol intake and *MTHFR* SNP rs1801133 (C677T), in which men with the '677TT' genotype who consumed ≥15 g of alcohol per day had the highest homocysteine concentration ($P_{interaction}$=0.002); but the interaction was not observed in women. Moreover, a prospective cohort study of 964 postmenopausal women [440], reported no interactions between alcohol intake and *APOE* genotype on lipid traits. A rise in homocysteine concentration is attributed to a deficiency in B vitamins and folate, and SNPs of *MTHFR* might affect homocysteine concentration by impairing folate metabolism [521]. However, it is unclear how alcohol intake modifies the activity of MTHFR, and the finding of the study [446] suggests a sex-specific response.

5.4.3.8 Interactions between smoking and genetic variants on cardiometabolic traits

Two studies [422, 461] investigated the interaction between smoking and genetic variants on cardiometabolic traits in Brazilians. In a cross-sectional study of 391 participants [461], smoking interacted with *APOA-IV* SNPs rs693 (XbaI), rs675 (Thr347Ser) and rs5110 (Gln360His), increasing BMI in individuals with the 'X*2' ($P_{interaction}$=0.007) and '347Ser' ($P_{interaction}$=0.02) alleles. However, men with the '360His' allele who were non-smokers had a larger WC than homozygotes for the 'Gln' allele ($P_{interaction}$=0.018) [461]. Similarly, in a cross-sectional study of 673 overweight adults (403 women and 270 men) [422], carriers of the 'S2' allele of *APOC3* SNP rs5128 had increased triglycerides and the effect was more pronounced in women who smoked than in non-smokers ($P_{interaction}$=0.009). Serum APOC3 concentration has been shown to be positively associated with triglyceride levels, and smoking has been reported to lower the concentration of APOC3 but only in women without central obesity [522], indicating a sex-specific response which is influenced by obesity traits.

5.4.3.9 Interactions between physical activity and genetic variants on cardiometabolic traits

Interactions between physical activity and genetic variants on cardiometabolic traits were investigated by nine Brazilian studies [309, 432, 433, 435, 446, 451, 461, 467, 474]. In a longitudinal study of 197 overweight or obese children [467], a physical exercise program (3 sessions/week for 12 weeks) interacted with adrenoceptor beta 2 (*ADRB2*) SNP rs1042714, decreasing triglyceride levels and triglyceride-glucose index ($P_{interaction}$=0.001 for both) more in carriers of the 'Glu27Glu' genotype than those carrying the 'Gln27' allele. A cross-sectional study of 1701 children and adolescents [474] also reported higher BMI and WC in individuals with the 'TT' genotype of fibronectin type III domain containing 5 (*FNDC5*) SNP rs16835198 compared to carriers of the 'G' allele only in those with lower levels of cardiorespiratory fitness (CRF) ($P_{interaction}$=0.038 and $P_{interaction}$=0.007 for WC and BMI, respectively); and lower limb strength ($P_{interaction}$=0.040 and $P_{interaction}$=0.044 for WC and BMI, respectively). Physical activity has been proposed to alter the expression of certain genes [523], and the findings of these studies indicate that, the effect of physical activity on lipid, glycaemic and anthropometric traits might be influenced by SNPs of *ADRB2* and *FNDC5* genes.

Similarly, a sedentary behaviour (a screen time of >378 min/day) was shown to increase cardiometabolic risk score in carriers of 'AA' genotype of *FTO* SNP rs9939609 with a low CRF but not in those with a high CRF in a cross-sectional study of 1215 children and adolescents ($P_{interaction}$=0.047) [432]. Along this line, a randomised controlled trial of 34 participants [451] reported that, a 45-minute walk on a treadmill at moderate intensity resulted in a reduction in SBP ($P_{interaction}$=0.02) and DBP ($P_{interaction}$<0.01) in carriers of the 'I' allele of *ACE* SNP rs4646994 compared with a non-exercise control session, but the reduction was not observed in participants with 'DD' genotype. However, five studies [309, 433, 435, 446, 461] did not identify significant interactions between physical activity and genetic variants on cardiometabolic traits as shown in **Table 5.1**.

5.4.3.10 Other gene-diet interactions in Brazilians

In the BOLD study consisting of 113 participants [309], a total fat intake of 25.36% TEI interacted with Betaine-Homocysteine S-Methyltransferase (*BHMT*) SNP rs492842, increasing vitamin B12 concentrations ($P_{interaction}$=0.034) in participants with the 'TT' genotype. A case-control interventional study of 126 obese women [132] also reported that, a hypocaloric diet (<600 kcal/day) for seven weeks was associated with a decreased abdominal circumference ($P_{interaction}$=0.04) among carriers of the '*A*' allele of *FTO* SNP

rs9939609. Furthermore, in a prospective cohort study of 3,701 women, breastfeeding (>6 months duration) interacted with *FTO* SNP rs9939609, decreasing BMI ($P_{interaction}$=0.03), fat mass ($P_{interactin}$=0.03), and WC ($P_{interaction}$=0.04) in carriers of the *'A'* allele [434].

In summary, research in Brazil stands out in comparison to the rest of the gene-lifestyle research in LACP for being the most abundant; twenty-nine studies investigated gene x lifestyle interactions in the Brazilian population as shown in **Table 5.1**, covering a wide range of cardiometabolic traits. Dietary fat intake and plasma fatty acid profile were the most frequently investigated dietary factors examined by seven and five studies respectively, although all the studies examining plasma fatty acid profile used data from the HS-SP. Carbohydrate intake was examined by only three studies, all of which used data from the BOLD study. Similarly, protein intake was investigated by only three studies, two of which used data from the BOLD study. Physical activity was the most frequently examined lifestyle factor, followed by smoking and alcohol intake. Breastfeeding was examined by only one study [434], and lifestyle factors such as socioeconomic status, level of education, and the effect of rural and urban environments were not investigated. Only one study was conducted in rural settings [425], but it was not focused on interaction of the rural environment with genetic variants. The *FTO* SNP *rs9939609* was the most studied, being explored by five studies [431-433, 435, 446]. Overall, the findings call for further research into lifestyle factors such as socioeconomic status, level of education and the effect of rural and urban environments as well as other dietary factors such as fruit and vegetable intake.

5.4.4 Gene-lifestyle Interactions in Mexicans

5.4.4.1 Interaction between dietary fat intake and genetic variants on CVD traits

The interaction between dietary fat intake and genetic variants on CVD-related traits was examined by five Mexican studies [429, 441, 443, 475, 476]. In a cross-sectional study of 224 participants with T2D [441], interactions between monounsaturated fatty acid (MUFA) intake and *APOE* genotype on blood lipid concentrations were reported. A low MUFA intake (<10–15% TEI) was found to be associated with higher total cholesterol (TC) ($P_{interaction}$=0.016), non-HDL ($P_{interaction}$=0.024) and LDL ($P_{interaction}$=0.030) only in carriers of the `E2´ allele of *APOE* SNP rs7412. Similarly, interactions between MUFA intake ($P_{interaction}$=0.001), total fat intake ($P_{interaction}$=0.001), dietary cholesterol intake ($P_{interaction}$=0.019) and Dopamine Receptor D2/Ankyrin Repeat and Kinase Domain Containing 1 (*DRD2/ANKK1*) SNP rs1800497, increasing triglyceride levels in carriers of the `A2A2´ genotype were observed in a cross-sectional study of 175 Mexican adults with T2D

[475]. MUFA intake has been linked to decreased triglyceride concentration [524] which is consistent with the findings of the first study [441]. However, the findings of the second study [475] imply that MUFA intake might not be beneficial for individuals with the `A2A2´ genotype of rs1800497. Both studies were conducted in participants with T2D which is known to affect lipid metabolism [525]. Moreover, as highlighted by the authors of the second study [475], the effect of dietary fat intake on triglycerides concentration may be influenced by other factors including physical activity and the level of insulin resistance.

A Mexican case-control study consisting of 100 participants with normal weight and 100 participants with obesity [443] also found significant interactions between SFA intake and leptin receptor (*LEPR*) SNP rs1137101 on TC ($P_{interaction}$=0.002) and triglyceride ($P_{interaction}$=0.02) levels. It was reported that, a SFA intake of ≥12 g/day was associated with a 3.8 times higher risk of hypercholesteroleamia and a 2.4 times higher risk of hypertriglycerideamia compared to an intake of <12 g/day in participants carrying the 'G' allele of rs1137101 [443]. An interaction between total fat intake with *LEPR* SNP rs1137101 on TC ($P_{interaction}$=0.001) was also reported in this study [443], where a high intake of total fat (≥83 g/d) was associated with a 4.1 times higher risk of hypercholesteroleamia in carriers of the 'G' allele of rs1137101. Similarly, in a prospective cohort study involving a dietary intervention in 41 participants with hypercholesterolaemia [476], interactions were observed between consumption of a diet low in SFA (<6% TEI/day) in addition to another diet containing 15 g of soluble fibre and 25 g of soy protein for 2 months and Glucose-Fructose Oxidoreductase Domain Containing 2 (*GFOD2*) SNP rs12449157 on TC ($P_{interaction}$=0.006) and LDL ($P_{interaction}$=0.025). Participants carrying the 'G' allele had a larger decrease in TC and LDL in response to the dietary intervention compared to subjects with the 'AA' genotype of rs12449157 [476]. In this study [476], baseline LDL and TC levels were higher in carriers of the 'G' allele, but they responded better to the dietary intervention, which indicates that the genetic risk of dyslipidaemia can be modified by a dietary intervention. However, in another study of 31 Mexican participants with dyslipidaemia [429] from the same cohort as above [476], using the same dietary intervention, no significant interactions were identified between the diet and Calpain 10 (*CAPN10*) SNPs rs5030952, rs2975762 and rs3792267 on lipid traits. It has been reported that SFA of different types and from different food sources might have different effects on cardiometabolic traits [294, 390], however both studies [429, 476] used the same dietary intervention. Nonetheless, factors such as physical activity have also been reported to

influence the effect of dietary fat intake on cardiometabolic traits [475], which could explain the differences in the findings.

5.4.4.2 Interaction between carbohydrate intake and genetic variants on cardiometabolic traits

Interactions between carbohydrate intake and genetic variants on cardiometabolic traits were examined by three Mexican studies [98, 454, 475]. In a cross-sectional study of 3591 adults [454], carbohydrate intake was negatively associated with HDL concentrations in premenopausal women carrying the risk allele (`C´) of ATP Binding Cassette Subfamily A Member 1 (*ABCA1*) SNP rs9282541 (*R230C*), but not in those carrying the `R´ allele ($P_{interaction}$=0.037). In another cross-sectional study of 215 healthy adults [98], a high sucrose intake (>5% TEI) significantly increased TC ($P_{interaction}$=0.034) and LDL ($P_{interaction}$=0.037) more in participants with `B1B2/B2B2´ genotype than those with `B1B1´ genotype of cholesteryl ester transfer protein (*CETP)* SNP rs708272. However, the interaction did not influence triglycerides, HDL, BMI nor waist circumference [98]. In contrast, the cross-sectional study discussed above [475], reported that the intake of maltose (0.68 ± 0.42 g/day) significantly decreased triglycerides ($P_{interaction}$=0.023) in carriers of the `A1´allele of *DRD2/ANKK1* SNP rs1800497. These findings indicate that carbohydrate intake might modulate lipid levels in Mexicans with certain genetic variants, but the mechanism through which carbohydrates affect lipid levels are unclear. Moreover, it has been reported that, the effect of carbohydrates on lipids might be dependent on glycaemic index or glycaemic load, and highly processed carbohydrates are linked to unfavourable lipid profiles [526].

5.4.4.3 Interaction between micronutrients and genetic variants on cardiometabolic traits

Two cross-sectional studies examined the interaction between micronutrients and genetic variants on cardiometabolic traits [447, 448]. In the first study which consisted of 231 healthy new-borns [447], a deficient maternal vitamin B12 (<2.0 mcg/d) was found to be associated with a smaller size baby at birth in mothers with the 'TT' genotype of *MTHFR* SNP rs1801133 ($P_{interaction}$=0.02) but a deficient maternal folate (<400 mcg/d) was not associated with anthropometric parameters (weight, length or BMI) of new-borns [447]. A low vitamin B12 intake (<2.0 mcg/d) was also associated with increased homocysteine levels ($P_{interaction}$=0.01) in carriers of the 'TT' genotype of *MTHFR* SNP rs1801133 in a cross-sectional study of 130 healthy women [448]. The 'TT' genotype of *MTHFR* is associated with decreased enzymatic activity and increased homocysteine concentration [527] and the

findings of these studies suggest that increasing the intake of vitamin B12 might improve foetal development in Mexican women with the 'TT' genotype.

5.4.4.4 Interaction between alcohol intake and genetic variants on cardiometabolic traits

The cross-sectional study of 130 healthy women discussed above [448], was the only study which examined alcohol intake and no interaction was found between alcohol intake and *MTHFR* SNP rs1801133 on homocysteine levels which could be due to the fact that 80% of the studied population consumed less than 1 cup/week of alcohol [448].

5.4.4.5 Interaction between physical activity and genetic variants on cardiometabolic traits

Interactions between physical activity and genetic variants on cardiometabolic traits were investigated by four Mexican studies [98, 415, 455, 458]. In the cross-sectional study discussed above [98], increased concentration of TC ($P_{interaction}$=0.033) was observed in individuals carrying the 'B2' allele of *CETP* SNP rs708272 who did not perform physical activity, compared to those with the 'B1B1' genotype. However, there were no interactions on TG, HDL, TG:HDL ratio, LDL, BMI or WC [98]. Similarly, interactions between physical fitness measured by muscular endurance (ME) and aerobic capacity with genetic variants were observed in a case-control study of 608 physically active adults [415], where higher levels of ME and aerobic capacity were associated with a lower WC in individuals with a high GRS based on 23 SNPs (**Table 5.1**) ($P_{interaction}$=0.0001 for both). In this study [415], a higher risk of obesity was found in older participants (≥40 years) with the 'AA' genotypes of *APOB* SNP rs512535 ($P_{interaction}$=0.004) and tumour necrosis factor (*TNFA*) SNP rs361525 ($P_{interaction}$=0.007) with low levels of ME. However, another cross-sectional study of 565 physically active participants [455] did not find significant interactions between physical fitness and six SNPs (*ADIPOQ* rs2241766, *ACSL1* rs9997745, *LIPC* rs1800588, *PPAR-α* rs1800206, *PPAR-γ* rs1801282 and *PPAR-γC1A* rs8192678) on glycaemic traits. Moreover, the fourth cross-sectional study which consisted of 394 participants [458], did not identify interactions between physical activity and *ADIPOQ* SNP –11391G/A on adiponectin levels.

5.4.4.6 Other gene-lifestyle interactions in Mexicans

In a cross-sectional study of 206 Mexican women [464], an interaction between polycyclic aromatic hydrocarbons (PAHs) and Paraoxonase 1 (*PON1*) SNP rs661 (Q192R) on serum asymmetric dimethylarginine (ADMA) was observed, where individuals carrying the 'R' allele had higher ADMA levels compared to those with the 'QQ' genotype in response to higher levels of urinary 1-hydroxypyrene ($P_{interaction}$=0.02). Increased levels of ADMA (P<0.01) and fatty acid-binding protein 4 (P<0.001) were also identified in individuals with

the 'RR' genotype of *PON1* SNP rs661 with higher urinary arsenic levels (>45.0 ug/g of creatinine) in comparison with participants with the 'QQ' genotype in a sample of 185 Mexican women [465]. The mechanisms of the interaction may be shared in the case of exposure to PAHs as these are also involved in the generation of reactive oxygen species [528].

Overall, different cardiometabolic traits have been investigated in Mexico, where eleven out of fifteen studies found significant gene-lifestyle interactions [98, 415, 441, 443, 447, 448, 454, 464, 465, 475, 476] as shown in **Table 5.1**. Dietary fat intake was the most frequently examined dietary factor, being investigated by five studies [429, 441, 443, 475, 476]; followed by carbohydrate intake, which was examined by three studies [98, 454, 475]. Physical activity was the most frequently examined lifestyle factor, while alcohol intake was investigated by only one study. Lifestyle factors such as smoking, socioeconomic status, level of education and the impact of rural and urban environments were not investigated. Moreover, dietary factors such as consumption of protein, complex carbohydrates, and fruits and vegetables have not been investigated, highlighting a need for further research.

5.4.5 Gene-lifestyle interactions in Costa Ricans

5.4.5.1 Interactions between dietary fat intake and genetic variants on CVD-related traits

The interaction between dietary fat intake and genetic variants on CVD-related traits was examined by six Costa Rican studies [421, 442, 457, 459, 468, 477]. In a cross-sectional study of 420 participants [442], SFA intake interacted with *APOE* genotype and influenced blood lipid concentrations. A higher SFA intake (13.5% energy) was associated with higher levels of very-low density lipoprotein cholesterol (VLDL) ($P_{interaction}$=0.03) and lower concentration of HDL ($P_{interaction}$=0.02) in carriers of the *'E2'* allele. However, no significant interactions were identified between SFA intake and *APOE* genotype on lipids in a case-control study involving 1927 participants with myocardial infarction (MI) and 1927 matched controls [421]. In another cross-sectional study of 336 participants [457], SFA intake was found to interact with *APOC3* genotype and impact on the concentration of TC ($P_{interaction}$=0.0004) and LDL ($P_{interaction}$=0.01). Homozygotes for the *APOC3-455T-625T* alleles had a 13% increase in TC and a 20% increase in LDL with a high SFA intake (>11% of energy intake), but the interaction was not significant in individuals with the *APOC3-455C-625del* allele [457]. In the case-control study discussed above [421], a significant interaction between SFA intake and *APOE* genotype on the risk of MI ($P_{interaction}$=0.0157) was also

reported, in which carriers of the '*E4'* allele had a 49% increased risk of MI compared to a 2.2 fold increased risk in those with the *'E2'* allele in response to a high SFA intake (>11.8% of energy intake).

APOE plays a key role in lipid metabolism, being a main component of triglyceride-rich lipoproteins and HDL, and a ligand for LDL receptor [442, 529] and it is believed that the metabolism of fatty acids is impaired in carriers of the '*E4'* allele which is considered a risk factor for CVDs [530]. However, the above findings indicate that, a high SFA intake is more detrimental to carriers of the '*E2'* allele than those carrying the '*E4'* allele, highlighting the potential role of SFA intake in modifying genetic risk.

In accordance with the findings above, a case-control study of 1805 participants with a first non-fatal MI and 1805 matched controls [459], reported an interaction between PUFA intake and *PPAR-*$\boldsymbol{\gamma}$ SNP rs1801282, influencing the risk of MI ($P_{interaction}$=0.03). Individuals with the 'Pro12/Pro12' genotype had a 34% reduced risk of MI per 5% increment in energy from PUFA compared to a 7% decreased risk in those carrying the *'Ala12'* allele [459]. Similarly, a case-control study of 1932 participants with a first non-fatal MI and 2055 matched controls [468], reported a significant interaction between long-chain omega-3 (LC n-3) PUFA intake and Proprotein Convertase Subtilisin/Kexin Type 9 (*PCSK9*) SNP rs11206510 on the risk of MI ($P_{interaction}$=0.012), where carriers of the 'C' allele had an odds ratio for MI of 0.84 per 0.1% increase in total energy from LC n-3 PUFA, compared to an odds ratio of 1.02 in participants without the 'C' allele [468]. Along similar lines, a case-control study of 1936 participants with a first non-fatal MI and 2035 matched controls [477] reported a significant interaction between omega-6 (n-6) PUFA intake and Phospholipase A2 Group IVA (*PLA2G4A*) SNP rs12746200 on the risk of MI ($P_{interaction}$=0.005), in which participants with the 'G' allele had a reduced risk of MI with an intake of n-6 PUFA above the median compared to those with the 'AA' genotype. However, there were no significant interactions with n-3 PUFA intake [477].

These findings indicate that the beneficial effect of PUFA intake reported by some studies [77, 531] might be limited in individuals with certain genetic variants. PPAR-$\boldsymbol{\gamma}$ is a nuclear receptor which is involved in adipogenesis and plays a role in the metabolism of glucose and fatty acids [532, 533], and the *'Ala12'* allele of PPAR-$\boldsymbol{\gamma}$ SNP rs1801282 has been reported to slow down the release of PUFA from adipocytes, which could explain the smaller reduction in the risk of MI in comparison with carriers of the 'Pro12/Pro12' genotype [459].

5.4.5.2 Interaction between other dietary factors and genetic variants on the risk of MI

Interactions between other dietary factors and genetic variants on the risk of MI were examined by three Costa Rican studies [426, 470, 478]. In a case-control study of 1560 incident cases of non-fatal MI and 1751 matched controls [426], sugar sweetened beverage (SSB) intake interacted with a GRS based on 3 SNPs of chromosome 9p21 (rs4977574, rs2383206 and rs1333049), increasing the risk of MI ($P_{interaction}$=0.03). SSB intake also interacted with rs4977574, increasing the risk of MI in carriers of the 'G' allele ($P_{interaction}$=0.005), but there was no interaction with fruit juice intake [426]. In another case-control study of 2014 participants with a first acute non-fatal MI and 2014 matched controls [470], an increased risk of MI with increasing coffee intake was observed in carriers of the 'C' allele (also known as "slow metabolizers of caffeine") of Cytochrome P450 Family 1 Subfamily A Member 2 (*CYP1A2*) SNP rs762551 compared to carriers of the 'AA' genotype ($P_{interaction}$=0.04). Similarly, in a case-control study consisting of 2042 participants with a first non-fatal MI and 2042 control subjects [478], cruciferous vegetable intake (0.86 servings/day of half a cup) interacted with Glutathione S-Transferase Theta 1 (*GSTT1*) SNP rs17856199, lowering the risk of MI in carriers of the `*1´ allele, but not in individuals with the `*0*0´ genotype ($P_{interaction}$=0.006). These findings indicate that, dietary factors other than fat intake, might also influence the risk of MI in Costa-Ricans with certain genetic variants.

5.4.5.3 Interaction between smoking and genetic variants on the risk of MI

Interaction between smoking and genetic variants on the risk of MI was investigated by three Costa Rican case-control studies [466, 471, 478], two of which found significant interactions [466, 478]. In a case-control study of 492 participants with a first non-fatal MI and 518 matched controls [466], an interaction was observed between smoking status and Paraoxonase 1 ($PON1_{192}$) SNP rs661 on the risk of MI ($P_{interaction}$=0.04), where the $PON1_{192Arg}$ allele was associated with an increased risk of MI only in non-smokers. Similarly, in the case-control study discussed above [478], the combined intake of cruciferous vegetables (>5 servings/day) and smoking (1-10 cigarettes/day) in carriers of the *`*1´* allele of rs17856199, lowered the risk of MI ($P_{interaction}$=0.008). However, there were no significant interactions with *GSTM1* or *GSTP1* genotype on the risk of MI [478]. Moreover, in the third Costa Rican case-control study which involved 873 participants with a first non-fatal MI and 932 control subjects [471], no significant interactions were observed between smoking and *CYP1A1* SNP rs1048943 or *CYP1A2* SNP rs762551 on the risk of MI. Smoking has been linked to increased risk of MI [534, 535] although the mechanisms are unclear. Smoking is also believed to

impair the activity of PON1, which is linked to increased risk of CVDs [536, 537], but this is not supported by the findings of the studies above, suggesting that Costa Ricans with certain genetic variants might respond differently to smoking.

5.4.5.4 Other gene-lifestyle interactions in Costa Ricans

One case-control study consisting of 1534 participants with a first non-fatal MI and 1534 matched controls [420], investigated the interaction between a lifestyle cardiovascular risk score comprising of physical activity, smoking, alcohol consumption, waist-to-hip ratio, and socioeconomic status; and a GRS based on 14 SNPs (**Table 5.1**) on the risk of MI, and no significant interactions were identified.

The research in Costa Rica has mainly focused on CVD traits in adults, with an emphasis on the risk of MI, and dietary fat intake has been the most frequently examined exposure. Socioeconomic status was examined by one study [420], and lifestyle factors such as educational level, the effect of rural and urban environments as well as dietary factors such as consumption of protein, fibre and complex carbohydrates have not been explored, highlighting a need for further research.

5.4.6 Gene-lifestyle interactions in LACP diaspora

5.4.6.1 Interaction between dietary fat intake and genetic variants on anthropometric traits

Interaction between dietary fat intake and genetic variants on anthropometric traits were investigated by six studies [137, 428, 445, 453, 472, 480], all of which used data from the Boston Puerto Rican Health Study (BPRHS). In a cross-sectional study of 930 Puerto Ricans from the BPRHS [137], a high intake of SFA (≥22 g/day) was associated with a 7.9% higher BMI in individuals with the 'CC' genotype of *APOA2* SNP rs5082 than those carrying the 'T' allele ($P_{interaction}$=0.003); but the SNP had no effect on BMI when SFA intake was low (<22 g/day). This study also observed that, among individuals with a high SFA intake (≥22 g/d), those with the 'CC' genotype had a higher risk of obesity than participants carrying the 'T' allele of the SNP rs5082 [Odds ratio (OR) = 1.84; 95% confidence interval (CI) = 1.38 - 2.47; P<0.0001). A similar finding was reported in a prospective cohort study of 920 participants from the BPRHS [428], where a high intake of SFA (≥9.3% of total energy) was linked to higher BMI ($P_{interaction}$=0.006), WC ($P_{interaction}$=0.02), and hip circumference (HC) ($P_{interaction}$=0.002) in participants carrying the minor allele ('T') of LDL receptor related protein 1 (*LRP1*) SNP rs1799986 compared to individuals with the 'CC' genotype; but the SNP had no effect on anthropometric traits when SFA intake was low (<9.3% of total energy).

The 'CC' genotype of *APOA2* rs5082 is believed to affect body fat distribution by lowering plasma concentration of APOA2 and these findings indicate that, a low SFA intake might attenuate this genetic risk [137, 538].

An interaction of total fat intake with *APOA1*-75 on WC was also reported in a longitudinal study of 821 participants of the BPRHS [445], in which individuals carrying two copies of the major allele had a lower WC with a low total fat intake than those carrying the minor allele ($P_{interaction}$=0.005). A longitudinal study performed in 1171 participants (333 men and 838 women) of the BPRHS [472] also observed that, women with the 'TT' genotype of lipoprotein lipase (*LPL)* SNP rs320 had lower BMI ($P_{interaction}$=0.002) and WC ($P_{interaction}$=0.001) with a high intake of PUFA but this was not observed in minor allele ('G') carriers and there were no significant interactions in men. In contrast, another longitudinal study of 1340 participants (395 men and 945 women) of the BPRHS [480] found that, men with the 'GG' genotype of brain derived neurotrophic factor (*BDNF)* SNP rs6265 had higher BMI ($P_{interaction}$=0.042), WC ($P_{interaction}$=0.018) and HC ($P_{interaction}$=0.009) with a low PUFA intake (<8.76% of energy) than those carrying the 'A' allele but no difference was observed when PUFA intake was high (≥8.76% of energy) and the interaction was not observed in women. Interaction between Mediterranean diet with *TCF7L2* SNP rs7903146 on obesity-related traits was also observed in a cross-section study of 1120 Puerto Ricans of the BPRHS [453], where carriers of the 'T' allele had lower WC (99.2 ± 0.9 vs 102.2 ± 0.9 cm; $P_{interaction}$=0.026) and weight (77.3 ± 1.0 vs 80.9 ± 1.0 kg; $P_{interaction}$=0.024) with a high Mediterranean diet score than individuals with 'CC' genotype. However, there were no significant differences between the genotypes when the Mediterranean diet score was low. The findings suggest that a high intake of PUFA and Mediterranean diet might be beneficial in reducing the genetic risk of obesity-related traits in a sex-specific manner and call for further research into the mechanisms involved.

5.4.6.2 Interaction between dietary fat intake and genetic variants on CVD traits

Interaction between total fat intake and genetic variants on CVD traits were reported by three studies [444, 445, 456]. In a longitudinal study of 802 participants of the BPRHS [444], a significant interaction was observed between total fat intake and *APOA5* SNP -1131T < C on plasma triglycerides ($P_{interaction}$=0.032), where a high total fat intake (≥31% of total energy) was associated with a higher plasma triglyceride concentration in individuals with the '1131C' allele, although no difference between the genotypes was observed when total fat intake was low. This study [444] also observed an interaction between *APOA5* SNP S19W with total fat intake on SBP ($P_{interaction}$=0.002) and DBP ($P_{interaction}$=0.007), where participants

with the minor allele ('G') had a higher SBP with a low total fat intake (<31% of total energy), and a lower SBP with a high total fat intake in comparison with individuals with the 'CC' genotype. The study on 821 participants of the BPRHS discussed above [445], also reported significant interactions between total fat intake and *APOC3* -640 on DBP ($P_{interaction}$=0.003), *APOA4* N147S and *APOA5* S19W on SBP ($P_{interaction}$=0.001 and $P_{interaction}$=0.002, respectively). It was observed that, homozygous for the major allele of *APOA1*-75, *APOA4* N147S and *APOA5* S19W had lower SBP with a low intake of total fat (<31% of total energy) than those carrying the minor allele; while heterozygous for *APOC3* -640 had lower DBP with a high total fat intake (≥31% from energy) [445]. However, a randomized crossover trial involving 41 adults from Dominican, Puerto Rican and other Caribbean Hispanic origins [456], did not find significant interactions between a high fat diet and hepatic lipase (*LIPC*) SNP rs1800588 on HDL, LDL, TC or plasma glucose concentrations. A high intake of total fat has been associated with an unfavourable lipid profile and high blood pressure [539] and the above findings indicate that, this association might be influenced by variants of several genes.

5.4.6.3 Interaction between carbohydrate intake and genetic variants on cardiometabolic traits

Two studies investigated the interaction between carbohydrate intake and genetic variants on cardiometabolic traits [479, 481]. In a longitudinal study involving 920 participants of the BPRHS [479], a significant interaction was observed between Perilipin 1 (*PLIN 1*) SNP 1482 G > A and complex carbohydrate intake on WC ($P_{interaction}$=0.002), where individuals carrying the 'A' allele had a higher WC with a low intake of complex carbohydrate (<144 g/day) and a lower WC with a high intake of complex carbohydrate (≥144 g/day) than those with the 'GG' genotype. Similarly, a cross-sectional study of 153 children descendent from Hispanic ancestry [481], identified significant interaction between carbohydrate intake (211.4 g/day) and total sugar intake (96.1 g/day), increasing hepatic fat fraction in carriers of the `GG´ genotype of Patatin like phospholipase domain containing 3 (*PNPLA3*) SNP rs738409 ($P_{interaction}$=0.04 and $P_{interaction}$=0.01, respectively), but the interaction was not observed in individuals carrying the 'C' allele. It has been reported that, body weight might be influenced by the type of carbohydrate consumed [540] which is supported by the findings of these studies, but the results also indicate that genetic variants might also play a role.

5.4.6.4 Interaction between micronutrient intake and genetic variants on cardiometabolic traits

The interaction between micronutrient intake and genetic variants on cardiometabolic traits was investigated by two studies [462, 469]. A cross-sectional study involving 1,734 Mexican Americans [469] reported a significant interaction between vitamin E and *APOB* SNP rs693 on LDL ($P_{interaction}$=8.94×10-7), and between vitamin A and *PCSK9* SNP rs11206510 on LDL ($P_{interaction}$=7.65×10-5), but the direction of the interactions is unclear. Similarly, in the longitudinal study of 1,144 Puerto Ricans of the BPRHS discussed above [462], a significant interaction between vitamin D status and *IRS1* rs2943641 on the risk of T2D was identified in women in which minor allele homozygotes ('TT') had a lower risk of T2D compared with 'C' allele carriers only when 25(OH)D was higher than the median [>17 ng/mL (42.4 nmol/L)] ($P_{interaction}$=0.007), but the interaction was not observed in men. The findings of these studies indicate that micronutrients might modulate the association between genetic variants and lipid and glycaemic traits, but further studies are needed to replicate and elucidate the mechanisms involved.

5.4.6.5 Interaction between physical activity and genetic variants on cardiometabolic traits

Only one study [482] examined the interaction between physical activity and genetic variants on cardiometabolic traits. This study [482] was a prospective cohort study of 9645 adult Puerto Ricans, Mexicans, Dominicans, Cuban, Central American, and South American from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) cohort, USA, and a positive association was observed between a GRS based on 97 SNPs (**Table 5.1**) and BMI, but the effect of the GRS was stronger in the first tertile of moderate to vigorous physical activity compared to the third tertile ($P_{interaction}$=0.005). Significant interactions following the same pattern were observed for fat mass ($P_{interaction}$=0.003), fat percentage ($P_{interaction}$=0.003) and fat mass index ($P_{interaction}$=0.002) [482].

In summary, research in LACP diaspora has mainly focused on Puerto Ricans residing in USA and most of this evidence (10 out of 13 studies) comes from the same study (BPRHS). Dietary fat intake has been the most frequently studied, with carbohydrate intake being examined by only two studies. Similarly, physical activity was investigated by only one study and lifestyle factors such as socioeconomic status, level of education, and the effect of rural and urban environments have not been explored.

5.4.7 Gene-lifestyle interactions in Chileans

5.4.7.1 Interaction between carbohydrate intake and genetic variants on glycaemic traits

Two gene-diet interaction studies were reported in Chileans [430, 463]. The first study [430] was a cross-sectional study of 2828 healthy Chilean adults, and a significant interaction was observed between consumption of SSB and a weighted genetic risk score (wGRS) based on 16 T2D risk SNPs (**Table 5.1**) on log-fasting glucose ($P_{interaction}$=0.02), where the strongest effect was observed between the highest SSB intake (≥2 servings/day of 330ml) and the highest wGRS. In this study [430], SSB intake also interacted with additive effects of Transcription Factor 7 Like 2 (*TCF7L2*) SNP rs7903146 ($P_{interaction}$=0.002) and with the 'G/G' genotype of Melatonin Receptor 1B (*MTNR1B*) SNP rs10830963 ($P_{interaction}$=0.001), increasing log-fasting glucose levels. The second Chilean study [463] was a non-randomized controlled trial performed in 97 healthy women and 147 women with polycystic ovary syndrome, and there were no reported interactions between a high glycaemic carbohydrate intake (75g of glucose) during an oral glucose tolerance test and Insulin Receptor Substrate 1 (*IRS-1*) SNP rs1801278 on glycaemic traits. In Chile, research has been limited to diabetes traits as outcomes and simple carbohydrates as exposure, reflecting a need for further research into other dietary and lifestyle factors such as socioeconomic status, level of education and the effect of rural and urban environments.

5.4.8 Gene-lifestyle interactions in Colombians

Two gene-lifestyle interaction studies were conducted in Colombians [436, 437]. The first study [436] was a case-control study involving 212 normal weight, 112 overweight and 100 obese teenagers and no significant interactions were observed between physical activity and three SNPs (Uncoupling Protein 3 (*UCP3*) rs1800849, *FTO* rs17817449 and *CAPN10* rs3842570) on excess weight. However, sub-group analysis showed that, a sedentary lifestyle was associated with an increased risk of excess weight only in those with the 'GG' or 'TT' genotype of *FTO* rs17817449 (p=0.0005); and 'CC' genotype of *UCP3* rs1800849 (*P*=0.0032) [436]. It was also observed that, even with an active lifestyle (1.6 – 1.9 metabolic equivalent task (MET) minute/day), individuals with the 'II' genotype of *CAPN10* rs3842570 had a higher risk of excess body weight compared to those carrying the 'D' allele (*P*=0.0212) [436]. The second study which was also a cross-sectional study involved 1081 Colombian teenagers [437], and there were no interactions between lifestyle factors (socioeconomic stratum, level of education and maternal breastfeeding) and ten SNPs on BMI (**Table 5.1**).

As both studies [436, 437] were conducted in teenagers and focused on obesity traits, there is a need for further research into other cardiometabolic traits in the wider Colombian population.

5.4.9 Gene-lifestyle interactions in Argentinians

Only one study [460] was conducted in Argentinians, and this was a cross-sectional study consisting of 572 healthy Argentinian men. This study [460] reported a significant interaction between smoking status and *PPAR-γ* SNP rs1801282 on the risk of MetS ($P_{interaction}$=0.031) where among the non-smokers, carriers of the *`Pro/Ala´* genotype (*P*=0.0059) and the *`Ala12´* allele (*P*=0.009) had a higher risk of MetS than non-carriers. It is unclear whether there were significant interactions between smoking status and rs1801282 genotype on the other outcomes investigated in the study [460] (**Table 5.1**), since the *p*-values given are for associations stratified by smoking status. The study adjusted for BMI and age only, but the pathophysiological mechanism of MetS is multifactorial [541], and hence other factors should be considered simultaneously. There have been no studies in Argentina examining the interactions of genetic variants with dietary factors, physical activity, or other lifestyle factors apart from smoking status.

5.5 Summary of the findings of commonly investigated interactions across the countries

The most commonly investigated interactions in LACP related to dietary fat intake and genetic variants on blood lipids. A high intake of olive oil was associated with lower LDL in Brazilian men with the *'E2'* allele of *APOE* [438], while a low MUFA intake was linked to higher TC, non-HDL and LDL in Mexicans carrying the *'E2'* allele of *APOE* [441]. In contrast, increased TG concentration in response to a high MUFA intake was observed in Mexicans who were homozygotes for the A2 allele of *DRD2/ANKK1* SNP rs1800497. A high PUFA intake was also associated with increased concentration of LDL in Brazilian carriers of the *'E4'* allele, and reduced concentration of TG in those carrying the *'E2'* allele of *APOE* [438]. However, a low PUFA intake was linked to increased TG and VLDL concentration in Brazilian women with the *'E4'* allele of *APOE* [439].

Furthermore, a high SFA intake was associated with higher VLDL and lower HDL concentrations in Costa Rican carriers of the *'E2'* allele of *APOE* [442], but no significant interactions were identified between SFA intake and *APOE* genotype on blood lipids in a Costa-Rican case-control study involving participants with MI [421]. However, a high SFA intake was linked to increased concentrations of TC and LDL in Costa Ricans who were

homozygotes for the *APOC3-455T-625T* alleles [457]. Similarly, a high SFA intake was associated with increased TC and TG concentrations in Mexicans with the 'G' allele of *LEPR* SNP rs1137101 [443]; while a low SFA intake was linked to a decrease in TC and LDL concentrations in Mexicans with the 'G' allele of *GFOD2* SNP rs12449157 [476].

The inconsistencies in the findings of the above studies call for further research into the interaction between sub-types of fat and genetic variants on blood lipids. The sources of dietary fat also need to be considered since SFA from different food sources have been reported to have different effects on cardiometabolic traits [390].

5.6 Discussion

This is the first systematic review to investigate gene-lifestyle interactions on cardiometabolic diseases in LACP, highlighting several gene-lifestyle interactions with effects being significant in Brazilians, Mexicans, Costa Ricans, Chileans, Argentinians, Colombians and LACP diaspora. The most frequently studied genes have been *FTO*, examined in Colombians, Mexicans, and Brazilians, *APOE* explored in Costa Ricans, Mexicans, and Brazilians, and *TCF7L2* investigated in Chileans, Mexicans, Brazilians and LACP diaspora. The concentration of blood lipids such as HDL and LDL was the most widely investigated trait, followed by BMI and WC; MI was examined by eleven studies and one study looked at hepatic fat accumulation, while diseases such as stroke and liver cirrhosis were not investigated. Research has identified gene-lifestyle interactions that describe effects which are population-, gender-, and ethnic-specific. The findings of this review indicate that most of the gene-lifestyle interactions were conducted once, necessitating replication to strengthen the evidence.

Another issue that could affect the results is the accuracy of the methods used to measure exposure variables such as dietary intake and physical activity [393, 542]. Some studies used 24-hour recall questionnaires and self-reporting methods [139, 419, 420, 449, 454, 469], which might have induced recall bias, inadequate estimations, daily variation bias, and over and underreporting of values [152, 395]. Measurement of dietary intake is a crucial part of gene-diet interaction studies as under or overestimation of dietary intake can weaken or reverse the association between dietary factors and cardiometabolic traits [152, 543]. Moreover, other studies used food frequency questionnaires with no information on whether they were tested for validity. Genotyping errors can also affect the results of gene-diet interactions by leading to deviations from the true genotype [169, 544].

Sample size has also been highlighted as a key methodological issue in gene-lifestyle interaction studies [393, 542]. For complex traits where the main effects of genetic variants are often modest, a large sample size is required to detect small interaction effects [393, 394].Thus, it is important that studies are adequately powered to detect true interactions [542]. Nonetheless, most of the studies had small sample sizes and only a few included information on statistical power to detect interactions. There is also the risk of false-positive finding when there is no correction for multiple comparisons [169, 545], but only a few of the studies provided information on correction for multiple comparisons.

Overall, the included studies are majorly cross-sectional, indicating a need for longitudinal/prospective studies. The findings reflect gaps in covering the genetic risks and the socioeconomic variables to which the LACP are exposed; 27 out of 33 LACP have not conducted gene-lifestyle interaction studies yet. Only five studies have been conducted in contexts of low socioeconomic status, and from these, only two studies investigated gene-socioeconomic status interactions [420, 437]. Moreover, no studies have examined the impact of rural and urban environments on the genetic predisposition to cardiometabolic diseases, highlighting a gap in knowledge in LACP. The higher number of nutrigenetic studies in Brazil compared to the other countries could be attributed to several factors including existing data on genetic studies [546-551], GWA studies done mainly in Brazil [552-554], increased awareness on nutrigenetics in Brazil or more research facilities available in Brazil compared to other LACP. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and the built environment. Moreover, the molecular mechanisms that underlie the gene-lifestyle interactions identified by this systematic review need to be explored. The strength of this review is the comprehensive search strategy and the inclusion of all dietary/lifestyle exposures and cardiometabolic traits. Another strength is the use of standardized tools to assess the quality of the studies. However, the study has some limitations.

5.7 Conclusion

In conclusion, this systematic review has identified several gene-lifestyle interactions on cardiometabolic disease traits in Brazilians, Mexicans, Costa Ricans, Chileans, Argentinians, Colombians and LACP diaspora, highlighting effects which are population-, gender-, and ethnic-specific. However, the lack of replication of most of the gene-lifestyle

interactions made it difficult to evaluate the evidence. Moreover, most of the studies were cross-sectional meaning that they preclude causal assumptions hence a temporal relationship cannot be established. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and the built environment. Moreover, the molecular mechanisms that underlie the gene-lifestyle interactions identified by this systematic review need to be explored.

Chapter 6 Impact of lipid genetic risk score and saturated fatty acid intake on central obesity in an Asian Indian population

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Ramatu Wuni's contribution: I started this study by writing up a data analysis plan which was approved by my primary supervisor. I then cleaned the raw dataset, evaluated the variables and log-transformed non-normally distributed variables prior to the analysis. I performed all the statistical analyses using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA). I interpreted the results, carried out a literature search and wrote the manuscript. I revised the manuscript based on comments and suggestions from the co-authors. I formatted the manuscript according to the guidelines of Nutrients before it was submitted for publication. I also wrote the responses to the reviewers' comments and revised them based on suggestions from the co-authors.

6.1 Abstract

Abnormalities in lipid metabolism have been linked to the development of obesity. We used a nutrigenetic approach to establish a link between lipids and obesity in Asian Indians, who are known to have a high prevalence of central obesity and dyslipidaemia. A sample of 497 Asian Indian individuals (260 with type 2 diabetes and 237 with normal glucose tolerance) (mean age: 44 ± 10 years) were randomly chosen from the Chennai Urban Rural Epidemiological Study (CURES). Dietary intake was assessed using a previously validated questionnaire. A genetic risk score (GRS) was constructed based on cholesteryl ester transfer protein (*CETP*) and lipoprotein lipase (*LPL*) genetic variants. There was a significant interaction between GRS and saturated fatty acid (SFA) intake on waist circumference (WC) ($P_{interaction}$=0.006). Individuals with a low SFA intake (≤23.2 g/day), despite carrying ≥2 risk alleles, had a smaller WC compared to individuals carrying <2 risk alleles (Beta=−0.01 cm; *P*=0.03). For those individuals carrying ≥2 risk alleles, a high SFA intake (>23.2 g/day) was significantly associated with a larger WC than a low SFA intake (≤23.2 g/day) (Beta=0.02 cm, *P*=0.02). There were no significant interactions between GRS and other dietary factors on any of the measured outcomes. We conclude that a diet low in SFA might help reduce the genetic risk of central obesity confirmed by *CETP* and *LPL* genetic variants. Conversely, a high SFA diet increases the genetic risk of central obesity in Asian Indians.

6.2 Introduction

Asian Indians are more prone to developing type 2 diabetes (T2D) and cardiovascular diseases (CVDs) at a lower body mass index (BMI) than Caucasians, due to the 'Asian Indian phenotype', which is characterised by central obesity, dyslipidaemia, and increased levels of total fat, visceral fat, insulin resistance and faster decline in beta cell function [105, 119, 120]. The location of body fat is thought to be more important in predicting adverse cardiovascular events [555-557]. Central obesity has been linked to several conditions, including insulin resistance and increased mortality from CVDs [558-561], necessitating studies to fully understand the underlying mechanisms for the development of central obesity in Asian Indians.

Abnormalities in lipid metabolism have been linked to the development of obesity, and lipoprotein lipase (LPL), a key enzyme in lipid metabolism, contributes to the development of obesity through its role in the partitioning of lipids to different tissues [472, 561, 562]. Cholesteryl ester transfer protein (CETP), mainly expressed in adipose tissue, is also a major enzyme in lipid metabolism, which mediates the transport of cholesteryl esters and triglycerides (TG) between high-density lipoprotein cholesterol (HDL) and apolipoprotein B (ApoB)–containing lipoproteins such as very-low-density lipoprotein (VLDL) [64]. Increased CETP activity results in lower HDL concentration, which is associated with higher risk of CVDs [46]. Consumption of a high saturated fatty acid (SFA) diet has also been shown to contribute to obesity by decreasing cholesterol efflux due to reduced expression of peroxisome proliferator-activated receptors involved in lipid metabolism [68, 69, 386]. Genome-wide association (GWA) and candidate gene studies have demonstrated that lipid levels are influenced by single nucleotide polymorphisms (SNPs) in lipid-pathway genes [94, 107, 108, 126, 201, 204]. SNPs of the *CETP* gene have been associated with HDL concentrations [94, 95, 97, 195, 197, 199], while SNPs of the *LPL* gene have been associated with both HDL and TG levels [94, 193, 205, 339]. A recent review of GWA studies of lipids [130] showed that *CETP* SNPs had the highest number of associations with lipids, followed by *LPL* SNPs. *CETP* and *LPL* SNPs have also been associated with obesity-related traits [127, 563].

Several studies have shown significant interactions between genetic variants and lifestyle factors regarding the association between lipid profile and obesity-related traits [105, 126-128, 245], but the findings have been inconsistent. Moreover, it has been shown that the effect size of individual SNPs is modest and less likely to accurately predict the risk of complex diseases, and a more effective approach involves combining several risk alleles to generate a genetic risk score (GRS) [128, 370]. Nonetheless, studies investigating

interactions between GRS and dietary factors on lipid and obesity-related traits have not been adequately performed in Asian Indians. Hence, the aim of this study was to examine the effect of a GRS and its interaction with dietary factors on lipid and obesity-related traits in Asian Indian adults with and without T2D.

6.3 Methods

6.3.1 Study participants

A sample of 497 individuals (260 with T2D and 237 with normal glucose tolerance (NGT)) were randomly chosen from an epidemiological study called the Chennai Urban Rural Epidemiological Study (CURES), details of which have been given in previous publications [18, 105, 126-128, 131, 251, 280, 564, 565]. Briefly, a total of 26,001 adults residing in the urban part of Chennai in Southern India were recruited by systematic random sampling between 2001 to 2003, and those who reported having T2D (1529 individuals) were tested to confirm their diagnosis [105, 564]. The follow-up study was conducted between 2012 to 2013 and consisted of 2410 participants (**Figure 6.1**). The sample for the current study was selected from the follow-up cohort. Participants were excluded if they were taking lipid-lowering medication such as statins and fibrates. Ethical approval was granted by the Madras Diabetes Research Foundation Institutional Ethics Committee and written informed consent was obtained from study participants [105].

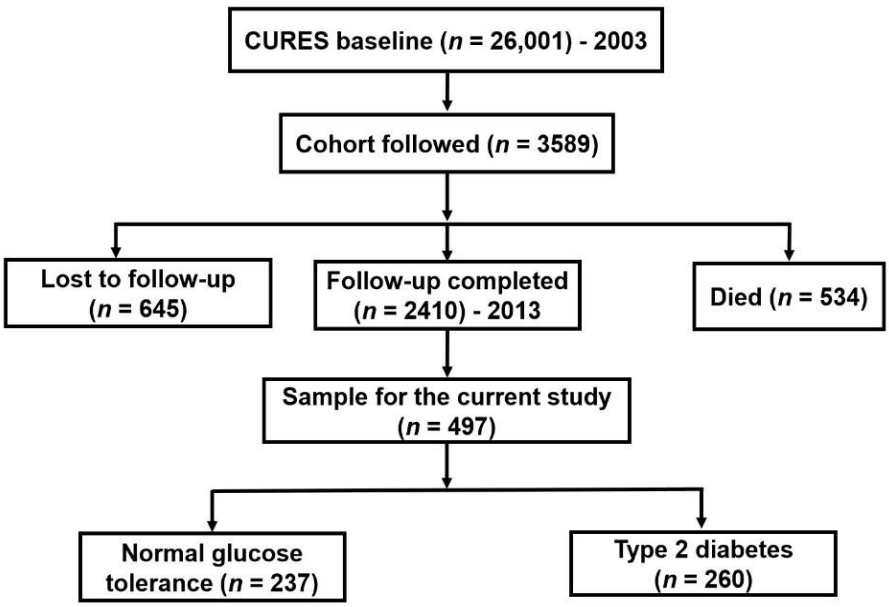

Figure 6.1 A flow chart showing the selection of participants from the CURES

6.3.2 Anthropometric and biochemical measurements

Anthropometric measurements including height, weight, waist circumference (WC), hip circumference, and waist–hip ratio (WHR) were obtained using standardized techniques. BMI was calculated as weight in kilograms (kg) divided by the square of the height in meters (m). Individuals with BMI <25 kg/m^2 were classified as non-obese and those with BMI ≥25 kg/m^2 were classified as obese, in accordance with the World Health Organisation Asia Pacific Guidelines [283]. Biochemical analyses were conducted using Hitachi-912 Auto Analyzer (Hitachi, Mannheim, Germany) with kits supplied by Roche Diagnostics (Mannheim). Serum total cholesterol was measured by cholesterol oxidase-phenol-4-amino-antipyrene peroxidase method and HDL by direct method-polyethylene glycol-pretreated enzymes. Serum TG was measured by glycerol phosphatase oxidase-phenol-4-amino-antipyrene peroxidase method, and low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula [330]. Serum insulin concentration was estimated using an enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark), fasting plasma glucose (FPG) by glucose oxidase-peroxidase method, and glycated haemoglobin (HbA1c) by high-performance liquid chromatography using a Variant™ machine (Bio-Rad, Hercules, CA, USA).

6.3.3 Dietary assessment

Dietary intake was assessed by an interviewer using a previously validated semi-quantitative food frequency questionnaire (FFQ) containing 222 items [282]. Participants were asked to estimate how much and how often they consumed various food items in the FFQ (number of times per day, week, month, year or never). The FFQ was designed to estimate the usual dietary intake of participants on a meal-by-meal basis. Open-ended questions were used to enable participants to estimate the frequency of their usual dietary intake. To help in estimating portion sizes, participants were shown common household measures such as spoons and cups and pictures of different sizes of fruits. The data were analysed using the Nutritional Epidemiology ('EpiNu') software to estimate average daily intake of macronutrients and total energy. Consumption of SFA, polyunsaturated fatty acid (PUFA), monounsaturated fatty acid (MUFA) and other macronutrients was estimated from the FFQ using the 'EpiNu' software which contains information on the nutritional content of commonly consumed food in the Chennai area. The 'EpiNu' software was developed for the local population using recipes from various sources including home-made and fast-food. Details of the development of the FFQ and the 'EpiNu' software are published elsewhere [282].

6.3.4 SNP selection and genotyping

Five SNPs (*CETP* SNP: rs4783961; and *LPL* SNPs: rs327, rs3200218, rs1800590 and rs268) were selected for this study based on their association with lipid-related traits in different ethnic groups, including Asian Indians [94, 127, 201, 204, 566-569]. Two SNPs (rs268 and rs1800590) had a minor allele frequency <5% (**Supplementary Table S6.1**), and hence, they were excluded. The remaining three SNPs (rs327, rs3200218 and rs4783961) were included in the current analysis. The genotyping methodology has been previously published [19]. Briefly, the DNA was extracted from whole blood using the phenol–chloroform method, and the SNPs were genotyped by the polymerase chain reaction-restriction fragment length polymorphism method.

6.3.5 Construction of GRS

An additive model was used to construct an unweighted GRS by adding the number of risk alleles across the three SNPs (rs327, rs3200218 and rs4783961) for each participant. The risk alleles were defined as alleles previously reported to be associated with dyslipidaemia or obesity-related traits. The risk alleles were not weighed due to limited available information on effect sizes of the SNPs for the Asian Indian population. Moreover, it has been demonstrated that assigning weights to risk alleles only has minimal effect [370], and hence, we used an unweighted GRS. The 3-SNP GRS ranged from 0 to 5 and based on the median GRS (2 risk alleles), participants were placed into two groups: low-risk group (for individuals with a GRS <2 risk alleles) and high-risk group (for individuals with a GRS ≥2 risk alleles).

6.3.6 Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA) and the data analysis plan is attached as an appendix (**Appendix C**). Normality test was performed by Shapiro–Wilk test, and all biochemical and anthropometric variables were log-transformed before the analysis. Results of descriptive statistics for continuous variables are presented as means and standard deviation (SD) and categorical variables as percentages [105]. Allele frequencies were determined by gene counting and a goodness-of-fit Chi-square test was performed to examine if the observed genotype counts were in Hardy-Weinberg equilibrium (HWE) (**Supplementary Table S6.1**). The three SNPs were all in HWE (P>0.05), and the alleles had a frequency greater than 5%. An independent sample t test was used to compare the means of the quantitative variables between individuals with low GRS (<2 risk alleles)

and those with high GRS (≥2 risk alleles). A Chi-squared test was performed to compare categorical variables such as smoking status between individuals in the low (GRS <2 risk alleles) and high-risk (GRS ≥2 risk alleles) groups.

Linear and logistic regression analyses were used to examine the association of the 3-SNP GRS with continuous and categorical outcomes, with adjustment for age, sex, BMI, T2D, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake wherever appropriate. Interactions between GRS and dietary factors were analysed by adding the interaction term in the regression models. For GRS–diet interactions, total energy was adjusted for, in addition to the other covariates. The dietary factors investigated in this study were consumption of fat, carbohydrate, protein, and dietary fibre. GRS–diet interactions reaching statistical significance (P<0.05) were investigated further by stratifying individuals based on the quantity of dietary intake. A significant interaction of GRS with total fat was explored further to include subtypes of fats (SFA, PUFA and MUFA). A median intake of total fat, SFA, MUFA, and PUFA was used to classify individuals into two groups, 'low' (lower than median) and 'high' (higher than median) group, and association between GRS and the outcome was then analysed for each group.

6.4 Results

6.4.1 Characteristics of the study participants

The mean age of the study participants was 44 ± 10 (**Table 6.1**). At baseline, there were no significant differences in anthropometric traits (BMI, WC and WHR), lipid sub-fractions (HDL, LDL, TG, and total cholesterol), systolic blood pressure (SBP) and diastolic blood pressure (DBP), or glycaemic traits (FPG, fasting serum insulin, insulin resistance and HbA1c) between participants with low GRS (<2 risk alleles) and those with high GRS (≥2 risk alleles). Furthermore, consumption of macronutrients did not differ significantly between participants with low GRS (<2 risk alleles) and those with high GRS (≥2 risk alleles) as shown in Table 1. Smoking was higher among individuals with high GRS (≥2 risk alleles) compared to those with low GRS (<2 risk alleles) (P=0.03). The baseline HDL concentration was significantly higher in women than in men (43.5 ± 1.3 vs. 38.7 ± 1.3 mg/dL; $P=2.3 \times 10^{-8}$).

Table 6.1 Characteristics of the study participants

	All Participants (*n*=497)	**GRS<2 (*n*=239)**	**GRS≥2 (*n*=258)**	***P* value ***
Age (years)	44 ± 10	45 ± 10	44 ± 9	0.34
Sex [Men (%),Women (%)]	225 (45), 272 (55)	106 (47), 133 (49)	119 (53), 139 (51)	0.69
BMI (kg/m^2)	24.6 ± 4.5	24.7 ± 4.7	24.4 ± 4.3	0.41
WC (cm)	87 ± 11	88 ± 12	87 ± 11	0.39
WHR	0.92 ± 0.08	0.92 ± 0.09	0.91 ± 0.08	0.57
Obese cases (%)	209 (42)	109 (52)	100 (48)	0.12
HDL (mg/dL)	42 ± 10	42 ± 10	42 ± 10	0.79
LDL (mg/dL)	119 ± 32	118 ± 32	119 ± 32	0.81
TG (mg/dL)	165 ± 150	166 ± 120	164 ± 173	0.87
Total cholesterol (mg/dL)	191 ± 40	192 ± 42	190 ± 38	0.64
Systolic BP (mmHg)	122 ± 20	123 ± 22	120 ± 18	0.15
Diastolic BP (mmHg)	76 ± 11	76 ± 12	75 ± 11	0.60
Fasting plasma glucose (mg/dL)	126 ± 65	126 ± 64	127 ± 67	0.79
Fasting serum insulin (μIU/mL)	9 ± 6	9 ± 6	9 ± 7	0.89

Insulin resistance	3 ± 2	3 ± 2	2 ± 2	0.44
HbA1c (%)	7 ± 2	7 ± 2	7 ± 2	0.91
Fat (g)	67 ± 27	67 ± 26	67 ± 27	0.83
Carbohydrate (g)	410 ± 136	410 ± 134	411 ± 138	0.92
Protein (g)	72 ± 24	73 ± 24	72 ± 23	0.63
Dietary fibre (g)	32 ± 12	32 ± 12	32 ± 11	0.77
Energy (kcal/day)	2560 ± 822	2560 ± 809	2559 ± 834	0.99
Total SFA (g)	25 ± 11	25 ± 11	25 ± 11	0.91
Total MUFA (g)	20 ± 8	20 ± 8	21 ± 9	0.79
Total PUFA (g)	19 ± 9	18 ± 9	19 ± 10	0.77
Plant protein (g/day)	41 ± 14	40 ± 13	42 ± 14	0.23
Animal protein (g/day)	23 ± 13	23 ± 12	22 ± 13	0.75
Smokers (%)	88 (18)	33 (38)	55 (63)	0.03
Alcohol drinkers (%)	123 (25)	52 (42)	71 (58)	0.14
T2D cases (%)	260 (52)	131 (50.4)	129 (49.6)	0.28

Data are mean ± standard deviation or frequencies where appropriate. *P values for the differences in means/frequencies between participants with low GRS and those with high GRS. p values were calculated using independent sample t test for continuous variables and Chi-square test

for categorical variables. BMI – body mass index; WC – waist circumference; WHR – waist hip ratio; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; TG – triglycerides; HbA1c – glycated haemoglobin; SFA – saturated fatty acids; MUFA – monounsaturated fatty acids; PUFA – polyunsaturated fatty acids.

6.4.2 Association of GRS with lipid and obesity-related traits

There was no significant association between GRS and any of the outcomes measured (HDL, LDL, TG, total cholesterol, SBP, DBP, BMI, WC, WHR and obesity) after adjusting for the confounding factors, age, sex, BMI, T2D, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake where appropriate (**Supplementary Tables S6.2 and S6.3**).

6.4.3 Interaction of GRS with dietary factors on lipid and obesity related traits

A significant interaction was observed between GRS and total fat intake on WC ($P_{interaction}$=0.03) after adjusting for age, sex, T2D, duration of diabetes, anti-diabetic medication, smoking status, alcohol intake, and total energy intake (**Table 6.2**). When individuals were stratified based on the median intake of total fat, there were no significant associations between GRS and total fat intake on WC, and when sub-types of fat were investigated (**Figure 6.2**), there was a significant interaction of GRS with SFA intake on WC ($P_{interaction}$=0.006) and MUFA intake on WC ($P_{interaction}$=0.004). In the low SFA intake group (≤ 23.2 g/day), individuals carrying ≥2 risk alleles had a smaller WC compared to those carrying <2 risk alleles (Beta =−0.01 cm, *P*=0.03), while in the high SFA intake group (>23.2 g/day), there was no significant difference in WC between participants carrying ≥2 risk alleles and those carrying <2 risk alleles. For those individuals carrying ≥2 risk alleles, a high SFA intake (> 23.2 g/day) was significantly associated with a larger WC than a low SFA intake (≤23.2 g/day) (Beta=0.02 cm, *P*=0.02). When individuals were grouped based on the median MUFA intake, there was no association between GRS and MUFA intake on WC. To examine whether the interactions of GRS with fat intake and SFA intake on WC were mediated by lipids, we included the four lipid subfractions (HDL, LDL, TG and total cholesterol) as confounding factors in addition to other confounding factors and found that the interaction was no longer significant for total fat intake ($P_{interaction}$=0.08), but it remained significant for SFA intake ($P_{interaction}$=0.02).

Table 6.2 Interaction of GRS with dietary factors on blood lipids, blood pressure, obesity-related traits, and obesity

Trait	GRS * Fat (g)	GRS * Carbohydrate (g)	GRS * Protein (g)	GRS * Dietary Fibre (g)
	Beta Coefficient ± SE ($P_{interaction}$)	**Beta Coefficient ± SE ($P_{interaction}$)**	**Beta Coefficient ± SE ($P_{interaction}$)**	**Beta Coefficient ± SE ($P_{interaction}$)**
BMI (kg/m²)	0.05 ± 0.04 (0.21) [a]	0.04 ± 0.05 (0.36) [a]	0.04 ± 0.05 (0.35) [a]	−0.01 ± 0.04 (0.77) [a]
WC (cm)	0.06 ± 0.03 (**0.03**) [a]	0.05 ± 0.03 (0.18) [a]	0.07 ± 0.04 (0.07) [a]	0.00 ± 0.03 (0.93) [a]
Waist hip ratio	0.01 ± 0.02 (0.52) [b]	0.00 ± 0.02 (0.98) [b]	0.01 ± 0.02 (0.58) [b]	−0.01 ± 0.02 (0.62) [b]
Common obesity	−1.76 ± 1.14 (0.12) [a]	0.10 ± 0.08 (0.20) [a]	−2.52 ± 1.41 (0.08) [a]	−0.35 ± 1.26 (0.78) [a]
HDL (mg/dL)	−0.04 ± 0.05 (0.42) [b]	−0.07 ± 0.06 (0.23) [b]	−0.07 ± 0.06 (0.21) [b]	−0.04 ± 0.05 (0.47) [b]
LDL (mg/dL)	0.02 ± 0.06 (0.82) [b]	0.02 ± 0.08 (0.79) [b]	−0.01 ± 0.08 (0.90) [b]	−0.02 ± 0.07 (0.81) [b]
TG (mg/dL)	0.10 ± 0.12 (0.39) [b]	−0.01 ± 0.15 (0.97) [b]	−0.02 ± 0.15 (0.89) [b]	0.08 ± 0.13 (0.57) [b]
Total cholesterol (mg/dL)	0.02 ± 0.04 (0.70) [b]	−0.00 ± 0.06 (0.98) [b]	−0.02 ± 0.06 (0.65) [b]	−0.00 ± 0.05 (0.98) [b]
Systolic BP (mmHg)	0.03 ± 0.03 (0.35) [b]	0.03 ± 0.04 (0.49) [b]	0.03 ± 0.04 (0.48) [b]	0.04 ± 0.03 (0.25) [b]
Diastolic BP (mmHg)	0.02 ± 0.03 (0.50) [b]	0.01 ± 0.04 (0.87) [b]	0.03 ± 0.04 (0.51) [b]	0.01 ± 0.04 (0.72) [b]

GRS – genetic risk score; BMI – body mass index; WC – waist circumference; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; TG – triglycerides. *P* values were obtained from linear regression analysis for continuous traits and logistic regression analysis for obesity. [a] *P* values adjusted for age, sex, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, alcohol

intake, and total energy intake. [b] *P* values adjusted for age, sex, BMI, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, alcohol intake, and total energy intake. Log-transformed variables were used for the analysis. *P*-value in bold represents statistically significant interaction.

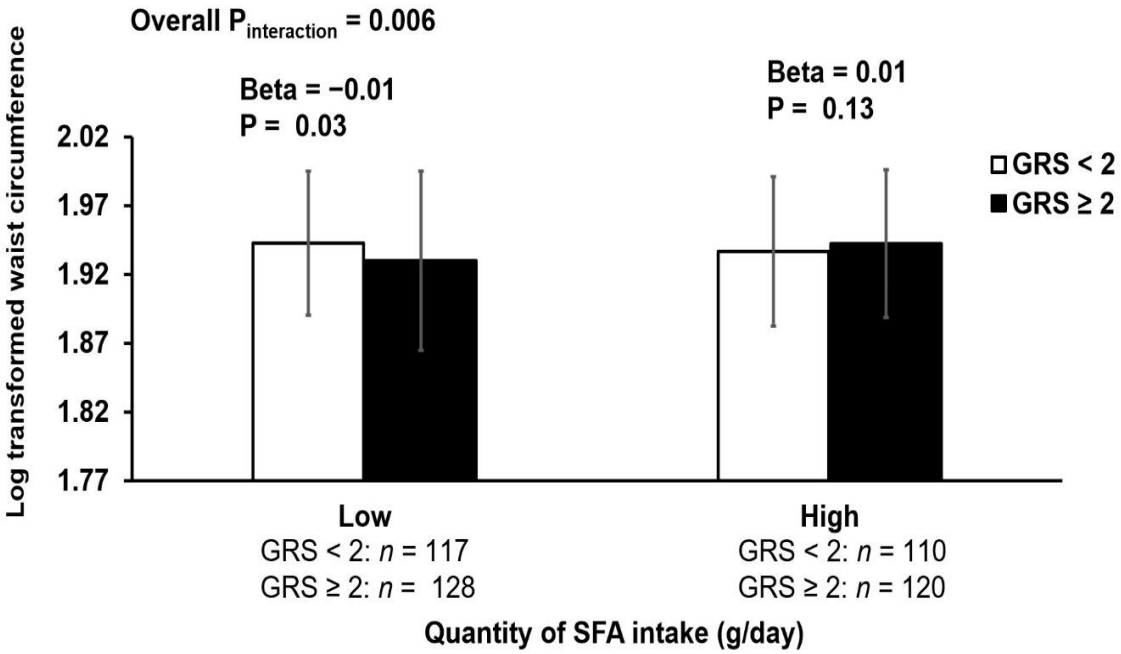

Figure 6.2 Interaction of GRS with SFA intake on log-transformed waist circumference.

P values adjusted for age, sex, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake. Low (≤23.2) and high (>23.2) refer to lower or equal to median and higher than median intake of SFA (g/day) respectively. In the low SFA intake group (≤23.2 g/day), individuals carrying 2 or more risk alleles had a smaller waist circumference compared to those carrying less than 2 risk alleles (Beta =−0.01, *P*=0.03), and in the high SFA intake group (>23.2 g/day), there was no significant difference in waist circumference between participants carrying 2 or more risk alleles and those carrying less than 2 risk alleles.

6.5 Discussion

Our study has shown that SFA intake may modify the effect of lipid-pathway genes on central obesity in Asian Indians. Our findings indicate that the combined effect of *LPL* and *CETP* SNPs (rs327, rs3200218 and rs4783961) on obesity traits may be altered by SFA intake, where consumption of high amounts of SFA may increase the combined genetic risk of central obesity posed by *LPL* and *CETP* SNPs while a low intake of SFA may help to reduce this risk. These findings are of public health importance considering the burden of central obesity in Asian Indians [119, 255, 570-572]. Our results suggest that Asian Indians with a higher genetic risk for central obesity are responsive to SFA intake and could benefit from dietary modifications to help prevent central obesity in Asian Indians.

An examination of the fatty acid profile of commonly consumed foods in India showed that milk and milk products were the main source of SFA and the median intake of SFA was 8.7% of total energy intake per day [573]. However, some of the commonly consumed food, such as potato chips, contained high amounts of palmitic acid, which could be attributed to the type of cooking oil used in their preparation [573]. The WHO's dietary guidelines [71] state that SFA consumption should be less than 10% of total energy intake, and the National Dietary Guidelines Consensus Group [574] recommends that for Asian Indians who have higher LDL concentration (≥100 mg/dL), SFA intake should be <7% of total energy intake per day. Moreover, intake of SFA at 8.6% of total energy was found to be associated with increased risk of T2D in Indians [573]. In the present study, the median intake of SFA was 8.5% of total energy intake, which is within the WHO's dietary guidelines [71], but as Indians are predisposed to dyslipidaemia, reducing SFA even further as recommended by the National Dietary Guidelines Consensus Group [574] might help to prevent central obesity in individuals with a high genetic risk.

Abnormalities in lipid metabolism have been linked to the development of obesity [386, 575]. We used a nutrigenetic approach to see if dietary intake can modify this link by employing a GRS from the two lipid pathway genes, *CETP* and *LPL*, which have been shown to have the strongest effect on lipid concentrations [94, 95, 130, 193, 195, 197, 199, 202]. To account for the effect of T2D on lipid levels, we adjusted for T2D status, anti-diabetic medication, and duration of T2D in our analysis. We found significant interactions between GRS and total fat, SFA and MUFA intake on WC, where a low intake of SFA (≤23.2 g/day) was found to be associated with a smaller WC in individuals with a higher genetic risk compared to those with a lower genetic risk. We also found that a high SFA intake (>23.2 g/day) was significantly associated with a larger WC than a low SFA intake (≤23.2 g/day) in individuals

with a high genetic risk. Our findings are in agreement with the results of a double-blind, randomized, crossover, controlled-feeding trial performed in 101 participants from Canada and the United States [386] where consumption of a diet low in SFA and high in unsaturated fatty acids resulted in increased serum-mediated cholesterol efflux which showed a negative association with WC (Beta=−0.25, *P*=0.01) and abdominal adiposity (Beta=−0.33, *P*=0.02). A parallel controlled-feeding trial performed in 20 individuals who were centrally overweight [68] also showed that consumption of a high SFA diet resulted in an increase in the expression of inflammatory genes in adipose tissue and a decrease in the expression of genes involved in fatty acid β-oxidation and synthesis of triglycerides, which could explain the increase in WC with a high SFA intake observed in our study. *LPL* was chosen as one of the candidate genes for the present nutrigenetic study, given that significant associations between *LPL* SNPs and obesity traits have been reported by previous studies in addition to their association with lipid traits. In a case-control study of 944 Koreans [567], the *LPL* SNP rs3200218, which is in the 3′-UTR, was shown to be associated with WHR (*P*=0.009), and in a previous study in CURES participants [127], carriers of the minor allele (G) of *LPL* SNP rs1800590 had a larger WC (*P*=0.03) and higher BMI (*P*=0.003) compared to those carrying two copies of the major allele (T). Increased risk of common obesity (2.73-fold increase) among carriers of the minor allele of *LPL* rs1800590 was also observed in Northern Indians [566]. Furthermore, LPL is a rate-restricting enzyme for the hydrolysis of TG in chylomicrons and VLDL [562], and it has been suggested that the level of LPL activity in muscle relative to that in adipose tissue determines body mass composition and contributes to obesity by influencing the rate at which fatty acids derived from TG are used or stored [561]. This suggests that SNPs that alter LPL activity in muscle and adipose tissue could affect obesity related traits. It has also been shown that SFAs are associated with a lower postprandial oxidation rate [576] and decreased energy expenditure [577] than MUFA.

Another important candidate gene for the study is *CETP*, the SNPs in which have been reported to influence obesity and lipid-related traits. The 'A' allele of the SNP rs4783961 has been shown to influence the concentration of CETP mass in plasma by producing binding motifs for transcription factor SP3, which modulates *CETP* promoter activity [578, 579], but studies examining the association of rs4783961 with obesity traits are limited. However, the 'A' allele of rs4783961 has been linked to higher HDL concentration in Taiwanese [580] (an increase of 1.71 mg/dL per allele, standard error (SE)=0.52; *P*=0.001) and African Americans [204] (Beta=4.6, SE=1.3; *P*=0.0009). A study involving 10,366 African American, 26,647 European American, 1410 Hispanics and 717 Chinese American participants from nine

cohorts [117] also reported that the 'A' allele of rs4783961 was associated with increased HDL concentration in all the cohorts, but the effect size was larger in African Americans (0.17 to 0.24) than in European Americans (0.09 to 0.15) (P=2 × 10^{-10}). The mechanism under which rs4783961 affects obesity traits are unclear, although it has been proposed that *CETP* SNPs might affect deposition of fat in visceral adipose tissue by being in linkage with SNPs of other genes [65]. Nonetheless, association of other *CETP* SNPs with obesity traits have been previously reported. A cross-sectional study of 1005 Spanish individuals who were obese [581] reported that participants carrying the 'A' allele of *CETP* SNP rs1800777 compared to non-carriers had higher WC (Delta: 5.6 ± 2.1 cm; P=0.02), WHR (Delta: 0.04 ± 0.01 cm; P=0.01) and fat mass (Delta: 4.4 ± 1.1 kg; P=0.04). Similarly, a study performed in 571 Chinese individuals [563] observed that participants with the 'GT' genotype of *CETP* SNP rs3764261 had a reduced risk of central obesity (Odds ratio (OR) = 0.631, 95% confidence interval (CI) = 0.460–0.865; P=0.004), and a study involving 3575 Dutch participants [582] reported that the minor allele of *CETP* SNP rs5882 was associated with a decreased prevalence of central obesity (OR=0.90, 95% CI=0.83–0.97; P=0.007).

Our findings of significant interactions between GRS and dietary fat intake on WC are consistent with a previous study [575]. This study [575], which consisted of 199 overweight/obese Spanish adolescents and involved a weight loss intervention, showed that each minor allele of *CETP* SNP rs1800777 was associated with a −1.4 kg decrease in body weight after 10 weeks (P=1.5 × 10^{-4}). Studies examining CETP and obesity have mainly focused on the impact of body weight on CETP mass and activity [583-585]. A study involving 21 morbidly obese female participants (BMI >40 kg/m^2) [583] who underwent a weight loss procedure concluded that weight loss was associated with a marked decrease in CETP mass and activity. Another study involving 51 normal weight individuals [585] also reported that participants with a body weight of around 46 kg had 15% lower serum CETP compared to those with a body weight of about 55 kg. However, an anti-adipogenic effect of CETP in the presence of apolipoprotein CIII (apoCIII) was reported by an animal study involving *CETP* and *apoCIII* transgenic mice [586], where obesity induced by a high-fat diet was reversed by the expression of *CETP*. As this study did not look at *CETP* SNPs, it is unclear whether different *CETP* SNPs will have the same effect. Individually, the SNPs in our study did not show any significant interaction with dietary factors. The discrepancies in findings between our study and others could be because of allele frequencies and effect sizes which differ between populations [105, 130]. Another plausible explanation is differences in dietary pattern and the methods used to assess dietary intake [105]. Moreover, a systematic review

of observational studies [587] concluded that SFAs were not linked to CVDs, and an analysis of data from randomized controlled trials [588] indicated that replacing SFA with linoleic acid was effective in lowering total cholesterol but there was no benefit in terms of lower risk of CVDs or death. However, large cohort studies [294, 390] have indicated that the effect of SFA is dependent on the type and food sources of SFA. The European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort study of 37,421 participants [390] observed that total dietary SFA had no association with T2D, but SFA derived from cheese and long-chain SFAs were negatively associated with T2D. The EPIC-InterAct case-cohort study of 27,296 participants [294] also reported that even-chain SFAs including palmitic acid and myristic acid had a positive association with T2D, while odd-chain and longer-chain SFAs had a negative association with T2D.

The strength of our study is the use of a GRS based on two established lipid pathway genes in a well characterised population. Our study is the first of its kind to investigate the link between lipids and obesity from a nutrigenetic perspective. Another strength is the use of validated questionnaires and the robust sensitivity analysis incorporating conventional risk factors including alcohol consumption and smoking as confounding factors. Nonetheless, our study has several limitations. The small sample size could have influenced the lack of association between GRS and the measured outcomes (lipids and obesity). Another limitation is that we did not investigate different types or sources of SFAs. As this is a cross-sectional study, it is not possible to determine causality between fat intake and WC. Despite our robust sensitivity analysis, we cannot rule out residual confounding from unidentified factors [105]. However, we were able to replicate previously reported interactions between GRS and fat intake on WC.

6.6 Conclusion

Our findings suggest that dietary fatty acid intake may modify the effect of SNPs in lipid-pathway genes on central obesity in Asian Indians. The results indicate that a diet low in SFA might help to reduce the genetic risk of central obesity while a high SFA diet might increase the genetic risk of central obesity in Asian Indians. These findings support the WHO's dietary guidelines for preventing unhealthy weight gain by limiting SFA intake to less than 10% of total energy intake, and they indicate that personalised nutrition based on GRS might be an effective strategy for the management of central obesity in Asian Indians who have a high genetic risk, but additional studies with large sample sizes are needed to confirm our findings.

Chapter 7 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)

Published (The published version of the paper is attached as an appendix at the end of the thesis)

Wuni, R., Curi-Quinto, K., Liu, L., Espinoza, D., Aquino, A. I., del Valle-Mendoza, J., Aguilar-Luis, M. A., Murray, C., Nunes, R., Methven, L., Lovegrove, J. A., Penny, M., Favara, M., Sánchez, A. & Vimaleswaran, K. S. 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). *Clinical Nutrition ESPEN* **2025**, *66*, 83-92. https://doi.org/10.1016/j.clnesp.2024.12.027

Ramatu Wuni's contribution: For this study, I provided the DNA sequences for the single nucleotide polymorphisms (SNPs) to be genotyped, which was then sent to LGC Genomics, London. I also merged the genetic data from LGC Genomics with the phenotypic data. I cleaned the final dataset, evaluating the variables and ensuring that non-normally distributed variables were log-transformed prior to the analysis. Before starting the analysis, I prepared a data analysis plan which was approved by my primary supervisor. I performed all the statistical analyses using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA). I interpreted the results, carried out a literature search and wrote the manuscript. I revised the manuscript based on comments from the co-authors. I also formatted the manuscript according to the guidelines of Clinical Nutrition ESPEN before it was submitted for publication. I also wrote the responses to the reviewers' comments and revised them based on suggestions from my primary supervisor.

7.1 Abstract

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]. 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 sub-study of the Young Lives study. Thirty-nine single nucleotide polymorphisms (SNPs) known to be associated with cardiometabolic traits at a genome-wide significance level ($P<5\times10^{-8}$) were used to construct a genetic risk score (GRS). 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 grams/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 ($P_{interaction}$=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. 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.

7.2 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 [589]. These diseases place a significant burden on low- and middle-income countries, where more than three-quarters of CVD deaths occur [25, 589]. 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 [590]. 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 [591], 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) [592]. Moreover, Peru experienced a substantial increase in fatalities related to CVDs (77.8%) between 2020 to 2022 [593].

Obesity is associated with increased risk of CVDs [559, 584, 594-597] which is partly driven by atherogenic dyslipidaemia [584, 598]. Although the underlying mechanisms are complex, adipose tissue dysfunction results in several metabolic and cardiovascular disturbances including impaired lipid metabolism [598-600]. 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 [584, 601, 602]. A meta-analysis of 97 prospective cohort studies with a total of 1·8 million participants [594] 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] [594]. Numerous studies have indicated that obesity and other risk factors for cardiometabolic diseases result from multiple factors including genetic and environmental factors [18, 104-106, 130, 131, 304, 603], 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 [604-606] as well as a decline in physical activity [607, 608].

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 [8, 609, 610] and blood lipid levels [5, 10, 11]. 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, 104, 105, 245, 611-613]. 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 [104, 245, 370, 613].

7.3 Methods

7.3.1 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 multicentre 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 2,053 children aged 6 to 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 [614]. The sample covers the diversity of living standard conditions observed in the country [614]. 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 [615].

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 S7.1**). 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. 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.

7.3.2 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-gram 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) [616, 617].

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 minutes; two consecutive BP measurements (systolic, SBP and diastolic, DBP) were taken three minutes 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 [618]. 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 [330] 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 minutes (16,000 x g) and

the supernatant (50 μL) used for analysis, following the manufacturer's instructions (samples were diluted 1:2 prior to analysis).

7.3.3 Dietary assessment

Dietary intake information was assessed using an online 47-item semi-quantitative food frequency questionnaire (FFQ) previously validated in the YLS [152]. 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 [619, 620]. 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 [620, 621].

7.3.4 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 S7.1**): alpha-ketoglutarate-dependent dioxygenase (*FTO*) SNP rs1558902 [8, 622-625]; transmembrane protein 18 (*TMEM18*) SNP rs13021737 [8, 352, 626-629]; melanocortin 4 receptor (*MC4R)* SNP rs6567160 [7, 8, 629-631]; glucosamine-6-phosphate deaminase 2 (*GNPDA2*) SNP rs10938397 [7, 8, 401, 632]; SEC16 homolog B, endoplasmic reticulum export factor (*SEC16B*) SNP rs543874 [8, 352, 629, 632, 633]; BCDIN3 domain containing RNA methyltransferase (*BCDIN3D*) SNP rs7138803 [8, 352, 401, 629, 632]; transcription factor AP-2 beta (*TFAP2B*) SNP rs2207139 [8, 352, 401, 628]; neuronal growth regulator 1

(*NEGR1*) SNP rs3101336 [8, 626-629]; adenylate cyclase 3 (*ADCY3*) SNP rs10182181 [8, 626, 627, 634]; ETS variant transcription factor 5 (*ETV5) SNP* rs1516725 [5, 8, 401, 626]; glutaminyl-peptide cyclotransferase like (*QPCTL*) SNP rs2287019 [8, 629, 632, 635]; G protein-coupled receptor class C group 5 member B *(GPRC5B)* SNP rs12446632 [8, 401, 629, 634]; mitochondrial carrier 2 (*MTCH2*) SNP rs3817334 [626, 627, 633, 634]; centriolar protein (*POC5*) SNP rs2112347 [7, 8, 629, 632]; mitogen-activated protein kinase 5 (*MAP2K*) SNP rs16951275 [8, 628, 636]; zinc finger CCCH-type containing 4 (*ZC3H4*) SNP rs3810291 [7, 8, 630, 632]; FPGT-TNNI3K read through (*FPGT-TNNI3K)* SNP rs12566985 [8, 628, 637]; leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2 (*LINGO2*) SNP rs10968576 [8, 352, 633, 638]; cell adhesion molecule 1 (*CADM1*) SNP rs12286929 [8, 627, 629]; protein kinase D1 (*PRKD1*) SNP rs12885454 [8, 632, 633]; AGBL carboxypeptidase 4 (*AGBL4*) SNP rs657452 [8, 352, 627]; polypyrimidine tract binding protein 2 (*PTBP2*) SNP rs11165643 [7, 8, 352, 626]; NLR family CARD domain containing 3 (*NLRC3)* SNP rs758747 [8, 627]; syntaxin binding protein 6 (*STXBP6*) SNP rs10132280 [8, 629, 632]; Huntingtin interacting protein 1 (*HIP1) SNP* rs1167827 [8, 633]; cell adhesion molecule 2 (*CADM2*) SNP rs13078960 [8]; far upstream element binding protein 1 (*FUBP1*) SNP rs12401738 [8, 634]; olfactomedin 4 (*OLFM4*) SNP rs12429545 [626, 628, 632]; RAS p21 protein activator 2 (*RASA2*) SNP rs16851483 [8, 628]; hypoxia inducible factor 1 subunit alpha inhibitor (*HIF1AN*) SNP rs17094222 [8, 633]; hepatocyte nuclear factor 4 gamma (*HNF4G*) SNP rs17405819 [627, 629, 639]; toll like receptor 4 (*TLR4*) SNP rs1928295 [8, 352]; neurexin 3 (*NRXN3*) SNP rs7141420 [8, 401]; inflammation and lipid regulator with UBA-like and NBR1-like domains (*ILRUN* or *C6orf106*) SNP rs205262 [8]; fragile histidine triad diadenosine triphosphatase (*FHIT*) SNP rs2365389 [8, 633]; neuron navigator 1 (*NAV1*) SNP rs2820292 [8]; tripartite motif containing 66 (*TRIM66*) SNP rs4256980 [8, 629]; erb-b2 receptor tyrosine kinase 4 (*ERBB4*) SNP rs7599312 [8, 623]; and lysine acetyltransferase 8 (*KAT8*) SNP rs9925964 [8, 627].

Blood samples for genotyping (3ml) 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 –80ºC during transportation. Genotyping was completed by LGC Genomics, London, UK (http://www.lgcgroup.com/services/genotyping), using the competitive allele-specific PCR-KASP® assay.

7.3.5 Construction of 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 [105, 369]. Moreover, assigning weights to risk alleles has been reported to have little effect [370]. 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 S7.1**. 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.

7.3.6 Statistical analyses

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 S7.2**).

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 and the data analysis plan is attached as an appendix (**Appendix D**).

7.3.7 Characteristics of the study participants

The characteristics of the participants included in this study are summarised in **Table 7.1**. 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 × 10^{-24}), fasting glucose (P=0.001) and HbA1c (P=1.92 × 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 × 10^{-12}), total fat (P=0.000002), carbohydrate (P=5.2 × 10^{-14}) and protein (P=1.0 × 10^{-9}) than women, whereas fibre intake did not vary between sexes (P=0.60).

Table 7.1 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	**1.0×10^{-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	**1.92×10^{-16}**
Energy (kcal/day)	3304.0	1427.7	2870.8	1116.6	3660.4	1553.4	**6.8×10^{-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)	**5.2×10^{-14}**
Protein [(g/day)/ % energy]	172.8 (21)	80.5 (4)	151.0 (21)	62.6 (3)	190.7 (21)	88.8 (4)	**1.0×10^{-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	**2.6×10^{-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.

P values for the differences in means between men and women were calculated using independent sample t test.

7.3.8 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 S7.3**). No regional effects were observed when participants were stratified according to region of residence.

7.3.9 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 7.2**). As shown in **Figure 7.1**, 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 **Figure 7.2**. 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 7.2**, 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 7.2**, 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.

Table 7.2 Interaction of GRS with dietary macronutrient intake on cardiometabolic traits

		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)			
Trait		**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** (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.

** 457 participants had data for waist circumference.

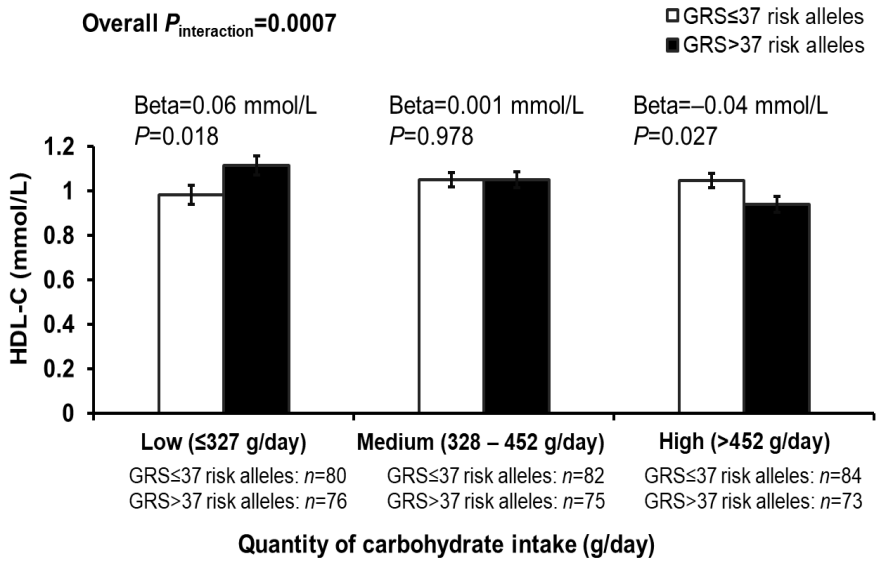

Figure 7.1 Interaction of GRS and carbohydrate intake on HDL-C concentration

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.

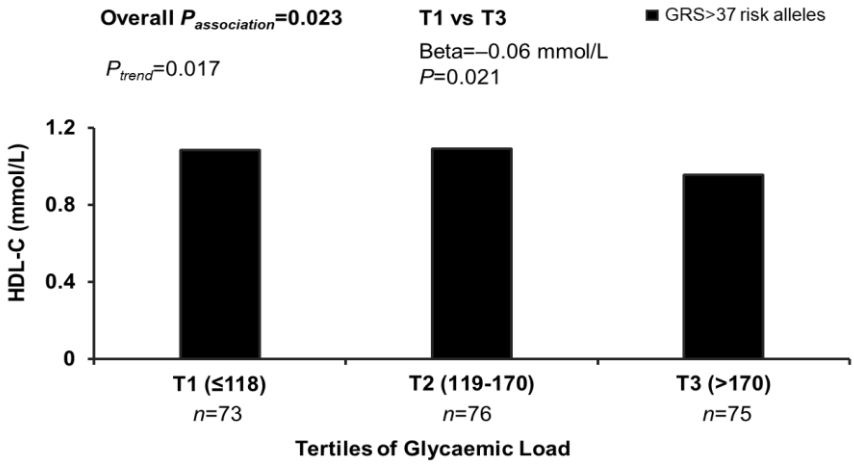

Figure 7.2 Association of glycaemic load (GL) with HDL-C concentration in individuals with a high GRS.

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.

7.4 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.

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 [592], and is related to a higher risk of CVDs [48, 640, 641], our findings have considerable public health implications. According to the dietary guidelines for Americans (2020–2025) [642], carbohydrates should make up 45–65% of total daily calories. The WHO [643] 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%, which is within the recommended intake for Americans [642]. 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 [≥40mg/dL (1.03mmol/L)], but lower than the recommended level for women [≥50mg/dL (1.30 mmol/L)] [644]. A 1mg/dL (0.03mmol/L) increase in the concentration of HDL-C has been associated with a 2–3% lower risk of coronary heart disease [645]. However, it has been recognised that, the concentration of HDL-C does not necessarily correlate with the function of HDL [32, 50].

In line with our findings, a cross-sectional study of 8,314 Korean adults from the Ansan and Ansung cohort of the Korean Genome and Epidemiology Study [646] 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 [646]. Moreover, the carbohydrate intake (% of TEI) in

the current study was lower than the Korean study [646]. 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 [647] 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 [647] 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 [648, 649]. The first study [648] consisted of 1,026 adults from the Insulin Resistance Atherosclerosis Study [648] where GL was found to be inversely associated with the concentration of HDL-C (Beta =–0.0009, P<0.001). Accordingly, the second study [649] which involved 5,011 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 [650]. 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 [35, 651]. 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 [652, 653]. Different types of carbohydrates however, can have varying effects on HDL-C concentration [654] and it has been suggested that GL serves as a measure of both the quality and quantity of dietary carbohydrates [649]. Foods with a high GL tend to induce more pronounced glycaemic and insulinemic reactions compared to those with a low GL

[655]. 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 [106] indicated that, the concentration of HDL-C might be influenced 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 [438], 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* [442]. 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.

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 [392, 656, 657] and lipid abnormalities which significantly increase the risk of developing atherosclerotic CVDs later in life [658-662]. 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 [393, 394]. The cross-sectional design also prevents establishment of causality [105]. Moreover, we did not investigate types of carbohydrates which can have varying effects on cardiometabolic traits [663, 664]. Additionally, using recalled FFQ rather than weighed diet diaries or biomarkers of intake can lead to underestimation of dietary intake [154, 665].

7.5 Conclusion

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 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.

Chapter 8 Barriers in translating existing nutrigenetics insights to precision nutrition for cardiometabolic health in ethnically diverse populations

Published (The published version of the paper is attached as an appendix at the end of the thesis)

Wuni, R. & Vimaleswaran, K. S. Barriers in Translating Existing Nutrigenetics Insights to Precision Nutrition for Cardiometabolic Health in Ethnically Diverse Populations. *Lifestyle Genomics* **2024**, *17*, 122-135. https://doi.org/10.1159/000541909

Ramatu Wuni's contribution: For this review, I conducted a literature search using different databases including PubMed and Google Scholar. I wrote the manuscript and revised it based on comments from my primary supervisor. I formatted the manuscript according to the guidelines of Lifestyle Genomics before it was submitted for publication. I also wrote the responses to the comments from the reviewers.

8.1 Abstract

Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of cardiovascular disease mortality (more than three-quarters) occurring in low- and middle-income countries. There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors. Despite the remarkable progress, several factors need to be considered before the translation of nutrigenetics insights into personalised and precision nutrition in ethnically diverse populations. Some of these factors include variations in genetic predispositions, cultural and lifestyle factors as well as socioeconomic factors. This review aimed to explore the factors that need to be considered in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities. Several factors might influence variations among individuals with regards to dietary exposures and metabolic responses and these include genetic diversity, cultural and lifestyle factors as well as socioeconomic factors. A multi-omics approach involving disciplines such as metabolomics, epigenetics and the gut microbiome might contribute to improved understanding of the underlying mechanisms of gene-diet interactions and the implementation of precision nutrition although more research is needed to confirm the practicality and effectiveness of this approach. Conducting gene-diet interaction studies in diverse populations is essential and studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention studies will be required to further strengthen the evidence and facilitate their application in clinical practice. Nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. Conducting gene-diet interaction studies in diverse populations is essential giving the genetic diversity and variations in dietary patterns. Integrating data from disciplines such as metabolomics, epigenetics and the gut microbiome could help in early identification of individuals at risk of cardiometabolic diseases as well as the implementation of precise dietary interventions for preventing and managing cardiometabolic diseases.

8.2 Introduction

Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of cardiovascular disease (CVD) mortality (more than three-quarters) occurring in low- and middle-income countries (LMICs) [25]. According to the Centres for Disease Control and Prevention [26], individuals in LMICs are often affected by cardiometabolic diseases during the peak of their productivity, which, coupled with huge healthcare expenses and limited employment opportunities worsens the financial burden of cardiometabolic diseases in these countries. Thus, cardiometabolic diseases present severe health and economic consequences for individuals, families, and communities [25], necessitating further research into the prevention and management of these conditions. Risk factors such as dyslipidaemia, hypertension and obesity have been shown to be influenced by genetic factors [5-9]. However, unlike monogenic disorders like sickle cell anaemia which are usually caused by mutations in a single gene [666], most cardiometabolic diseases, such as CVDs are influenced by numerous genes and are also impacted by environmental factors [132, 165, 167, 667, 668].

There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors [163-168]. Thus, a genetic variant might not always pose a higher risk of a disease as its effects might be modulated by the environmental factors that interact with it [109]. Defined as the scientific field that investigates the impact of genetic variability on individual responses to diet [18], nutrigenetics focuses on understanding gene-diet interactions that predispose to specific diseases, offering the potential to design personalised dietary guidelines for preventing and managing cardiometabolic diseases [19, 20].

Gene-diet interaction studies have been extended to cover previously under-represented populations [99, 137-141], although there is still limited research in some areas [542, 669] and most studies have not been replicated [169, 542]. Despite the remarkable progress in nutrigenetics research, several factors need to be considered before the translation of existing nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations [17, 670]. Ethnic diversity covers a broad range of factors including variations in genetic predispositions, cultural and lifestyle factors which can hinder the worldwide application of nutrigenetics findings [671]. Therefore, this review aims to explore the potential barriers and challenges in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities.

8.3 Genetic diversity

One of the main challenges (shown in **Figure 8.1**) in translating existing nutrigenetics insights to personalised and precision nutrition in various ethnic groups is the genetic diversity that exists among populations. Numerous studies have shown that individuals of different ethnic backgrounds have distinct genetic variations that impact how their bodies metabolise certain nutrients [18, 106, 130-132]. Therefore, research covering populations that represent different ethnicities is required to gain a better understanding of the genetic variations and specific nutritional requirements within these groups. Research by the Gene–Nutrient Interactions (GeNuIne) collaboration identified that, the genetic influence on obesity in different Asian populations was influenced by different dietary factors [18, 104, 105, 128, 131, 170, 565, 613]. Using a genetic risk score (GRS), it was observed that, South Asians with a higher GRS had a greater susceptibility to obesity when consuming a high-carbohydrate diet, whereas South East and Western Asian populations with a higher GRS displayed an increased risk of central obesity in response to a high-protein diet [18]. Similarly, research by the Diabetes Heart Study [114-116] indicates that African Americans have elevated levels of circulating arachidonic acid (AA) in comparison to individuals of European ancestry. Notable differences were also observed in allele frequencies of various SNPs within the fatty acid desaturase (*FADS*) gene cluster which have been shown to play a significant role in determining circulating levels of fatty acids. In particular, the 'GG' genotype of the SNP rs174537, which is linked to elevated AA levels was present in 81% of African Americans compared to 46% of European Americans [116]. Thus, while research conducted on individuals of European descent suggests that only a small fraction of dietary linoleic acid is converted to AA in humans, this minimal conversion rate may not be consistent across all populations [114-116]. Given that AA and its metabolites play crucial roles in immune responses and inflammation, thereby influencing the onset and advancement of various diseases including diabetes and CVDs [133, 134], tailored dietary recommendations regarding the intake of PUFA might be beneficial for this population.

One of the most widely studied genes in relation to cardiometabolic diseases is the Apolipoprotein E (*APOE*) gene [95, 124, 203-205, 672] and variations in the frequency of the E4 isoform of the gene, which is associated with increased risk of CVDs, have been reported [112, 113]. African and Asian populations tend to have higher frequencies of the E4 isoform (29-40% in Central Africa) compared to Caucasians [112, 113] which could contribute to differences in susceptibility to certain diseases among these populations. Furthermore, within Europe there are regional variations in the frequency of the E4 isoform, ranging from

5-10% in Spain, Portugal, Italy, and Greece; up to 16% in France, Belgium, and Germany; and further rises to up to 23% in the Scandinavian peninsula, with the Saami population of Finland showing frequencies as high as 31% [112, 113]. However, the link between the E4 isoform and increased low-density lipoprotein cholesterol levels is more pronounced in populations with diets high in saturated fat and cholesterol compared to other groudps [673, 674], suggesting that interventions targeting a reduction in saturated fatty acids (SFA) intake could be effective for CVD prevention and management in populations with a high frequency of the E4 isoform.

The use of a GRS has been shown to be effective in assessing the genetic contribution to complex traits such as dyslipidaemia since it allows the combined effects of multiple genetic variants to be analysed [370, 371, 675]. A weighted GRS, which takes into account the effect sizes of the risk alleles, is used by some studies [369, 676, 677]. However, most of the published data on effective sizes come from GWA studies which have been conducted in populations of European ancestry and it has been reported that effective sizes may vary across populations [105, 369], suggesting that using a weighted GRS might not be ideal for populations which are under-represented in GWA studies. In a study by the National Heart, Lung, and Blood Institute's Candidate Gene Association Resource (CARe), consisting of 10,366 African American, 26,647 European American, 1410 Hispanic, and 717 Chinese American individuals from nine cohorts [117], there were marked differences in effect sizes across the ethnic groups for some of the SNPs, and this has also been reported in a review of nutrigenetic studies [130]. The effect size of the cholesteryl ester transfer protein (*CETP*) SNP rs4783961, the 'A' allele of which is associated with higher concentration of high-density lipoprotein cholesterol (HDL-C), was uniformly larger in African American cohorts (0.17 to 0.24) compared to European Americans (0.09 to 0.15) [117]. In contrast, another HDL-C-associated SNP, rs17231506, also in *CETP*, had larger effect sizes in European Americans and Hispanics (0.21 to 0.28) compared to African Americans (0.06 to 0.26). A potential reason for this finding as explained by the authors [117] is that, African Americans and European Americans possess the same underlying causal variant within a gene, yet because of ethnicity-specific variations in the frequencies of major and minor alleles, a SNP might have varying degrees of correlation with the underlying variant, resulting in varying effect sizes and degrees of association.

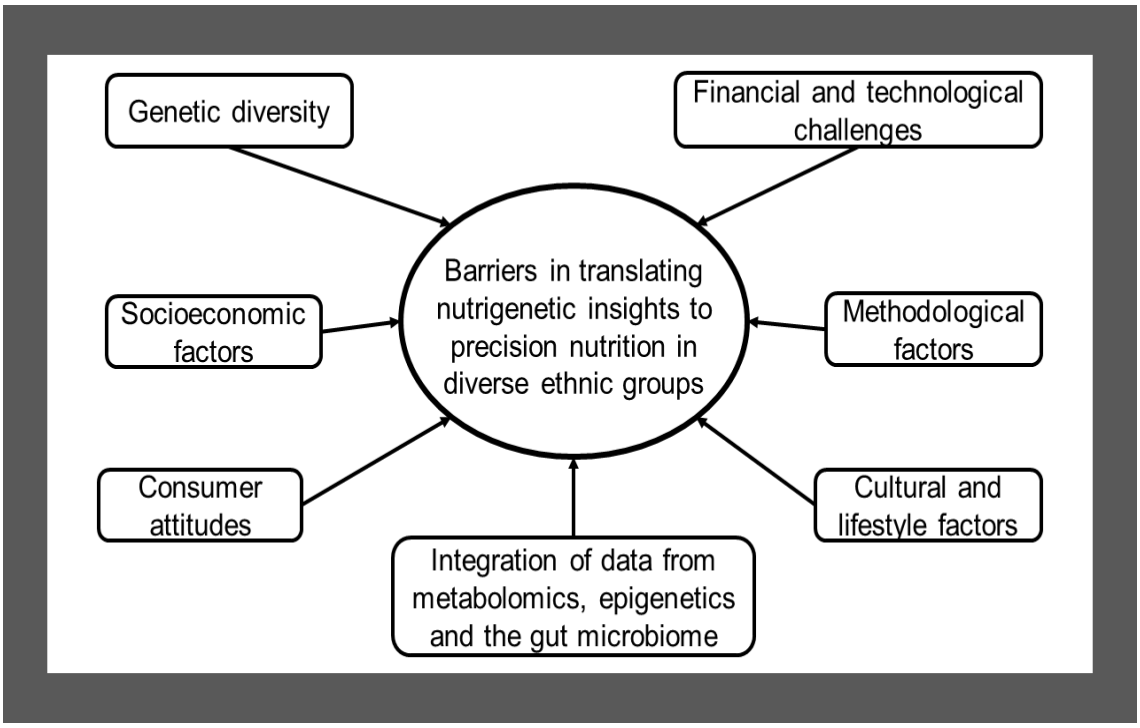

Figure 8.1 Barriers affecting the translation of existing nutrigenetics insights to precision nutrition in ethnically diverse populations

8.4 Methodological factors

Aside genetic diversity, another barrier that affects the translation of nutrigenetics is the lack of replication in most gene-diet interaction studies [106, 169, 678]. Conducting replication studies, especially in diverse populations is vital in enhancing the reliability of findings and facilitating their application in clinical practice [109]. In a systemic review of gene-diet interaction studies in relation to CVDs [169], it was observed that many of the studies that identified significant interactions had not been replicated, with only a small number of studies examining the same dietary and genetic factors. Similarly, a lack of replication was reported in a systemic review of gene-lifestyle interaction studies conducted by our team [106] in which it was identified that most of the studies were conducted only once. Furthermore, a systematic review of nutrigenetic studies focusing on omega-3 fatty acid and plasma lipid, lipoprotein, and apolipoproteins [678] highlighted a lack of replication of previously identified interactions. To strengthen the evidence and enhance comparability across studies, it is important for studies to be replicated in independent samples [106, 169].

In addition to the lack of replication, sample size has been cited as a methodological issue that affects the quality of the evidence generated by gene-diet interaction studies [106, 130, 169, 678]. A large sample size improves the power to detect interactions with minimal effect sizes and this is especially important for multifactorial traits where the main effects of genetic variants is often subtle [169, 393, 394]. Moreover, there is a scarcity of genotype-based dietary intervention studies [18]. It has been highlighted that, dietary intervention studies can help to raise the evidence level of gene-diet interactions identified in observational studies once they have been replicated [109]. In a 12-week randomised controlled trial involving 145 participants with overweight or obesity, participants were first identified as being responsive to fat or carbohydrate based on a GRS, before being randomised to a high-fat or high-carbohydrate diet [679]. Although no differences in weight loss were observed between participants who were randomised to the appropriate diet based on their genotype and those who were not [679], studies utilising this approach could help to determine the effectiveness of dietary interventions based on genotypes and facilitate the translation of nutrigenetics into precision nutrition.

8.5 Cultural and lifestyle factors

Cultural and lifestyle factors also need to be considered in translating nutrigenetics and implementing precision nutrition. Ethnic groups often have longstanding dietary traditions, specific food preferences, and cooking practices that have been passed down through generations, making them a fundamental part of their cultural identity [680, 681]. Therefore, incorporating precision nutrition based on nutrigenetics into these cultural practices without compromising their valued traditions might be challenging. A systematic review of 20 qualitative studies revealed that the food preferences of individuals of Asian, African and other minority ethnic communities was impacted by social and cultural elements besides nutritional and health considerations [680]. It was observed that individuals from African, Asian and other minority ethnic backgrounds place significant value on traditional foods, viewing them as symbols of their ethnic identity and belonging [680]. Similarly, in African Americans, despite a disproportionate prevalence of cardiometabolic diseases in comparison to white Americans [682, 683], adherence to dietary guidelines has been found to be influenced by a preference for a dietary intake that reflects a cultural tradition known as “soul food” [682]. This diet often consists of fatty meats, added fat, sugar and salt and involves methods of cooking such as deep frying and others that raise the amount of calories and sodium in the diet [682]. Accordingly, African Caribbean individuals living in Britain

were found to prioritize spending on traditional foods such as yams over potatoes, thereby preserving their cultural food preferences [684]. Moreover, specific practices such as adhering to a vegetarian diet, avoidance of pork and beef and following certain cooking procedures are considered valuable to people of Asian and African backgrounds [680, 685]. Moreover, the concept of 'local food' has attracted a lot of attention in recent years, with many consumers preferring products that have travelled short distances or directly marketed by producers [686-688]. However, the extent to which individuals adhere to their traditional dietary practices is influenced by several factors, with younger individuals more likely to adopt new dietary habits [681, 689].

With regard to diet and cardiometabolic diseases, examining the overall dietary pattern is believed to offer several advantages since foods and the nutrients they contain often have synergistic effects, which can make it difficult to identify the influence of a single food or nutrient [690]. Moreover, it has been shown that it is not specific nutrients but rather the overall dietary pattern that exerts the most significant impact on cardiometabolic diseases [690-692]. Dietary pattern is defined as the regular consumption of various foods, drinks, and nutrients in specific quantities and combinations, including the frequency at which they are consumed [693]. Recognising a dietary pattern could lead to a stronger correlation with a specific health indicator and provide a broader and more inclusive understanding of how nutrients and other bioactive compounds in our food are consumed, as well as how patterns of consumption affect health outcomes [693, 694]. In a study involving South Asian Surinamese, African Surinamese and Dutch participants in the Netherlands [695], three dietary patterns, categorised as 'noodle/rice and white meat', 'red meat, snacks, and sweets' and 'vegetables, fruits, and nuts' were identified. In contrast to Dutch participants, those of Surinamese origin had a stronger adherence to the 'noodle/rice and white meat' pattern, which reflected the dietary preferences typical of the traditional Surinamese diet. Dutch participants on the other hand showed a higher level of adherence to the 'red meat, snacks, and sweets' and 'vegetables, fruits, and nuts' patterns [696]. Variations in dietary consumption and factors shaping dietary behaviours across different ethnic groups were also observed in a systematic review of 49 studies [121]. Consumption of fruits and vegetables was found to be low in populations of African ancestry and higher in Hispanic and Latino populations while fish consumption was low in White and Hispanic populations. In contrast, White and Asian populations were found to have the highest dairy intake (2.17 and 1.3 servings per day, respectively) compared to populations of African ancestry (0.58 servings per day) [121]. These findings indicate a low tendency towards fruit

and vegetable consumption as well as reduced intake of dairy in African ancestry populations in comparison to the other ethnic groups, highlighting a need for ethnic-specific initiatives. It should be noted that within the same ethnic group, there are variations in dietary pattern depending on whether they are living in developed countries or in their native countries [696], indicating that public health priorities with regards to diet and disease prevention might differ based on geographic location.

Traditional diets for certain ethnic groups have often been associated with health benefits [697]. The traditional South Asian diet in particular is composed mainly of fresh fruits and vegetables along with beans, legumes, nuts and spices [697]. However, a rise in type 2 diabetes (T2D) and CVDs has been seen in South Asians [18, 105] and this has partly been linked to unhealthy modifications to the traditional diet, shifting from nutrient-rich fresh produce to refined products and the use of large amounts of saturated cooking oils [697]. Similarly, the traditional African diet is enriched with fresh vegetables such as okra, spinach and other green leafy vegetables [698, 699]. Nonetheless, a shift away from traditional meals towards processed foods and soft drinks has been reported across African countries [700]. Hence understanding cultural and lifestyle factors that shape food preferences and dietary habits is vital in translating existing nutrigenetic insights to various ethnic groups.

8.6 Socioeconomic factors

Socioeconomic and geographical disparities are also important factors to consider in the translation of nutrigenetics to precision nutrition. Ethnic populations may experience disparities in access to healthcare, technologies, and resources required for implementing precision nutrition effectively. The allocation of money to healthcare has been reported to vary across countries depending on their level of economic development, with high-income countries allocating on average, $3,000 per person towards healthcare, while low-income countries only spend around $30 per person [122]. Similarly, a report by the World Health Organisation [396] indicated that healthcare costs in low-income countries were mainly covered by individuals paying directly (44%) and aid from external sources (29%), while government funding played a predominant role in high-income countries (70%). Moreover, socioeconomic and political factors also influence the distribution of food, adjustments in food composition or the implementation of optional taxes on unhealthy food products as well as the adoption of dietary guidelines promoting the consumption of healthy options such as fruits and vegetables [701, 702].

Aside cost and infrastructure, the knowledge and attitudes of healthcare providers, including dietitians, towards nutrigenetics are crucial for its integration into clinical practice, which may also be influenced by socioeconomic-related educational opportunities [172]. Healthcare professionals need to understand genetic influences on public health, evaluate the clinical relevance and utility of genetic tests as well as analyse the individual's background in order to recommend genetic assessments, screening or lifestyle adjustments [703]. It has been highlighted that nutritional genetics has emerged as a relatively new field over the past two decades, with much of its scientific knowledge not integrated into healthcare education [704]. Consequently, healthcare professionals lack the essential foundation to provide effective nutrigenetic counselling [704]. Available evidence on knowledge and attitudes of healthcare professionals towards nutrigenetics mainly comes from studies conducted in high income countries and the findings indicate a general lack of awareness among healthcare professionals [705-708]. In a survey of 390 dietitians in the UK [706], it was observed that, despite being involved in the management of polygenic conditions such as diabetes, obesity and CVDs which are influenced by both genetic and dietary factors, majority of the participants were not engaged in activities related to genetics or nutrigenetics and expressed low confidence in undertaking such activities. Similarly, a survey involving 1,844 dietitians from Australia (390), the USA (461), and the UK (993) [707] revealed that, the participants had limited knowledge, engagement, and confidence in nutrigenetics. Giving the lack of resources in LMICs, knowledge and awareness of nutrigenetics is likely to be even lower. In this regard, initiatives such as the GeNuIne Collaboration are required [131]. Through funding from the British Nutrition Foundation (BNF), the GeNuIne collaboration was started at the University of Reading in 2013, and it has been instrumental not only in conducting nutrigenetics studies in diverse ethnic groups, but also in facilitating training and resource development to improve the ability of professionals and policymakers in low-income countries to effectively apply nutrigenetics findings within their domains [18, 106, 131, 170, 172, 173].

8.7 Financial and technological challenges

Funding from public bodies is vital for developing innovative approaches within nutrition programmes, promote collaboration among scientists, facilitate the distribution of nutrigenetics information through modern virtual communication technologies as well as establishing a well-trained public health nutrition workforce [709]. Several studies have highlighted the necessity for enhancing capacity in public health nutrition across individual,

organisational, and systemic levels [709-712]. However, global initiatives such as the Scaling Up Nutrition (SUN) movement which is focused on addressing the complex causes of malnutrition through the implementation of evidence-based, nutrition-specific interventions in developing countries, face challenges due to financial constraints in most countries [713].

In a report by Sight and Life [714] it was noted that, personalised nutrition appears not only feasible and rational but also cost-effective in terms of developing effective nutrition interventions to alleviate the burden of diseases and improve health outcomes in LMICs. However, several implementation challenges were highlighted including how to extend the application of personalised nutrition approaches to benefit a larger population giving the financial constraints, deciding which methods offer the greatest potential for successful adoption, what resources are necessary to expand the implementation of personalised nutrition and whether there is sufficient support and interest in introducing personalised nutrition approaches to LMICs [714]. Moreover, it has been recognised that the integration of nutrigenetics into healthcare systems requires a multisystem approach that includes the gut microbiome, and environmental factors [20], which poses a huge challenge in LMICs. According to Sight for Life [714], personalised nutrition approaches that are more specific are less readily available in LMICs and these include genetic and microbiome analysis and counselling, alongside tools for assessing metabolic markers such as glucose monitors and energy intake sensors.

8.8 Consumer attitudes towards nutrigenetics and personalised nutrition

There is a growing interest in nutrigenetics and personalised nutrition, although at present, accessibility is limited to a narrow group of highly motivated individuals with high socioeconomic status [715]. Commercial companies offering nutrigenetic testing exist mostly in Europe and North America [716], with the aim of enabling consumers to identify their genetic susceptibility to diseases and offering personalised dietary recommendations to promote health [716, 717]. The growing interest in direct-to-consumer (DTC) genetic testing has been associated with social elements such as enhanced internet access to information and a cultural shift towards individuals taking greater responsibility for their health and lifestyle choices, while relying less on conventional expert guidance [718]. However, there are concerns about the accuracy and usefulness of the health-related data provided by DTC genetic testing companies as well as potential adverse outcomes if consumers or their healthcare providers misinterpret such information [719-722]. In a

study of 1,648 participants [723], it was observed that before undertaking personalised DTC genetic testing, consumers were mostly interested in information about ancestry (73.7%), traits (72.2%) and disease risks (71.9%). In terms of susceptibility to disease, heart disease (68%), breast cancer (67%), and Alzheimer's disease (66%) attracted a high level of interest [723]. It should be noted that the participants were mostly women, Caucasian and from a high socioeconomic background [723]. Similarly, a survey of 1,048 customers of DTC genetic testing [718] indicated that, the customers' individual circumstances and subjective understanding of disease susceptibility were linked to specific health-related behaviours they undertake upon receiving their test results. More specifically, various aspects of the participants' lives such as having a chronic condition, a family history of diseases tested by the DTC service, self-reported health issues and regular visits to a doctor were significantly correlated with several health-related behaviours individuals displayed following receipt of their results [718]. Along these lines, a survey of 2,037 customers of DTC services showed that the response to genetic testing was influenced by both the perceived severity and sense of control over the condition of interest. Higher perceived severity and lower perceived control were linked to increased, though not clinically significant, levels of anxiety and distress [724].

With regard to attitudes of the general public towards personalised nutrition, a survey of 9,381 participants across nine European countries (the UK, Germany, Ireland, Spain, Greece, Poland, Portugal, the Netherlands, and Norway) [725] indicated that the trust and preference consumers have for personalised nutrition services are key indicators of their likelihood to embrace such services. Variations in trust in the national health service as a regulatory body and source of information, as well as trust in dietitians and nutritionists as service providers were observed across the countries, although in all the countries, family doctors emerged as the most relied-upon sources of information [725]. Similarly, a study conducted in the UK and Ireland by Food4Me [726] identified that there was a preference for government-led services delivered in person, which was believed to enhance trust, transparency, and overall value. In both countries, paying for nutritional advice was associated with heightened commitment and motivation to adhere to guidelines [726]. Furthermore, a study involving 438 Dutch participants [727] showed that consumers acceptance of personalised nutrition was positively influenced by consensus among expert stakeholders, benefits for consumers or scientists, ease of implementation, and freedom of choice. In line with these findings, a study consisting of 1,425 Canadian participants [728] revealed that most of the participants (93.3%) regarded dietitians as the most suitable

professionals to provide personalised dietary advice based on nutrigenetic testing. In this study [728], health and disease prevention were cited as the primary benefits for nutrigenetic testing and there were concerns regarding accessibility to genetic testing through telemarketing companies and spam as well as companies using personal genetic data to promote sales [728]. Although there is limited data on the attitudes of consumers in LMICs towards nutrigenetics, previous studies by our group indicated a reluctance to give blood samples for genetic testing. Hence individuals from various socio-demographic backgrounds may have varying levels of trust in service providers, regulators and online information delivery. Consequently, preferences regarding the manner and source of personalised nutrition services might vary across countries and cultural settings [725].

8.9 Integration of data from multiple fields

Precision nutrition is centred around integrating data from multiple disciplines such as metabolomics, epigenetics and the gut microbiome as this is argued to be important in enhancing the scientific understanding of inter-individual variability in response to dietary interventions, although the practicality and effectiveness of this process are still being explored [180, 181]. So far, progress has been made in the mechanistic understanding of dietary interventions through the integration of omics technologies such as metabolomics and the gut microbiome [182]. Metabolomics focuses on analysing small molecules (metabolites) found in biological samples to understand changes in metabolism under various conditions [180]. Metabolites are the direct products of dietary consumption and metabolism, enabling a more accurate assessment of biological and physiological pathways as well as the related biomarkers for diet or disease [182]. Metabolic profiles have been linked to variations in nutritional needs and responses to diet, which offers the potential to stratify populations with similar metabolic and phenotypic profiles, enabling the development of tailored dietary recommendations [729]. Moreover, an accurate assessment of dietary intake is essential in understanding the link between diet and diseases, and methods currently used to assess dietary intake such as food frequency questionnaires, weighed food diaries and 24-h recalls are prone to errors including under estimation of energy intake [180]. By applying metabolomics, specific biomarkers associated to foods eaten can be obtained, and this involves participants consuming specific foods and the collection of biofluid samples over time [180]. These biomarkers could provide useful information to supplement self-reported dietary intake [729].

Using metabolomics, a possible explanation of the mechanisms underlying the health benefits of low glycaemic index (GI) diets was reported in a 6-month parallel randomised trial involving 122 adult participants with overweight and obesity [730]. An analysis of plasma metabolites revealed that, a low GI diet resulted in higher levels of serine, lower levels of valine and leucine, and alterations in a group of two sphingomyelins, two lysophosphatidylcholines, and six phosphatidylcholines. These changes in plasma amino acids and lipid species were found to be correlated with changes in body weight, glucose levels, insulin, and certain inflammatory markers [730]. Similarly, a metabolomic study identified underlying risks for T2D, insulin resistance and related comorbidities through analysis of blood metabolites in participants who had normoglycaemia and no clinical symptoms [731]. In this study [731], metabolomic analysis was performed at baseline and after the implementation of a personalised lifestyle intervention for 100 days. By combining metabolites associated with specific disease risks and calculating risk scores, the baseline analysis showed that some of the participants had moderate to high risks for insulin resistance, T2D and CVDs. However, when the analysis was repeated following the personalised lifestyle intervention, specific metabolites that were previously outside the normal range had returned to the normal range, thereby reducing potential health risks during the second time point [731].

The gut microbiome supports the host by interacting directly or indirectly with host cells through the production of bioactive molecules, and this interaction allows the gut microbiome to regulate various biological processes related to immunity and energy balance [183]. This ability to interact with the host depends on the types of bacteria present and their distribution within the gut microbial community [732]. The application of the gut microbiome in precision nutrition involves using the gut microbiome as a biomarker to predict how specific dietary components affect host health, and the use of this information to design precision dietary interventions aimed at promoting health [183]. It has been highlighted that, the way individuals respond to certain dietary interventions may be influenced by the composition and function of the gut microbiota which differs among individuals with distinct metabolic profiles [732]. In a study involving 14 men with obesity [733], controlled diets supplemented with resistant starch or non-starch polysaccharide and a weight-loss diet were found to result in distinct changes in the microbiota composition. The resistant starch diet was linked to an increase in several Ruminococcaceae phylotypes, while the non-starch polysaccharide primarily resulted in an increase in Lachnospiraceae phylotypes, and the weight-loss diet significantly decreased Bifidobacteria. It was concluded

that since the dietary response of an individual's microbiota varied significantly and was inversely related to its diversity, individuals could be classified as responders or non-responders based on the characteristics of their intestinal microbiota [733]. In another study involving a cohort of 800 participants with no previous diagnosis of T2D [734], variations in post-prandial glycaemic responses to similar standardized meals were observed. A machine learning algorithm was then developed by integrating blood parameters, dietary habits, anthropometric data, physical activity and gut microbiota information from the same cohort and was found to be effective in predicting personalised postprandial glycaemic responses to real-life meals. Subsequently, a blinded randomised controlled dietary intervention based on the algorithm resulted in significantly reduced postprandial responses and consistent changes in gut microbiota composition [734].

Epigenetics covers the molecular processes that can alter the activity of genes without changing the DNA sequence, and these processes include DNA methylation, histone modifications and alterations in noncoding RNAs [184]. Epigenetic changes might explain individual differences in metabolic health and responses to diet, and have the potential to identify novel biomarkers for precision nutrition and targets for precise interventions [185]. Similarly, transcriptomics technologies have been applied in nutrition research to understand the molecular and signalling pathways associated with nutrients [735]. In an interventional study, a transcriptomic approach was used to assess the impact of a high-carbohydrate or high-protein diet on gene expression profiles in blood leukocytes [736]. The findings showed that, the high-carbohydrate breakfast resulted in changes in the expression of genes related to glycogen metabolism, while the high-protein breakfast led to changes in the expression of genes associated with protein biosynthesis [736]. Another interventional study [737], utilising a transcriptomic approach to assess the postprandial effect of consuming different fatty acids on the gene expression profiles of peripheral blood mononuclear cells reported that, intake of PUFA was associated with a decrease in the expression of genes in liver X receptor signalling, while consumption of SFA led to an increase in the expression of these genes. Consumption of PUFA also resulted in an increase in the expression of genes linked to cellular stress responses, while MUFA had a moderate effect on several genes [737]. The findings suggest that data from multiple individuals undergoing postprandial gene expression profiling in peripheral blood mononuclear cells could enable the stratification of gene expression profiles as ‘healthy’ or ‘unhealthy’, as well as the identification of particular meals that could be categorized as healhty or unhealthy for such individuals [180].

With regard to obesity, a significant interaction was observed between SFA intake and the *APOA2* SNP rs5082 on the risk of obesity in a study of 3462 participants from three populations in the United States [the Framingham Offspring Study (1,454 whites), the Genetics of Lipid Lowering Drugs and Diet Network Study (1,078 whites), and the Boston–Puerto Rican Centers on Population Health and Health Disparities Study (930 Hispanics of Caribbean origin)] [137]. This finding was also replicated in Chinese, Asian Indians and whites from the Valencia Region of Spain [738]. Individuals with the 'CC' genotype had an increased risk of obesity compared to those with the 'TT' or 'TC' genotypes only when their SFA intake was high (≥22g/day) [137, 738]. To explore the mechanisms underlying this interaction, the authors performed a multi-omics study involving methylome, transcription and metabolomic analyses from three different populations (the Boston Puerto Rican Health Study, the Genetics of Lipid Lowering Drugs and Diet Network Study, and the Framingham Heart Study)[538]. The epigenetic state of the *APOA2* regulatory region was found to be linked to SFA intake and the rs5082 genotype, causing differences in *APOA2* expression between the 'CC' and 'TT' genotypes on a high-SFA diet and influencing branched-chain amino acid and tryptophan metabolism [538]. Therefore, integrating data from nutrigenetics, metabolomics, the gut microbiome, epigenetics, phenotypic traits and lifestyle factors might help in designing personalised and precise nutrition interventions. Machine learning and artificial intelligence enables the integration of data from various fields by identifying patterns in large datasets and grouping similar data to create predictive models and algorithms [739]. A machine learning model utilising age, systolic blood pressure, routine blood and urine tests as well as dietary intake values has been reported to be effective in identifying young, asymptomatic individuals at higher risk of CVDs [740]. Similarly, integrating data on lifestyle factors, gut microbiome, clinical variables, subcutaneous adipose tissue gene expression and metabolomics derived from serum, urine and faeces, was found to be effective in identifying biomarkers linked to insulin sensitivity [741]. Thus, integrating data from multiple disciplines could help in designing personalised and precise dietary interventions for the prevention and management of cardiometabolic diseases, although the effectiveness and practicality of this approach are still being explored (**Figure 8.2**).

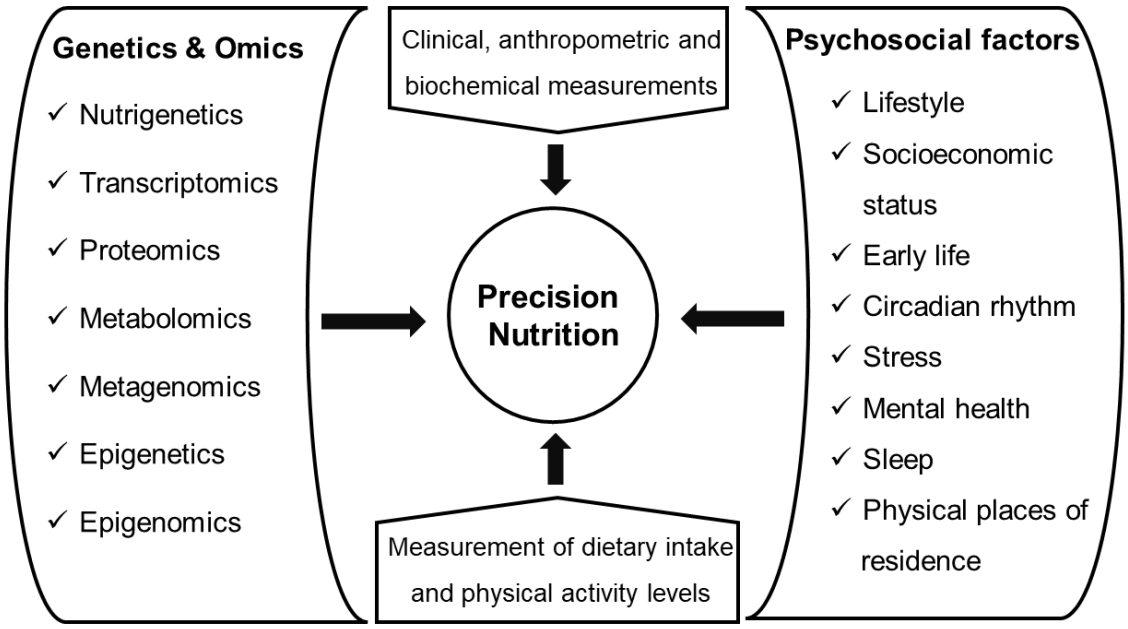

Figure 8.2 List of factors that should be considered for the implementation of precision nutrition

8.10 Conclusion

Nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. Several factors might influence variations among individuals with regards to dietary exposures and metabolic responses and these include genetic diversity, cultural and lifestyle factors as well as socioeconomic factors. A multi-omics approach involving disciplines such as metabolomics, epigenetics and the gut microbiome might contribute to improved understanding of the underlying mechanisms of gene-diet interactions and the implementation of precision nutrition although more research is needed to confirm the practicality and effectiveness of this approach. Therefore, conducting gene-diet interaction studies in diverse populations is essential to improve their clinical application worldwide. To bridge the gap between existing nutrigenetic insights and their application in clinical practice, it is vital for initial findings to be replicated in independent samples, followed by dietary intervention studies. Studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention studies will be required to further strengthen the evidence and facilitate

their application in clinical practice. The issues discussed in this review are particularly important, given the current diverse climate, which poses significant risks to food security and diet quality, making vulnerable populations across the world susceptible to various forms of malnutrition [742].

Chapter 9 Discussion and conclusion

9.1 Discussion

Nutrigenetics is an innovative field that investigates the impact of genetic variability on individual responses to diet, offering the potential to design personalised dietary guidelines for preventing and managing cardiometabolic diseases. Thus, a genetic variant might not always pose a higher risk of a disease as its effects might be modulated by the environmental factors that interact with it [109]. Dietary factors may interact with an individual's genetic characteristics and impair metabolic processes, which may contribute to the development of lipid-related traits such as CVDs [20]. Therefore, understanding gene-diet interactions that predispose to altered blood lipid levels could help to design personalised or precise dietary guidelines for preventing and managing lipid-related traits [19, 20]. The findings of this thesis add to the field of nutrigenetics by showing the presence of genetic heterogeneity in gene-diet interactions on lipid-related traits in different ethnic groups. These findings will contribute to improved understanding of how genetic and dietary factors interact to alter the susceptibility to CVDs in different ethnic groups. Additionally, factors that need to be considered to facilitate the translation of nutrigenetics to personalised and precision nutrition in diverse ethnic groups have been examined in this thesis, which is important, given the current diverse climate, which poses significant risks to food security and diet quality, making vulnerable populations across the world susceptible to various forms of malnutrition [742].

Studies investigating gene-diet interactions have produced inconsistent results which can be attributed to genetic heterogeneity and small sample sizes. As a result, these findings could not be utilised to design personalised dietary guidelines for each ethnic group [18, 131]. Although nutrigenetic studies have been extended to cover previously under-represented populations, there is still limited research in some developing countries due to insufficient funding, a lack of expertise and inadequate infrastructure [131, 170]. In this thesis, a genetic approach was used to investigate the association of SNPs as a GRS with lipid-related traits in different ethnic groups. In addition, a nutrigenetic approach was used to examine the interaction of the GRS with dietary factors (intake of fat, carbohydrate and protein) on lipid-related traits.

Gene-diet interactions were examined in the following populations: Brazilian young adults, Asian Indian adults, and Peruvian young adults. The inclusion of individuals from different ethnic groups with different genetic characteristics enabled the objectives of the

project to be met through the identification of ethnic-specific gene-diet interactions and the generation of evidence which can be utilised to design personalised dietary guidelines based on ethnicity. The studies included two cross-sectional cohort studies: [the Obesity, Lifestyle and Diabetes in Brazil (BOLD) study, Brazilian young adults, *n*=190; and the Study of Obesity, Nutrition, Genes and Social factors (SONGS), Peruvian young adults, *n*=468] and a case-control study [the Chennai Urban Rural Epidemiological Study (CURES), Asian Indian adults, *n*=497]. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA) and the R software version 4.3.1 [372]. Linear and logistic regression models were used to test for associations and interactions. The models were adjusted for age, sex, BMI, type 2 diabetes, smoking status, physical activity, and total energy intake, wherever appropriate. The findings from this thesis are summarised below.

9.2 A nutrigenetic update on *CETP* gene-diet interactions on lipid-related outcomes

The global burden of CVDs is well recognised and ischaemic heart disease alone accounted for 9 million deaths in 2019, making it the top cause of death in all parts of the world [186]. An abnormal lipid profile, usually indicated by low concentrations of HDL-C and elevated levels of LDL-C or TG, is considered a major risk factor for CVDs [107, 187]. Several studies have demonstrated *CETP*-diet interactions on blood lipids; however, the findings have been inconsistent [99, 100, 189-192]. The objective of this review was to identify and discuss nutrigenetic studies assessing the interactions between *CETP* SNPs and dietary factors on blood lipids.

Significant interactions were identified between 17 dietary factors and 8 SNPs of the *CETP* gene on blood lipids in the following populations: Mexican, Iranian, Spanish, White American, Chinese, Malay, Indian, Irish, French, Japanese, New Zealander, Dutch, Greek, Icelandic, Inuit, Canadian, Taiwanese and residents of the USA. The SNPs showing significant interactions with dietary factors (such as total fat intake, MUFA, n-3 PUFA, Mediterranean diet, olive oil and sesame-canola oil) were TaqIB (rs708272 G>A); rs5882 (I405V); rs3764261 (C>A); rs1800775 (C-629A); rs183130(C-4502T); rs4783961 (G-971A); rs289714 (C>T) and rs1800774 (C>A). The macronutrient investigated by majority of the studies was dietary fat, comprising of total fat, SFA, MUFA and PUFA. Total fat intake accounted for majority of the interactions across different SNPs, being associated with unfavourable lipid outcomes in some individuals but not others.

Overall, the findings suggest that *CETP* SNPs might alter blood lipid profiles by modifying responses to diet, but further research utilising large sample sizes in multiple ethnic groups is warranted to identify individuals at risk of adverse lipid response to diet which is essential in developing dietary guidelines that are tailored to specific groups of people.

9.3 Higher intake of dairy is associated with lower cardiometabolic risks and metabolic syndrome in Asian Indians

There is conflicting evidence about the association between dairy products and cardiometabolic risk (CMR) [256, 266, 267, 270]. This study aimed to assess the association of total dairy intake with CMR factors and to investigate the association of unfermented and fermented dairy intake with CMR in Asian Indians who are known to have greater susceptibility to type 2 diabetes and CVDs compared to white Europeans [105, 119, 120, 255]. The study comprised of 1033 Asian Indian adults with normal glucose tolerance chosen from the CURES. Dietary intake was assessed using a validated open-ended semi-quantitative food frequency questionnaire.

In line with previous studies [256, 266-269], dairy consumption was found to have a protective effect against metabolic syndrome (MS). We found a reduced risk with an increased intake of dairy products, where consumption of ≥5 cups per day of total, ≥4 cups per day of unfermented or ≥2 cups per day of fermented dairy was associated with a reduced risk of high fasting plasma glucose. A total dairy intake of ≥5 cups per was also associated with a lower risk of high blood pressure, low HDL-C and MS. Consumption of ≥4 cups per day of unfermented dairy was also associated with a decreased incidence of high BMI; while an intake of ≥2 cups per day of fermented dairy was also associated with a lower risk of MS.

Given that Asian Indians have high prevalence of CVDs and T2D [105, 119, 255, 274], these findings are of public health importance. India is the largest producer of milk and it is commonly consumed by all classes of income groups, providing value for money and nutrients [275]. The results indicate that increasing the consumption of dairy products might help to reduce the risk of MS and its individual components in Asian Indians.

9.4 Interaction between genetic risk score and dietary fat intake on lipid-related traits in Brazilian young adults

CVDs are a top cause of mortality globally, accounting for 32% of all deaths worldwide in 2019 [305]. Over three-quarters of mortality from CVDs has been reported to occur in low- and middle-income countries [305], highlighting the enormous impact of CVDs in these countries. In Brazil, ischaemic heart disease and stroke accounted for most deaths in 2019, with a percentage increase of 18 and 14%, respectively from 2009 [306]. GWA studies have implicated several genetic loci for the development of dyslipidaemia, a key risk factor for CVDs [95, 124, 201, 204, 318], but these variants account for a small proportion of variability in blood lipid concentrations, and there is growing evidence that an interaction between genetic variants and environmental factors is responsible for part of the missing heritability [105, 106, 126-129]. Only a few studies have utilised a GRS to assess the interactions between dietary intake and genetic variants on CVD traits in Brazilians [139, 319, 327], with even fewer studies focusing on young adults. Hence, the aim of this study was to assess the genetic associations and the interaction of the GRS with dietary factors on lipid-related traits in Brazilian young adults. The study consisted of 190 Brazilian young adults, and dietary intake was assessed using three 24-hour dietary recalls. The GRS was constructed using 7 SNPs known to be associated with lipid-related traits at a genome-wide significance level: *CETP* rs3764261, glucokinase regulator (*GCKR*) rs1260326, endothelial lipase (*LIPG*) rs7241918, sortilin 1 (*SORT1*) rs629301, hepatic lipase (*LIPC*) rs1532085, apolipoprotein AI (*APOAI*) rs964184 and ATPase plasma membrane Ca2+ transporting 1 (*ATP2BI*) rs2681472.

The findings provide evidence that the genetic risk for disturbances in blood lipids concentration might be modulated by dietary fat intake. Significant interactions were found between the GRS and total fat intake on TG:HDL-C ratio; and between the GRS and SFA intake on TG:HDL-C ratio. Increased consumption of total fat (>31.5% of energy) and SFA (>8.6% of energy) was associated with higher TG:HDL-C ratio in participants carrying ≥6 risk alleles compared to those with <6 risk alleles. The results suggest that the TG:HDL ratio in Brazilian young adults with a high genetic risk for disturbances in lipid-related traits might be responsive to dietary fat intake; hence, interventions targeting a reduction in total fat and SFA intake could potentially benefit these individuals.

The ratio of TG:HDL-C has been identified as an independent predictor of CHD, mortality from CVDs and insulin resistance [74, 75, 375, 376]. Hence, our findings have

significant public health implications in terms of prevention and management of dyslipidaemia in individuals with a high genetic risk.

9.5 Interactions between genetic and lifestyle factors on cardiometabolic disease-related outcomes in Latin American and Caribbean populations: A systematic review

Cardiometabolic diseases such as hypertension and T2D are accountable for most NCD deaths and impose an economic burden on low- and middle-income countries [396]. In LACP, the prevalence of hypertension, T2D and obesity is 47, 22, and above 20%, respectively [397, 398]. The aetiology of cardiometabolic diseases is multifactorial where studies have demonstrated an interaction between the environment, genetic, behavioural, physiological, and socioeconomic factors [18, 170, 171, 281, 399, 400]. Therefore, this systematic review was conducted to identify gene-lifestyle interactions that modify the risk of cardiometabolic diseases in LACP.

We identified 122 significant interactions between genetic and lifestyle factors on cardiometabolic traits and the vast majority of studies come from Brazil (29), Mexico (15) and Costa Rica (12) with *FTO*, *APOE*, and *TCF7L2* being the most studied genes. The results of the gene-lifestyle interactions suggest effects which are population-, gender-, and ethnic-specific. Most of the gene-lifestyle interactions were conducted once, necessitating replication to reinforce these results. The findings of this review indicate that 27 out of 33 LACP have not conducted gene-lifestyle interaction studies and only five studies have been undertaken in low-socioeconomic settings. Most of the studies were cross-sectional, indicating a need for longitudinal/prospective studies. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and the built environment.

9.6 Impact of lipid genetic risk score and saturated fatty acid intake on central obesity in an Asian Indian population

Asian Indians are more prone to developing type 2 diabetes (T2D) and cardiovascular diseases (CVDs) at a lower body mass index (BMI) than Caucasians, due to the 'Asian Indian phenotype', which is characterised by central obesity, dyslipidaemia, and increased levels of total fat, visceral fat, insulin resistance and faster decline in beta cell function [105, 119, 120]. The location of body fat is thought to be more important in predicting adverse cardiovascular events [555-557]. Central obesity has been linked to several conditions, including insulin

resistance and increased mortality from CVDs [559, 560], necessitating studies to fully understand the underlying mechanisms for the development of central obesity in Asian Indians. Therefore, this study utilised a nutrigenetic approach to establish a link between lipids and obesity in Asian Indians. The sample consisted of 497 Asian Indian individuals (260 with type 2 diabetes and 237 with normal glucose tolerance) with a mean age of 44 ± 10 years. The participants were randomly chosen from the Chennai Urban Rural Epidemiological Study (CURES). Dietary intake was assessed using a previously validated questionnaire and a GRS was constructed using three SNPs of established lipid-pathway genes (*CETP* SNP rs4783961 and *LPL* SNPs rs327 and rs3200218).

This study has shown that SFA intake may modify the effect of lipid-pathway genes on central obesity in Asian Indians. The findings indicate that the combined effect of *LPL* and *CETP* SNPs (rs327, rs3200218 and rs4783961) on obesity traits may be altered by SFA intake, where consumption of high amounts of SFA may increase the combined genetic risk of central obesity posed by *LPL* and *CETP* SNPs while a low intake of SFA may help to reduce this risk. These findings are of public health importance considering the burden of central obesity in Asian Indians. The results suggest that Asian Indians with a higher genetic risk for central obesity are responsive to SFA intake and could benefit from dietary modifications to help prevent central obesity.

9.7 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)

Cardiometabolic diseases including CVDs remain a threat to global public health, and in 2019, around 32% of worldwide mortality was attributable to CVDs [589]. These diseases place a significant burden on low- and middle-income countries, where more than three-quarters of CVD deaths occur [25, 589]. 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 [590]. Similarly, a high prevalence of dyslipidaemia, in particular, low concentration of HDL-C (48%) has been reported in LACP [592]. Moreover, Peru experienced a substantial increase in fatalities related to CVDs (77.8%) between 2020 to 2022 [593].

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 [8, 609, 610] and blood lipid levels [5, 10, 11]. 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, 104, 105, 245, 611-613]. To our knowledge, no studies have examined gene-lifestyle interactions on cardiometabolic traits in the Peruvian population. Hence, this study aimed to assess the interaction between 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 [104, 245, 370, 613]. The study consisted of 468 urban Peruvian young adults and dietary intake was assessed using a previously validated food frequency questionnaire.

The GRS was constructed using 39 SNPs which have shown an association with cardiometabolic traits at a genome-wide significance level: alpha-ketoglutarate-dependent dioxygenase (*FTO*) rs1558902; transmembrane protein 18 (*TMEM18*) rs13021737; melanocortin 4 receptor (*MC4R)* rs6567160; glucosamine-6-phosphate deaminase 2 (*GNPDA2*) rs10938397; SEC16 homolog B, endoplasmic reticulum export factor (*SEC16B*) rs543874; BCDIN3 domain containing RNA methyltransferase (*BCDIN3D*) rs7138803; transcription factor AP-2 beta (*TFAP2B*) SNP rs2207139; neuronal growth regulator 1 (*NEGR1*) rs3101336; adenylate cyclase 3 (*ADCY3*) rs10182181; ETS variant transcription factor 5 (*ETV5)* rs1516725; glutaminyl-peptide cyclotransferase like (*QPCTL*) rs2287019; G protein-coupled receptor class C group 5 member B *(GPRC5B)* rs12446632; mitochondrial carrier 2 (*MTCH2*) SNP rs3817334; centriolar protein (*POC5*) SNP rs2112347; mitogen-activated protein kinase 5 (*MAP2K*) SNP rs16951275; zinc finger CCCH-type containing 4 (*ZC3H4*) rs3810291; FPGT-TNNI3K read through (*FPGT-TNNI3K)* SNP rs12566985; leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2 (*LINGO2*) rs10968576; cell adhesion molecule 1 (*CADM1*) SNP rs12286929; protein kinase D1 (*PRKD1*) SNP rs12885454; AGBL carboxypeptidase 4 (*AGBL4*) SNP rs657452; polypyrimidine tract binding protein 2 (*PTBP2*) rs11165643; NLR family CARD domain containing 3 (*NLRC3)* rs758747; syntaxin binding protein 6 (*STXBP6*) rs10132280; Huntingtin interacting protein 1 (*HIP1)* rs1167827; cell adhesion molecule 2 (*CADM2*) rs13078960; far upstream element binding protein 1 (*FUBP1*) rs12401738; olfactomedin 4 (*OLFM4*) rs12429545; RAS p21 protein activator 2 (*RASA2*) rs16851483; hypoxia inducible factor 1 subunit alpha inhibitor (*HIF1AN*) rs17094222; hepatocyte nuclear factor 4 gamma (*HNF4G*) rs17405819; toll like receptor 4 (*TLR4*) rs1928295; neurexin 3 (*NRXN3*) rs7141420; inflammation and lipid regulator with UBA-like and NBR1-like domains (*ILRUN* or *C6orf106*) rs205262; fragile histidine triad diadenosine triphosphatase (*FHIT*)

rs2365389; neuron navigator 1 (*NAV1*) rs2820292; tripartite motif containing 66 (*TRIM66*) rs4256980; erb-b2 receptor tyrosine kinase 4 (*ERBB4*) rs7599312; and lysine acetyltransferase 8 (*KAT8*) rs9925964.

This study indicates that carbohydrate intake might modulate genetic influences on HDL-C concentration in urban Peruvian young adults. A significant interaction was observed between the 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 a higher concentration of HDL-C than those with a low GRS (≤37 risk alleles). In the third tertile of carbohydrate intake (>452 grams/day), participants with a high GRS had a lower concentration of HDL-C than those with a low GRS. Furthermore, for participants with a high GRS, there were lower concentrations of HDL-C across tertiles of glycaemic load. 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 [592], and is related to a higher risk of CVDs [48, 640, 641], these findings have considerable public health implications.

9.8 Barriers in translating existing nutrigenetics insights to precision nutrition for cardiometabolic health in ethnically diverse populations

Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of CVD mortality (more than three-quarters) occurring in low- and middle-income countries [25]. There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors [163-168]. Despite the remarkable progress in nutrigenetics research, several factors need to be considered before the translation of existing nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations [17, 670]. Therefore, this review aimed to explore the potential barriers and challenges in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities.

The findings indicate there are numerous factors that can affect the translation of existing nutrigenetics insights to personalised and precision nutrition in diverse populations including genetic diversity, methodological factors, cultural and lifestyle factors as well as socioeconomic factors. Additionally, integration of data from disciplines such as metabolomics, epigenetics and the gut microbiome could help to facilitate the

implementation of precision nutrition based on nutrigenetics. Therefore, conducting gene-diet interaction studies in diverse populations is essential to improve their clinical application worldwide. To bridge the gap between existing nutrigenetic insights and their application in clinical practice, it is vital for initial findings to be replicated in independent samples, followed by dietary intervention studies. Studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention studies will be required to further strengthen the evidence and facilitate their application in clinical practice.

9.9 General trends observed across the studies

Variations in the intake of macronutrients were observed among the three ethnic groups studied (**Table 9.1**). Brazilian young adults had the highest intake of total fat as percentage of calories (32±6%) compared to Peruvian young adults (29 ± 6%) and Asian Indian adults (23 ± 5%). The intake in Brazilian young adults exceeded the recommended total fat intake of less than 30% of total energy intake [71] while the intakes in Peruvian young adults and Asian Indian adults were within the recommended level. Asian Indian adults however had the highest carbohydrate intake as percentage of calories (64 ± 7%). Brazilian and Peruvian young adults had a similar carbohydrate intake of 51 ± 7% and 51 ± 8% respectively. The recommended intake range of carbohydrates for adolescents aged 14 and older as well as adults is 45-65% of total daily energy intake [642], indicating that all the groups met the recommended range. With regard to protein intake, Peruvian young adults had the highest intake as percentage of calories (21 ± 4%), followed by Brazilian young adults (17 ± 1%) and Asian Indian adults (11 ± 1%).

The sampling strategy used in the studies could have influenced the comparison of dietary intake across the three groups. The Brazilian and Peruvian populations consisted of young adults aged 19 to 24 and 19 to 21 years respectively, while the Asian Indian population included adults and elderly individuals aged 20 to 88 years. It has been highlighted that younger individuals are more likely to adopt new dietary habits than older individuals [689]. Therefore, offering dietary advice to younger population could be an effective approach to preventing diseases later in life such as obesity and CVDs. Additionally, participants for the BOLD and SONGS studies were recruited from urban areas, while the CURES study included individuals recruited from both urban and rural areas. There is a need

for further research covering both urban and rural populations and accounting for confounding factors such as socioeconomic status. Furthermore, different methods were used to collect dietary intake data which could also influence the assessment of dietary intake across the groups. Three 24-h dietary recalls were used in the BOLD study, while an FFQ was used in the CURES and SONGS studies.

As shown in **Table 9.1**, Asian Indian adults had the highest mean BMI (25 ±5) and WC (87 ± 11) compared to the other groups. Asian Indian adults also had the highest concentrations of TG (165 ± 150 mg/dL), LDL-C (119 ± 32 mg/dL) and TC (191 ± 40 mg/dL). Brazilian young adults on the other hand had the highest concentration of HDL-C (55 ± 1), while Peruvian young adults had an HDL-C concentration similar to that of Asian Indian adults (42 ± 13 mg/dL vs 42 ± 10 mg/dL). With regard to the gene-diet interactions, an interaction between GRS and SFA intake on TG:HDL ratio was observed in Brazilian young adults, while an interaction between GRS and SFA intake on WC was observed in Asian Indian Adults, suggesting that different outcomes might be influenced by similar gene-diet interactions in different ethnic groups. In Peruvian young adults however, an interaction between GRS and carbohydrate intake on the concentration of HDL-C was observed. Generalising these findings is difficult due to the heterogeneity among these ethnic groups and the small sample sizes of the populations studied.

Table 9.1 A comparison of macronutrient intakes, anthropometric and biochemical parameters among the BOLD, CURES and SONGS studies

Parameter	**BOLD (Brazilian)** *n*=190	**CURES (Asian Indian)** *n*=497	**SONGS (Peruvian)** *n*=468
Age (years)	21 ± 2	44 ± 10	20 ± 1
Sex (Men/Women)	49/141	225/272	258/210
BMI (kg/m^2)	23 ± 1	25 ± 5	24 ± 4
WC (cm)	72 ± 1	87 ± 11	81 ± 10
TG (mg/dL)	76 ± 2	165 ± 150	96 ± 60
HDL-C (mg/dL)	55 ± 1	42 ± 10	42 ± 13
LDL-C (mg/dL)	99 ± 1	119 ± 32	77 ± 24
TC (mg/dL)	174 ± 1	191 ± 40	138 ± 36
TG:HDL ratio	2 ± 2	N/A	N/A
SBP (mmHg)	107 ± 1	122 ± 20	104 ± 11
DBP (mmHg)	64 ± 1	76 ± 11	67 ± 8
Energy (kcal/day)	1735 ± 1	2560 ± 822	3304 ± 1428
Total fat (% of energy)	32 ± 6	23 ± 5	29 ± 6
Carbohydrate (% of energy)	51 ± 7	64 ± 7	51 ± 8
Protein (% of energy)	17 ± 1	11 ± 1	21 ± 4

BOLD – Obesity, Lifestyle and Diabetes in Brazil; CURES – Chennai Urban Rural Epidemiological Study; SONGS – Study of Obesity, Nutrition, Genes and Social factors; BMI – body mass index; WC – waist circumference; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; TG:HDL-C – ratio of triglycerides to high-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure.

9.10 Limitations and strengths

The studies included in this project have some limitations that need to be considered. One of the main limitations is the small sample size of some of the studies, which could have influenced our findings since large sample sizes improve the power to detect interactions with modest effect sizes [393, 394]. However, we were able to detect significant interactions in all the populations studied. Additionally, a cross-sectional design was used in all the studies which prevents the establishment of a causal relationship between the GRS-diet interactions and the lipid-related traits. Another limitation is the use of self-reported measures to assess dietary intake, which can introduce bias through overestimation and underestimation of dietary intake [152, 395]. However, validated questionnaires were used to reduce potential errors. The CURES study included participants with T2D which could have introduced selection bias, but T2D was adjusted for in the analysis. Furthermore, we did not investigate types or food sources of SFA which have been reported to have different effects on CVD traits [294, 390]. Moreover, we did not investigate types of carbohydrates which can also have varying effects on cardiometabolic traits [663, 664].

The main strengths of this thesis include the use of well-defined populations and the development of various GRSs using multiple genetic variants. The GRS approach has been shown to be more effective in assessing the genetic contribution to complex traits such as blood lipid concentrations since single variants often have moderate effect sizes and hence less likely to accurately predict the genetic risk of multifactorial traits [370, 371, 675]. The study in the Peruvian population (SONGS) is the first gene-diet interaction study in Peru, capturing different regions of Peru (Coast, Highland and the Jungle), as well as the first to be conducted in adolescents, an unstudied non-Caucasian group which has an increasing prevalence of CVDs [392, 656, 657] and lipid abnormalities which significantly increase the risk of developing atherosclerotic CVDs later in life [658-662]. Moreover, validated FFQs were used in the CURES [282] and SONGS [152] studies to assess the populations' long-term macronutrient intake, while in the BOLD study, the multiple-pass method [332] was used to enhance the accuracy of the 24-h dietary recalls. All the studies employed trained personnel to enhance the accuracy of the assessments.

9.11 Future prospects

In this thesis, a significant interaction was identified between SFA intake and WC, an indicator of central obesity, in Asian Indians. The results suggest a link between lipids and central obesity, calling for further research in this area. Asian Indians are more prone to developing cardiometabolic diseases, and these findings indicate that lipid abnormalities could play a role in the development of central obesity which is an independent biomarker of cardiometabolic disease [558, 560]. Future studies should focus on using a large number of lipid-related SNPs to construct a GRS which can then be used to confirm a link between lipids and central obesity in a large sample. Once the findings have been confirmed, dietary intervention studies focusing on low SFA diets in genetically susceptible individuals could help to further confirm the findings. Similarly, low HDL-C concentration has been identified as the most common lipid abnormality in LACP [592] and findings from this thesis indicate that SFA intake might modulate genetic influences on the ratio of TG:HDL-C in Brazilians while carbohydrate intake might modify genetic influences on the concentration of HDL-C in Peruvians.

Looking at the dietary patterns of these populations, a shift from nutrient-rich fresh produce to refined products and the use of large amounts of cooking oil has been reported among South Asians [697]. Additionally, some of the commonly consumed foods in India such as potato chips have been found to contain high amounts of palmitic acid, which can be attributed to the type of cooking oil used [573]. Although milk and milk products have been found to be a main source of SFA in India, the CURES dairy intake study found a negative association between dairy intake and cardiometabolic risk factors, suggesting that SFA from dairy sources might not be accountable for the increased risk of cardiometabolic diseases. In Brazil, the dietary pattern is characterised by increased consumption of processed foods rich in fat and added sugar [384, 385]. Furthermore, the fat content of processed foods in Brazil was found to be composed of high amounts of SFA, ranging from 9.3 to 12 grams per 100 grams of food products [317]. A shift in dietary pattern has also been reported in Peru in which there is increased consumption of high-caloric foods and sugar sweetened beverages [604-606]. An analysis of the primary food sources that contribute to energy intake in urban populations from eight Latin American countries [604] showed that Peru had the highest proportion of energy derived from carbohydrates (62.9 %). Given that a high carbohydrate intake was found to be linked to low-HDL-C concentration in individuals with a high GRS, dietary guidelines targeting a reduction in carbohydrate intake might be beneficial for Peruvian individuals who are genetically susceptible to low HDL-C

concentration. As with Asian Indians, interventions targeting a reduction in SFA intake might be effective in preventing and managing lipid abnormalities in Brazilian individuals with a high genetic risk.

These gene-diet interactions require replication in longitudinal and interventional studies with larger sample sizes prior to implementing public health guidelines. It has been highlighted that dietary intervention studies can help to raise the evidence-level of gene-diet interactions once they have been replicated [109]. In a 12-week RCT, a GRS was used to identify participants as being responsive to fat or carbohydrate before randomisation to a high-fat or high carbohydrate diet [679]. Studies utilising this approach could help to determine the effectiveness of dietary interventions based on genotypic information and facilitate the clinical application of nutrigenetics.

Additionally, the underlying mechanisms of the gene-diet interactions are unclear, indicating a need for mechanistic studies. Understanding the mechanisms involved is important in enhancing the validity of the findings, and this will require a collaborative approach among experts in biological, statistical and computational sciences to design models based on real biological phenomena [143]. Moreover, examining the overall dietary pattern is believed to offer several advantages since foods and the nutrients they contain often have synergistic effects, which can make it difficult to identify the influence of a single food or nutrient [690]. By using metabolomics, specific biomarkers associated with food intake and dietary patterns can be identified to supplement the information obtained from self-reported dietary intake, thus enabling a more objective and reliable measurement of dietary exposure [729, 743]. It is also important to examine gene-diet interactions in groups at risk of lipid-related traits such as the elderly.

The findings from this thesis support the use of personalised nutrition to prevent or manage cardiometabolic diseases. Genetic information can help to determine an individual's susceptibility to lipid-related traits such as CVDs which can be altered by dietary intake. While gene-diet interaction studies have been extended to cover previously under-represented populations, a systematic review conducted as part of this thesis [106] identified that, 27 out of 33 countries in Latin America and the Caribbean had not conducted gene-diet interaction studies. Hence, further nutrigenetic research in LMICs is required given the enormous burden of NCDs, variations in genetic susceptibility, and cultural practices leading to distinct environmental exposures [106, 130, 143]. The GeNuIne Collaboration was established to address this gap in human nutrition research in LMICs, and

this initiative has identified significant gene-diet interactions on cardiometabolic traits in these regions [18, 131].

Finally, nutrigenomic research has provided insights into the molecular actions of nutrients and other dietary components as well as their roles in maintaining both normal and impaired cellular homeostasis [743]. Nutrigenomics involves the application of biochemistry, physiology, nutrition, genomics, proteomics, metabolomics, transcriptomics, and epigenomics to explore the interactions between genes and nutrients at the molecular level [744]. Integrating data from nutrigenetics and nutrigenomic approaches such as metabolomics, epigenetics and the gut microbiome is argued to be important in enhancing the scientific understanding of inter-individual variability in response to dietary interventions, although the practicality and effectiveness of this process are still being explored [180, 181]. So far, progress has been made in the mechanistic understanding of dietary interventions through the integration of omics technologies such as metabolomics and the gut microbiome [182]. Metabolomics focuses on analysing small molecules (metabolites) found in biological samples to understand changes in metabolism under various conditions [180]. Metabolites are the direct products of dietary consumption and metabolism, enabling a more accurate assessment of biological and physiological pathways as well as the related biomarkers for diet or disease [182]. The gut microbiome supports the host by interacting directly or indirectly with host cells through the production of bioactive molecules, and this interaction allows the gut microbiome to regulate various biological processes related to immunity and energy balance [183]. The application of the gut microbiome in precision nutrition involves using the gut microbiome as a biomarker to predict how specific dietary components affect host health, and the use of this information to design precision dietary interventions aimed at promoting health [183]. Epigenetics on the other hand covers the molecular processes that can alter the activity of genes without changing the DNA sequence, and these processes include DNA methylation, histone modifications and alterations in noncoding RNAs [184]. Epigenetic changes might explain individual differences in metabolic health and responses to diet, and have the potential to identify novel biomarkers for precision nutrition and targets for precise interventions [185].

In summary, nutrigenetics is considered the cornerstone of personalised/precision nutrition [17, 178]. Differences in dietary responses and susceptibility to cardiometabolic diseases is attributable to genetic variations, particularly, in the form of SNPs [17, 670]. Nutrigenetic research has the potential to predict the risk of various cardiometabolic diseases, and with personalised dietary interventions, these diseases could be prevented or

managed more effectively [745]. Although significant gene-diet interactions have been identified by various studies, many of the studies have not been replicated and there is a need for large scale longitudinal and dietary intervention studies covering different ethnic groups to raise the evidence level and facilitate the translation of nutrigenetics to personalised and precision nutrition.

9.12 Conclusion

In LACP, CVDs are the top cause of mortality and a key contributor to disability, and this is mainly attributed to CVD risk factors. Similarly, the CVD epidermic in India is marked by an early onset, greater relative risk, a higher fatality rate and an increased number of premature deaths. The findings of this thesis indicate that personalised nutrition based on GRS could be an effective strategy for preventing and managing CVD risk factors in these populations. In Asian Indians, interventions targeting a reduction in SFA intake might help to reduce the genetic risk of central obesity, while in Brazilians these interventions might benefit individuals with a genetic susceptibility to disturbances in blood lipid concentrations. In Peruvians, on the other hand, dietary guidelines focusing on lowering the intake of carbohydrates could help to reduce the genetic risk of low HDL-C concentration. In the CURES dairy intake study, a negative association was found between dairy intake and cardiometabolic risk factors in Asian Indians, indicating that while dairy is a source of SFA, increased consumption of dairy products might be beneficial for Asian Indians.

With regard to nutrigenetic studies examining the *CETP* gene, total fat intake accounted for majority of the interactions across different SNPs of the gene, being associated with unfavourable lipid outcomes in some populations but not others. In LACP, several gene-lifestyle interactions on cardiometabolic traits have been identified in Brazilians, Mexicans, Costa Ricans, Chileans, Argentinians, Colombians and LACP diaspora, highlighting effects which are population-, sex- and ethnic-specific. However, most of the studies were conducted once, necessitating replication to reinforce the results.

The evidence indicates that nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. However, numerous factors need to be considered before the translation of existing nutrigenetic insights to personalised and precision nutrition in diverse populations including genetic diversity, cultural and lifestyle factors as well as socioeconomic factors. Additionally, integration of data from disciplines such as metabolomics, epigenetics and the gut microbiome could help to facilitate the implementation of precision nutrition based on nutrigenetics. Therefore, conducting gene-

diet interaction studies in diverse populations is essential to improve their clinical application worldwide. To bridge the gap between existing nutrigenetic insights and their application in clinical practice, it is vital for initial findings to be replicated in independent samples from ethnically diverse populations. Once findings have been replicated in independent samples, dietary intervention studies will be required to further strengthen the evidence and facilitate their application in clinical practice. Studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes.

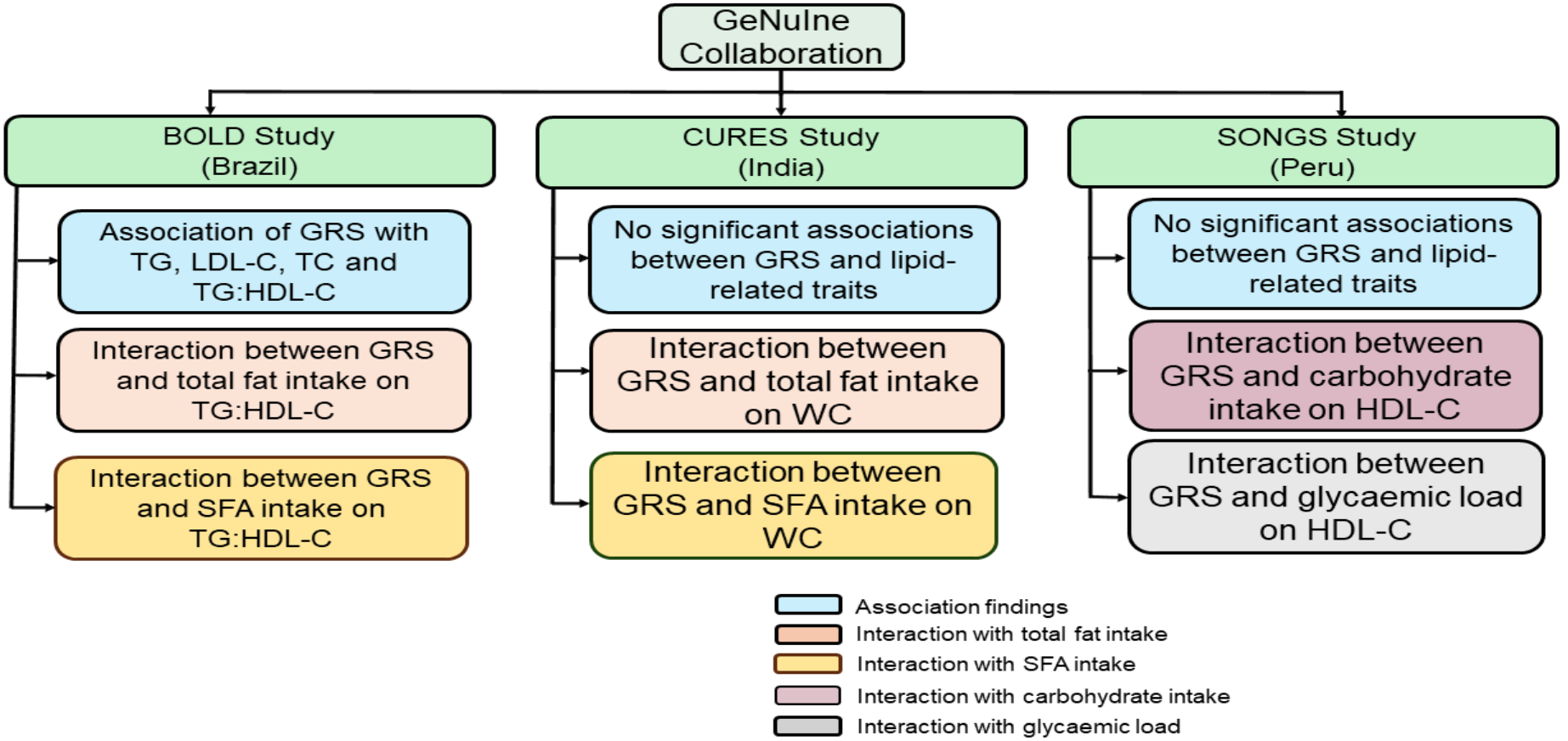

Figure 9.1 The main findings of the thesis

GeNuIne – Gene-Nutrient Interactions; BOLD – Obesity, Lifestyle and Diabetes in Brazil; CURES – Chennai Urban Rural Epidemiological Study; SONGS – Study of Obesity, Nutrition, Genes and Social factors; GRS – genetic risk score; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TC – total cholesterol; TG:HDL-C – ratio of triglycerides to high-density lipoprotein cholesterol; WC – waist circumference.

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Appendix A - Data analysis plan: Higher intake of dairy is associated with lower cardiometabolic risks and metabolic syndrome in Asian Indians

In this document:

1. Background
2. Study data and design
3. Statistical analyses
4. Expected outcomes
5. Proposed deadline

1. Background

Asian Indians have been shown to have distinct biochemical and clinical characteristics that put them at risk of type 2 diabetes (T2D) and cardiovascular diseases (CVDs) [105, 119, 120, 255]. The distinct features include central obesity, dyslipidaemia, insulin resistance, increased levels of visceral fat, total fat, and propensity to beta cell dysfunction [105, 119, 120, 255]. The increasing prevalence of cardiometabolic risk factors has been linked to genetic and environmental factors [18, 105, 126, 128, 265] and there is growing interest in the role of different types of food in the development of these risk factors [105, 128, 256, 265]. Several studies have reported a protective effect of dairy consumption on the risk of cardiometabolic diseases [256, 266-269]. However, one study [270] reported that a low dairy intake was linked to lower cardiometabolic risks than a high dairy intake.

a. Aims and objectives of the study

To test the association between dairy intake and cardiometabolic risks.

b. Hypothesis

Dairy intake is associated with lower cardiometabolic risks.

2. Study data and design

Participants for this study were randomly selected from the Chennai Urban Rural Epidemiological Study (CURES), which is a cross-sectional epidemiology study conducted on a representative sample of the population of Chennai, formerly Madras, in southern India [105, 280]. The sample for the current study consists of 1,033 adults with normal glucose tolerance [105, 280].

a. Phenotypes (exposure, outcome, covariates)

- Main exposure

Dairy intake

- Main outcome

Levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), and fasting plasma glucose (FPG); blood pressure; body mass index (BMI); waist circumference (WC); general obesity and central obesity.

- Confounders

- Sex
- Age
- BMI
- Smoking status
- Physical activity
- Total energy intake
- Tea and coffee intake

3. Statistical analyses

a. Descriptive statistics

Descriptive characteristics will be presented as median and interquartile range for continuous variables, and as proportions for categorical variables [105] as detailed in **Table 1**. The Kruskal-Wallis test will be used to compare differences between the medians of continuous variables, and the Chi-Squared test will be used to test for differences in proportions [105]. BMI will be calculated as weight in kg divided by the square of the height (m^2). Individuals with BMI <25 kg/m^2 will be classified as non-obese and those with BMI ≥25 kg/m^2 will be classified as obese, in accordance with the World Health Organisation (WHO) Asia Pacific Guidelines [283].

b. Graphs

Bar graphs will be used for levels of HDL-C, LDL-C, TG, TC, FPG and blood pressure according to dairy intake. A bar graph will also be used for BMI, risk of central obesity and general obesity according to dairy intake.

c. Models

The Cox proportional hazards model will be used to test for association between dairy intake and cardiometabolic risk. The lowest, medium and highest intakes of total dairy, unfermented and fermented dairy will be derived by stratifying the

data into deciles and regrouping as lowest (quartile 1(Q1)–quartile 4 (Q4)), medium (Q5–Q8) and highest intake (Q9–Q10) to test the association with cardiometabolic risk using the regression model. The hazard ratio (HR) for incidence of cardiometabolic risk in each group of dairy intake (lowest, medium and highest intake) and its subdivision (fermented and unfermented) will be calculated using the Cox proportional hazards model, adjusting for age, sex, BMI, smoking status, physical activity level, total energy, tea and coffee intake where appropriate [105] as shown in **Table 1**. The linear trend across the lowest, medium and highest dairy intake and incidence of cardiometabolic risk will be tested using the regression model [287]. Differences between the dairy product and its subdivisions will be assessed using the Kruskal-Wallis test for all the continuous variables. A *P* value <0.05 will be considered statistically significant.

d. Software

SAS software version 9.4

4. Expected outcomes

The findings from this project are expected to be published in a journal and will be written up as a chapter of my thesis.

5. Proposed deadline

20-04-2022

Table 1 Statistical analyses

Objectives	Statistical test used	Reason for statistical test used	Outcome of statistical test used	Covariates (When appropriate)
1. To produce descriptive statistics for the study participants who had completed an assessment on demographics and fasting biochemical/anthropometric measurements.				
To generate descriptive statistics of the participants who completed the study assessment on demographics, anthropometric and biochemical outcomes of interest.	Descriptive statistics Or Descriptive statistics frequencies	Descriptive for continuous variables Frequencies for categorical variables	To determine the median and inter-quartile range of the anthropometric and biochemical variables as well as frequencies for categorical variables: age (years), height (cm), weight (kg), waist circumference (cm), obese cases (%), PAL, smoking status, SBP and DBP (mmHg), serum TC, HDL-C, LDL-C, TG (mg/dL), FPG (mg/dL), and total energy (kcal).	
2. To test the relationship between dairy intake and anthropometric/fasting biochemical measurements (TC, HDL-C, LDL-C, TG, FPG, SBP, DBP, BMI, and WC)				
To test the association between dairy intake and anthropometric/biochemical traits while adjusting for covariates.	Univariate linear regression	The exposure/independent variable [dairy intake (low, medium and high)] is a categorical variable and the outcome/dependent variable (anthropometric trait/biochemical trait) is a continuous variable.	To identify the effect of dairy intake on cardiometabolic traits.	- Age, sex, BMI, smoking status, PAL, total energy, tea and coffee intake will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C and TG), FPG, or blood pressure. - BMI will not be adjusted for when obesity/BMI is the outcome [105].

3. To test the relationship between dairy intake and cardiometabolic risk				
To test the association between dairy intake and cardiometabolic risk while adjusting for covariates.	Cox proportional hazard analysis	The exposure/independent variable [dairy intake (low, medium and high)] is a categorical variable and the outcome/dependent variable (general obesity, central obesity and cardiometabolic risk) is a categorical variable.	To identify the effect of dairy intake on general obesity, central obesity and cardiometabolic risk.	- Age, sex, BMI, smoking status, PAL, total energy, tea and coffee intake will be adjusted for when the outcome is a lipid trait or blood pressure. - BMI will not be adjusted for when obesity is the outcome [105].

BMI – body mass index; WC – waist circumference; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; FPG – fasting plasma glucose; PAL – physical activity level

Appendix B - Data analysis plan: Interaction between genetic risk score and dietary fat intake on lipid-related traits in Brazilian young adults

In this document:

1. Background
2. Study data and design
3. Statistical analyses
4. Expected outcomes
5. Proposed deadline

1. Background

Cardiovascular diseases (CVDs) remain a leading cause of death and disability worldwide [746] and one of the major risk factors is dyslipidaemia which is characterised by a decrease in the concentration of high-density lipoprotein cholesterol (HDL-C) and an elevation in the levels of triglycerides (TG) or low-density lipoprotein cholesterol (LDL-C) [3, 107]. Dyslipidaemia is a complex trait and genome-wide association (GWA) studies have identified several loci associated with blood lipid levels [94-96, 200, 204, 321]. However, these variants account for a small proportion of variability in lipid traits, and there is growing evidence that an interaction between genetic variants and environmental factors is responsible for part of the missing heritability of complex traits [105, 126-129]. Single variants often have small effect sizes and an effective approach to assessing the genetic contribution to complex traits is the use of a genetic risk score (GRS) which allows the combined effect of multiple variants to be analysed [245, 319].

a. Aims and objective of the study

To investigate whether dietary factors interact with GRS to influence lipid-related traits. The dietary factors to be considered include dietary intake of fat, carbohydrate, and protein.

b. Hypothesis

GRS and dietary factors interact to modify lipid-related traits.

2. Study data and design

The sample consists of 203 healthy young adults aged 19-24 years from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) cross-sectional study [128, 319]. Participants

were recruited between March and June 2019 from the Federal University of Goiás (UFG). The study was performed as part of the Gene-Nutrient Interactions (GeNuIne) collaboration which is aimed at investigating how genetic and lifestyle factors interact to influence chronic diseases in diverse ethnic groups, with the goal of preventing and managing chronic diseases through personalised nutrition [18, 131, 170, 171].

a. Phenotypes (exposure, outcome, covariates)

- Main exposure

  GRS

- Main outcome

  Lipid traits: HDL-C, LDL-C, TG, total cholesterol (TC) and TG:HDL-C ratio.

  Blood pressure: Systolic blood pressure (SBP) and diastolic blood pressure (DBP).

  Obesity-related traits: Waist circumference (WC) and body mass index (BMI).

- Confounders
  - Sex
  - Age
  - BMI

3. Statistical analyses

a. Descriptive statistics

Descriptive characteristics of the study participants by sex will be presented as means and standard deviation for continuous variables, and as percentages for categorical variables [105] as detailed in **Table 1**. An independent sample t-test will be used to compare the means of continuous variables and a goodness of fit Chi-squared test will be performed to examine if the observed genotype counts are in Hardy-Weinberg equilibrium [105]. Normality test will be done by Shapiro-Wilk test and variables which are not normally distributed will be log-transformed before the analysis. BMI will be calculated as weight in kg divided by the square of the height (m^2).

b. Graphs

Bar graphs will be used to display lipid levels, blood pressure and dietary factor, stratified by GRS. A bar graph will also be used for obesity-related traits and dietary factor, stratified by GRS.

c. Models

Linear and logistic regression models will be used to test for genetic associations with the continuous and categorical outcomes respectively adjusting for age, sex, and BMI where appropriate [105] as shown in **Table 1**. Interactions between GRS and dietary intake will be analysed by adding the interaction terms in the models and adjusting for total energy intake in addition to the covariates above [105]. Interactions between GRS and dietary intake reaching statistical significance (P<0.05) will be explored further by grouping participants based on the quantity of dietary intake [128]. A median dietary intake will be used to classify participants into 'low' (lower than median) and 'high' (higher than median) groups. Participants will also be grouped based on tertiles of dietary intake into first, second and third tertiles [245]. Seven SNPs (*CETP* rs3764261, *GCKR* rs1260326, *LIPG* rs7241918, *SORT1* rs629301, *LIPC* rs1532085, *APOA1* rs964184, and *ATP2B1* rs2681472) will be used to generate an unweighted GRS. An unweighted GRS will used because information on effect sizes is often limited to certain traits [245, 369]. Moreover, effect sizes may vary between populations and data from a GWA conducted in one population may not apply to another population [105, 369]. The unweighted GRS will be calculated by adding the risk alleles across the seven SNPs for each participant [564]. The SNPs have been selected based on their associations with lipid traits at a genome-wide significance level ($P<5\times10^{-8}$) [94, 124, 195, 200, 201, 203, 205, 207, 208, 357].

d. Software

SPSS version 28 and R software version 4·3·1

4. Expected outcomes

The findings from this project are expected to be published in a journal and will be written up as a chapter of my thesis.

5. Proposed deadline

30-06-2022

Table 1 Statistical analyses

Objectives	Statistical test used	Reason for statistical test used	Outcome of statistical test used	Covariates (When appropriate)
1. To check whether the selected SNPs are in Hardy-Weinberg equilibrium (HWE)				
To determine whether the observed genotype counts are in HWE.	Goodness of fit Chi-Squared test	To compare the observed genotype counts with the expected values under HWE.	To test whether the study population is in HWE for the loci under study [105].	
2. To produce descriptive statistics for the study participants who had completed an assessment on demographics and biochemical and anthropometric measurements.				
To generate descriptive statistics of the participants who completed the study assessment on demographics, anthropometric and biochemical outcomes of interest.	Descriptive statistics Or Descriptive statistics frequencies	Descriptive for continuous variables Frequencies for categorical variables	To determine the mean and standard deviation of the demographic, anthropometric and biochemical variables: age (years), height (cm), weight (kg), waist circumference (cm), serum TC, HDL-C, LDL-C, TG (mg/dL), TG:HDL-C ratio, SBP (mmHg), DBP (mmHg), total fat (g), total fat (% energy), total SFA(g), MUFA (g), PUFA (g), carbohydrate (g), carbohydrate (% energy), protein (g), protein (% energy), and total energy (kcal).	

3. To test the association between the GRS and fasting biochemical/anthropometric measurements (TC, HDL-C, LDL-C, TG, TG:HDL-C ratio, SBP, DBP, BMI, and WC)				
To test the association between GRS and anthropometric/biochemical traits while adjusting for covariates.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (anthropometric trait/biochemical trait) is a continuous variable.	To identify the effect of genetic variants on lipid-related traits.	- Age, sex, and BMI will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C, TG and TG:HDL-C ratio) or blood pressure. - BMI will not be adjusted for when the outcome is an obesity related trait or BMI [105].
4. To test the interaction between the GRS and dietary factors on fasting biochemical/anthropometric measurements (TC, HDL-C, LDL-C, TG, TG:HDL-C ratio, SBP, DBP, BMI and WC)				
To test the interaction between macronutrients and GRS on fasting biochemical and anthropometric traits.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (fasting biochemical trait/anthropometric trait) is a continuous variable.	To determine the effect of the genetic variants and the macronutrients: carbohydrate, protein, and fat on fasting biochemical and anthropometric traits.	- Age, sex, and BMI will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C, TG and TG:HDL-C ratio) or blood pressure [105]. - BMI will not be adjusted for when the outcome is an obesity related trait or BMI [105]. - Total energy will be adjusted for when the dietary variable is measured in grams.
To test whether the interactions are caused by high, low or medium intake of these macronutrients.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable	To determine the effect of the genetic variants and the macronutrients: carbohydrate, protein, and	- Age, sex, and BMI will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C, TG and

		(fasting biochemical/anthropometric trait) is a continuous variable.	fat on fasting biochemical and anthropometric traits. Data will be split based on tertiles of carbohydrate, protein, and fat.	TG:HDL-C ratio) or blood pressure. - BMI will not be adjusted for when an obesity-related trait or BMI is the outcome [105]. - Total energy will be adjusted for when the dietary variable is measured in grams.
NOTES				
When examining fat, carbohydrate and proteins in grams, total energy intake will be adjusted for. When using the percentage energy intake of the macronutrients, there is no need to adjust for total energy intake.	Computer variables	For GRS - Carbohydrate interactions: 1g of carbohydrate = 4 kcal For GRS - Fat interactions: 1g of fat = 9 kcal For GRS - Protein interactions: 1g protei*n*=4 kcal		

GRS – genetic risk score; BMI – body mass index; WC – waist circumference; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure.

Appendix C - Data analysis plan: Impact of lipid genetic risk score and saturated fatty acid intake on central obesity in an Asian Indian population

In this document:

1. Background
2. Study data and design
3. Statistical analyses
4. Expected outcomes
5. Proposed deadline

1. Background

Evidence has shown that Asian Indians are more prone to insulin resistance and diabetes in comparison with Europeans owing to what is described as the 'Asian Indian' phenotype, which is characterised by higher levels of insulin, total fat and central obesity despite having a lower body mass index (BMI) [105, 119]. A number of studies have demonstrated that cardiometabolic traits such as lipid levels and obesity are influenced by single nucleotide polymorphism (SNPs) in the lipoprotein lipase (*LPL*) and cholesteryl ester transfer protein (*CETP*) genes [126, 189, 242, 747, 748]. However, the effect size of individual SNPs is small and a more effective approach involves combining several risk alleles [370] to generate a genetic risk score (GRS) [245].

a. Aims and objective of the study

To test for interaction between GRS and dietary factors on cardiometabolic traits.

b. Hypothesis

GRS and dietary factors interact to modify cardiometabolic traits.

2. Study data and design

Participants for this case-control study were randomly selected from the Chennai Urban Rural Epidemiological Study (CURES), which is a cross-sectional epidemiology study conducted on a representative sample of the population of Chennai, formerly Madras, in southern India [105, 280]. The sample for the current study consists of 497 unrelated individuals, 260 with type 2 diabetes (cases) and 237 with normal glucose tolerance (NGT) (controls) [105, 280].

a. Phenotypes (exposure, outcome, covariates)

- Main exposure

  GRS

- Main outcome

  Levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total cholesterol (TC), body mass index (BMI), waist circumference (WC), general obesity and central obesity.

- Confounders
  - Sex
  - Age
  - BMI
  - Type 2 diabetes

3. Statistical analyses

a. Descriptive statistics

Descriptive characteristics will be presented as means and standard deviation (SD) for continuous variables, and as percentages for categorical variables [105] as detailed in **Table 1**. An independent sample t-test will be used to compare the means of continuous variables, and a goodness of fit Chi-squared test will be used to examine if the observed genotype counts are in Hardy-Weinberg equilibrium [105]. Variables which are not normally distributed will be log-transformed before the analysis [564]. BMI will be calculated as weight in kg divided by the square of the height (m^2). Individuals with BMI <25 kg/m^2 will be classified as non-obese and those with BMI ≥25 kg/m^2 will be classified as obese, in accordance with the World Health Organisation (WHO) Asia Pacific Guidelines [283]. The dietary factors to be investigated are total dietary intake of fat, carbohydrate and protein.

b. Graphs

Bar graphs will be used for levels of HDL-C, LDL-C, TG, TC and dietary factor, stratified by GRS. A bar graph will also be used for BMI and dietary factor, stratified by GRS.

c. Models

Linear and logistic regression models will be used to test for genetic associations with the continuous and categorical outcomes respectively adjusting for age, sex, BMI and type 2 diabetes where appropriate [105] as shown in **Table 1**. Interactions between GRS and dietary intake will be analysed by adding the

interaction terms in the models and adjusting for total energy intake in addition to the covariates above [105]. Interactions between GRS and dietary intake reaching statistical significance (P<0.05) will be explored further using binary analysis [128]. A median intake of total fat, saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) will be used to classify individuals into two groups: 'lower than median group' and 'higher than median group' [245]. Participants will also be grouped using tertiles of carbohydrate intake (% energy) as: first tertile; second tertile; and third tertile [105]. Five SNPs (*CETP* SNP: rs4783961; and *LPL* SNPs: rs327, rs3200218, rs1800590 and rs268) will be used to generate an unweighted GRS. The risk alleles will not be weighed due to limited available information on effect sizes of the SNPs for the Asian Indian population. Moreover, it has been demonstrated that assigning weights to risk alleles only has minimal effect [370]. The GRS will be calculated by adding the risk alleles across the SNPs [564]. The SNPs have been selected based on previously reported associations with lipid traits, obesity and type 2 diabetes [99, 126, 190, 747].

d. Software

SPSS version 26

4. Expected outcomes

The findings from this project are expected to be published in a journal and will be written up as a chapter of my thesis.

5. Proposed deadline

25-08-2021

Table 1 Statistical analyses

Objectives	Statistical test used	Reason for statistical test used	Outcome of statistical test used	Covariates (When appropriate)
1. To check whether the selected SNPs are in Hardy-Weinberg equilibrium (HWE)				
To determine whether the observed genotype counts are in HWE.	Goodness of fit Chi-Squared test	To compare the observed genotype counts with the expected values under HWE.	To test whether the study population is in HWE for the loci under study [105].	
2. To produce descriptive statistics for the study participants who had completed an assessment on demographics and biochemical and anthropometric measurements				
To generate descriptive statistics of the participants who completed the study assessment on demographics, anthropometric and biochemical outcomes of interest.	Descriptive statistics Or Descriptive statistics frequencies	Descriptive for continuous variables Frequencies for categorical variables	To determine the mean and standard deviation of the anthropometric and biochemical variables as well as frequencies for categorical variables: age (years), height (cm), weight (kg), waist circumference (cm), WHR, obese cases (%), diabetes cases (%), fasting blood glucose (mg/dL), fasting serum insulin (µIU/ml), glycated haemoglobin (HbA1c), PAL (sedentary (%), moderate (%), vigorous (%), serum TC, HDL-C, LDL-C, TG (mg/dL), total fat (g), total fat (% energy), SFA(g), MUFA (g), PUFA (g), carbohydrate (g), carbohydrate (% energy), protein (g), protein (% energy), and total energy (kcal).	

3. To test the relationship between the GRS and anthropometric/fasting biochemical measurements (TC, HDL-C, LDL-C, TG, SBP, DBP, BMI, and WC)				
a. To test the association between GRS and anthropometric/biochemical traits while adjusting for covariates.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (anthropometric/biochemical trait) is a continuous variable.	To identify the effect of genetic variants on anthropometric/biochemical traits.	- Age, sex, BMI and T2D will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C and TG) or blood pressure. - BMI will not be adjusted for when obesity/BMI is the outcome [105].
b. To test the association between the GRS and obesity while adjusting for covariates.	Logistic regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (general and central obesity) is a categorical variable.	To identify the effect of genetic variants on general and central obesity.	Age, sex and T2D.
4: To test the interaction between the GRS and dietary factors on fasting biochemical/anthropometric measurements (TC, HDL-C, LDL-C, TG, SBP, DBP, BMI, and WC)				
a. To test the interaction between macronutrients and GRS on fasting biochemical and anthropometric traits.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (fasting biochemical/anthropometric trait) is a continuous variable.	To determine the effect of the genetic variants and the macronutrients: carbohydrate, protein and fat on fasting biochemical and anthropometric traits.	- Age, sex, BMI and T2D will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C and TG) or blood pressure [105]. - BMI will not be adjusted for when obesity/BMI is the outcome [105]. - Total energy will be adjusted for when the dietary variable is measured in grams.
b. To test whether the interactions are caused by high, low or medium intake of these macronutrients.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the	To determine the effect of the genetic variants and the macronutrients: carbohydrate, protein and	- Age, sex, BMI and T2D will be adjusted for when the outcome is a lipid trait (TC,

		outcome/dependent variable (fasting biochemical/anthropometric trait) is a continuous variable.	fat on fasting biochemical and anthropometric traits. Data will be split based on tertiles of carbohydrate, protein, and fat.	HDL-C, LDL-C and TG) or blood pressure. - BMI will not be adjusted for when obesity/BMI is the outcome [105]. - Total energy will be adjusted for when the dietary variable is measured in grams.
NOTES				
When examining fat, carbohydrate and protein in grams, total energy intake will be adjusted for. When using the percentage energy intake of the macronutrients, there is no need to adjust for total energy intake.	Computer variables	For GRS - Carbohydrate interactions: 1g of carbohydrate = 4 kcal For GRS - Fat interactions: 1g of fat = 9kcal For GRS - Protein interactions: 1g protei*n*=4 kcal		

GRS – genetic risk score; BMI – body mass index; WC – waist circumference; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; PAL – physical activity level

Appendix D - Data analysis plan: 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)

In this document:

1. Background
2. Study data and design
3. Statistical analyses
4. Expected outcomes
5. Proposed deadline

1. Background

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 [589]. These diseases place a significant burden on low- and middle-income countries, where more than three-quarters of CVD deaths occur [25, 589]. Dyslipidaemia, obesity and hyperglycaemia are major risk factors for cardiometabolic diseases [74, 749-751] and multiple factors including genetic, environmental and lifestyle factors have been implicated in the development of these traits [18, 104, 105, 130, 327, 611]. Interactions between genetic variants and lifestyle factors including dietary intake have been reported to contribute to interindividual variation in lipid, glycaemic and obesity related traits in several populations [104, 107, 245, 251, 327, 613, 752, 753]. However, to our knowledge, no studies have examined gene-diet interactions on cardiometabolic traits in the Peruvian population. Hence, the aim of this study is to examine the association of a genetic risk score (GRS) and its interaction with dietary factors on cardiometabolic traits in the Peruvian population. The GRS approach has been shown to be more effective in predicting the genetic risk of complex traits such as dyslipidaemia where the effect size of single variants is often modest [104, 245, 370, 613].

a. Aims and objectives of the study

To determine whether dietary factors interact with GRS to influence cardiometabolic traits. The dietary factors to be considered are dietary intakes of macronutrients (fat, carbohydrate and protein).

b. Hypothesis

Dietary factors and GRS interact to modify cardiometabolic traits.

2. Study data and design

This study is 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 multicentre 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 2,053 children aged 6 to 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 [614]. The sample covers the diversity of living standard conditions observed in the country [614].

Participants for this sub-study come from 12 of the original 20 clusters and include 833 urban participants. 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.

a. Phenotypes (exposure, outcome, covariates)

- Main exposure

  GRS

- Main outcome

  Lipid traits: HDL-C, LDL-C, TG, and TC.

  Blood pressure: Systolic blood pressure (SBP) and diastolic blood pressure (DBP).

  Glycaemic traits: Fasting glucose, fasting insulin and glycated haemoglobin (HbA1c).

  Obesity-related traits: waist circumference and body mass index (BMI).

- Confounders
  - Sex
  - BMI
  - Smoking status
  - Physical activity level
  - Family history of diabetes

3. Statistical Analyses

a. Descriptive Statistics

Descriptive characteristics of the study participants will be presented as means and standard deviation for continuous variables, and as percentages for categorical variables [105] as detailed in **Table 1**. An independent sample t-test will be used to compare the means of continuous variables and the Chi-squared test will be performed to examine if the observed genotype counts are in Hardy-Weinberg equilibrium [105]. Normality test will be done by Shapiro-Wilk test and non-normally distributed variables will be log-transformed before the analysis. BMI will be calculated as weight in kilograms (kg) divided by the square of the height (m^2).

a. Graphs

Bar graphs will be used to display lipid levels, blood pressure, glycaemic traits, obesity-related traits and lifestyle factors stratified by GRS.

b. Models

Linear and logistic regression models will be used to test for genetic associations with the continuous and categorical outcomes respectively, adjusting for sex, BMI, physical activity level, smoking status and family history of diabetes where appropriate [105] as shown in **Table 1**. Interactions between GRS and dietary factors will be analysed by adding the interaction terms in the models and adjusting for total energy intake in addition to the covariates above if the dietary intake variable is in grams [105]. Interactions between GRS and dietary intake reaching statistical significance (P<0.05) will be explored further by grouping participants based on the quantity of dietary intake [128]. The median of the interacting variable will be used as a cut-off point to classify participants into 'low' (lower than or equal to median) and 'high' (higher than median) groups. Participants will also be grouped based on tertiles of the interacting variable into first, second and third tertiles [245]. An unweighted GRS will be constructed using 39 SNPs of metabolic pathway genes: alpha-ketoglutarate-dependent dioxygenase (*FTO*) SNP rs1558902 [8, 622-625]; transmembrane protein 18 (*TMEM18*) SNP rs13021737 [8, 352, 626-629]; melanocortin 4 receptor (*MC4R)* SNP rs6567160 [7, 8, 629-631]; glucosamine-6-phosphate deaminase 2 (*GNPDA2*) SNP rs10938397 [7, 8, 401, 632]; SEC16 homolog B, endoplasmic reticulum export factor (*SEC16B*) SNP rs543874 [8, 352, 629, 632, 633]; BCDIN3

domain containing RNA methyltransferase (*BCDIN3D*) SNP rs7138803 [8, 352, 401, 629, 632]; transcription factor AP-2 beta (*TFAP2B*) SNP rs2207139 [8, 352, 401, 628]; neuronal growth regulator 1 (*NEGR1*) SNP rs3101336 [8, 626-629]; adenylate cyclase 3 (*ADCY3*) SNP rs10182181 [8, 626, 627, 634]; ETS variant transcription factor 5 (*ETV5) SNP* rs1516725 [5, 8, 401, 626]; glutaminyl-peptide cyclotransferase like (*QPCTL*) SNP rs2287019 [8, 629, 632, 635]; G protein-coupled receptor class C group 5 member B *(GPRC5B)* SNP rs12446632 [8, 401, 629, 634]; mitochondrial carrier 2 (*MTCH2*) SNP rs3817334 [626, 627, 633, 634]; centriolar protein (*POC5*) SNP rs2112347 [7, 8, 629, 632]; mitogen-activated protein kinase 5 (*MAP2K*) SNP rs16951275 [8, 628, 636]; zinc finger CCCH-type containing 4 (*ZC3H4*) SNP rs3810291 [7, 8, 630, 632]; FPGT-TNNI3K read through (*FPGT-TNNI3K)* SNP rs12566985 [8, 628, 637]; leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2 (*LINGO2*) SNP rs10968576 [8, 352, 633, 638]; cell adhesion molecule 1 (*CADM1*) SNP rs12286929 [8, 627, 629]; protein kinase D1 (*PRKD1*) SNP rs12885454 [8, 632, 633]; AGBL carboxypeptidase 4 (*AGBL4*) SNP rs657452 [8, 352, 627]; polypyrimidine tract binding protein 2 (*PTBP2*) SNP rs11165643 [7, 8, 352, 626]; NLR family CARD domain containing 3 (*NLRC3)* SNP rs758747 [8, 627]; syntaxin binding protein 6 (*STXBP6*) SNP rs10132280 [8, 629, 632]; Huntingtin interacting protein 1 (*HIP1) SNP* rs1167827 [8, 633]; cell adhesion molecule 2 (*CADM2*) SNP rs13078960 [8]; far upstream element binding protein 1 (*FUBP1*) SNP rs12401738 [8, 634]; olfactomedin 4 (*OLFM4*) SNP rs12429545 [626, 628, 632]; RAS p21 protein activator 2 (*RASA2*) SNP rs16851483 [8, 628]; hypoxia inducible factor 1 subunit alpha inhibitor (*HIF1AN*) SNP rs17094222 [8, 633]; hepatocyte nuclear factor 4 gamma (*HNF4G*) SNP rs17405819 [627, 629, 639]; toll like receptor 4 (*TLR4*) SNP rs1928295 [8, 352]; neurexin 3 (*NRXN3*) SNP rs7141420 [8, 401]; inflammation and lipid regulator with UBA-like and NBR1-like domains (*ILRUN* or *C6orf106*) SNP rs205262 [8]; fragile histidine triad diadenosine triphosphatase (*FHIT*) SNP rs2365389 [8, 633]; neuron navigator 1 (*NAV1*) SNP rs2820292 [8]; tripartite motif containing 66 (*TRIM66*) SNP rs4256980 [8, 629]; erb-b2 receptor tyrosine kinase 4 (*ERBB4*) SNP rs7599312 [8, 623]; and lysine acetyltransferase 8 (*KAT8*) SNP rs9925964 [8, 627]. The risk alleles will not be weighed because information on effect sizes is often limited to certain traits [245, 369]. Moreover, data on effect sizes from a GWA conducted in one population may

not be applicable to another population because of variations in effect sizes [105, 369]. The unweighted GRS will be calculated by adding the risk alleles across the SNPs for each participant [564]. The SNPs have been selected based on their association with cardiometabolic traits at a genome-wide significance level ($P<5 \times 10^{-8}$) as shown in **Table 2**. The risk alleles of the SNPs and the traits they have been associated with are presented in **Table 2**.

c. Software

SPSS version 28

4. Expected outcomes

The findings from this project are expected to be published in a journal and will be written up as a chapter of my thesis.

5. Proposed deadline

30-05-2023

Table 1 Statistical analyses

Objectives	Statistical test used	Reason for statistical test used	Outcome of statistical test used	Covariates (When appropriate)
1. To check whether the selected SNPs are in Hardy-Weinberg equilibrium (HWE)				
To determine whether the observed genotype counts are in HWE.	Goodness of fit Chi-Squared test	To compare the observed genotype counts with the expected values under HWE.	To test whether the study population is in HWE for the loci under study [105].	
2. To produce descriptive statistics for the study participants who had completed an assessment on demographics, biochemical and anthropometric measurements.				
To generate descriptive statistics of the participants who completed the study assessment on demographics, anthropometric and biochemical outcomes of interest.	Descriptive statistics or Descriptive statistics frequencies	Descriptive for continuous variables Frequencies for categorical variables	To determine the mean and standard deviation of the anthropometric and biochemical variables as well as frequencies for categorical variables: age (years), height (cm), weight (kg), waist circumference (cm), BMI (kg/m^2), obese cases (%), serum TC, HDL-C, LDL-C, TG (mmol/L), SBP (mmHg), DBP (mmHg), fasting glucose, fasting insulin, HbA1c, total fat (g), total fat (% energy), total SFA(g), MUFA (g), PUFA (g), carbohydrate (g), carbohydrate (% energy), protein (g), protein (% energy), and total energy (kcal).	
3. To test the association between the GRS and anthropometric and biochemical measurements [TC, HDL-C, LDL-C, TG, SBP, DBP, fasting glucose, fasting insulin, HbA1c, BMI, and WC]				

To test the association between GRS and anthropometric/biochemical traits while adjusting for covariates.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (anthropometric/biochemical trait) is a continuous variable.	To identify the effect of genetic variants on anthropometric and biochemical traits.	- Sex, BMI, smoking status, physical activity level and family history of T2D will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C and TG) or blood pressure. - BMI will not be adjusted for when the outcome is an obesity related trait or BMI [105].
4. To test the interaction between the GRS and dietary factors on fasting biochemical/anthropometric measurements (TC, HDL-C, LDL-C, TG, SBP, DBP, fasting glucose, fasting insulin, HbA1c, BMI, and WC).				
a. To test the interaction between macronutrients and GRS on fasting biochemical and anthropometric traits.	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the outcome/dependent variable (fasting biochemical/anthropometric trait) is a continuous variable.	To determine the effect of the genetic variants and the macronutrients: carbohydrate, protein and fat on fasting biochemical and anthropometric traits.	- Sex, BMI, smoking status, physical activity level and family history of T2D will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C, and TG) or blood pressure [105]. - BMI will not be adjusted for when the outcome is an obesity related trait or BMI [105]. - Total energy will be adjusted for when the dietary variable is measured in grams.
a. To test whether the interactions are caused by high, low or	Univariate linear regression	The exposure/independent variable (GRS) is a categorical variable, and the	To determine the effect of the genetic variants and the macronutrients:	- Sex, BMI, smoking status, physical activity level and family history of

medium intake of these macronutrients.		outcome/dependent variable (fasting biochemical/anthropometric trait) is a continuous variable.	carbohydrate, protein and fat on fasting biochemical and anthropometric traits. Data will be split using the median of the dietary variable: carbohydrate, protein and fat; or based on tertiles of the dietary variable.	T2D will be adjusted for when the outcome is a lipid trait (TC, HDL-C, LDL-C, and TG) or blood pressure. - BMI will not be adjusted for when an obesity-related trait or BMI is the outcome [105]. - Total energy will be adjusted for when the dietary variable is measured in grams.
NOTES				
When examining fat, carbohydrate and protein in grams, total energy intake will be adjusted for. When using the percentage energy intake of the macronutrients, there is no need to adjust for total energy intake.	Computer variables	For GRS - Carbohydrate interactions: 1g of carbohydrate = 4 kcal For GRS - Fat interactions: 1g of fat = 9 kcal For GRS – Protein interactions: 1g protein=4 kcal		

GRS – genetic risk score; BMI – body mass index; WC – waist circumference; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; HbA1c – glycated haemoglobin.

Table 2 Single nucleotide polymorphisms to be included in the GRS and the reported traits by genome-wide association (GWA) studies

SNP	Gene name	Gene Symbol	Chromosome Location	Location of SNP	Alleles Risk/Other	Traits	GWA Study
rs1558902	*Alpha-ketoglutarate dependent dioxygenase*	*FTO*	16:53769662	Intronic	A/T	HDL-C, BMI, HC, WC, HbA1c and obesity	Locke et al. (2015) [8] Ligthart et al. (2016) [622] Tachmazidou et al. (2017) [623] Wheeler et al. (2017) [624] Scherag et al. (2010) [625]
rs13021737	*Transmembrane protein 18*	*TMEM18*	2:632348	Intergenic	G/A	BMI	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Hoffmann et al. (2018) [627] Justice et al. (2017) [628] Pulit et al. (2019) [629] Koskeridis et al. (2022) [352]
rs6567160	*Melanocortin 4 receptor*	*MC4R*	18:60161902	Upstream	C/T	HDL-C, TG, WHR, T2D, BMI	Locke et al. (2015) [8] Pulit et al. (2019) [629] Vujkovic et al. (2020) [631] Martin et al. (2021) [7] Mahajan et al. (2018) [630]
rs10938397	*Glucosamine-6-phosphate deaminase 2*	*GNPDA2*	4:45180510	Intergenic	G/A	HDL-C, LDL-C, BMI, WC, obesity	Locke et al. (2015) [8] Martin et al. (2021) [7] Berndt et al. (2013) [401]

							Shungin et al. (2015) [632]
rs543874	*SEC16 homolog B, endoplasmic reticulum export factor*	*SEC16B*	1:177920345	Upstream	G/A	HDL-C, BMI, HC, WHR	Locke et al. (2015) [8] Pulit et al. (2019) [629] Koskeridis et al. (2022) [352] Shungin et al. (2015) [632] Huang et al. (2022) [633]
rs7138803	*BCDIN3 domain containing RNA*	*BCDIN3D*	12:49853685	Intergenic	A/G	HDL-C, BMI, HC, WHR, obesity	Locke et al. (2015) [8] Pulit et al. (2019) [629] Koskeridis et al. (2022) [352] Berndt et al. (2013) [401] Shungin et al. (2015) [632]
rs2207139	*Transcription factor AP-2 beta*	*TFAP2B*	6:50877777	Intergenic	G/A	BMI	Locke et al. (2015) [8] Justice et al. (2017) [628] Koskeridis et al. (2022) [352] Berndt et al. (2013) [401]
rs3101336	*Neuronal growth regulator 1*	*NEGR1*	1:72285502	Intronic	C/T	BMI	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Hoffmann et al. (2018) [627] Justice et al. (2017) [628] Pulit et al. (2019) [629]
rs10182181	*Adenylate cyclase 3*	*ADCY3*	2:24927427	Intergenic	G/A	BMI	Locke et al. (2015) [8]

							Akiyama et al. (2017) [626] Hoffmann et al. (2018) [627] Winker et al. (2015) [634]
rs1516725	*ETS variant transcription factor 5*	*ETV5*	3:186106215	Intronic	C/T	BMI	Locke et al. [8] Akiyama et al. (2017) [626] Berndt et al. (2013) *[401]* Graham et al. (2021) [5]
rs2287019	*Glutaminyl-peptide cyclotransferase like*	*QPCTL*	19:45698914	Intronic	C/T	LDL-C, TC, SBP, BMI, WC, WHR,	Locke et al. (2015) [*8*] Pulit et al. (2019) [629] Shungin et al. (2015) [632] Lee et al. (2022) [635]
rs12446632	*G protein-coupled receptor class C group 5 member B*	*GPRC5B*	16:19924067	Intergenic	G/A	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Berndt et al. (2013) [401]
rs3817334	*Mitochondrial carrier 2*	*MTCH2*	11:47,607,569	Intronic	T/C	BMI	Akiyama et al. (2017) [626] Hoffman et al. (2018) [627] Huang et al. (2022) [633] Winker et al. (2015) [634] Speliotes et al. (2010) [754]
rs2112347	*POC5 centriolar protein*	*POC5*	5:75719417	Upstream	T/G	HDL-C, LDL-C, TG BMI, WC, HC,	Locke et al. (2015) [8] Pulit et al. (2019) [629] Martin et al. (2021) [7]

						WHR, body fat percentage	Shungin et al. (2015) [632]
rs16951275	*Mitogen-activated protein kinase 5*	*MAP2K5*	15:67784830	Intronic	T/C	BMI	Locke et al. (2015) [8] Justice et al. (2017) [628] Wood et al. (2016) [636]
rs3810291	*zinc finger CCCH-type containing 4*	*ZC3H4*	19:47065746	3 prime UTR	A/G	HDL-C, TG, BMI, WC, T2D, HC	Locke et al. (2015) [8] Martin et al. (2021) [7] Mahajan et al. (2018) [630] Shungin et al. (2015) [632]
rs12566985	*FPGT-TNNI3K readthrough*	*FPGT-TNNI3K*	1:74536509	Intronic	G/A	BMI	Locke et al. (2015) [8] Felix et al. (2022) [637]
rs10968576	*Leucine rich repeat and Ig domain containing 2*	*LINGO2*	9:28414341	Intronic	G/A	HDL-C, BMI, WC	Locke et al. (2015) [8] Koskeridis et al. (2022) [352] Huang et al. (2022) [633] Liu et al. (2017) [638]
rs12286929	*Cell adhesion molecule 1*	*CADM1*	11:115151684	Intergenic	G/A	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Pulit et al. (2019) [629]
rs12885454	*Protein kinase D1*	*PRKD1*	14:29267632	Exonic	C/A	BMI, WC	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Shungin et al. (2015) [632] Huang et al. (2022) [633]

rs657452	*AGBL carboxypeptidase 4*	*AGBL4*	1:49124175	Intronic	A/G	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Koskeridis et al. (2022) [352]
rs11165643	*Polypyrimidine tract binding protein 2*	*PTBP2*	1:96458541	Intergenic	T/C	BMI, body fat percentage	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Koskeridis et al. (2022) [352] Martin et al. (2021) [7]
rs758747	*NLR family CARD domain containing 3*	*NLRC3*	16:3577357	5 prime UTR	T/C	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) *[627]*
rs10132280	*Syntaxin binding protein 6*	*STXBP6*	14:25458973	Intergenic	C/T	BMI, WC, HC, WHR	Locke et al. (2015) [8] Pulit et al. (2019) [629] Shungin et al. (2015) [632] Graff et al. (2017) [639]
rs1167827	*Huntingtin interacting protein 1*	*HIP1*	7:75533848	3 prime UTR	G/A	BMI	Locke et al. (2015) [8] Huang et al. (2022) [633]
rs13078960	*Cell adhesion molecule 2*	*CADM2*	3:85758440	Intronic	G/T	BMI	Locke et al. (2015) [*8*]
rs12401738	*Far upstream element binding protein 1*	*FUBP1*	1:77981077	Intronic	A/G	BMI	Locke et al. (2015) [*8*] Winkler et al. 2015 [634]
rs12429545	*Olfactomedin 4*	*OLFM4*	13:53528071	Intronic	A/G	BMI, WC	Akiyama et al. (2017) [626] Justice et al. (2017) [628] Shungin et al. (2015) [632]

rs16851483	*RAS p21 protein activator 2*	*RASA2*	3:141556594	Intronic	T/G	BMI	Locke et al. (2015) [8] Pulit et al. (2019) [629]
rs17094222	*Hypoxia inducible factor 1 subunit alpha inhibitor*	*HIF1AN*	10:100635683	Intergenic	C/T	BMI	Locke et al. (2015) [8] Huang et al. (2022) [633]
rs17405819	*Hepatocyte nuclear factor 4 gamma*	*HNF4G*	8:75894349	Intergenic	T/C	BMI	Hoffman et al. (2018) [627] Pulit et al. (2019) [629] Graff et al. (2017) [639]
rs1928295	*Toll like receptor 4*	*TLR4*	9:117616205	Intergenic	T/C	BMI	Locke et al. (2015) [8] Koskeridis et al. (2022) *[352]*
rs7141420	*Neurexin 3*	*NRXN3*	14:79433111	Intronic	T/C	BMI, obesity	Locke et al. (2015) [8] Berndt et al. (2013) *[401]*
rs205262	*Inflammation and lipid regulator with UBA-like and NBR1-like domains*	*C6orf106*	6:34595387	Intronic	G/A	BMI	Locke et al. (2015) [8]
rs2365389	*Fragile histidine triad diadenosine triphosphatase*	*FHIT*	3:61250788	Intronic	C/T	BMI	Locke et al. (2015) [8] Huang et al. (2022) [633]
rs2820292	*Neuron navigator 1*	*NAV1*	1:201815159	Intronic	C/A	BMI	Locke et al. (2015) [8]
rs4256980	*Tripartite motif containing 66*	*TRIM66*	11:8652392	Intronic	G/C	BMI	Locke et al. (2015) [8] Pulit et al. (2019) [629]
rs7599312	*Erb-b2 receptor tyrosine kinase 4*	*ERBB4*	2:212548507	Regulatory region	G/A	BMI	Locke et al. (2015) [8] Tachmazidou et al. (2017) [623]
rs9925964	*Lysine acetyltransferase 8*	*KAT8*	16:31118574	Splice region	A/G	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627]

SNP – single nucleotide polymorphism; GRS – genetic risk score; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; SBP – systolic blood pressure; HbA1c – glycated haemoglobin.

Appendix E - Supplementary Material

Appendix E1 - Supplementary Table S2.1 Lipid-related genes identified by genome-wide association studies

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
Khushdeep et al. (2019) [94]						
CELSR2 rs646776	6.19×10^{-3}				Northern India, healthy individuals *n*=1036	45 – 60 (Men) 44 – 60 (Women)
CELSR2 rs646776			4.59×10^{-3}			
CETP rs3764261		6.291×10^{-12}				
CETP rs1532624		5.279×10^{-9}				
CETP rs1800775		3.968×10^{-10}				
LPL rs10096633		0.1				
LPL rs12678919		0.2				
CETP rs9989419		1.35×10^{-3}				
LPL rs4128744		0.03				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CETP rs4783961		1.32×10^{-4}				
ZNF259 rs964184				2.99×10^{-6}		
BUD13 rs7350481				6.03×10^{-7}		
ZNF259 rs6589567				1.73×10^{-4}		
LPL rs10096633				1.09×10^{-6}		
LPL rs4128744				9.78×10^{-6}		
QKI rs9458854	0.01					
QKI rs9458855	0.01					
REEP3 rs7083226	9.42×10^{-4}					
REEP3 rs7083226			0.01			
TMCC2 rs2290265			0.01			
FAM129C rs4544358		0.28				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
FAM241B rs12771265				4.73×10^{-6}		
FAM241B rs4746882				2.71×10^{-5}		
LOC100506207 rs9393071				1.01×10^{-5}		
Zhou et al. (2013) [193]						
DOCK7 rs11207995	3.27×10^{-9}				Han Chinese Healthy individuals *n*=3,451	63.0 ± 8.1 (Cohort 1) 37.5 ± 11.1 (Cohort 2)
HMGCR rs10045497	3.80×10^{-6}					
HMGCR rs10045497			4.93×10^{-7}			
LPL rs328				1.91×10^{-8}		
LPL rs328		9.75×10^{-12}				
ABO rs507666	2.91×10^{-7}					
ABO rs507666			9.25×10^{-8}			
APOA1/C3/A4/A5 rs651821				1.35×10^{-28}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LIPC rs2043085		3.02×10^{-7}				
TOMM40 rs1160985			6.13×10^{-6}			
CETP rs3764261		6.65×10^{-12}				
Tekola-Ayele et al. (2015) [755]						
KSR2 rs11610896				1.70×10^{-5}	African (Ghana and Nigeria) *n*=1427	45.73 ± 16.02
KSR2 rs7964157				9.92×10^{-6}		
KSR2 rs11610896				1.14×10^{-5}		
KSR2 rs7964157				2.06×10^{-5}		
EDEM1-GRM7 rs1377212		7.20×10^{-6}				
EDEM1-GRM7 rs1377212		1.54×10^{-5}				
EDEM1-GRM7 rs1377212		1.71×10^{-5}				
EDEM1-GRM7 rs116357511		2.16×10^{-5}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
EDEM1-GRM7 rs116357511		2.11×10^{-5}				
Deek et al. (2019) [194]						
Unknown rs4288204		2.29×10^{-6}			Lebanese patients Patients undergoing cardiac catherisation: *n*=7,710 T2D: *n*=775	62.32 ± 11.01
RORA rs2062091		6.06×10^{-6}				
CETP rs3764261		6.70×10^{-7}				
CYP2B6 rs17799912		5.41×10^{-7}				
Graff et al. (2017) [756]						
CD86 rs114378860	6.62×10^{-9}				Hispanic/Latino TC: *n*=12,731 TG & HDL: n=12,730 LDL: *n*=12,467	18 - 74
DNAH5 rs183336356	2.80×10^{-7}					
RP1-39 J2.1; SMOC2 rs77635931				2.54×10^{-7}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
SYNE1 rs78768981		9.29×10^{-9}				
DAGLB/GRID2IP rs77071750		1.01×10^{-7}				
AUTS2 rs191891263		2.06×10^{-11}				
APOC3 rs184637772		2.57×10^{-6}				
DNAL1 rs149886784			1.05×10^{-8}			
Hebbar et al. (2018) [757]						
RPS6KA1 rs1002487				7.17×10^{-11}	Arab (Kuwait) Healthy and Diabetic individuals *n*=1,913	46.77 ± 13.79
LAD1 rs11805972				8.55×10^{-11}		
OR5V1 rs7761746				1.89×10^{-9}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CTTNBP2, LSM8 rs39745				3.63×10^{-9}		
PGAP3 rs2934952				3.17×10^{-9}		
RP11-191L9.4, CERK rs9626773				1.42×10^{-9}		
ST6GALNAC5 rs10873925				4.11×10^{-8}		
SPP2, ARL4C rs4663379				8.38×10^{-9}		
NPY1R rs10033119				8.79×10^{-9}		
LINC00911, FLRT2 rs17709449				5.12×10^{-8}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CDK12, NEUROD2 rs11654954				2.18×10^{-8}		
CDK12, NEUROD2 rs11654954				3.75×10^{-8}		
STARD3 rs9972882				1.81×10^{-8}		
Kathiresan et al. (2008) [95]						
CELSR2, PSRC1, SORT1 rs646776			8×10^{-8}		European (Denmark, Norway, Sweden) *n*=2,758 Type 2 diabetic cases and controls	61.5 ± 10.5
Unknown rs599839			9×10^{-8}			
CILP2, PBX4 rs16996148			0.04			
APOB rs693			7×10^{-7}			
APOE-C1-C4- C2 rs4420638			3×10^{-13}			
HMGCR rs12654264			0.0004			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LDLR rs6511720			9×10^{-7}			
GALNT2 rs4846914		3×10^{-4}				
ABCA1 rs3890182		3×10^{-5}				
APOA1-C3-A4-A5, ZNF259, BUD13 rs28927680		0.31				
CETP rs1800775		3×10^{-13}				
LIPC rs1800588		3×10^{-5}				
LIPG, ACAA2 rs2156552		0.02				
LPL rs328		3×10^{-4}				
BCL7B, TBL2, MLXIPL rs17145738				0.003		
TRIB1 rs17321515				7×10^{-4}		
GALNT2 rs4846914				9×10^{-5}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CILP2, PBX4 rs16996148				0.05		
ANGPTL3, DOCK7, ATG4C rs12130333				0.0006		
APOA1-C3-A4-A5, ZNF259, BUD13 rs28927680				$6x10^{-5}$		
APOB rs693				$7×10^{-4}$		
GCKR rs780094				$4×10^{-8}$		
LPL rs328				$4×10^{-7}$		
Oh et al. (2020) [195]						
GCKR rs780092				$4.82×10^{-9}$	Korean Metabolic Syndrome cases and controls Cases: *n*=1,362 Controls: *n*=6,061	53.5 ± 9.5 (Cases) 49.9 ± 10.2 (Controls)

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
GCKR rs780093				2.55×10^{-12}		
GCKR rs780094				6.49×10^{-12}		
GCKR rs1260326				3.89×10^{-12}		
GCKR rs1260333				5.20×10^{-12}		
C2orf16 rs1919127				1.18×10^{-8}		
C2orf16 rs1919128				7.39×10^{-9}		
APOA5 rs662799				4.97×10^{-34}		
APOA5 rs2075291				3.67×10^{-19}		
APOA5 rs2266788				9.26×10^{-15}		
ZPR1 rs603446				6.24×10^{-9}		
ZPR1 rs964184				1.47×10^{-14}		
BUD13 rs2075295				4.56×10^{-10}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
BUD13 rs11216126				1.34×10^{-11}		
BUD13 rs1558861				5.85×10^{-14}		
APOA5 rs662799		2.26×10^{-16}				
APOA5 rs2075291		9.28×10^{-9}				
ALDH1A2 rs4775041		2.28×10^{-8}				
ALDH1A2 rs10468017		7.27×10^{-8}				
ALDH1A2 rs1800588		5.62×10^{-8}				
HERPUD1 rs72786786		1.65×10^{-10}				
HERPUD1 rs173539		1.13×10^{-8}				
HERPUD1 rs247616		1.29×10^{-16}				
HERPUD1 rs247617		7.70×10^{-17}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
HERPUD1 rs3764261		5.27×10^{-17}				
HERPUD1 rs4783961		9.93×10^{-9}				
CETP rs708272		6.09×10^{-8}				
CETP rs7499892		1.57×10^{-8}				
CETP rs2303790		5.31×10^{-11}				
Zhu et al. (2017) [243]						
APOA5 rs651821				7.8×10^{-16}	Han Chinese Metabolic Syndrome cases and controls Cases: *n*=862 Controls: *n*=880	59.9 ± 10.7 (Cases) 55.3 ± 12.0 (Controls)
BUD13 rs180326				3.9×10^{-7}		
TPBG||UBE2CBP rs209411		9.5×10^{-6}				
TLE1||FLJ43950 rs7864030		1.0×10^{-6}				
APOA5 rs651821		6.5×10^{-7}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
STRBP||CRB2 rs10985976			6.2×10^{-6}			
MYO19 rs12602787			3.6×10^{-6}			
CUX1 rs420437			3.3×10^{-6}			
APOC1 rs445925			4.1×10^{-12}			
APOA5 rs651821				7.8×10^{-16}		
Wu et al. (2013) [196]						
APOE rs7412			2.7×10^{-53}		Filipino Women Mothers: *n*=1,782 Offspring: *n*=1,719	48.4 ± 6.1 (Mothers) 21.5 ± 0.3 (Offspring)
APOE rs7412	1.5×10^{-30}					
APOA5 rs662799				5.7×10^{-24}		
GCKR rs780092				1.8×10^{-09}		
CETP rs1800775		3.4×10^{-9}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
TOM1 rs138777		4.0×10^{-5}				
LPL rs328				1.6×10^{-3}		
MLXIPL rs17145738				4.2×10^{-3}		
ANGPTL3 rs2131925				5.1×10^{-3}		
LIPC rs588136		1.5×10^{-12}				
LIPG rs2156552		4.6×10^{-3}				
MMAB-MVK rs10774708		0.011				
ABO rs2519093			3.0×10^{-5}			
APOB rs1367117			7.4×10^{-3}			
TIMD4 rs6882076	4.0×10^{-3}					
DNAH11 rs5008148	0.012					
Chasman et al. (2009) [339]						

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
PCSK9 rs11591147			1.6×10^{-7}		White American Women: n=6,382	52 (49–58)
CELSR2, PSRC1, SORT1 rs646776			4.9×10^{-19}			
APOB rs506585			9.3×10^{-09}			
GCKR rs1260326				1.3×10^{-16}		
LPL rs328				4.7×10^{-11}		
LPL rs331		9.1×10^{-7}		1.7×10^{-9}		
APOA5-APOA1 rs3135506				5.5×10^{-12}		
APOA5-APOA1 rs662799				2.9×10^{-15}		
APOA5-APOA1 rs12225230		5.3×10^{-5}				
LIPC rs1532085		1.3×10^{-10}				
Keller et al. (2013) [758]						

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
TMPRSS2 rs2298857		3.85×10^{-7}			Eastern Germany (The Sorbs) *n*=839	46 ± 16
SSTR1 rs1954021		7.39×10^{-6}				
FRMD1 rs3816859		8.79×10^{-6}				
SOX6 rs297360		9.02×10^{-6}				
Unknown rs7081043		9.68×10^{-6}				
ABHB5 rs883212			4.80×10^{-7}			
MIST rs10488946			1.78×10^{-6}			
HTR5A rs1730206			2.91×10^{-6}			
FAM112A rs3127065			3.03×10^{-6}			
ABHB5 rs17583742			3.08×10^{-6}			
TNFSF4 rs10127728			6.41×10^{-6}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
PCSK5 rs10869740				1.86×10^{-6}		
REPS1 rs9484217				4.66×10^{-6}		
C6ORF166 rs4707385				4.93×10^{-6}		
Waterworth et al. (2010)[c] [197]						
PCSK9 rs11206510		0.52	1.2×10^{-10}	0.04	White European (British, Swedish, Finnish and Italian) *n*=17,543	31[d] (0.0) – 75[d] (5.0)
CELSR2 rs660240		0.22	1.2×10^{-26}	0.56		
APOB rs515135		0.47	2.4×10^{-20}	0.25		
HMGCR rs12916		0.80	1.4×10^{-11}	0.64		
TRIB1 rs2954021		1.3×10^{-4}	1.4×10^{-7}	6.3×10^{-11}		
BUD13, ZNF259, APOA5-A4-C3-A1 rs1558861		1.7×10^{-7}	2.0×10^{-6}	2.0×10^{-30}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LDLR rs2738459		0.34	6.6×10^{-6}	0.31		
SF4–CILP2 rs10401969		0.26	9.5×10^{-12}	8.4×10^{-14}		
APOE-C1-C4-C2 rs4420638		2.0×10^{-7}	1.7×10^{-40}	5.5×10^{-7}		
GALNT2 rs10489615		3.8×10^{-9}	0.25	2.4×10^{-4}		
APOB rs11902417		3.7×10^{-7}	4.0×10^{-3}	2.7×10^{-7}		
LPL rs325		7.8×10^{-25}	0.34	4.9×10^{-24}		
ABCA1 rs3890182		4.7×10^{-7}	0.43	0.16		
ZNF259, APOA5-A4-C3-A1 rs964184		1.6×10^{-11}	6.4×10^{-6}	9.0×10^{-53}		
MYO1H, KCTD10, UBE3B, MMAB, MVK rs9943753		3.2×10^{-6}	0.20	0.51		
LIPC rs261334		4.9×10^{-22}	0.65	0.01		
CETP rs9989419		1.3×10^{-32}	0.58	0.67		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
GFOD2–LCAT rs12449157		2.3×10^{-7}	0.31	0.02		
LIPG rs2156552		1.7×10^{-12}	0.01	0.02		
DOCK7, ANGPTL3 rs1168013		0.97	6.7×10^{-3}	6.4×10^{-8}		
APOB rs6544366		5.3×10^{-7}	3.8×10^{-3}	1.9×10^{-7}		
GCKR rs1260333		0.08	0.36	1.7×10^{-19}		
BAZ1B, BCL7B, TBL2, MLXIPL rs1178979		8.0×10^{-3}	2.5×10^{-3}	2.3×10^{-12}		
LPL rs10105606		1.7×10^{-14}	0.94	3.6×10^{-25}		
TRIB1 rs2954029		4.5×10^{-5}	9.2×10^{-7}	1.8×10^{-11}		
BUD13, ZNF259, APOA5-A4-C3-A1 rs4938303		9.6×10^{-8}	0.02	4.1×10^{-21}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CETP, LOC100130044, NLRC5 rs16965220		0.04	0.01	9.6×10^{-6}		
CILP2–ZNF101 rs2304130		0.55	1.1×10^{-7}	3.9×10^{-8}		
Dumitrescu et al. (2011) [759]						
SGSM2 rs2429917			7.01×10^{-06}		African *n*=66	7.2 ± 4
Intergenic rs12190789			3.32×10^{-06}			
CD96 rs16858329				4.29×10^{-06}		
Intergenic rs6477578				6.13×10^{-06}	European *n*=282	7.0 ± 5
FRMD3 rs10868008			1.66×10^{-06}		Mexican *n*=63	6.4 ± 4
FRMD3 rs11140077			1.66×10^{-06}			
Hiura et al. (2009) [96]						
CETP rs3764261		6.17[e]			Japanese *n*=900	59.8 ± 7.3 (Men)

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
Unknown rs10945991		5.90[e]				58.2 ± 6.8 (Women)
ZNF665 rs6509732		5.50[e]				
SLC23A2 rs6133175		4.98[e]				
FLJ45139 rs467571		4.97[e]				
Unknown rs10485472		4.90[e]				
Unknown rs1469918		4.82[e]				
Unknown rs6790597		4.78[e]				
Unknown rs12225506		4.72[e]				
BCL2L14 rs1544669		4.70[e]				
Unknown rs12206635		4.64[e]				
C14orf118 rs2246454		4.62[e]				
Unknown rs980861		4.58[e]				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
RAP1GAP rs12134357		4.49[e]				
TMEM200A rs17059002		4.45[e]				
PSMB6, PLD2 rs11654690		4.44[e]				
CCT8L2 rs2236639		4.42[e]				
ACCN1 rs280049		4.34[e]				
ESRRG rs7547186		4.31[e]				
Unknown rs7550051		4.31[e]				
Unknown rs4656747		4.30[e]				
ADARB2 rs2813397		4.29[e]				
Unknown rs12586473		4.27[e]				
SLC23A2 rs3914810		4.27[e]				
Unknown rs10493889		4.24[e]				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
Unknown rs9956878		4.17[e]				
CLASP1 rs10496565		4.14[e]				
TMC2 rs4815298		4.13[e]				
Unknown rs6990139		4.13[e]				
GABRR1 rs9359845		4.12[e]				
UGT3A1 rs2242225		4.11[e]				
TAF1B rs450286		4.04[e]				
Unknown rs12453139		4.04[e]				
Unknown rs4404877		4.01[e]				
Smith et al. (2010) [198]						

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
HERPUD1/CETP rs247616		6.6×10^{-7}			Individuals of European ancestry in the USA *n*=525	4 – 48
MRPS6/KCNE2 rs8131349			1.4×10^{-8}			
APOE/APOC1 rs7412			1.6×10^{-8}			
C6orf170/GJA1 rs7738656			2.5×10^{-7}			
KIF4B/SGCD rs10044666			4.7×10^{-7}			
MRPS6/KCNE2 rs8131349	4.6×10^{-8}					
ABLIM2 rs6829649	9.6×10^{-8}					
C6orf170/GJA1 rs7738656	2.1×10^{-7}					
ST3GAL1/ZFAT rs4897695	2.7×10^{-7}					
Tan et al. (2012) [209]						
RYR2 rs16835705	1.15×10^{-6}				Chinese Men *n*=1,999	37.54 ± 11.10

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LPL rs328	4.90×10^{-8}					
SLCO5A1 rs10504457	1.05×10^{-6}					
APOA5 rs651821	6.10×10^{-15}					
ALDH2 rs671	4.85×10^{-6}					
Intergenic rs1532085	1.01×10^{-6}					
TOMM40 rs157581	8.48×10^{-7}					
Zabaneh et al. (2010) [199]						
CETP rs3764261		1.3×10^{-48}			Men of Indian Asian descent from West London *n*=2,684	50.0 ± 11.0
CETP rs9989419		1.4×10^{-20}				
LPL rs2083637		1.9×10^{-10}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LPL rs4523270		1.0×10^{-07}				
FLJ41733 rs496300		3.9×10^{-07}				
FADS1 rs174546		6.0×10^{-07}				
FADS2 rs1535		6.5×10^{-07}				
Lettre et al. (2011)[c] [97]						
GALNT2 rs2144300		0.0015			African American *n*=8,090	24.4[d] ± 3.8 – 73.4[d] ± 2.9
PPP1R3B rs9987289		4.3×10^{-5}				
LPL rs10503669		7.2×10^{-5}				
Unknown rs10096633		1.5×10^{-9}				
ABCA1 rs3905000		0.054				
Unknown rs13284054		0.0011				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
FADS1, FADS2, FADS3 rs174547		0.068				
Unknown rs1535		6.7×10^{-5}				
LIPC rs1800588		1.5×10^{-8}				
Unknown rs8034802		1.3×10^{-9}				
CETP rs3764261		8.6×10^{-18}				
Unknown rs247617		1.2×10^{-43}				
LCAT rs255052		6.6×10^{-11}				
PLTP rs7679		0.22				
Unknown rs6065904		7.4×10^{-5}				
DOCK7 rs10889353			0.0040			
Unknown rs10889335			1.2×10^{-4}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CELSR2, PSRC1, SORT1 rs12740374			1.3×10^{-16}			
PCSK9 rs10493178			4.7×10^{-12}			
APOB rs562338			3.1×10^{-7}			
Unknown rs503662			2.5×10^{-9}			
LDLR rs6511720			7.2×10^{-8}			
APOE, APOC1, APOC4, APOC2 rs1160985			7.2×10^{-21}			
Carlson et al. (2020) [200]						
APOB rs754523	6.25×10^{-6}				Samoans n=2,849	44.8 ± 11.1 (Women) 45.6 ± 11.1 (Men)
PDE4D rs7711093	3.01×10^{-6}					
LUCAT1 rs10072084	9.48×10^{-6}					
FILIP1 rs2951921	9.04×10^{-7}					

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
ZHX2 rs7841763	4.82×10^{-6}					
APOA1 rs964184	5.37×10^{-5}					
SIRT2 rs10405150	6.34×10^{-6}					
ZNF283 rs16976816	9.78×10^{-6}					
APOE rs1160985	2.13×10^{-13}					
STON1-GTF2A1L rs6739536		1.58×10^{-6}				
MGAT1 rs1038143		3.72×10^{-6}				
AKAP7 rs3777486		3.09×10^{-6}				
CSMD1 rs1626142		7.67×10^{-6}				
RAB21 rs328733		2.57×10^{-6}				
ZNF10 rs2292029		4.05×10^{-6}				
HS6ST3 rs16953620		8.48×10^{-6}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LIPC rs10438284		4.00×10^{-7}				
CETP rs289708		1.19×10^{-11}				
LIPG rs16950739		1.07×10^{-7}				
APOE rs1160985		0.003				
CDH4 rs817687		2.31×10^{-6}				
APOB rs754523			3.25×10^{-6}			
KALRN rs6789134			3.22×10^{-6}			
ZHX2 rs7841763			1.80×10^{-6}			
SH2D4B rs10509415			7.96×10^{-6}			
ALG10 rs3912355			2.12×10^{-6}			
ALG10B rs10880642			5.56×10^{-6}			
CPNE8 rs11169807			4.77×10^{-6}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LINC02408 rs17104016			9.29×10^{-6}			
LINC00922 rs254371	9.04×10^{-6}					
ZNF283 rs16976816	1.78×10^{-6}					
APOE rs1160985	2.61×10^{-20}					
GCKR rs780094				9.84×10^{-7}		
CD200 rs2399416				5.12×10^{-6}		
SPIN1 rs7861888				4.24×10^{-6}		
APOA1 rs964184				2.37×10^{-17}		
KIRREL3 rs3018434				4.16×10^{-6}		
APOE rs1160985a				0.312		
Kurano et al. (2016) [201]						
CELSR2 rs660240			4.56×10^{-5}		Japanese, healthy individuals	20 – Over 40

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
					n=2,994	
CELSR2 rs646776			4.93×10^{-5}			
CELSR2 rs629301			3.22×10^{-5}			
PSRC1 rs599839			7.86×10^{-5}			
CELSR2 rs629301			3.22×10^{-5}			
APOB rs1367117			3.19×10^{-2}			
HMGCR rs12916			1.19×10^{-4}			
HMGCR rs3846662			1.10×10^{-4}			
HMGCR rs12916			1.19×10^{-4}			
TIMD4-HAVCR1 rs58198139			2.25×10^{-4}			
TIMD4 rs6882076			2.86×10^{-4}			
HPR rs2000999			9.65×10^{-3}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
TOMM40 rs1160985			2.69×10^{-6}			
APOC1 rs4420638			1.39×10^{-5}			
PABPC4 rs4660293		4.24×10^{-2}				
LOC100130996 rs1779824		2.45×10^{-2}				
GALNT2 rs2144300		1.69×10^{-2}				
LPL rs327		2.58×10^{-4}				
LPL rs328		6.47×10^{-7}				
LPL-RPL30P9 rs17482753		1.33×10^{-6}				
LPL rs328		6.47×10^{-7}				
ABCA1 rs12686004		3.05×10^{-2}				
ABCA1 rs1883025		5.33×10^{-3}				
FADS1 rs174548		6.81×10^{-3}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
FADS1 rs174547		6.86×10^{-3}				
FADS1 rs174546		9.05×10^{-3}				
MMAB rs7134594		1.38×10^{-2}				
NCOR2-SCARB1 rs838880		1.10×10^{-3}				
LIPC rs1800588		2.14×10^{-4}				
RPL28P4-LIPC rs1532085		7.30×10^{-4}				
LIPC rs1800588		2.14×10^{-4}				
CETP rs12708980		4.79×10^{-3}				
HERPUD1-CETP rs9989419		1.12×10^{-6}				
HERPUD1-CETP rs3764261		1.18×10^{-16}				
CETP rs1800775		1.01×10^{-2}				
NUTF2 rs2271293		4.76×10^{-2}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
PSKH1 rs16942887		4.98×10^{-2}				
HNF4A rs1800961		6.83×10^{-3}				
DOCK7 rs1748195				0.001273		
GCKR rs780092				0.01145		
GCKR rs1260326				0.00072		
GCKR rs780094				0.003526		
TIMD4 rs6882076				0.002649		
TBL2 rs17145738				0.000647		
TBL2 rs2286276				0.000277		
LPL rs327				2.81×10^{-8}		
LPL-RPL30P9 rs17410996				1.75×10^{-8}		
LPL-RPL30P9 rs17410996				1.75×10^{-8}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LPL-RPL30P9 rs10105606				2.24×10^{-7}		
LPL-RPL30P9 rs7841189				1.75×10^{-8}		
LPL-RPL30P9 rs17482753				2.26×10^{-8}		
LPL rs328				4.47×10^{-8}		
XKR6 rs7819412				0.01766		
TRIB1-LINC00861 rs17321515				0.0137		
SIK3 rs2075292				8.80×10^{-7}		
APOA5 rs651821				1.01×10^{-30}		
RPL15P15, BUD13 rs4938303				0.01347		
Coram et al (2013) [202]						

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
PCSK9 rs17111684			2.40×10^{-17}		African American Women HDL: *n*=7,917 LDL: *n*=7,861 TG: *n*=7,918	50–79
APOB rs12713956			3.74×10^{-08}			
GCKR rs4665972c				1.05×10^{-08}		
ABCG8 rs4245791			1.24×10^{-09}			
CD36 rs2366858		5.59×10^{-10}				
PPP1R3B rs1461729		7.39×10^{-09}				
LPL rs326		1.23×10^{-08}				
LPL rs326				1.02×10^{-08}		
APOA/APOC rs6589566				4.99×10^{-14}		
APOA/APOC chr11: 116,799,496		1.08×10^{-12}				
CETP rs247617		1.48×10^{-44}				
LDLR rs17249141			2.43×10^{-17}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LOC55908 rs12979813		1.99×10^{-09}				
APOE rs1160985			1.87×10^{-21}			
APOC1 rs12721054				2.86×10^{-19}		
PPP1R3B rs1461729		7.39×10^{-09}				
Unknown rs13046373		2.26×10^{-08}				
GCKR rs780094				7.35×10^{-09}	Hispanic American Women *n*=3,506 (HDL) *n*=3,425 (LDL) *n*=3,506 (TG	50–79
LPL rs17410962				7.35×10^{-09}		
APOA/APOC rs964184		2.81×10^{-12}				
APOA/APOC rs964184				3.66×10^{-33}		
CETP rs247617		3.48×10^{-16}				
Aulchenko et al. (2008)[c] [203]						
TMEM57 rs10903129	5.4×10^{-10}	0.02	1.8×10^{-5}	0.48	Different European	18–104

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
					countries including Austria and Finland *n*=17,797–22,562	
DOCK7 rs1167998	6.4×10^{-10}	3.8×10^{-3}	1.1×10^{-5}	2.0×10^{-12}		
DOCK7 rs10889353	3.7×10^{-12}	1.8×10^{-3}	7.9×10^{-6}	8.2×10^{-11}		
CELSR2 rs646776	8.5×10^{-22}	6.2×10^{-3}	7.8×10^{-23}	0.63		
APOB rs693	8.7×10^{-23}	1.3×10^{-7}	3.6×10^{-17}	1.4×10^{-4}		
APOB rs6754295	1.8×10^{-6}	4.4×10^{-8}	1.6×10^{-7}	2.5×10^{-8}		
APOB rs673548	7.4×10^{-05}	7.4×10^{-7}	3.6×10^{-5}	1.1×10^{-8}		
GCKR rs780094	0.02	0.12	0.85	3.1×10^{-20}		
ABCG5 rs6756629	1.5×10^{-11}	0.74	2.6×10^{-10}	0.26		
HMGCR rs3846662	2.5×10^{-19}	0.57	1.5×10^{-11}	0.03		
DNAH11 rs12670798	9.2×10^{-7}	0.14	6.1×10^{-9}	0.68		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
MLXIPL rs2240466	0.80	0.02	0.44	1.1×10^{-12}		
LPL rs2083637	0.73	5.5×10^{-18}	0.76	1.0×10^{-14}		
LPL rs10096633	0.91	6.1×10^{-16}	0.53	1.9×10^{-18}		
TRIB1 rs6987702	3.3×10^{-9}	0.44	2.9×10^{-6}	5.2×10^{-5}		
ABCA1 rs3905000	5.0×10^{-5}	8.6×10^{-13}	0.90	0.20		
MADD-FOLH1 rs7395662	0.63	6.0×10^{-11}	0.31	0.54		
FADS2/3 rs174570	1.5×10^{-10}	3.9×10^{-6}	4.4×10^{-13}	2.9×10^{-5}		
APO(A1/A4/A5/C3) rs12272004	7.3×10^{-7}	0.01	9.9×10^{-4}	5.4×10^{-13}		
LIPC rs1532085	3.7×10^{-7}	9.7×10^{-36}	0.60	0.33		
CETP rs1532624	0.01	9.4×10^{-94}	3.3×10^{-3}	1.1×10^{-3}		
CTCF-PRMT8 rs2271293	0.14	8.3×10^{-16}	0.33	0.04		
LIPG rs4939883	2.4×10^{-7}	1.6×10^{-11}	0.06	0.11		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LDLR rs2228671	9.3×10^{-24}	0.54	4.2×10^{-14}	0.59		
NCAN rs2304130	2.0×10^{-15}	0.75	1.5×10^{-7}	2.9×10^{-6}		
TOMM40-APOE rs2075650	2.9×10^{-19}	1.9×10^{-4}	9.3×10^{-19}	2.4×10^{-4}		
TOMM40-APOE rs157580	5.1×10^{-17}	3.6×10^{-7}	2.1×10^{-19}	1.2×10^{-8}		
TOMM40-APOE rs439401	3.7×10^{-4}	2.7×10^{-3}	1.1×10^{-2}	1.8×10^{-9}		
Adeyemo et al (2012) [204]						
CILP2/SF4 rs10401969				0.006	African Americans non-diabetic *n*=887	45.5 ± 12.4 (Men) 46.4 ± 13.3 (Women)
STARD3 rs11869286		0.02				
LPL rs12678919				0.01		
CYP7A1 rs2081687			0.04			
ANGPTL3 rs2131925	0.04					
APOE rs4420638		0.02				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
SORT1 rs629301			0.005			
IRS1 rs2943652		0.01				
CETP rs173539		0.0003				
CETP rs1800775		0.03				
CETP rs4783961		0.0009				
UBASH3B rs6589939	0.005					
Hoffmann et al (2018) [9]						
FAF1 rs144432213				6.1×10^{-9}	Non-Hispanic white Latino East Asian African American South Asian *n*=94, 674	45.2 – 57.8
NFIA rs55878063		1.5×10^{-8}				
DR1 rs145882729		6.1×10^{-10}				
PIGC rs7519429				1.4×10^{-10}		
LAMC1 rs4651135	1.2×10^{-8}		h			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
OPTC rs6695980				2.8×10^{-8}		
RP11-95P13.1 rs2791547				3.1×10^{-10}		
TIA1 rs2706770	1.1×10^{-8}					
TGOLN2 rs10198423		5.1×10^{-9}				
AC096670.3 rs77004761				6.7×10^{-10}		
TIA1 rs2706770	1.1×10^{-8}					
TGOLN2 rs10198423		5.1×10^{-9}				
AC096670.3 rs77004761				6.7×10^{-10}		
IL1RN rs55709272	1.8×10^{-8}					
KPNA1 rs72285796			4.3×10^{-12}			
RP11-550I24.2 rs78086267				1.8×10^{-8}		
ETV5 rs112545201		2.5×10^{-19}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
TMPRSS11E rs13114070	1.6×10^{-8}					
TET2 rs201330646		2.2×10^{-9}				
FCHO2 rs62362194		4.2×10^{-8}				
C5orf56 rs2522061			4.4×10^{-11}			
RP11-32D16.1 rs1651274		3×10^{-9}				
GNMT rs10948059		8.1×10^{-9}				
GSTA5 rs12529923		1.4×10^{-8}				
RP3-332B22.1 rs181937009				1.7×10^{-9}		
RGS17 rs1281955		2.2×10^{-8}				
TRGC2 rs2534596		2.1×10^{-8}				
CALCR rs2299247				1.3×10^{-9}		
SH2D4A rs2958557				2.6×10^{-8}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
SNTB1 rs13248499		1.4×10^{-11}				
DENND4C rs202246180	3.1×10^{-8}					
DFNB31 rs74551598	1.6×10^{-8}					
OIT3 rs57176252			1.2×10^{-8}			
RP11-159H3.2 rs7079858		4.9×10^{-8}				
NAP1L4 rs7935422		1.5×10^{-8}				
TRIM5 rs11601507			6.6×10^{-9}			
MACROD1 rs11231698				5.9×10^{-9}		
Sabatti et al (2009) [205]						
APOB rs673548				2.01×10^{-8}	Northern Finland Birth Cohort *n*=4,763	31
GCKR rs1260326				3.56×10^{-10}		
LPL rs10096633				5.16×10^{-8}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
Unknown rs2624265				4.31×10^{-7}		
NR1H3 rs2167079		5.13×10^{-8}				
NR1H3 rs7120118		3.57×10^{-8}				
LIPC rs1532085		1.77×10^{-10}				
CETP rs3764261		6.97×10^{-29}				
LCAT rs255049		3.06×10^{-8}				
Unknown rs9891572		2.33×10^{-7}				
CELSR2-PSRC1 SORT1 rs646776			2.19×10^{-12}			
CR1L rs4844614			2.38×10^{-7}			
APOB rs693			2.99×10^{-11}			
FADS1-FADS2 rs174537			2.10×10^{-7}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
FADS1-FADS2 rs102275			1.52×10^{-7}			
FADS1-FADS2 rs174546			1.30×10^{-7}			
FADS1-FADS2 rs174556			3.49×10^{-7}			
FADS1-FADS2 rs1535			3.65×10^{-7}			
LDLR rs11668477			1.51×10^{-7}			
APO cluster rs157580			4.96×10^{-8}			
AR rs5031002			2.37×10^{-7}			
ANGPTL3-DOCK7-ATG4C rs1167998				1.60×10^{-4}		
ANGPTL3-DOCK7-ATG4C rs12130333				3.60×10^{-3}		
GALNT2 rs4846914				2.80×10^{-1}		
APOB rs693				3.40×10^{-3}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
GCKR rs780094				5.03×10^{-9}		
BCL7B-TBL2-MLXIPL rs17145738				2.70×10^{-5}		
LPL rs328				4.50×10^{-8}		
TRIB1 rs6982636				1.43×10^{-2}		
APOA1/C3/A4/A5, ZNF259, BUD13 rs12292921				1.35×10^{-3}		
LIPC rs4775041				5.85×10^{-1}		
NCAN-CILP2-PBX4 rs16996148				8.40×10^{-1}		
GALNT2 rs4846914		5.60×10^{-4}				
LPL rs328		7.18×10^{-6}				
ABCA1 rs2740491		3.12×10^{-4}				
ABCA1 rs3847303		3.22×10^{-3}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
APOA1/C3/A4/A5, ZNF259, BUD13 rs28927680		Not given				
MVK-MMAB rs2338104		4.40×10^{-2}				
LIPC rs4775041		1.70×10^{-2}				
LIPC rs1800588		4.11×10^{-3}				
CETP rs3764261		6.97×10^{-29}				
CETP rs1800775		1.32×10^{-9}				
LCAT rs255052		2.36×10^{-7}				
LIPG-ACAA2 rs2156552		1.15×10^{-2}				
PCSK9 rs12117661			1.95×10^{-12}			
CELSR2-PSRC1-SORT1 rs646776			2.19×10^{-12}			
APOB rs693			2.99×10^{-11}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
APOB rs562338			1.97×10^{-7}			
HMGCR rs12654264			2.63×10^{-5}			
B3GALT4 rs2254287			6.98×10^{-1}			
LDLR rs6511720			1.48×10^{-9}			
NCAN-CILP2-PBX4 rs16996148			8.20×10^{-1}			
APO cluster rs2075650			1.05×10^{-5}			
Heid et al. (2008) [206]						
CETP rs1800775		6.05×10^{-15}			German n=1643	33 – 93
PRICKLX10 rs17569297		1.51×10^{-6}				
CETP rs9989419		1.86×10^{-6}				
PRICKLX10 rs10506210		2.22×10^{-6}				
UBXD2 rs16831992		2.44×10^{-6}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CACNA2D4 rs11062008		3.73×10^{-6}				
SORCS2 rs734526		5.34×10^{-6}				
SHB rs10973646		6.32×10^{-6}				
PBX1 rs4657374		1.04×10^{-5}				
DKFZP434C171 rs248426		1.06×10^{-5}				
ENST00000277244 rs1970528		1.08×10^{-5}				
NUP160 rs6485788		1.22×10^{-5}				
EDARADD rs600988		1.29×10^{-5}				
EDARADD rs660351		1.41×10^{-5}				
ITGB8 rs11973964		$1.59\times^{-5}$				
EDARADD rs585537		$1.63\times^{-5}$				
SCARB1 rs12831105		$1.72\times^{-5}$				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
DGKH rs10492434		$1.97\times^{-5}$				
ITGB8 rs6973059		$2.21\times^{-5}$				
ITGKB rs3768371		$2.22\times^{-5}$				
NCAM1 rs7111410		2.31×10^{-5}				
LPL rs17482753		2.71×10^{-5}				
FZD10 rs1532724		2.83×10^{-5}				
ENST00000357331 rs2526100		3.03×10^{-5}				
NCAM1 rs4936266		3.13×10^{-5}				
EDARADD rs2463198		3.22×10^{-5}				
SYNE1 rs11752725		3.26×10^{-5}				
CTNNA2 rs1861700		3.56×10^{-5}				
LPL rs1919484		3.79×10^{-5}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
PBX1 rs3767364		3.83×10^{-5}				
ITGB8 rs6954502		3.91×10^{-5}				
TNNI3 rs2288529		4.58×10^{-5}				
CNDP1 rs12961730		4.62×10^{-5}				
SCARB1 rs11615630		4.79×10^{-5}				
NCAM1 rs2846915		5.37×10^{-5}				
ENST00000357331 rs12699252		5.39×10^{-5}				
LPL rs7461111		5.60×10^{-5}				
ITGB8 rs17365098		5.80×10^{-5}				
PARVG rs139265		5.89×10^{-5}				
TYRP1 rs7863023		5.97×10^{-5}				
NFYA rs7760860		6.07×10^{-5}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
LPL rs17411024		6.66×10^{-5}				
NRXN3 *rs766024*		7.03×10^{-5}				
SORCS2 rs16840358		7.45×10^{-5}				
LOC387882 rs11112741		7.89×10^{-5}				
C14orf147 rs10130824		8.03×10^{-5}				
LPL rs1837842		8.55×10^{-5}				
CRYBA4 rs5761635		9.04×10^{-5}				
CDKL2 rs6851864		9.12×10^{-5}				
ENST00000078131 rs2478884		9.12×10^{-5}				
PBX1 rs3767368		9.37×10^{-5}				
CNDP1 rs9319909		9.59×10^{-5}				
SHB rs943938		9.61×10^{-5}				

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
SYT5 rs12461195		9.94×10^{-5}				
LPL rs17411126		1.67×10^{-4}				
LPL rs17489268		2.01×10^{-4}				
LPL rs271		2.30×10^{-4}				
LPL rs10503669		2.58×10^{-4}				
LPL rs17411031		3.07×10^{-4}				
LIPG rs7240405		3.19×10^{-4}				
LIPG rs2156552		3.71×10^{-4}				
LIPG rs1943981		4.41×10^{-4}				
LIPG rs4939883		8.45×10^{-4}				
Saxena et al. (2007)[c] [92]						

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
GCKR rs780094				3.7×10^{-8}	Finnish and Swedish T2D: *n*=1,464 Controls: *n*=1,467	Not given
GCKR rs780094				8.7×10^{-8}		
APOE cluster rs4420638			3.4×10^{-13}			
APOB rs693			7.1×10^{-7}			
CETP rs1800775		2.5×10^{-13}				
LPL rs17482753		3.6×10^{-5}				
LIPC rs261332		3.4×10^{-5}				
LPL rs17482753				4.9×10^{-7}		
APOA5 rs481843				3.3×10^{-5}		
Sandhu et al. (2008)[c] [357]						
APOC1 rs4420638			1.2×10^{-20}		White European	39–79

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
PSRC1 rs599839			1.7×10^{-15}		(British, Swedish, Finnish and Italian) *n*=11,685	
CELSR2 rs4970834			3.0×10^{-11}			
APOB rs562338			1.4×10^{-9}			
APOB rs7575840			1.9×10^{-9}			
APOB rs478442			8.1×10^{-9}			
APOB rs4591370			8.2×10^{-9}			
APOB rs4560142			8.3×10^{-9}			
APOB rs576203			9.0×10^{-9}			
APOB rs506585			1.0×10^{-8}			
APOB rs488507			2.0×10^{-8}			
APOB rs538928			2.7×10^{-8}			
BCAM rs10402271			4.1×10^{-8}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
APOB rs693			4.4×10^{-8}			
TOMM40 rs2075650			7.1×10^{-14}		British Birth Cohort *n*=4,337	39 - 79
BCL3 rs4803750			2.4×10^{-11}			
CELSR2 rs646776			4.3×10^{-9}			
APOB rs1713222			1.0×10^{-8}			
LDLR rs2228671			1.1×10^{-8}			
LDLR rs11668477			1.5×10^{-8}			
BCAM rs4605275			4.7×10^{-8}			
CELSR2 rs646776			3.0×10^{-14}		White European (British, Swedish, Finnish and Italian) *n*=9,988	39–79
CELSR2 rs629301			3.1×10^{-14}			
CELSR2 rs12740374			3.2×10^{-14}			
CELSR2 rs660240			3.8×10^{-14}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
CELSR2 rs602633			5.7×10^{-14}			
CELSR2 rs599839			7.8×10^{-11}			
CELSR2 rs611917			1.5×10^{-10}			
CELSR2 rs4970834			6.7×10^{-10}			
CELSR2 rs6657811			2.0×10^{-8}			
Surakka et al (2012) [760]						
SRGAP2 rs2483058		3.98×10^{-8}			European (Monozygotic women twin-pairs) *n*=1,720	20 - 80
SRGAP2 rs9242		1.08×10^{-7}				
CD47 rs17826288				8.16×10^{-7}		
Wallace et al (2008) [123]						

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
ApoA5 rs6589567	7.76×10^{-7}				British (Hypertensive) *n*=1,955	Median*n*=58 Interquartile range 49 - 65
CELSR2 rs4970834	1.70×10^{-6}					
Unknown rs10514542	6.98×10^{-6}					
TBPL2 rs4470077	9.04×10^{-6}					
Unknown rs11017236		5.67×10^{-7}				
Unknown rs11826048		9.70×10^{-7}				
COLQ rs905648		4.58×10^{-6}				
PSRC1, CELSR2 rs599839			1.05×10^{-7}			
Unknown rs11889082			1.22×10^{-6}			
NA rs6470600			8.68×10^{-6}			

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
APOA5 rs6589566				2.89×10^{-11}		
LPL rs17482753				1.17×10^{-9}		
GCKR rs780094				4.99×10^{-7}		
Unknown rs17545624				2.13×10^{-6}		
Weissglas-Volkov et al (2013) [207]						
APOA5 rs964184				5.5×10^{-35}	Mexican *n*=2,240	Not given
GCKR rs1260326				2.2×10^{-13}		
LPL rs12678919				2.7×10^{-10}		
MLXIPL rs2286276				2.2×10^{-6}		
TIMD4 rs2036402				3.4×10^{-6}		
CILP2 rs2228603				3.0×10^{-5}		

Gene & SNP	Lipid Trait & *P*-value[ab]				Population & Sample Size	Age Group
	TC	HDL	LDL	TG		
ANGPTL3 rs10889337				3.3×10^{-5}		
CETP rs1532624		1.39×10^{-24}				
LIPC rs1077835		2.1×10^{-14}				
LOC55908 rs2278426		3.44×10^{-9}				
ABCA1 rs9282541		6.4×10^{-26}				
Unknown rs4149310		5.54×10^{-8}				

[a] *P* values are for the discovery stage of the genome-wide association study.

[b] For meta-analysis where the combined *P*-value is provided, this has been given in the table.

[c] Meta-analysis.

[d] Lowest mean age and highest mean age.

[e] *P* values are expressed as -Log10P.

SNP – single-nucleotide polymorphism; TC – total cholesterol; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; TG – triglycerides; T2D – type 2 diabetes.

Appendix E2 - Supplementary Table S2.2 Observational studies examining interaction between *CETP* polymorphisms and diet on blood lipids

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/A	Mexican - Mestizo *n*=215	36.9 ± 11.7	Energy, proteins, fat, SFA, MUFA, PUFA, ratio n-6:n-3, carbohydrates, simple carbohydrates, sucrose, cholesterol and fiber.	Cross-sectional; three – day food intake record.	TC, HDL, LDL and TG	Among participants with a higher intake of sucrose (≥5% of the total kcal/day), those carrying the minor allele (A) had higher TC (mean TC (mg/dL): 200.19 vs 165.55, $P_{interaction}$=0.034) and higher LDL (mean LDL (mg/dL): 128.64 vs 99.29, $P_{interaction}$=0.037) compared with those carrying 2 copies of the major allele (G). None of the other SNP-diet interactions were statistically significant.	Campos-Perez et al. (2020) [98]
TaqIB (rs708272) (G > A)	A/G	Iranian patients with T2D without dyslipedaemia: *n*=129 Patients with T2D and dyslipedemia:	52.9 ± 0.6	Energy, total fat, PUFA, MUFA, cholesterol, carbohydrate, fiber and alcohol intake.	Cross-sectional; food frequency questionnaire.	HDL	Among participants without dyslipidaemia, a higher intake of total fat (>34.9 % from total energy intake) was associated with higher HDL in individuals with 2 copies of the major	Kalantar et al. (2018) [99]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
		n=55					allele (G) compared with those carrying 2 copies of the minor allele (A) (mean HDL (mg/dL) for high total fat vs low total fat intake (≤34.9% from total energy) in 'GG': 58.6 ± 4.1 vs 36.5 ± 6.5; $P_{interaction}$=0.02). None of the other SNP-diet interactions were statistically significant.	
TaqIB (rs708272) (G > A)	A/	Spanish Patients with T2D, obesity, hypertension or dyslipedaemia: *n*=4210	66.9 ± 6.3	Energy, total fat, SFA, MUFA, PUFA, proteins, carbohydrates and alcohol intake.	Nested case-control Food frequency questionnaire.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Corella et al. (2010b) [223]
TaqIB (rs708272) (G > A)	A/	Spanish patients with CHD: *n*=557 Healthy controls:	53.9 ± 7.3	Alcohol consumption.	Nested case-control; validated computerised diet history questionnaire.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Corella et al. (2010a) [222]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
		n=1180						
TaqIB (rs708272) (G > A)	A/G	Men with T2D without CVD in the USA (96% white participants) *n*=603	40 - 75	Energy, total fat, animal fat, vegetable fat, cholesterol, PUFA, MUFA, trans fat, SFA and alcohol intake.	Prospective cohort; food-frequency questionnaire.	HDL, LDL, TG and non-HDL cholesterol.	A higher intake of total fat (>33.5% from total energy intake), animal fat (>19.9% from total energy intake), SFA (>11.47% from total energy intake) and MUFA (>12.75% from total energy intake) was associated with lower HDL in participants with 2 copies of the major allele (G) compared with those with AA genotype ($P_{interaction}$=0.003, 0.02, 0.02 and 0.04 respectively). None of the other SNP-diet interactions were statistically significant.	Li et al. (2007)[190]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/A	Multi-ethnic Chinese: *n*=2858 Malay: *n*=761 Asian Indian: *n*=588	37.2[c] – 41.1[c]	Energy, percentage of energy as fat and cholesterol intake.	Cross-sectional; food frequency questionnaire.	TC, HDL, LDL and TG	In Malay and Asian Indian participants, a higher dietary cholesterol (cholesterol intake as continuous) was linked to higher HDL in participants with 2 copies of the A allele compared with those with GG genotype ($P_{interaction}$=0.046 for Malay; $P_{interaction}$=0.023 for Indian). The interaction was not statistically significant in Chinese. None of the other SNP-diet interactions were statistically significant.	Tai et al. (2003) [100]
TaqIB (rs708272) (G > A)	A/A	Irish and French Male MI patients: *n*=608 Healthy controls: *n*=724	52.7[c] - 53.7[c]	Alcohol consumption.	Case-control; questionnaire.	HDL, LDL, TG and VLDL	Among healthy controls, a higher intake of alcohol (≥75g /day) was associated with higher levels of HDL in participants carrying the minor allele (A) (30% higher for 'AA' and 13%	Fumeron et al. (1995) [217]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							higher for 'GA') compared with those with GG genotype ($P_{interaction}$<0.0001). None of the other SNP-diet interactions were statistically significant.	
TaqIB (rs708272) (G > A)	A/A	Multi-ethnic (11 US States) CHD patients: *n*=505 Healthy controls: *n*=999	62[c] – 66[c]	Alcohol consumption.	Nested case-control; food frequency questionnaire.	TC, HDL, LDL and TG	In healthy controls, a higher alcohol intake (≥15 g/day) was linked to higher HDL in participants carrying the minor allele (A), with those carrying 2 copies having the highest HDL ($P_{interaction}$<0.01). None of the other SNP-diet interactions were statistically significant.	Jensen et al. (2008) [101]
TaqIB (rs708272) (G > A)	A/A	Japanese (Western Japan) *n*=1729	57.2 ± 15.7	Alcohol consumption.	Cross-sectional; questionnaire.	TC, HDL and TG	A higher alcohol intake (≥2 drinks/day) was associated with higher HDL in men carrying the minor allele (A) compared with men carrying 2 copies of the	Tsujita et al. (2007) [216]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							major allele (G) (mean HDL (mmol/l): 'GG', 1.37 ± 0.03; 'GA', 1.44 ± 0.03; 'AA', 1.49 ± 0.05; $P_{interaction}$=0.049). In women, consumption of any amount of alcohol was linked to higher HDL in individuals with 2 copies of the A allele compared with those with GG or GA genotypes (mean HDL (mmol/l): 'GG', 1.57±0.03; 'GA', 1.57±0.03; 'AA', 1.79±0.06; $P_{interaction}$=0.022). None of the other SNP-diet interactions were statistically significant	
TaqIB (rs708272) (G > A)	A/G and A	Hei Yi Zhuang Chinese Healthy participants *n*=758	39.9[c] – 42.4[c]	Alcohol consumption.	Cross-sectional; questionnaire.	TC, HDL, LDL and TG	In participants with 2 copies of the major allele (G), those who consumed any amount of alcohol had higher HDL (mean HDL (mmol/l): 2.09 ± 0.46 vs	Zhou et al. (2008) [215]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							1.94 ± 0.38; *P*<0.01) and TG (mean TG (mmol/l): 1.42 ± 2.71 vs 0.94 ± 0.36; P< 0.05) and lower LDL (mean LDL (mmol/l): 2.24 ± 0.65 vs 2.65 ± 3.01; *P*<0.01) compared with those who did not drink alcohol. In heterozygotes (GA), HDL was higher in drinkers than non-drinkers (mean HDL (mmol/l): 2.17 ± 0.55 vs 2.02 ± 0.50; *P*<0.05). Those with GA genotype who drank any amount of alcohol also had lower TG than individuals with GG who drank any amount of alcohol (mean TG (mmol/l): 1.01 ± 0.86 vs 1.42 ± 2.71; *P*<0.05). None of the other SNP-diet interactions were statistically significant.	

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/	Scottish Healthy participants *n*=220	39 ± 11	Alcohol consumption.	Cross-sectional; questionnaire.	TC, HDL, LDL, VLDL and TG	None of the SNP-diet interactions were statistically significant.	Freeman et al. (1994) [221]
TaqIB (rs708272) (G > A)	A/	White American and African American *n*=15,792	53.7 ± 0.5	Alcohol consumption.	Longitudinal; dietary questionnaire.	TC and HDL	None of the SNP-diet interactions were statistically significant.	Volcik et al. (2007) [220]
TaqIB (rs708272) (G > A)	A/	White British Healthy men *n*=2773	56 ± 3.4	Alcohol consumption.	Longitudinal; questionnaire.	TC, HDL and TG	None of the SNP-diet interactions were statistically significant.	Talmud et al. (2002) [219]
TaqIB (rs708272) (G > A)	A/	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	n-3 PUFA in red blood cells (RBCs) and total energy intake.	Cross-sectional: gas chromatographic analysis; food frequency questionnaire.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Rudkowska et al. (2013b) [237]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	Total energy, total fat and total SFA intake.	Cross-sectional; food frequency questionnaire.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Rudkowska et al. (2013a) [192]
TaqIB (rs708272) (G > A)	A/	White American *n*=8,968 African American *n*=2, 677	53.6 ± 0.5	Energy, protein, carbohydrate, total fat, SFA, MUFA, PUFA, cholesterol and fiber intake.	Cross-sectional; food frequency questionnaire.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Nettleton et al. (2007) [761]
TaqIB (rs708272) (G > A)	A/	Finnish Male alcohol drinkers: *n*=98 Male healthy non-alcoholic controls: *n*=82	41.6 ± 9.7	Alcohol consumption.	Cross-sectional; interview.	TC, HDL, LDL, VLDL, TG and VLDL-TG	None of the SNP-diet interactions were statistically significant.	Hannuksela et al. (1994) [218]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
rs5882 (I405V) (G > A)	G/G	Iranian *n*=4700	40.9 ± 13.9	Energy, carbohydrate, protein, total fat, MUFA, PUFA, SFA, fish and fiber intake.	Longitudinal: 3.6 years of follow-up; food frequency questionnaire.	TC, HDL, LDL and TG	Higher total fat intake was associated with increased levels of TG in participants carrying the minor allele (G) compared to those carrying 2 copies of the major (A) allele (mean changes in TG (mg/dL) across quartiles of total fat intake: −1.90, 2.6, 6.06, 8.88; $P_{interaction}$=0.001). Higher MUFA intake was also linked to increased levels of TG in G allele carriers compared to participants with AA genotype (mean changes in TG (mg/dL) across quartiles of MUFA intake: −3.03, 1.73, 8.06, 8.85; $P_{interaction}$=0.001); while higher carbohydrate intake correlated with decreased levels of TG in those carrying the G	Hosseini-Esfahani et al. (2019) [231]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							allele (changes in TG (mg/dL) across quartiles of carbohydrate intake: 6.65, 7.29, 4.42, −3.28; $P_{interaction}$=0.01). None of the other SNP-diet interactions were statistically significant.	
rs5882 (I405V) (G > A)	G/G	Iranian Participants with Metabolic Syndrome (MetS): *n*=441 Healthy controls: *n*=844	36.9 ± 10.5	Energy, carbohydrate, protein, total fat, PUFA, MUFA, trans-fatty acids, cholesterol and omega3 fatty acids.	Nested case-control: 3 years of follow-up; food frequency questionnaire.	HDL and TG	Minor allele (G) carriers had a lower risk of low HDL with a lower intake of MUFA and a higher risk of low HDL with a higher intake of MUFA (9.6-11% of total energy intake) compared to participants with AA genotype ($P_{interaction}$=0.02). None of the other SNP-diet interactions were statistically significant.	Esfandiar et al. (2018) [232]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
rs5882 (I405V) (G > A)	G/G	Multi-ethnic (USA) n=101	36.2 ± 5.8	Energy, total fat, SFA, MUFA and PUFA intake.	Cross-sectional analysis from an ongoing clinical trial (NCT02740439)7 -day food record.	TC, HDL and TG	A higher MUFA intake (>31g/day) was linked to lower TG in participants carrying the minor allele (G) ($P_{interaction}$=0.006). None of the other SNP-diet interactions were statistically significant.	Hannon et al. (2020) [189]
rs5882 (I405V) (G > A)	G/A	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	n-3 PUFA in red blood cells (RBCs) and total energy intake.	Cross-sectional: gas chromatographic analysis; food frequency questionnaire.	TC, HDL, LDL and TG.	A higher level of n-3 PUFA in RBCs was associated with lower TC in participants with 2 copies of the major allele (A) compared to those with 'GG' or 'AG' genotype (β (mmol/l) = -0.0290 ± 0.0307; $P_{interaction}$=0.0334) and higher HDL in carriers of the A allele compared to those with 'GG' genotype (β (mmol/l) = 0.0263 ± 0.0115 for 'AG' genotype, β (mmol/l) = 0.0017 ± 0.0131 for 'AA'	Rudkowska et al. (2013b) [237]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							genotype; $P_{interaction}$=0.0271). None of the other SNP-diet interactions were statistically significant.	
rs5882 (I405V) (G > A)	G/A	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	Total energy, total fat and SFA intake.	Cross-sectional; food frequency questionnaire.	TC, HDL, LDL and TG	In participants with 2 copies of the major allele (A), a higher total fat intake resulted in a greater increase in TC compared with participants with 'GG' or 'AG' genotype (β (mmol/l) = 0·0024 ± 0·0026; $P_{interaction}$=0.046). None of the other SNP-diet interactions were statistically significant.	Rudkowska et al. (2013a) [192]
rs5882 (I405V) (G > A)	G/	Spanish *n*=1315	49.7 ± 0.2	Plasma selenium	Cross-sectional; inductively coupled-plasma mass spectrometry.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Galan-Chilet et al. (2015) [252]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
rs5882 (I405V) (G > A)	G/	Irish and French Male participants MI patients: *n*=568 Healthy controls: *n*=668	53.2 ± 8.5	Alcohol consumption.	Case-control; questionnaire.	HDL	None of the SNP-diet interactions were statistically significant.	Corbex et al. (2000) [248]
rs5882 (I405V) (G > A)	G/G	Icelandic Healthy participants Men: *n*=152 Women: *n*=166	15 - 78	Alcohol consumption.	Cross-sectional; questionnaire.	HDL and TG	In men, alcohol consumption was associated with higher HDL (13.7% higher HDL than 'AA' genotype) in carriers of 2 copies of the minor allele (G) compared with men with AG and AA genotypes ($P_{interaction}$=0.026). None of the other SNP-diet interactions were statistically significant.	Gudnason et al. (1997) [236]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
rs3764261 (C > A)	A/A	Iranian *n*=4,700	40.9 ± 13.9	Energy, carbohydrate, protein, total fat, MUFA, PUFA, SFA, fish and fiber intake.	Longitudinal: 3.6 years of follow-up; food frequency questionnaire.	TC, HDL, LDL and TG	A higher fish intake was associated with a larger decrease in TC in participants carrying the minor allele (A) (mean changes in TC (mg/dL) with quartiles of fish intake: 8.02, 6.93, 6.54, 5.58) compared to those with CC genotype (mean changes in TC (mg/dL) with quartiles of fish intake: 3.65, 6.62, 4.57, 8.93) ($P_{interaction}$=0.02). None of the other SNP-diet interactions were statistically significant.	Hosseini-Esfahani et al. (2019) [231]
rs3764261 (C > A)	A/	Iranian Participants with MetS: *n*=441 Healthy controls: *n*=844	36.9 ± 10.5	Energy, carbohydrate, protein, total fat, PUFA, MUFA, trans-fatty acids, cholesterol and omega3 fatty acids.	Nested case-control: 3 years of follow-up; food frequency questionnaire.	HDL and TG	None of the SNP-diet interactions were statistically significant.	Esfandiar et al. (2018) [232]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
rs3764261 (C > A)	A/A	Indian (Lucknow, Nagpur, Hyderabad and Bangalore) *n*=3342	39.9 ± 10.3	Average daily fat intake	Cross-sectional; food frequency questionnaire.	TC, HDL, LDL and TG	Participants carrying the minor allele (A) who had a higher dietary fat intake (≥76.98g/day) had increased levels of TC (β (mmol/l) = 0.097 ± 0.041; $P_{interaction}$=0.018) and LDL (β (mmol/l) = 0.085 ± 0.041; $P_{interaction}$=0.042). None of the other SNP-diet interactions were statistically significant.	Walia et al. (2014) [242]
rs3764261 (C > A)	A/	White American Participants with CVD *n*=772	66.2 ± 9.4	Cholesterol and total caloric intake.	Cross-sectional; food frequency questionnaire.	TC	None of the SNP-diet interactions were statistically significant.	Kim et al. (2013) [762]
C-629A (rs1800775) (C > A)	C/	Multi-ethnic Chinese: *n*=1366 Malay: *n*=467 Indian: *n*=387	39.1 ± 12.3	Cholesterol, energy intake and percentage of energy as fat.	Cross-sectional; food frequency questionnaire.	HDL	None of the SNP-diet interactions were statistically significant.	Tai et al. (2003) [100]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
C-629A (rs1800775) (C > A)	C/A	Irish and French Men MI patients: *n*=568 Healthy controls: *n*=668	53.2 ± 8.5	Alcohol consumption.	Case-control; questionnaire.	HDL	Among participants carrying the A allele, alcohol consumption was associated with higher HDL in healthy participants ($P_{interaction}$<0.002) and patients who were not treated with lipid-lowering medication ($P_{interaction}$<0.001). None of the other SNP-diet interactions were statistically significant.	Corbex et al. (2000) [248]
C-629A (rs1800775) (C > A)	C/	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	n-3 PUFA in red blood cells (RBCs) and total energy intake.	Cross-sectional: Gas chromatographic analysis; Food frequency questionnaire.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Rudkowska et al. (2013b) [237]
C-629A (rs1800775) (C > A)	C/	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	Total energy, total fat and SFA intake.	Cross-sectional, food frequency questionnaire.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Rudkowska et al. (2013a) [192]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
C-629A (rs1800775) (C > A)	C/C	Taiwanese *n*=9075	53.5 ± 0.4	Coffee consumption.	Cross-sectional; questionnaire.	HDL	Coffee consumption was associated with lower HDL in women carrying the minor allele (C) compared to women with 'AA' genotype (β = -1.8095 (standard error not given) for 'AC' genotype, β (mg/dL) = -2.8151 for 'CC' genotype; $P_{interaction}$<0.0001); and in men carrying the 'C' allele compared to men with the 'AA' genotype [β (mg/dL) = -1.9623 for 'AC' genotype, β (mg/dL) = -2.7153 for 'CC' genotype; $P_{interaction}$<0.0001] None of the other SNP-diet interactions were statistically significant.	Hsu et al. (2019) [247]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
C-4502T (rs183130) (C > T)	T/	Spanish Patients with T2D, Obesity, Hypertension or Dyslipedemia. *n*=4210	66.9 ± 6.3	Energy, total fat, SFA, MUFA, PUFA, protein, carbohydrate and alcohol intake.	Nested case-control Food frequency questionnaire	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Corella et al. (2010b) [223]
C-4502T (rs183130) (C > T)	T/T and C	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	n-3 PUFA in red blood cells (RBCs) and total energy intake.	Cross-sectional: gas chromatographic analysis; food frequency questionnaire.	TC, HDL, LDL and TG.	A higher level of n-3 PUFA in RBCs was associated with lower TC in carriers of the minor allele (T) compared to those with 'CC' genotype [β (mmol/l) = −0.0632 ± 0.0241 for CT, β (mmol/l) = −0.0421 ± 0.0343 for TT; $P_{interaction}$=0.0326] and lower TG in heterozygotes compared to those with TT genotype [β (mmol/l) = −0.0095 ± 0.0051 vs 0.0073 ± 0.0073; $P_{interaction}$=0.0300].	Rudkowska et al. (2013b) [237]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							None of the other SNP-diet interactions were statistically significant.	
C-4502T (rs183130) (C > T)	T/	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	Total energy, total fat and SFA intake.	Cross-sectional, food frequency questionnaire.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Rudkowska et al. (2013a) [192]
rs4783961 (G > A)	A/G	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	n-3 PUFA in red blood cells (RBCs) and total energy intake.	Cross-sectional: gas chromatographic analysis; food frequency questionnaire.	TC, HDL, LDL and TG.	A higher level of n-3 PUFA in RBCs was associated with lower TG (β (mmol/l) = -0.0106 ± 0.0057; $P_{interaction}$=0.0032) and lower TC:HDL ratio (β (mmol/l) = -0.0055 ± 0.0033; $P_{interaction}$=0.0483) in heterozygotes compared to participants with 2 copies of the minor allele (A).	Rudkowska et al. (2013b)[237]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
rs4783961 (G > A)	A/	Inuit (Nunavik Inuit) *n*=553	37.2 ± 8.5	Total energy, total fat and SFA intake.	Cross-sectional; food frequency questionnaire.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Rudkowska et al. (2013a) [192]
rs9989419 (A > G)	A/	Swiss *n*=5409	53.4 ± 10.8	Alcohol consumption.	Cross-sectional; reported alcohol consumption of the last 7 days.	TC, HDL and TG.	None of the SNP-diet interactions were statistically significant.	Marques-Vidal et al. (2010) [763]
rs6499861 (C > G)	G/	Swiss *n*=5409	53.4 ± 10.8	Alcohol consumption.	Cross-sectional; reported alcohol consumption of the last 7 days.	TC, HDL and TG.	None of the SNP-diet interactions were statistically significant.	Marques-Vidal et al. (2010) [763]
C>T/In9 (rs289714) (G > A)	G/A	Multi-ethnic (USA) *n*=101	36.2 ± 5.8	Energy, total fat, SFA, MUFA and PUFA intake.	Cross-sectional analysis from an ongoing clinical trial (NCT02740439)7 -day food record.	TC, HDL and TG	Among participants with 2 copies of the major allele (A), those with an intake of >92g of total fat /day had lower TG (103 ± 63 vs 135 ± 15 mg/dL) than those who consumed <31g of total	Hannon et al. (2020) [189]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							fat /day ($P_{interaction}$=0.001). None of the other SNP-diet interactions were statistically significant.	
rs1800774 (C > T)	T/C	Spanish *n*=1315	49.7 ± 0.2	Plasma selenium	Cross-sectional; inductively coupled-plasma mass spectrometry.	TC, HDL, LDL and TG	Higher plasma selenium levels were associated elevated LDL in all the three genotypes but participants with 2 copies of the major allele (C) had lower LDL compared to those with 'CT' and 'TT' genotypes [odds ratio per an interquintile range increase in plasma selenium (95% confidence interval): 0.97 (0.74 to 1.27) for 'CC', 1.76 (1.38 to 2.25) for 'CT', 3.20 (1.93 to 5.28) for 'TT' genotype; $P_{interaction}$=0.0002].	Galan-Chilet et al. (2015) [252]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
							None of the other SNP-diet interactions were statistically significant.	
rs4783962 (T > A / T > C)	T/	Spanish *n*=1315	49.7 ± 0.2	Plasma selenium	Cross-sectional; inductively coupled-plasma mass spectrometry.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Galan-Chilet et al. (2015) [252]
rs820299 (G > A / G > C)	G/	Taiwanese *n*=3000	49.2 ± 11.0	Alcohol consumption.	Cross-sectional; questionnaire.	HDL and TG	None of the SNP-diet interactions were statistically significant.	Lin et al. (2016) [764]
C373 (Ala > Pro)	Pro/	Irish and French Male participants MI patients: *n*=568 Healthy controls:	53.2 ± 8.5	Alcohol consumption.	Case-control; questionnaire.	HDL	None of the SNP-diet interactions were statistically significant.	Corbex et al. (2000) [248]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
		n=668						
C451 (Arg > Gln)	Gln/	Irish and French Male participants MI patients: *n*=568 Healthy controls: *n*=668	53.2 ± 8.5	Alcohol consumption.	Case-control; questionnaire.	HDL	None of the SNP-diet interactions were statistically significant.	Corbex et al. (2000) [248]
–631 (C > A)	A/	Irish and French Male participants MI patients: *n*=568 Healthy controls: *n*=668	53.2 ± 8.5	Alcohol consumption.	Case-control; questionnaire.	HDL	None of the SNP-diet interactions were statistically significant.	Corbex et al. (2000) [248]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
+524 (G > T)	T/	Irish and French Male participants MI patients: *n*=568 Healthy controls: *n*=668	53.2 ± 8.5	Alcohol consumption.	Case-control; questionnaire.	HDL	None of the SNP-diet interactions were statistically significant.	Corbex et al. (2000) [248]
rs1532624 (C > A)	A/	Multi-ethnic (USA) *n*=101	36.2 ± 5.8	Energy, total fat, SFA, MUFA and PUFA intake.	Cross-sectional analysis from an ongoing clinical trial (NCT02740439)7 -day food record.	TC, HDL and TG	None of the SNP-diet interactions were statistically significant.	Hannon et al. (2020) [189]
TaqIA (A1 > A2)	A2/	Finnish Male alcohol drinkers: *n*=98 Male healthy non-alcoholic controls: *n*=82	41.6 ± 9.7	Alcohol consumption.	Cross-sectional; interview.	TC, HDL, LDL, VLDL, TG and VLDL-TG.	None of the SNP-diet interactions were statistically significant.	Hannuksela et al. (1994) [218]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Design	Lipid Trait Examined	Results for Interaction[b]	References
EcoNI (N1 > N2)	N2/	Finnish Male alcohol drinkers: n=98 Male healthy non-alcoholic controls: *n*=82	41.6 ± 9.7	Alcohol consumption.	Cross-sectional; interview.	TC, HDL, LDL, VLDL, TG and VLDL-TG.	None of the SNP-diet interactions were statistically significant.	Hannuksela et al. (1994) [218]

[a] Alleles are reported in the forward direction in line with dbSNP.

[b] $P_{interaction}$ values are reported only for the significant SNP-diet interactions.

[c] Lowest mean age and highest mean age

SNP – single-nucleotide polymorphism; TC – total cholesterol; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; VLDL – very low-density lipoprotein cholesterol; TG – triglycerides; VLDL-TG – very low-density lipoprotein triglycerides; SFA – saturated fatty acids; PUFA – polyunsaturated fatty acids; MUFA – monounsaturated fatty acids; n-6 – omega 6 polyunsaturated fatty acids; n-3 – omega 3 polyunsaturated fatty acids; T2D – type 2 diabetes; CHD – coronary heart disease; CVD – cardiovascular disease; MI – myocardial infarction.

Appendix E3 - Supplementary Table S2.3 Interventional studies examining interaction between *CETP* polymorphisms and diet on blood lipids

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/G	Iranian patients with T2D: *n*=95 Healthy controls: *n*=73	48.0 ± 1.7	Sesame oil, Canola oil and Sesame-canola oil.	Randomised triple-blind crossover trial; Three diets: Sesame oil; canola oil; 40% sesame oil and 60% canola oil. 4-week washout period with sunflower oil; three 9-week intervention periods, separated by 4-week washout periods.	TC, HDL, LDL and TG	In healthy participants, none of the SNP-diet interactions were statistically significant. In patients with T2D, carriers of 2 copies of the major allele (G) had a reduction in lipid ratios after intake of sesame oil and sesame-canola oil (change in LDL: HDL (mg/dL), -1.29, $P_{interaction}$=0.027; change in TC: HDL (mg/dL), -2.82, $P_{interaction}$=0.024; and change in TG: HDL (mg/dL), -7.00; $P_{interaction}$=0.025). None of the other SNP-diet interactions were statistically significant.	Ramezani-Jolfaie et al. (2020) [227]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/G	Spanish Prepubertal children with mild hypercholesterolemia *n*=36	8.4 ± 2.9	MUFA from virgin olive oil.	Crossover: Cow's skim milk vs cow's skim milk enriched with virgin olive oil; 2 periods of 6 weeks.	HDL, LDL and TG.	Intake of olive-oil-enriched skim milk resulted in a higher increase in HDL [mean change in HDL (mmol/) (95% confidence interval) l: 0.179 (0.096 to 0.262) vs 0.089 (0.032 to 0.146); $P_{interaction}$<0.001] and a decrease in LDL:HDL ratio [mean change in LDL:HDL (mmol/l) (95% confidence interval): -0.470 (-0.729 to 0.211) vs -0.097 (-0.275 to 0.081); $P_{interaction}$<0.001] in participants with 2 copies of the major allele (G) compared with carriers of the minor allele (A). None of the other SNP-diet interactions were statistically significant.	Estévez-González et al. (2010) [211]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/G	Iranian Patients with MetS *n*=80	38.91 ± 6.90	Artichoke leaf extract (ALE)	Double-blind RCT: 1800 mg /day of ALE vs placebo for 12 weeks.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Rezazadeh et al. (2018) [765]
TaqIB (rs708272) (G > A)	A/	Spanish Participants at high risk of CVD *n*=650	Unavailable	Mediterranean diet	Three diets: Mediterranean diet with olive oil; Mediterranean diet with nuts; and control (low-fat diet); 3 months.	Plasma lipids	None of the SNP-diet interactions were statistically significant.	Frances et al. 2006 (Abstract) [210]
TaqIB (rs708272) (G > A)	A/	Brazillian Participants with moderate primary Hypercholesterolemia *n*=60	20–60	Plant sterol ester (PSE)	Double-blind cross-over: 20g /day margarine with (PSE) vs 20g /day margarine without PSE; 4 weeks. Food record.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Lottenberg et al. (2003) [766]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/G	New Zealander Men with Hypercholesterolaemia *n*=85	48.5 ± 9.5	Kiwifruit	RCT: 4-week healthy diet, followed by 4-week healthy diet vs healthy diet plus 2 kiwifruit per day.	TC, HDL, LDL and TG	In participants with 2 copies of the major allele (G), consumption of kiwifruit resulted in lower TG:HDL ratio than the control diet (mean change in TG:HDL ratio (mmol/l), -0.23 ± 0.58 vs 0.09 ± 0.56, P = 0.03; $P_{interaction}$<0.05). None of the other SNP-diet interactions were statistically significant.	Gammon et al. (2014) [228]
TaqIB (rs708272) (G > A)	A/A	Han Chinese Healthy participants *n*=56	22.9 ± 1.8	Carbohydrate and fat intake.	Washout diet of 31% fat and 54% carbohydrate for 7 days; followed by high carbohydrate/low fat diet (HC/LF) of 70% carbohydrate and 15% fat for 6 days.	TC, HDL, LDL and TG	After the HC/LF diet, carriers of the minor allele (A) had higher HDL (mean HDL (mg/dL): 56.14 ± 10.69 after washout diet vs 59.77 ± 10.62 after high carbohydrate/ low fat; $P_{interaction}$<0.05). None of the other SNP-diet interactions were statistically significant.	Du et al. (2010) [224]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/	New Zealander *n*=70	48.25 ± 9.5	Energy, carbohydrate, protein, total fat, SFA, PUFA, MUFA and dietary cholesterol.	Single crossover trial; high SFA vs high PUFA; two 4-week phases.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Aitken et al. (2006) [767]
TaqIB (rs708272) (G > A)	A/	Multi-ethnic (British, German, Danish and Italian) *n*=117	57.7 ± 5.4	Isoflavone-enriched cereal bars.	Double-blind RCT: Cereal bars enriched with Isoflavone (genistein – to – daidzein ratio of 2:1; 50mg/day) or placebo cereal bars for 8 weeks with a washout period of 8 weeks before crossover.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Hall et al. (2006) [768]
TaqIB (rs708272) (G > A)	A/	Dutch Healthy participants *n*=112	33 ± 16	Rapeseed oil and plant stanol ester.	A low erucic acid rapeseed oil-based margarine and shortening for 4 weeks; followed by the same margarine (control) or 1 of 2	HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Plat and Mensink (2002) [769]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
					treatment groups: the same margarine and shortening + vegetable-oil-based plant stanol ester mixture or the same margarine and shortening + wood – based plant stanol ester mixture for 8 weeks.			
TaqIB (rs708272) (G > A)	A/A	Greek Men and postmenopausal women heterozygous for Familial Hypercholesterolemia (HFH) men: *n*=41 women: *n*=39 Healthy controls: *n*=11	44.37 ± 12.15	Fatty meal	Oral fat tolerance test: 12-hour overnight fast followed by consumption of fatty meal within 20 minutes.	TC, HDL and TG	Among all participants, none of the SNP-diet interactions were statistically significant. In HFH participants, women with the minor allele (A) had lower TG after 4 hours of fat intake (239 ± 65 vs 279 ± 95 mg/dL; *P*=0.03) compared with men with the A allele.	Anagnostopoulou et al. (2009) [226]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
TaqIB (rs708272) (G > A)	A/	New Zealander *n*=55	45.5 ± 9.5	SFA and PUFA.	Double cross-over: Lipid-lowering diet (baseline diet) for 3 weeks; high SFA vs high PUFA; 4 weeks.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Wallace et al. (2000a) [320]
TaqIB (rs708272) (G > A)	A/	New Zealander *n*=46	45.5 ± 9.9	SFA and PUFA.	Double cross-over: Lipid-lowering diet (baseline diet) for 3 weeks; high SFA; high PUFA for 4 weeks.	TC, HDL, LDL, TG, light LDL and dense LDL.	None of the SNP-diet interactions were statistically significant.	Wallace et al. (2000b) [770]
TaqIB (rs708272) (G > A)	A/A	Dutch Healthy participants *n*=405	29 ± 12	SFA, trans fat, dietary cholesterol and coffee diterpenes cafestol and kahweol.	7 trials with SFA; 2 trials with trans fat; 8 trials with dietary cholesterol; and 9 trials with coffee diterpenes cafestol and kaweol.	TC, HDL and LDL.	Participants with 2 copies of the minor allele (A) had higher changes in HDL in response to SFA (mean change in HDL (mmol): 0.08 ± 0.02 for 'AA', 0.03 ± 0.01 for 'GA', 0.04 ± 0.02 for 'GG' genotype; *P*=0.04) than participants with 'GG' or 'GA' genotype. Changes in LDL in response to dietary cholesterol were smaller	Weggemans et al. (2001) [225]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
							in participants carrying the major allele (G) than those with AA genotype (mean change in LDL mmol/l: 0.27 ± 0.14 for 'GG', 0.35 ± 0.08 for 'GA', 0.75 ± 0.15 for 'AA'; GG vs AA, *P*=0.03; GA vs AA, P = 0.01). None of the other SNP-diet interactions were statistically significant.	
rs5882 (I405V) (G > A)	G/ A	Canadian Sedentary men (12 pairs of monozygotic twins). *n*=24	21 ± 2.0	Overfeeding.	Overfeeding by 1000Kcal /day, 6 days per week for a period of 100 days.	TC, HDL, LDL, VLDL, TG, HDL_2 and HDL_3,	Overfeeding was associated with decreased HDL (mean change in HDL (mmol/l): -0.12 ± 0.04 vs 0.02 ± 0.04; *P*=0.02), HDL_2 (mean change in HDL_2 (mmol/l), -0.08 ± 0.03 vs 0.03 ± 0.03; *P*=0.04) and HDL_3 (mean change in HDL_3 (mmol/l), -0.04 ± 0.02 vs -0.004 ± 0.02; *P*=0.002) in carriers of 2 copies of the major allele	Terán-García et al. (2008) [240]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
							(A) compared to homozygotes for the minor allele (G). None of the other SNP-diet interactions were statistically significant.	
rs5882 (I405V) (G > A)	G/	Brazillian Participants with moderate primary hypercholesterolemia *n*=60	20–60	Plant sterol ester	Double-blind cross-over: 20 g /day margarine with plant sterol ester (PSE) vs 20 g /day margarine without PSE for 4 weeks. Food record.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Lottenberg et al. (2003) [766]
rs5882 (I405V) (G > A)	G/	Canadian Individuals with mild hypercholesterolemia *n*=71	30 – 75	Plant sterol	Dual centre single blind randomised crossover trial. Margarine with 2g plant sterol/day vs margarine without plant sterol for 28-day periods.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	MacKay et al. (2015) [771]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
rs5882 (I405V) (G > A)	G/	Iranian Healthy participants *n*=85	20 ± 2	PUFA and SFA	A high PUFA:SFA (1.2) followed by a low PUFA:SFA (0.3). Two consecutive 28-day periods.	HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Darabi et al. (2009) [772]
rs5882 (I405V) (G > A)	G/	Israeli Healthy participants *n*=214	45.2 (14 - 74)	Energy intake, total fat, SFA and cholesterol.	Cross over: high SFA and cholesterol vs low SFA and low cholesterol. Two 4-week periods and a 4-week washout period.	TC, HDL, LDL and TG.	None of the SNP-diet interactions were statistically significant.	Friedlander et al. (2000) [773]
rs5882 (I405V) (G > A)	G/	Greek Men and postmenopausal women heterozygous for Familial Hypercholestrolemia men: *n*=41 women: *n*=39 Healthy participants: *n*=11	44.4 ± 12.2	Fatty meal	Oral fat tolerance test: 12 hour overnight fast followed by consumption of fatty meal within 20 minutes.	TC, HDL and TG	None of the SNP-diet interactions were statistically significant.	Anagnostopoulou et al. (2009) [226]

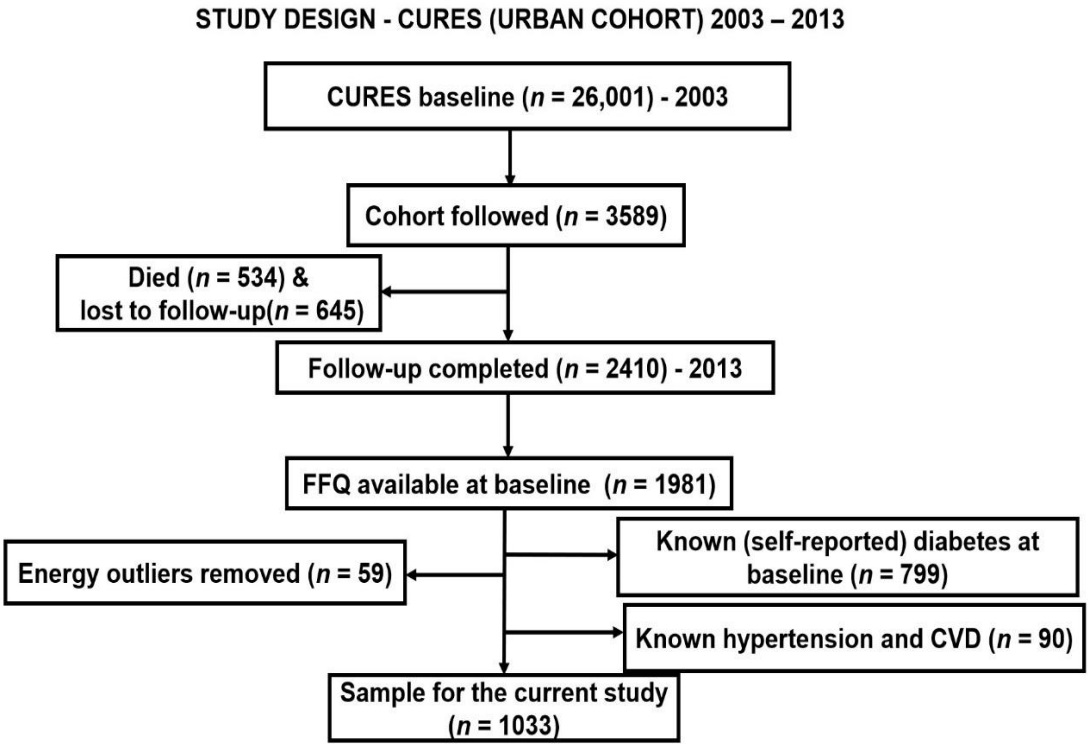
SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
rs3764261 (C > A)	A/A	Spanish ACS/CHD patients. with MetS: *n*=424	60.0 ± 0.3	Mediterranean diet and low-fat diet.	1-year dietary intervention involving Mediterranean diet (35% fat, 22% MUFA) vs Low-fat diet (28% fat, 12% MUFA).	TC, HDL, LDL and TG.	Intake of Mediterranean diet was associated with higher HDL (mean HDL (mg/dL): 41 vs. 38; $P_{interaction}$=0.006) and lower TG (mean TG (mg/dL): 130 vs 146; $P_{interaction}$=0.04) in participants carrying the minor allele (A) compared to those with CC genotype. None of the other SNP-diet interactions were statistically significant.	Garcia-Rios et al. (2018) [191]
rs3764261 (C > A)	A/C	US residents White: *n*=747 Black: *n*=111 Hispanic, Asian or other: *n*=36	51.0 ± 7.7	High-fat diet, low-fat diet and carbohydrate.	2-year randomised weight-loss trial (POUNDS LOST): Low-fat diet (20%) vs high-fat diet (40%) *n*=732 2-year RCT (DIRECT): Low-fat diet vs low carbohydrate (high fat) diet *n*=171	TC, HDL, LDL and TG	Among participants with 2 copies of the major allele (C), those in the high-fat diet (40% fat) group had a higher increase in HDL (11.7 vs 4.5%; $P_{interaction}$=0.01) and a larger decrease in TG (-25.1 vs. -11.7%; $P_{interaction}$=0.0007) compared with those in	Qi et al. (2015) [214]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
							the low-fat diet (20% fat) group. None of the other SNP-diet interactions were statistically significant.	
C-629A (rs1800775) (C > A)	C/	Multi-ethnic White: *n*=395 South and South East Asian: *n*=46 Black African: *n*=38	51.5 ± 9.5	SFA, MUFA, low fat, carbohydrate (CHO).	RCT: 4-week reference diet (~18% SFA, 12% MUFA, 38% total fat, 45% CHO) followed by 1 of 3 diets: a MUFA diet (~10% SFA, 20% MUFA, 38% total fat, 45% CHO); a low fat diet (~10% SFA, 11% MUFA, 28% total fat, 55% CHO); or the reference diet for 24 weeks.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Walker et al. (2011) [249]

SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
rs9989419 (A > G / A > T)	A/	Multi-ethnic White: *n*=395 South and South East Asian: *n*=46 Black African: *n*=38	51.5 ± 9.5	SFA, MUFA, low fat, carbohydrate (CHO).	RCT: 4-week reference diet (~18% SFA, 12% MUFA, 38% total fat, 45% CHO) followed by 1 of 3 diets: a MUFA diet (~10% SFA, 20% MUFA, 38% total fat, 45% CHO); a low fat diet (~10% SFA, 11% MUFA, 28% total fat, 55% CHO); or the reference diet for 24 weeks.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Walker et al. (2011) [249]
C>T/In9 (rs289714) (G > A / G > C)	C/	Canadian Sedentary men (12 pairs of monozygotic twins): *n*=24	21 ± 2.0	Overfeeding.	Overfeeding by 1000Kcal per day, 6 days per week for a period of 100 days.	TC, HDL, LDL, VLDL, TG, HDL_2 and HDL_3,	None of the SNP-diet interactions were statistically significant.	Terán-García et al. (2008) [240]

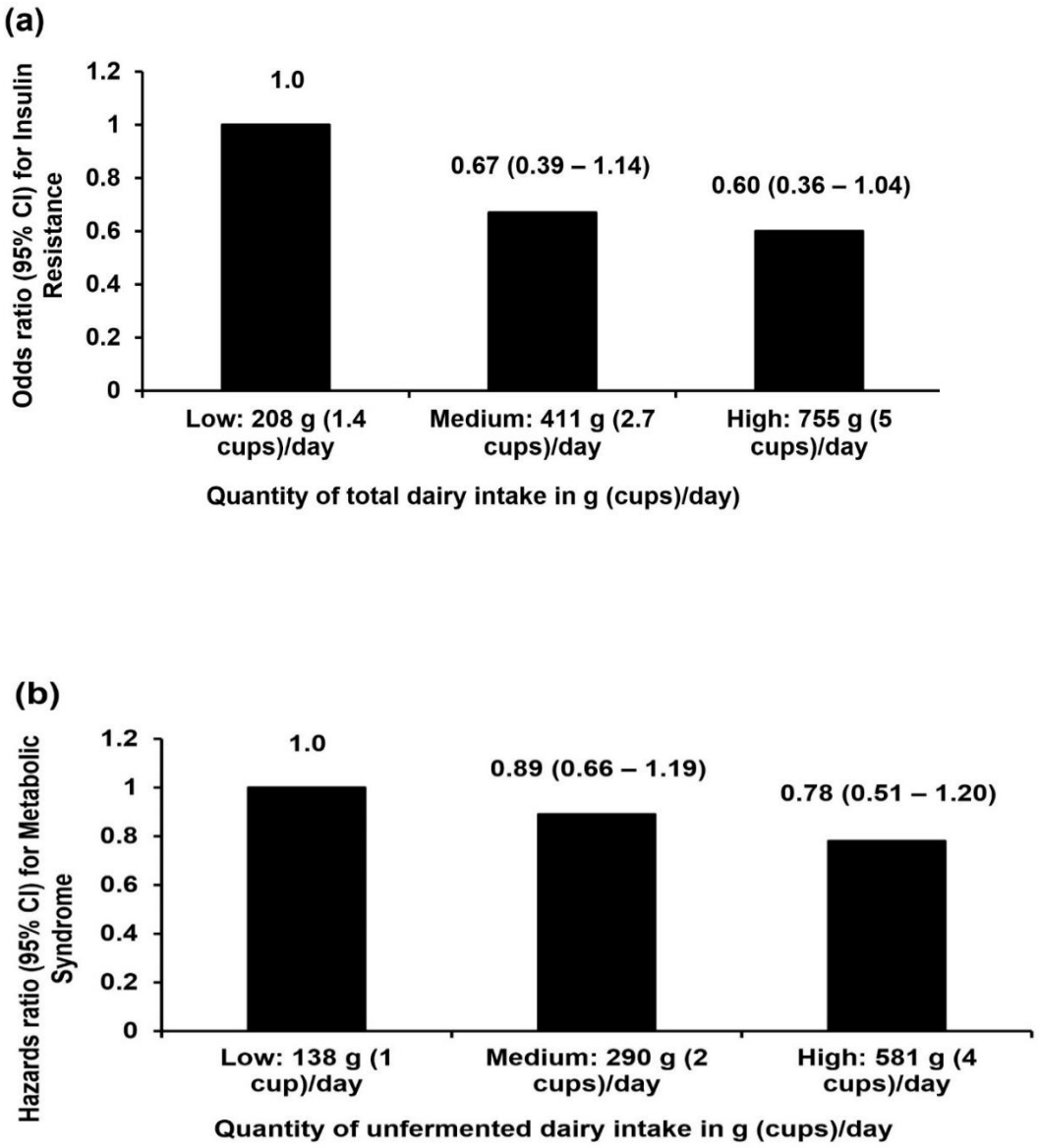
SNP (Nucleotide Change)[a]	Minor Allele/ Effect Allele	Ethnicity & Sample Size	Age (Years)	Dietary Factor	Intervention	Lipid Trait Examined	Results for Interaction[b]	References
rs173539 (C > T)	T/	Multi-ethnic White: *n*=395 South and South East Asian: *n*=46 Black African: *n*=38	51.5 ± 9.5	SFA, MUFA, low fat, carbohydrate (CHO).	RCT: 4-week reference diet (~18% SFA, 12% MUFA, 38% total fat, 45% CHO) followed by 1 of 3 diets: a MUFA diet (~10% SFA, 20% MUFA, 38% total fat, 45% CHO); a low fat diet (~10% SFA, 11% MUFA, 28% total fat, 55% CHO); or the reference diet for 24 weeks.	TC, HDL, LDL and TG	None of the SNP-diet interactions were statistically significant.	Walker et al. (2011) [249]

Appendix E4 - **Supplementary Figure S3.1** Selection of participants from the Chennai Urban Rural Epidemiological Study (CURES)



Supplementary Figure S3.1 A flow chart showing the selection of participants from the Chennai Urban Rural Epidemiological Study (CURES)

Appendix E5 - Supplementary Figure S3.2 Dairy intake and insulin resistance/metabolic syndrome



Supplementary Figure S3.2 Dairy intake and insulin resistance/metabolic syndrome

(a): The association of total dairy intake with insulin resistance in the Chennai urban adults. Model adjusted for age (years), sex, income, weight (kg), alcohol, energy (kcal), added sugar(g), total fat(g), saturated fatty acid (g), tea and coffee intake.

(b): Unfermented dairy intake and its association with Metabolic Syndrome. Data presented as median. Adjusted variables are age (years), sex, BMI, income, smoking, alcohol, major cooking oil, total poly unsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level, total energy (kcal), tea and coffee intake.

Appendix E6 - Supplementary Table S3.1 Tea and coffee consumption and its association with components of cardiometabolic risk

	Hazards Ratio (95% Confidence Interval)		
	Lowest intake	***Medium intake***	***Highest intake***
Tea and coffee (g/day) ***Milk (g/day) in the tea/coffee*** Serving in cup	170 (219) ***85*** 3/4 cups	470 (144) ***235*** 2.5 cups	1176(470) ***588*** 5 cups
Blood pressure (mmHg) ≥ 140/90	1 (ref)	0.84(0.65 – 1.07)	0.60(0.39 – 0.91)*
BMI (kg/m^2) ≥ 22.9	1 (ref)	0.78(0.59 – 1.03)	0.56(0.36 – 0.88)*
Waist circumference (cm) (> 80: F; > 90: M)	1 (ref)	0.91(0.76 – 1.09)	0.81(0.62 – 1.07)
Total cholesterol (> 200 mg/dL)	1 (ref)	0.63(0.44 – 0.90)	0.57(0.34 – 0.95)*
Triglyceride (> 150 mg/dL)	1 (ref)	0.73(0.54 – 0.99)*	0.60(0.38 – 0.93)*
High density lipoprotein (mg/dL) (≤ 40: F; ≤ 50: M)	1 (ref)	0.86(0.70 – 1.06)	0.77(0.55 – 1.08)
Low density lipoprotein (> 100 mg/dL)	1 (ref)	0.80(0.66 – 0.97)*	0.77(0.58 – 1.03)
Fasting plasma glucose (> 100 mg/dL)	1 (ref)	0.90(0.69 – 1.17)	1.02(0.69 – 1.50)

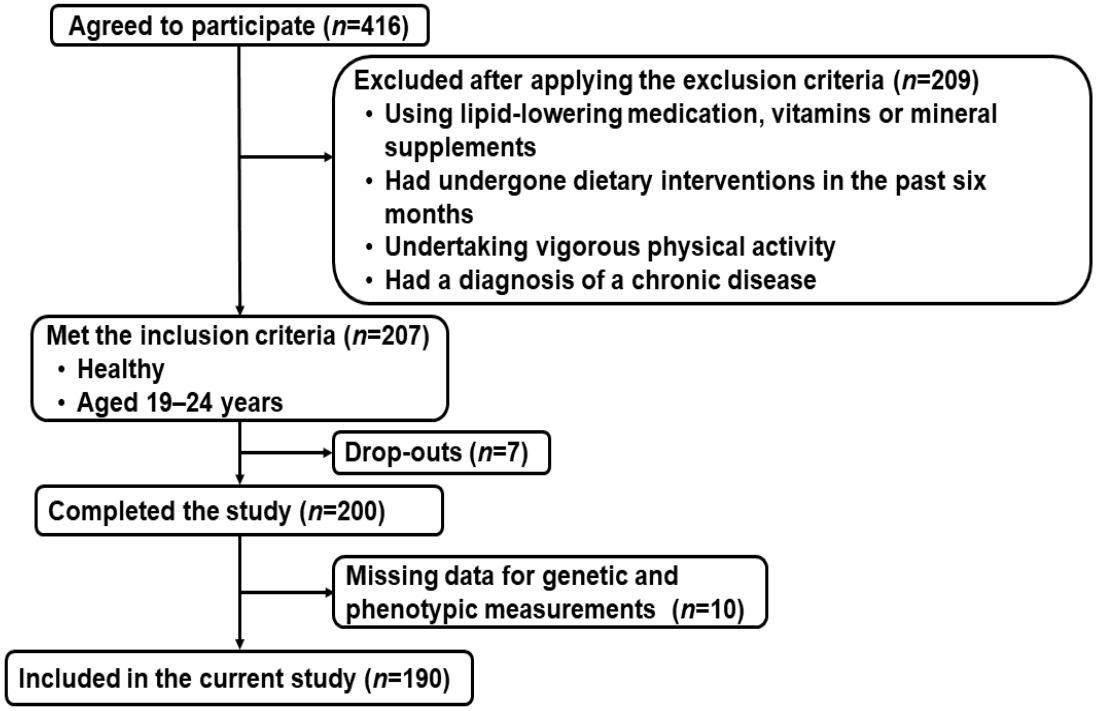
Data presented as median (interquartile range). **P*-value<0.05 considered as significant. Adjusted variables are age, sex, BMI, income, smoking, alcohol, major cooking oil, total poly unsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level, and total energy (kcal).

Appendix E7 - Supplementary Table S4.1 Allele frequencies and Hardy-Weinberg Equilibrium *P*-value (*n*=190)

Gene & SNP	Genotype Count	Allele Frequency in this study (%)	Hardy-Weinberg Equilibrium *P*-value
CETP rs3764261	GG = 107 GT = 70 TT = 13	G = 75 T = 25	0.74
GCKR rs1260326	CC = 82 CT = 81 TT = 27	C = 64 T = 36	0.34
LIPG rs7241918	TT = 150 TG = 36 GG = 4	T = 88 G = 12	0.30
SORT1 rs629301	TT = 117 TG = 59 GG = 14	T = 77 G = 23	0.10
LIPC rs1532085	GG = 67 GA = 91 AA = 32	G = 59 A = 41	0.91
APOA1 rs964184	CC = 115 CG = 68 GG = 7	C = 78 G = 22	0.43
ATP2B1 rs2681472	AA = 134 AG = 53 GG = 3	A = 84 G = 16	0.38

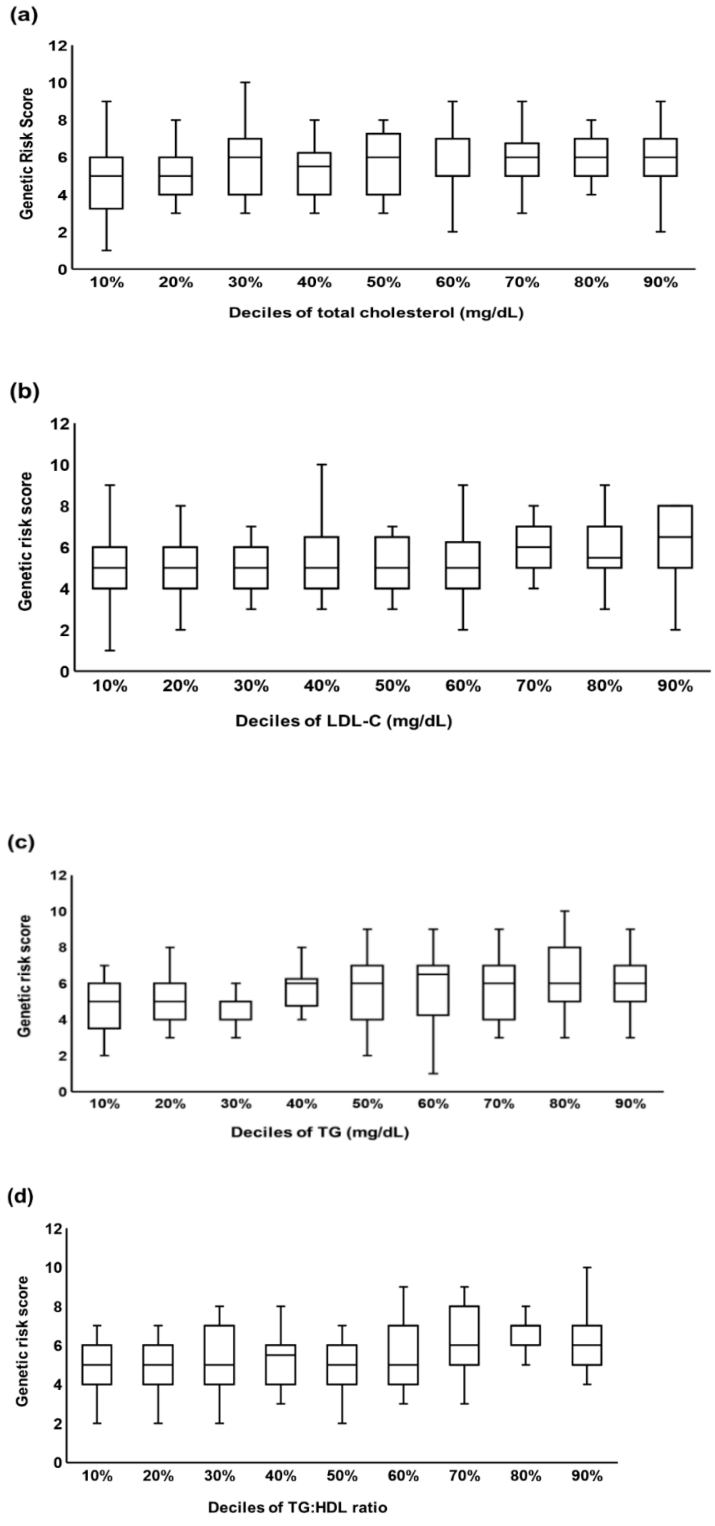
SNP – single nucleotide polymorphism; *CETP* – cholesteryl ester transfer protein; *GCKR* – glucokinase regulator; *LIPG* – endothelial lipase; *SORT1* – sortilin 1; *LIPC* – hepatic lipase; *APOA1* – apolipoprotein A1; *ATP2B1* – ATPase plasma membrane Ca2+ transporting 1.

Appendix E8 - Supplementary Figure S4.1 Selection of participants from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) cross-sectional study



Supplementary Figure S4.1 A flow chart showing the selection of participants from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) cross-sectional study.

Appendix E9 - Supplementary Figure S4.2 The distribution of the GRS across deciles of TC, LDL-C, TG and TG:HDL ratio



Supplementary Figure S4.2 The distribution of the GRS across deciles of TC, LDL-C, TG and TG:HDL ratio.

Section 1: Search strings

Appendix E10 - Supplementary Table S5.1 Number of hits and search strings per database

Search engine/database	Search string	Nº of HITS
Web of Science	Genetic*(all fields) and interaction*(all fields) and diet* (all fields) and Latin (all fields)	34
	Gene*(all fields) AND interact*(all fields) AND Caribbean (all fields) AND diet*(all fields)	47
	Genetic*(all fields) AND interact*(all fields) AND latin*(all fields) AND physical*(all fields)	25
	Gene*AND interact* AND caribbean AND physical*	12
	gene (All fields) and interaction (All fields) and haiti (All fields)	4
	gene (All fields) and interaction (All fields) and Cuba (All fields)	126
	gene (All fields) and interaction (All fields) and Dominican (All fields)	37
	gene (All fields) and interaction (All fields) and Jamaica (All fields)	70
	gene (All fields) and interaction (All fields) and Trinidad (All fields)	94
	gene (All fields) and interaction (All fields) and Bahamas (All fields)	16
	gene (All fields) and interaction (All fields) and Barbados (All fields)	17
	gene (All fields) and interaction (All fields) and Saint Lucia (All fields)	574
	gene (All fields) and interaction (All fields) and Grenada (All fields)	20
	gene (All fields) and interaction (All fields) and Grenadines (All fields)	1
	gene (All fields) and interaction (All fields) and Antigua and Barbuda (All fields)	0
	gene (All fields) and interaction (All fields) and Dominica (All fields)	10
	gene (All fields) and interaction (All fields) and Saint Kitts & Nevis (All fields)	0
	gene (All fields) and interaction (All fields) and Mexico (All fields)	3,116
	gene (All fields) and interaction (All fields) and Guatemala (All fields)	24
	gene (All fields) and interaction (All fields) and Honduras (All fields)	19
	gene (All fields) and interaction (All fields) and Nicaragua (All fields)	11
	gene (All fields) and interaction (All fields) and Salvador (All fields)	405

	gene (All fields) and interaction (All fields) and costa rica (All fields)	125
	gene (All fields) and interaction (All fields) and Panama (All fields)	145
	gene (All fields) and interaction (All fields) and Belize (All fields)	8
	gene (All fields) and interaction (All fields) and Brazil (All fields)	5,344
	gene (All fields) and interaction (All fields) and colombia (All fields)	571
	gene (All fields) and interaction (All fields) and argentina (All fields)	1,621
	gene (All fields) and interaction (All fields) and peru (All fields)	139
	gene (All fields) and interaction (All fields) and venezuela (All fields)	131
	gene (All fields) and interaction (All fields) and chile (All fields)	1,061
	gene (All fields) and interaction (All fields) and Ecuador (All fields)	106
	gene (All fields) and interaction (All fields) and bolivia (All fields)	29
	gene (All fields) and interaction (All fields) and paraguay (All fields)	33
	gene (All fields) and interaction (All fields) and uruguay (All fields)	229
	gene (All fields) and interaction (All fields) and guyana (All fields)	8
	gene (All fields) and interaction (All fields) and suriname (All fields)	2
PubMed	(((genetic*) AND (interaction*)) AND (diet*)) AND (latin)	45
	(gene-diet interaction) AND (latin*)	8
	(((genetic*) AND (interaction*)) AND (nutrient)) AND (Caribbean)	7
	(((genetic*) AND (interaction*)) AND (nutrient)) AND (latin)	16
	(((genetic*) AND (interaction*)) AND (physical)) AND (latin)	18
	(gene-nutrient interaction) AND (latin*)	3
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Puerto Rico"[Title/Abstract]	18
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Falkland"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Montserrat"[Title/Abstract]	0

	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Anguilla"[Title/Abstract]	15
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "British Virgin Islands"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Caicos"[Title/Abstract]	1
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Cayman Islands"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Caribbean Netherlands"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Maarten"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Aruba"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Curaçao"[Title/Abstract]	2
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Guiana"[Title/Abstract]	3
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Martinique"[Title/Abstract]	1
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Guadeloupe"[Title/Abstract]	4
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Suriname"[Title/Abstract]	0
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Guyana"[Title/Abstract]	3
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Uruguay"[Title/Abstract]	6
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Paraguay"[Title/Abstract]	1
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Bolivia"[Title/Abstract]	3
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Ecuador"[Title/Abstract]	4

	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Chile"[Title/Abstract]	18
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Venezuela"[Title/Abstract]	9
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Peru"[Title/Abstract]	11
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Argentina"[Title/Abstract]	19
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Colombia"[Title/Abstract]	22
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Brazil"[Title/Abstract]	126
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Belize"[Title/Abstract]	2
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Panama"[Title/Abstract]	7
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Costa Rica"[Title/Abstract]	14
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "salvador"[Title/Abstract]	13
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Honduras"[Title/Abstract]	4
	"gene"[Title/Abstract] AND "interaction"[Title/Abstract] AND "Guatemala "[Title/Abstract]	6
	((gene) AND (interaction)) AND (latin)	210
	((((polymorphism OR gene OR SNP OR single nucleotide polymorphism OR genetic variation OR genetic variant) AND ("gene-diet interaction" OR "diet-gene interaction" OR SNP-diet interaction OR diet-SNP interaction OR "gene-nutrient interaction" OR "nutrient-gene interaction" OR "gene-lifestyle interaction" OR "gene-environment interaction")) AND (carbohydrate OR protein OR fat OR fibre OR sugar OR SFA OR saturated fat OR monounsaturated fat OR polyunsaturated fat OR MUFA OR PUFA OR Mediterranean diet OR Nordic diet OR B12 OR vitamin D OR amino acids OR polyphenols OR egg intake OR caffeine	1,948

	intake OR green tea OR alcohol intake OR meat intake OR energy intake OR physical activity level OR social factors OR socioeconomic)) AND (Obesity OR weight OR BMI OR waist circumference OR waist hip ratio OR hip circumference OR adiposity OR diabetes OR fasting glucose OR insulin OR HbA1c OR cardiovascular disease OR coronary heart disease OR ischaemic heart disease OR stroke OR lipids OR HDL OR LDL OR VLDL OR total cholesterol OR triglycerides OR triacylglycerol OR blood lipids OR serum lipids OR metabolic syndrome)) AND (Latin American OR Caribbean OR Haiti OR Cuba OR Dominican Republic OR Jamaica OR Trinidad and Tobago OR Bahamas OR Barbados OR Saint Lucia OR Grenada OR St. Vincent and Grenadines OR Antigua and Barbuda OR Dominica OR Saint Kitts & Nevis OR Mexico OR Guatemala OR Honduras OR Nicaragua OR El Salvador OR Costa Rica OR Panama OR Belize OR Brazil OR Colombia OR Argentina OR Peru OR Venezuela OR Chile OR Ecuador OR Bolivia OR Paraguay OR Uruguay OR Guyana OR Suriname OR Guadeloupe OR Martinique OR French Guiana OR Curacao OR Aruba OR Sint Maarten OR Caribbean Netherlands OR Cayman Islands OR Turks and Caicos OR British Virgin Islands OR Anguilla OR Montserrat OR Falkland Islands OR Puerto Rico OR U.S. Virgin Islands)"	
Science Direct	Title, abstract, keywords: genetic AND interaction AND diet AND latin	6
	Title, abstract, keywords: gene-diet interaction AND latin	5
	Title, abstract, keywords: gene AND interaction AND latin	29
	Title, abstract, keywords: gene AND interaction AND caribbean	22
SciELO	(ab:(*genetic)) AND (ab:(interaction)) AND (ab:(latin))	7
	(ab:(gen)) AND (ab:(interaccion))	74
	(ab:(*genetic)) AND (ab:(interaction)) AND (ab:(caribbean))	3
Scopus	(ALL (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (latin*))	771
	(ALL (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (caribbean*))	414
	(ALL (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (diet*) AND TITLE-ABS-KEY (latin))	133

	(ALL (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (haiti))	9
	(ALL (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (cuba))	89
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Dominican Republic))	32
	(ALL (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (jamaica))	46
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Trinidad and Tobago))	27
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Bahamas))	27
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Barbados))	19
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Saint Lucia))	2
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Grenada))	8
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (St. Vincent & Grenadines))	0
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Antigua and Barbuda))	0
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Dominica))	24
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Saint Kitts & Nevis))	0
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Mexico))	1242
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Guatemala))	55
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Honduras))	26
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Nicaragua))	25
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (El Salvador))	110

	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Costa Rica))	154
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Panama))	160
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Belize))	32
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Brazil))	2238
	(ALL (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Colombia))	297
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction*) AND TITLE-ABS-KEY (argentina))	204
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Peru))	88
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Venezuela))	61
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Chile))	177
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Ecuador))	63
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Bolivia))	26
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Paraguay))	17
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Uruguay))	35
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Guyana))	9
	(TITLE-ABS-KEY (gene) AND TITLE-ABS-KEY (interaction) AND TITLE-ABS-KEY (Suriname))	5
Taylor & Francis Online	[Abstract: gene] AND [All: interaction] AND [All: latin]	733
MEDLINE (EBSCOhost)	AB gene AND AB interact AND AB latin	0
	AB gene AND AB interact AND AB caribbean	0
Cochrane trails	gene in Title Abstract Keyword AND "interaction" in Title Abstract Keyword AND "Latin" in Title Abstract Keyword - (Word variations have been searched)	7
	gene in Title Abstract Keyword AND "interaction" in Title Abstract Keyword AND	1

	"caribbean" in Title Abstract Keyword - (Word variations have been searched)	
ERIC (EBSCOhost)	AB gene AND AB interact AND AB latin	0
LILACS	gen [Palavras do resumo] and interacción [Palavras do resumo]	77
	interação [Palabras del resumen] and obesidade [Palabras del resumen]	114
	interação [Palabras del resumen] and genética [Palabras del resumen] and diabetes [Palabras del resumen]	23
	interação [Palabras del resumen] and genética [Palabras del resumen] and cardiovascular [Palabras del resumen]	33
IBECS	gen AND interacción	80
Google Scholar	genetic* interaction latin* "gene-interaction"	4,472

Section 2: Risk of bias assessment

Appendix E11 - Appraisal tool for Cross-sectional studies (AXIS)

Introduction

1. Were the aims/ Objectives of the study clear?

Methods

2. Was the study design appropriate for the stated aim(s)?
3. Was the sample size justified?
4. Was the target/reference population clearly defined? (Is it clear who the research was about?
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?
7. Were measures undertaken to address and categorize non-responders?
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?
9. Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialled, piloted or published previously? (Only dietary, nutritional, physical activity assessment were evaluated)
10. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., p-values, CIs)
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?

Results

12. Were the basic data adequately described?
13. Does the response rate raise concerns about non-response bias?
14. If appropriate, was information about non-responders described?
15. Were the results internally consistent?
16. Were the results for the analyses described in the methods, presented?

Discussion

17. Was the author´s discussion and conclusions justified by the results?
18. Were the limitations of the study discussed?
19. Were there any funding sources or conflicts that may affect the authors interpretations of the results?
20. Was ethical approval or consent of participants attained?

Appendix E12 - Supplementary Table S5.2 Summary outcome of assessment with the Appraisal Tool for Cross-Sectional Studies (AXIS)

	Vilella et al 2017	Young et al 2016	Valadez et al, 2020	Campos et al, 2000	Andrade et al 2010	Corella et al, 2009	Brown et al 2003	Ma et al, 2014	Lai et al 2010	Zheng et al 2014	Prieto et al 2019	Davis et al. 2010	Dumitrescu et al 2012	Oliveira et al 2017	Ramos-Lopez et al 2019	Paula et al 2010,	Schreiber et al 2013	Alsulami et al 2021	Oki et al 2017	Norde et al 2016,	Torres-Sánchez et al 2006	Hidalgo et al 2011	Fujii et al 2019	Tellechea et al 2009	Barcelos et al 2015	Campos-Perez et al 2020	Carvalho et al 2019	Fiegenbaum et al 2003	Fiegenbaum et al 2007	Garcia-Garcia et al 2014	Giovanella et al 2020	Norde et al 2018	Ochoa-Martinez et al	Ochoa-Martinez et al	Oki et al 2016
1)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5)	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	N	Y	Y	Y	Y	Y	Y
7)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8)	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9)	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y
11)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
13)	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
14)	N	Y	Y	Y	Y	Y	Y	y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15)	Y	Y	Y	Y	-	Y	Y	y	Y	-	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
16)	Y	Y	Y	Y	Y	Y	Y	y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
17)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
19)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
20)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Note: Numbered questions are listed apart.

Continuation of Supplementary Table S5.2

		Study 1	Orozco et al 2014	Muñoz et al 2017	Yu et al 2017	Alathari et al 2022	Dominguez-Rey et	Costa-Urrutia et al	Todendi et al 2021	Freire et al 2017	Sehn et al 2022	Mattei et al 2011	Mattei et al 2009	Surendran et al	Ma et al 2012
	Introduction														
1)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Methods														
2)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Results														
12)		N	N	N	N	N	N	N	N	N	N	N	N	N	N
13)		-	-	-	-	-	-	-	-	-	-	-	-	-	-
14)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
16)		N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Discussion														
17)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19)		N	N	N	N	N	N	N	N	N	N	N	N	N	N
20)		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Note: Numbered questions are listed apart.

Appendix E13 - Supplementary Table S5.3 Assessment with the Comments Appraisal Tool for Cross-Sectional Studies

	Introduction	**Method**										**Results**					**Discussion**			
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
Vilella et al. (2017)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
8. 24-h diet recall and global BMI values to establish percentiles in which participants were fixed into are both measures leading to bias **13**. > 5 % of the data were measing																				
Young et al. (2016)	Y	N	Y	N	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y
2. No methodology available in full text **4.** Only characteristics "Latino children and adults" **5**. N/A **8**. Physical activity was measured via a dichotomic question																				
Andrade et al. (2010)	Y	Y	Y	Y	Y	**N**	Y	Y	Y	**N**	Y	Y	N	Y	Y	Y	Y	Y	N	Y
6. In Brazil has the highest admixture index in the world an only European ancestry population were included. **10**. Not clarified in the methods																				
Ma et al. (2014)	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y
5. Subgroup representing a minority **9.** Food frequency questionnaire not adapted to the subgroup´s gastronomic culture																				
Zheng et al. (2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	-	Y	Y	Y	N	Y
15. Data available in graphs not in tables hence consistency of results was no possible to determine																				
Davis et al. (2010)	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y
4. Samples from other studies, brief description, "Hispanic children and adolescents" **5**. The sample was taken from protocols and measures conducted by a third party during the past 6 years. **6.** Hispanic children recruited from schools, community centers, health clinics, health fairs via word of mouth, flyers and in-person contact.																				
Barcelos et al. (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y
18. No limitations were discussed																				

Note: Questions are listed above, **Table S5.2** summarises **Table S5.3**.

Appendix E14 - Supplementary Table S5.4 Assessment using the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I)

ROBINS-I assessment	**1.1 Is there potential for confounding of the effect of exposure in this study? If N or PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered Y / PY / PN / N**
Smith et al 2008	PN
[Description]	"Dietary intake was assessed using a FFQ that was designed for and tested in this population". "The interactions were tested with control for potential confounders including age, sex, alcohol (never, past, current), smoking (never, past, current), physical activity, diabetes medications, and dietary fibre".
Smith et al 2013	PN
[Description]	"The modified FFQ, which includes foods commonly consumed by Hispanics and open-ended portion sizes, more accurately estimated nutrients and energy intake in older Hispanics than the original FFQ based on its improved correlation with dietary recall data" "The interactions were tested with control for potential confounders including age, sex, alcohol intake (g/d), smoking (current vs. never and former), physical activity, antiglycemic medication, and ancestral admixture."
Moon et al 2017	PN
[Description]	"Conducted various sensitivity analyses and subgroup analyses. Used a DXA and measured weight to the nearest 0.1kg.
Portillo et al 2022	PN
[Description]	Dietary questionnaire "applied by previously trained personnel" "Adjusted for possible confounders: adjusted for: age, sex, BMI, waist circumference, physical activity, schooling, socioeconomic level, smoking, consumptions: fruit, vegetables, sugar, processed meats, alcoholic beverages and % Amerindian ancestry"
Torres Sánchez et al 2014	PN
[Description]	Uses a validated questionnaire carried out by trained personnel, and the methodology is being replicated from 2 other studies. "The following known risk factors for foetal development were selected as potential confounders: maternal age (years), height (cm), education (years), paid occupation (yes/no), parity (none/1–2) and body mass index during the first trimester of pregnancy (kg/m2) and usage of vitamin supplements during pregnancy." "After adjusting separately for potential confounding variables in each model and correcting by bootstrap resampling..."

Horta et al 2018	PN
[Description]	Used DXA and stadiometer with accuracy, visceral and subcutaneous abdominal fat thickness were estimates with ultrasound. WC was measured twice. It acknowledges possible confounders and adjusts.
Guevara-Cruz et al 2014	PN
[Description]	Methodology explained thoroughly . Nutritionist assigned for the follow up. Analysis stratified and visible in tables.
Lopez-Ortiz et al 2016	PN
[Description]	"Dietary evaluations were carried out using 24-h recall questionnaires and 3-d dietary records, and these were applied to evaluate 2 weekdays and 1 weekend day using standardised measures of food portions; the information was collected by direct interview." "We compared changes in end points across genotype groups according to diet groups at 8 weeks. To assess the effects of genotype, dietary treatment and their interaction, we used a general linear model (GLM) repeated-measures analysis, and age was included in the model as a covariate."
Sir-Petermann et al 2004	PN
[Description]	Pre-established protocol, and clear inclusion and exclusion criteria,
Prieto et al 2016	PN
[Description]	Use of previously used and validated scale “lifestyle cardiovascular risk score (LCRS)”. Clear adjustment in analysis “We examined interaction and joint associations for each component of the LCRS separately and controlling for each other (i.e., adjusted for the other lifestyles in the LCRS).
Yang et al 2007	PN
[Description]	“Trained personnel visited all study participants”. “Generalized linear models adjusted for age, sex, body mass index, and physical activity were used to report the relationship between plasma lipid levels, saturated fat intake, and *APOE* genotype”.
Ruiz-Narvaez et al 2007	PN
[Description]	“Trained personnel visited all study participants at their homes for data collection, biological specimen collection, and anthropometric measurements.”
Hartiala et al 2012	PN

[Description]	Study that aims to replicate previous observations by another study. "Trained personnel visited all study participants at their homes for data collection". Use of fully adjusted model including age, sex, county of residence, % of total energy from fat, smoking, household income, history of diabetes, hypertension, or hypercholesteremia, obesity, and family history of MI.
Zheng et al 2016	PN
[Description]	Clear aim. Use of culturally adapted food-frequency questionnaire (FFQ) "FFQ that was developed and validated specifically for the Costa Rican population". Clear assessment of covariates plus transparency in statistical analysis.
Cornelis et al 2007	PN
[Description]	Clear objective, description of cases and matched controlled. Transparency in statistical analysis, and adjustment for confounding variables. Besides use of trained personnel and closed ended questionnaires: " All data were collected by trained fieldworkers during an interview using 2 questionnaires consisting of closed-ended questions"
Sen-Banerjee et al 2000	PN
[Description]	Clear purpose of the study, description of cases and controls, inclusion and exclusion criteria, transparency in statistical analysis, and adjustment for covariates. However, data sources from self-reported diabetes and hypertension, but it was validated using standardized definitions.
Costa-Urrutia et al 2017	PN
[Description]	Clear aim, inclusion and exclusion criteria, transparent statistical analysis and adjusted for covariates. Furthermore, pre-established power calculations.
Guevara-Cruz et al 2013	PN
[Description]	Clear aim, inclusion and exclusion criteria, transparent statistical analysis and adjustment for covariates, consideration of limitations in the study "the determination of only a single gene polymorphism and the subjects participating in this study belong to a specific ethnic group"
Nascimento et al 2018	PN
[Description]	Appropriate methods for aim, clear inclusion and exclusion criteria, adjustment for covariates and transparent statistical test, consideration of limitations "This study was limited to analysis of the biochemical variable sin these individuals, some of the, were analysed in a previous study that was limited to anthropometric variable analysis."
Nascimento et al 2019	PN
[Description]	Clear study design. Nevertheless, the small sample size may have influenced the identification of minor effects.

Cornelis et al 2004	PN									
[Description]	Clear aim and study design. Inclusion of univariate and multivariate analysis with adjustment for confounding variables.									
El-Sohemy et al 2007	PN									
[Description]	Case-control study clear inclusion and exclusion criteria, appropriate study design, adjustment for confounding variables, and use of validated and culturally adapted FFQ									
	1.1 Is there potential for confounding of the effect of exposure in this study? If N or PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered Y / PY / PN / N	If Y/PY to 1.1, answer 2.1 and 1.3 to determine whether there is a need to assess time-varying confounding:	**1.2. If Y or PY to 1.1: Was the analysis based on splitting, follow up time according to exposure received?**	If N or PN to 1.2, answer questions 1.4 to 1.6, which relate to baseline confounding	**1.3. If Y or PY to 1.2: Were exposure discontinuations or switches likely to be related to factors that are prognostic for the outcome?**	If N or PN to 1.3, answer questions 1.4 to 1.6, which relate to baseline confounding	Bias in selection of participants into the study	**2.1. Was selection of participants into the study (or into the analysis) based on variables measured after the start of the exposure?**	If N or PN to 2.1 go to 2.4	**2.4 Do start of follow-up and start of exposure coincide for most participants?**
Correa et al 2013	**PY**		**Y**		**Y**			**N**		**PY**
[Description]	No established calibration of instruments, however rigorous methods for estimating alcohol consumption.				"Completers, lost because of drop out, lost because of death" and it was measuring alcohol intake. Deaths and drop out could have been related.					"The baseline cohort population consisted of all residents aged ≥60 years on 1 January 1997, who were identified by means of a complete census of the town."

Appendix E15 - Supplementary Table S6.1 Allele frequencies and Hardy-Weinberg Equilibrium *P*-value (*n*=497)

Gene & SNP	**Genotype Count**	**Allele Frequency in this study (%)**	**Hardy-Weinberg Equilibrium *P*-value**
CETP rs4783961	GG = 152 GA = 241 AA = 104	G = 55 A = 45	0.64
LPL rs327	TT = 286 TG = 190 GG = 21	T = 77 G = 23	0.13
LPL rs3200218	AA = 407 AG = 83 GG = 7	A = 90 G = 10	0.25
LPL T93G (rs1800590)	TT = 480 TG = 17 GG = 0	T = 98 **G = 2**	0.70
LPL rs268	GG = 472 GA = 25 AA = 0	G = 97 **A = 3**	0.57

Values in bold have a minor allele frequency less than 5%. SNP – single nucleotide polymorphism; *CETP* – cholesteryl ester transfer protein; *LPL* – lipoprotein lipase.

Appendix E16 - Supplementary Table S6.2 Association of GRS with blood lipids, blood pressure and obesity-related traits

Trait	Mean ± Standard Deviation		*P* value
	GRS<2 (*n*=239)	GRS≥2 (*n*=258)	
BMI (kg/m^2)	24.3 ± 1.2	24.0 ± 1.2	0.70[a]
Waist circumference (cm)	87.1 ± 1.1	86.3 ± 1.1	0.65[a]
Waist hip ratio	0.90 ± 1.10	0.90 ± 1.10	0.73[b]
Systolic BP (mmHg)	121.3 ± 1.2	119.3 ± 1.2	0.51[b]
Diastolic BP (mmHg)	74.8 ± 1.2	74.4 ± 1.2	0.93[b]
HDL (mg/dL)	41.1 ± 1.3	41.4 ± 1.3	0.92[b]
LDL (mg/dL)	114.1 ± 1.3	114.7 ± 1.3	0.81[b]
TG (mg/dL)	138.4 ± 1.8	130.9 ± 1.8	0.43[b]
Total cholesterol (mg/dL)	188.2 ± 1.2	186.7 ± 1.2	0.74[b]

GRS – genetic risk score; BMI – body mass index; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; TG – triglycerides. *P* values were obtained from linear regression analysis using log-transformed variables.

[a] *P* values adjusted for age, sex, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake.

[b] *P* values adjusted for age, sex, BMI, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake. Log-transformed variables were used for the analysis.

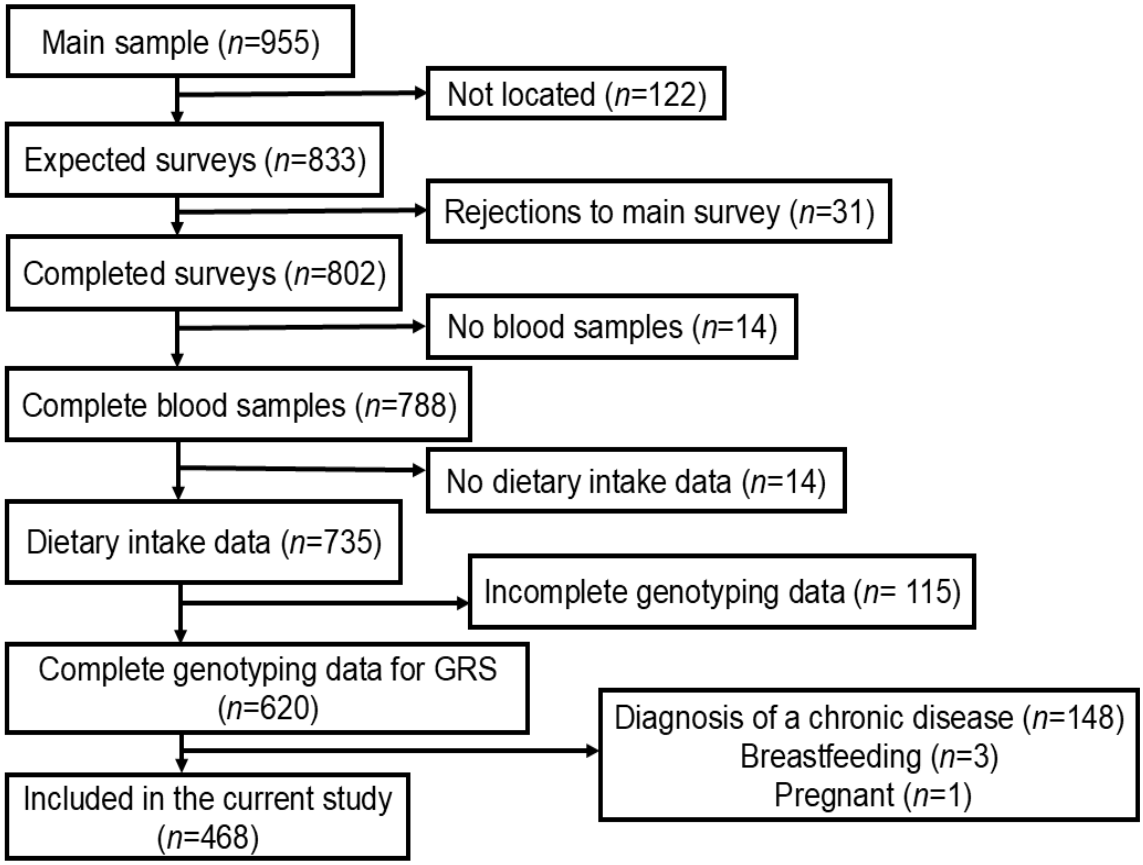
Appendix E17 - Supplementary Table S6.3 Association of GRS with obesity

Trait	Odds ratio (95% C.I)	*n*		*P* value
		GRS<2	GRS≥2	
Common obesity	1.34 (0.89 – 2.01)	214	236	0.16
Central obesity	1.20 (0.81 – 1.80)	227	248	0.37

GRS – genetic risk score.

P values were obtained from logistic regression analysis, adjusted for age, sex, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake. Log-transformed variables were used for the analysis.

Appendix E18 - Supplementary Figure S7.1 Selection of participants from the Study of Obesity, Nutrition, Genes and Social factors (SONGS)



Supplementary Figure S7.1 A flow chart showing the selection of participants from the Study of Obesity, Nutrition, Genes and Social factors (SONGS)

GRS, genetic risk score.

Data from the younger cohort living in imminently urban areas from the Children of the Millennium study which was collected between the months of July and October 2022 was used for this study. **Supplementary Figure S7.1** shows how the main sample of young people used in this study was obtained. Out of a sample of 833 participants, 96% of them consented to participate in the main survey and about 95% of the respondents consented to the various components of the laboratory survey, including taking anthropometric measurements, blood samples and blood pressure measurement.

Appendix E19 - Supplementary Table S7.1 Single nucleotide polymorphisms included in the GRS and the reported traits by genome-wide association (GWA) studies

SNP	Gene name	Gene Symbol	Chromosome Location	Location of SNP	Alleles Risk/Other	Traits	GWA Study
rs1558902	*Alpha-ketoglutarate dependent dioxygenase*	*FTO*	16:53769662	Intronic	A/T	HDL-C, BMI, HC, WC, HbA1c and obesity	Locke et al. (2015) [8] Ligthart et al., (2016) [622] Tachmazidou et al. (2017) [623] Wheeler et al. (2017) [624] Scherag et al. (2010) [625]
rs13021737	*Transmembrane protein 18*	*TMEM18*	2:632348	Intergenic	G/A	BMI	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Hoffmann et al. (2018) [627] Justice et al. (2017) [628] Pulit et al. (2019) [629] Koskeridis et al. (2022) [352]
rs6567160	*Melanocortin 4 receptor*	*MC4R*	18:60161902	Upstream	C/T	HDL-C, TG, WHR, T2D, BMI	Locke et al. (2015) [8] Pulit et al. (2019) [629] Vujkovic et al. (2020) [631] Martin et al. (2021) [7] Mahajan et al. (2018) [630]

rs10938397	*Glucosamine-6-phosphate deaminase 2*	*GNPDA2*	4:45180510	Intergenic	G/A	HDL-C, LDL-C, BMI, WC, obesity	Locke et al. (2015) [8] Martin et al. (2021) [7] Berndt et al. (2013) [401] Shungin et al. (2015) [632]
rs543874	*SEC16 homolog B, endoplasmic reticulum export factor*	*SEC16B*	1:177920345	Upstream	G/A	HDL-C, BMI, HC, WHR	Locke et al. (2015) [8] Pulit et al. (2019) [629] Koskeridis et al. (2022) [352] Shungin et al. (2015) [632] Huang et al. (2022) [633]
rs7138803	*BCDIN3 domain containing RNA*	*BCDIN3D*	12:49853685	Intergenic	A/G	HDL-C, BMI, HC, WHR, obesity	Locke et al. (2015) [8] Pulit et al. (2019) [629] Koskeridis et al. (2022) [352] Berndt et al. (2013) [401] Shungin et al. (2015) [632]
rs2207139	*Transcription factor AP-2 beta*	*TFAP2B*	6:50877777	Intergenic	G/A	BMI	Locke et al. (2015) [8] Justice et al. (2017) [628] Koskeridis et al. (2022) [352] Berndt et al. (2013) [401]
rs3101336	*Neuronal growth regulator 1*	*NEGR1*	1:72285502	Intronic	C/T	BMI	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Hoffmann et al. (2018) [627] Justice et al. (2017) [628]

							Pulit et al. (2019) [629]
rs10182181	*Adenylate cyclase 3*	*ADCY3*	2:24927427	Intergenic	G/A	BMI	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Hoffmann et al. (2018) [627] Winker et al. (2015) [634]
rs1516725	*ETS variant transcription factor 5*	*ETV5*	3:186106215	Intronic	C/T	BMI	Locke et al. [8] Akiyama et al. (2017) [626] Berndt et al. (2013) [401] Graham et al. (2021) [5]
rs2287019	*Glutaminyl-peptide cyclotransferase like*	*QPCTL*	19:45698914	Intronic	C/T	LDL-C, TC, SBP, BMI, WC, WHR,	Locke et al. (2015) [8] Pulit et al. (2019) [629] Shungin et al. (2015) [632] Lee et al. (2022) [635]
rs12446632	*G protein-coupled receptor class C group 5 member B*	*GPRC5B*	16:19924067	Intergenic	G/A	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Berndt et al. (2013) [401]
rs3817334	*Mitochondrial carrier 2*	*MTCH2*	11:47,607,569	Intronic	T/C	BMI	Akiyama et al. (2017) [626] Hoffman et al. (2018) [627] Huang et al. (2022) [633] Winker et al. (2015) [634] Speliotes et al. (2010) [754]

rs2112347	*POC5 centriolar protein*	*POC5*	5:75719417	Upstream	T/G	HDL-C, LDL-C, TG BMI, WC, HC, WHR, body fat percentage	Locke et al. (2015) [8] Pulit et al. (2019) [629] Martin et al. (2021) [7] Shungin et al. (2015) [632]
rs16951275	*Mitogen-activated protein kinase 5*	*MAP2K5*	15:67784830	Intronic	T/C	BMI	Locke et al. (2015) [8] Justice et al. (2017) [628] Wood et al. (2016) [636]
rs3810291	*zinc finger CCCH-type containing 4*	*ZC3H4*	19:47065746	3 prime UTR	A/G	HDL-C, TG, BMI, WC, T2D, HC	Locke et al. (2015) [8] Martin et al. (2021) [7] Mahajan et al. (2018) [630] Shungin et al. (2015) [632]
rs12566985	*FPGT-TNNI3K readthrough*	*FPGT-TNNI3K*	1:74536509	Intronic	G/A	BMI	Locke et al. (2015) [8] Felix et al. (2022) [637]
rs10968576	*Leucine rich repeat and Ig domain containing 2*	*LINGO2*	9:28414341	Intronic	G/A	HDL-C, BMI, WC	Locke et al. (2015) [*8*] Koskeridis et al. (2022) [352] Huang et al. (2022) [633] Liu et al. (2017) [638]
rs12286929	*Cell adhesion molecule 1*	*CADM1*	11:115151684	Intergenic	G/A	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Pulit et al. (2019) [629]
rs12885454	*Protein kinase D1*	*PRKD1*	14:29267632	Exonic	C/A	BMI, WC	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Shungin et al. (2015) [632]

							Huang et al. (2022) [633]
rs657452	*AGBL carboxypeptidase 4*	*AGBL4*	1:49124175	Intronic	A/G	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627] Koskeridis et al. (2022) [352]
rs11165643	*Polypyrimidine tract binding protein 2*	*PTBP2*	1:96458541	Intergenic	T/C	BMI, body fat percentage	Locke et al. (2015) [8] Akiyama et al. (2017) [626] Koskeridis et al. (2022) [352] Martin et al. (2021) [7]
rs758747	*NLR family CARD domain containing 3*	*NLRC3*	16:3577357	5 prime UTR	T/C	BMI	Locke et al. (2015) *[8]* Hoffman et al. (2018) [627]
rs10132280	*Syntaxin binding protein 6*	*STXBP6*	14:25458973	Intergenic	C/T	BMI, WC, HC, WHR	Locke et al. (2015) [8] Pulit et al. (2019) [629] Shungin et al. (2015) [632] Graff et al. (2017) [639]
rs1167827	*Huntingtin interacting protein 1*	*HIP1*	7:75533848	3 prime UTR	G/A	BMI	Locke et al. (2015) [8] Huang et al. (2022) [633]
rs13078960	*Cell adhesion molecule 2*	*CADM2*	3:85758440	Intronic	G/T	BMI	Locke et al. (2015) [*8*]
rs12401738	*Far upstream element binding protein 1*	*FUBP1*	1:77981077	Intronic	A/G	BMI	Locke et al. (2015) [*8*] Winkler et al. 2015 [634]
rs12429545	*Olfactomedin 4*	*OLFM4*	13:53528071	Intronic	A/G	BMI, WC	Akiyama et al. (2017) [626] Justice et al. (2017) [628]

							Shungin et al. (2015) [632]
rs16851483	*RAS p21 protein activator 2*	*RASA2*	3:141556594	Intronic	T/G	BMI	Locke et al. (2015) [8] Pulit et al. (2019) [629]
rs17094222	*Hypoxia inducible factor 1 subunit alpha inhibitor*	*HIF1AN*	10:100635683	Intergenic	C/T	BMI	Locke et al. (2015) [*8*] Huang et al. (2022) [633]
rs17405819	*Hepatocyte nuclear factor 4 gamma*	*HNF4G*	8:75894349	Intergenic	T/C	BMI	Hoffman et al. (2018) [627] Pulit et al. (2019) [629] Graff et al. (2017) [639]
rs1928295	*Toll like receptor 4*	*TLR4*	9:117616205	Intergenic	T/C	BMI	Locke et al. (2015) [8] Koskeridis et al. (2022) [352]
rs7141420	*Neurexin 3*	*NRXN3*	14:79433111	Intronic	T/C	BMI, obesity	Locke et al. (2015) [8] Berndt et al. (2013) [401]
rs205262	*Inflammation and lipid regulator with UBA-like and NBR1-like domains*	*C6orf106*	6:34595387	Intronic	G/A	BMI	Locke et al. (2015) [8]
rs2365389	*Fragile histidine triad diadenosine triphosphatase*	*FHIT*	3:61250788	Intronic	C/T	BMI	Locke et al. (2015) [8] Huang et al. (2022) [633]
rs2820292	*Neuron navigator 1*	*NAV1*	1:201815159	Intronic	C/A	BMI	Locke et al. (2015) [8]
rs4256980	*Tripartite motif containing 66*	*TRIM66*	11:8652392	Intronic	G/C	BMI	Locke et al. (2015) [8] Pulit et al. (2019) [629]
rs7599312	*Erb-b2 receptor tyrosine kinase 4*	*ERBB4*	2:212548507	Regulatory region	G/A	BMI	Locke et al. (2015) [8] Tachmazidou et al. (2017) [623]
rs9925964	*Lysine acetyltransferase 8*	*KAT8*	16:31118574	Splice region	A/G	BMI	Locke et al. (2015) [8] Hoffman et al. (2018) [627]

Abbreviations: SNP – single nucleotide polymorphism; GRS – genetic risk score; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; TC – total cholesterol; SBP – systolic blood pressure; HbA1c – glycated haemoglobin; BMI – body mass index; WC – waist circumference; WHR – waist-hip ratio; HC – hip circumference; T2D – type 2 diabetes; UTR – untranslated region.

Appendix E20 - Supplementary Table S7.2 Allele frequencies and Hardy-Weinberg Equilibrium *P*-value (*n*=468)

Gene & SNP	**Genotype Count**	**Allele Frequency in this study (%)**	**Hardy-Weinberg Equilibrium *P*-value**
FTO rs1558902	TT = 402 TA = 63 AA = 3	T = 93 A = 7	0.76
TMEM18 rs13021737	GG = 384 GA = 79 AA = 5	G = 90 A = 10	0.68
MC4R rs6567160	TT = 417 TC = 49 CC = 2	T = 94 C = 6	0.66
GNPDA2 rs10938397	AA = 193 GA = 201 GG = 74	A = 63 G = 37	0.08
SEC16B rs543874	AA = 292 GA = 148 GG = 28	A = 78 G = 22	0.12
BCDIN3D rs7138803	GG = 348 GA = 116 AA = 4	G = 87 A = 13	0.09
TFAP2B rs2207139	AA = 134 GA = 222 GG = 112	A = 52 G = 48	0.29
NEGR1 rs3101336	CC = 230 CT = 189 TT = 49	C = 69 T = 31	0.28
ADCY3 rs10182181	AA = 321 GA = 130 GG = 17	A = 82 G = 18	0.40
QPCTL rs2287019	CC = 422 TC = 46 TT = 0	C = 95 T = 5	0.26
GPRC5B rs12446632	GG = 453 AG = 15 AA = 0	G = 98 A = 2	0.72
MTCH2 rs3817334	TT = 166 CT = 215 CC = 87	T = 58 C = 42	0.24
POC5 rs2112347	TT = 142	G = 55	0.79

	TG = 229 GG = 97	T = 45	
MAP2K5 rs16951275	CC = 261 CT = 171 TT = 35	C = 74 T = 26	0.34
ZC3H4 rs3810291	GG = 170 GA = 227 AA = 71	G = 61 A = 39	0.74
FPGT-TNNI3K rs12566985	GG = 243 AG = 177 AA = 48	G = 71 A = 29	0.07
LINGO2 rs10968576	AA = 285 GA = 160 GG = 23	A = 78 G = 22	0.93
CADM1 rs12286929	GG = 137 GA = 228 AA = 103	A = 54 G = 46	0.66
PRKD1 rs12885454	CC = 316 CA = 136 AA = 16	C = 82 A = 18	0.77
AGBL4 rs657452	GG = 149 GA = 217 AA = 102	G = 55 A = 45	0.17
PTBP2 rs11165643	TT = 272 TC = 161 CC = 35	T = 75 C = 25	0.11
NLRC3 rs758747	CC = 351 TC = 105 TT = 12	C = 86 T = 14	0.23
STXBP6 rs10132280	CC = 280 AC = 159 AA = 29	A = 77 C = 23	0.32
HIP1 rs1167827	AA = 318 AG = 130 GG = 20	A = 82 G = 18	0.16
FUBP1 rs12401738	GG = 195 AG = 211 AA = 62	G = 64 A = 36	0.68
OLFM4 rs12429545	GG = 147 AG = 226 AA = 95	A = 56 G = 44	0.63
RASA2 rs16851483	GG = 141 TG = 229 TT = 98	G = 55 T = 45	0.78

CADM2 rs13078960	TT = 432 GT = 35 GG = 1	T = 96 G = 4	0.74
HIF1AN rs17094222	TT = 242 CT = 188 CC = 38	C = 72 T = 28	0.86
HNF4G rs17405819	TT = 207 CT = 214 CC = 47	T = 67 C = 33	0.44
TLR4 rs1928295	TT = 245 CT = 183 CC = 40	T = 72 C = 28	0.39
NRXN3 rs7141420	TT = 284 TC = 162 CC = 22	T = 78 C = 22	0.84
C6orf106 rs205262	AA = 381 GA = 81 GG = 6	A = 90 G = 10	0.48
FHIT rs2365389	TT = 366 TC = 93 CC = 9	T = 88 C = 12	0.28
NAV1 rs2820292	AA = 251 CA = 176 CC = 41	A = 72 T = 28	0.21
TRIM66 rs4256980	GG = 190 GC = 223 CC = 55	G = 64 C = 36	0.39
ERBB4 rs7599312	GG = 378 AG = 87 AA = 3	G = 90 A = 10	0.40
KAT8 rs9925964	AA = 133 GA = 232 GG = 103	A = 53 G = 47	0.92
ETV rs1516725	CC = 423 CT = 45	C = 95 T = 5	0.27

SNP – single nucleotide polymorphis; *FTO* – alpha-ketoglutarate-dependent dioxygenase; *TMEM18* – transmembrane protein 18; *MC4R* – melanocortin 4 receptor; *GNPDA2* – glucosamine-6-phosphate deaminase 2; *SEC16B* – SEC16 homolog B, endoplasmic reticulum export factor; *BCDIN3D* – BCDIN3 domain containing RNA methyltransferase; *TFAP2B* – transcription factor AP-2 beta; *NEGR1* – neuronal growth regulator 1; *ADCY3* – adenylate cyclase 3; *QPCTL* – glutaminyl-peptide cyclotransferase like; *GPRC5B* – G protein-coupled receptor class C group 5 member B; *MTCH2* – mitochondrial carrier 2; *POC5* –

centriolar protein; *MAP2K* – mitogen-activated protein kinase 5; *ZC3H4* – zinc finger CCCH-type containing 4; *FPGT-TNNI3K* – FPGT-TNNI3K readthrough; *LINGO2* – leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 2; *CADM1* – cell adhesion molecule 1; *PRKD1* – protein kinase D1; *AGBL4* – AGBL carboxypeptidase 4; *PTBP2* – polypyrimidine tract binding protein 2; *NLRC3* – NLR family CARD domain containing 3; *STXBP6* – syntaxin binding protein 6; *HIP1* – Huntingtin interacting protein 1; *FUBP1* – far upstream element binding protein 1; *OLFM4* – olfactomedin 4; *RASA2* – RAS p21 protein activator 2; *HIF1AN* – hypoxia inducible factor 1 subunit alpha inhibitor; *HNF4G* – hepatocyte nuclear factor 4 gamma; *TLR4* – toll like receptor 4; *NRXN3* – neurexin 3; *ILRUN* or *C6orf106* – inflammation and lipid regulator with UBA-like and NBR1-like domains; *FHIT* – fragile histidine triad diadenosine triphosphatase; *NAV1* – neuron navigator 1; *TRIM66* – tripartite motif containing 66; *ERBB4* – erb-b2 receptor tyrosine kinase 4; *KAT8* – lysine acetyltransferase 8; and *ETV5* – ETS variant transcription factor 5.

Appendix E21 - Supplementary Table S7.3 Association of GRS with cardiometabolic traits

Trait	Mean ± SE		
	GRS≤37 risk alleles (*n*=228)	**GRS>37 risk alleles (*n*=240)**	***P* value**
HDL-C (mmol/L)	1.02 ± 1.02	1.04 ± 1.02	0.634
LDL-C (mmol/L)	1.88 ± 1.02	1.89 ± 1.02	0.851
TAG (mmol/L)	0.97 ± 1.03	0.93 ± 1.03	0.368
TC (mmol/L)	3.45 ± 1.02	3.45 ± 1.02	0.993
SBP (mmHg)	102.95 ± 1.01	103.28 ± 1.01	0.693
DBP (mmHg)	66.03 ± 1.01	66.47 ± 1.01	0.512
Fasting glucose (mmol/L)	4.32 ± 0.05	4.44 ± 0.05	0.103
Fasting insulin (pmol/L)	51.75 ± 1.03	53.23 ± 1.03	0.550
HbA1c (%)	5.43 ± 1.00	5.43 ± 1.00	0.829
BMI (kg/m^2)	23.81 ± 1.01	24.00 ± 1.01	0.599
WC* (cm)	80.52 ± 1.01	80.61 ± 1.01	0.919

P values were obtained from linear regression analysis with adjustment for sex, family history of diabetes, smoking status, physical activity level, and BMI wherever appropriate. Log-transformed variables were used for the analysis (except fasting glucose) and values in bold represent significant associations. 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.

*The number of participants with data for waist circumference was 457.

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NUTRITION (K. PETERSEN, SECTION EDITOR)

A Nutrigenetic Update on *CETP* Gene–Diet Interactions on Lipid-Related Outcomes

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Abstract

Purpose of Review An abnormal lipid profile is considered a main risk factor for cardiovascular diseases and evidence suggests that single nucleotide polymorphisms (SNPs) in the cholesteryl ester transfer protein (*CETP*) gene contribute to variations in lipid levels in response to dietary intake. The objective of this review was to identify and discuss nutrigenetic studies assessing the interactions between *CETP* SNPs and dietary factors on blood lipids.

Recent Findings Relevant articles were obtained through a literature search of PubMed and Google Scholar through to July 2021. An article was included if it examined an interaction between *CETP* SNPs and dietary factors on blood lipids. From 49 eligible nutrigenetic studies, 27 studies reported significant interactions between 8 *CETP* SNPs and 17 dietary factors on blood lipids in 18 ethnicities. The discrepancies in the study findings could be attributed to genetic heterogeneity, and differences in sample size, study design, lifestyle and measurement of dietary intake. The most extensively studied ethnicities were those of Caucasian populations and majority of the studies reported an interaction with dietary fat intake. The rs708272 (TaqIB) was the most widely studied *CETP* SNP, where 'B1' allele was associated with higher *CETP* activity, resulting in lower high-density lipoprotein cholesterol and higher serum triglycerides under the influence of high dietary fat intake.

Summary Overall, the findings suggest that *CETP* SNPs might alter blood lipid profiles by modifying responses to diet, but further large studies in multiple ethnic groups are warranted to identify individuals at risk of adverse lipid response to diet.

Keywords Cholesteryl ester transfer protein · Polymorphisms · Diet · Lipids · Genetic Epidemiology

Background

The global burden of cardiovascular diseases (CVDs) is well recognised and ischaemic heart disease alone accounted for 9 million deaths in 2019, making it the top cause of death in all parts of the world [1]. An abnormal lipid profile (dyslipidaemia), indicated by low concentrations of high-density lipoprotein cholesterol (HDL) and elevated levels of low-density lipoprotein cholesterol (LDL) or triglycerides (TG), is considered a major risk factor for CVDs [2, 3]. The cardioprotective role of HDL is thought to be dependent on the function of HDL rather than the levels of HDL, which is reflected in individuals with scavenger receptor class B member 1 (*SCARB1*) gene mutations who have higher levels of HDL but higher CVD risk [4]. There is evidence to suggest that a combination of genetic susceptibility and environmental factors including diet is responsible for CVDs [5••, 6, 7]. Single nucleotide polymorphisms (SNPs) in lipid-related genes such as the cholesteryl ester transfer protein (*CETP*), lipoprotein lipase (*LPL*) and apolipoprotein E (*ApoE*) genes have been found to contribute to changes in lipid profiles in response to diet [8, 9, 10•]. Of these three genes, *CETP* has been shown to have more associations with blood lipids (Supplemental Table 1). *CETP* regulates the concentration and particle size of HDL cholesterol in the plasma (Fig. 1) and is considered to play an important role in reverse cholesterol transport which is a protective mechanism against atherosclerosis [11]. Increased *CETP* activity has been shown to result in lower HDL levels and is linked to higher risk of CVDs [12].

Several studies have demonstrated *CETP*–diet interactions on blood lipids; however, the findings have been

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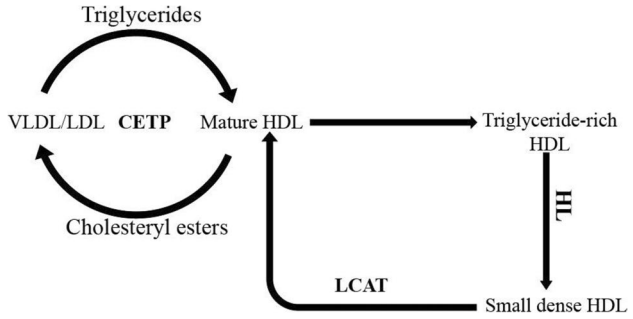

Fig. 1 The role of cholesteryl ester transfer protein in lipid metabolism

inconsistent [10•, 13–17]. The objective of this review was therefore to identify and discuss studies assessing the interactions between *CETP* SNPs and dietary factors on blood lipids and to identify the factors that can be attributed to these discrepancies.

Cholesteryl ester transfer protein (*CETP*) is a plasma glycoprotein which is secreted by the liver and is responsible for transporting cholesteryl esters and triglycerides between HDL and apolipoprotein B–containing lipoproteins such as very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) [18]. HDL is formed from lipid-free apolipoprotein A1 (ApoA1) in a process involving the removal of free cholesterol from peripheral tissues and the subsequent esterification of some of the free cholesterol into cholesteryl esters via the actions of adenosine triphosphate binding cassette transporter A1 and lecithin:cholesterol acyltransferase (LCAT) [11]. The enrichment of HDL with triglycerides makes it a substrate for hepatic lipase (HL) which then hydrolyses the triglycerides, resulting in dissociation of the lipid-free ApoA1 and a decrease in size of the HDL particle, forming small-dense HDL [18].

Materials and Methods

Selection of the Candidate Gene for the Review

To identify candidate genes which have been reported by genome-wide association (GWA) studies to influence blood lipid levels, a literature search was undertaken in December 2020, using the following keywords: (genome-wide association study OR genome-wide association scan OR genome-wide association analysis OR GWAS OR GWA) AND (Lipids OR HDL OR LDL OR VLDL OR total cholesterol OR triglycerides OR triacylglycerol OR blood lipids). The results showed that, out of 32 identified studies (Supplemental Table 1), 20 GWA studies reported statistically significant associations between *CETP* and lipids [19–38], while *LPL* was reported by 18 GWA studies [19, 20, 22, 24, 25, 28, 29, 31–41] and *APOE* was reported by 10 GWA studies [22, 24, 25, 27, 29, 30, 32, 33, 34, 37]. *CETP* was then chosen for the review as it had the highest number of hits compared to *LPL* and *APOE*.

Study identification

To identify published articles, a literature search was undertaken using PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Google Scholar (https://scholar.google.com/). The search covered the earliest date of indexing through to July 2021. For PubMed, the following key terms were used: (CETP OR cholesteryl ester transfer protein) AND (polymorphism OR gene OR SNP OR single nucleotide polymorphism OR genetic variation OR genetic variant OR rs3764261 OR rs1532624 OR rs1800775 OR rs9989419 OR rs4783961 OR rs708272 OR rs7499892 OR rs2303790 OR rs16965220 OR rs247616 OR rs289708 OR rs12708980 OR rs247617 OR rs173539) AND ('gene-diet interaction' OR 'diet-gene interaction' OR 'SNP-diet interaction' OR 'diet-SNP interaction' OR 'gene-nutrient interaction' OR 'nutrient-gene interaction') AND (carbohydrate OR protein OR fat OR fibre OR sugar OR SFA OR MUFA OR PUFA OR Mediterranean diet OR Nordic diet OR B12 OR amino acids OR polyphenols OR egg intake OR caffeine intake OR green tea OR alcohol intake OR meat intake) AND (lipids OR HDL OR LDL OR VLDL OR total cholesterol OR triglycerides OR triacylglycerol OR blood lipids OR serum lipids). The key terms for Google Scholar were (CETP AND 'gene-diet interaction' AND lipids). Only studies published in English were included.

Study Selection

The search strategies above yielded a total of 448 articles from the two databases (227 from PubMed and 221 from Google Scholar) as shown in Fig. 2. Titles of all the studies were first read to determine their relevance to the topic. Full-text of those found to be relevant were then read in detail to determine eligibility for inclusion. The criteria for inclusion in the review were as follows: gene–diet interaction studies involving *CETP* gene polymorphisms and blood lipids. Only studies conducted in humans were included and, after applying the inclusion and exclusion criteria, 49 articles were found to be eligible, of which one article was published as an abstract. The studies excluded after reading the full-text were those focusing on interaction between *CETP* and physical activity on lipids; gene–diet interaction on lipids not including *CETP*; and gene–diet interaction review articles. Full-text of 48 eligible studies was read in detail and the results were extracted for analysis (Supplemental Tables 2 and 3). The results of one study [42] which was published as an abstract were also extracted and included in

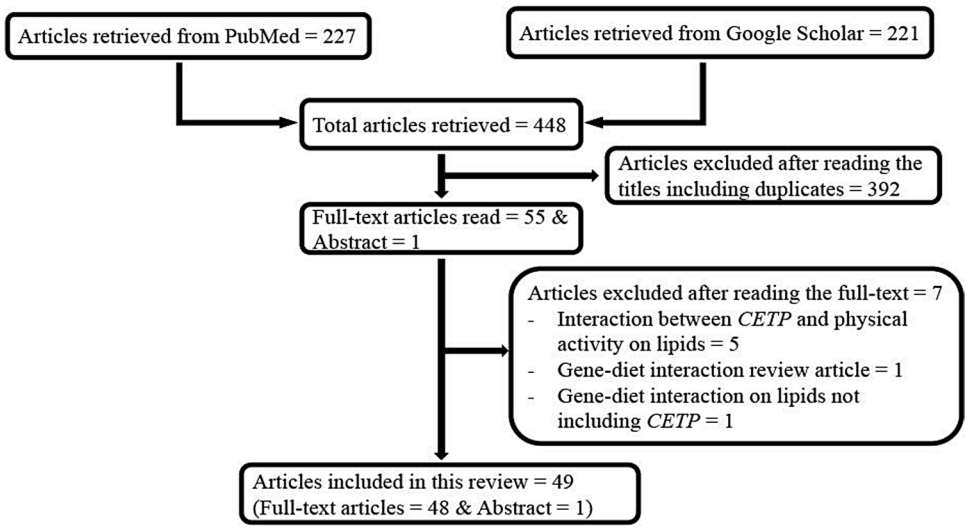

Fig. 2 Flowchart of studies identified in the literature for *CETP*–diet interaction on lipids

the tables. The studies consisted of 28 observational studies (Supplemental Table 2) and 21 interventional studies (Supplemental Table 3).

Data Extraction

The studies were identified by a single investigator and the following data were double-extracted independently by one reviewer: first author, publication year, location or ethnicity of participants, sample size, mean age, study design, reference SNP (rs) ID, genotype and minor allele. Corresponding authors were contacted to provide additional information where needed.

Results of Database Search

This section reviews studies examining the interaction between dietary factors and *CETP* SNPs on blood lipids. The rs708272 (TaqIB), the most widely studied *CETP* SNP, was investigated by 31 studies. The second most studied SNP was rs5882 (I405V), accounting for 16 studies. The *CETP* SNPs rs3764261 and rs1800775 were each examined by 6 studies. All the studies were conducted in adults except for one study which was carried out in prepubertal children [43]. The ethnicities covered by the studies included British, White American, Spanish, Mexican, Chinese and Iranian as shown in Fig. 3. A wide range of dietary factors were investigated by the 28 observational studies, and these included dietary carbohydrate, protein, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), coffee, sucrose, total energy intake and alcohol consumption. The 21 dietary intervention studies also focused on a variety of diets including Mediterranean diet, plant sterol ester, sesame oil, canola oil and rapeseed oil.

TaqIB (SNP rs708272 G > A)

The major allele ('G') is also called the 'B1' allele while the minor allele ('A') is also referred to as the 'B2' allele. Eight out of seventeen observational studies reported a significant association between TaqIB genotypes, dietary factors and blood lipids. In a cross-sectional study involving 129 Iranian patients with type 2 diabetes (T2D) without dyslipidaemia [15], a higher intake of total fat (>34.9% from total energy intake) was associated with higher HDL in participants with 'B1B1' genotype (mean HDL (mg/dl) for high total fat intake (>34.9% from total energy) vs low total fat intake (≤ 34.9% from total energy) = 58.6 ± 4.1 vs 36.5 ± 6.5; $P_{\text{interaction}} = 0.02$). Those with 'B2B2' genotype who had a higher intake of total fat (>34.9% from total energy) also had higher HDL (mean HDL (mg/dl) for high total fat intake (>34.9% from total energy) vs low total fat intake (≤ 34.9% from total energy) = 59.0 ± 4.2 vs 55.8 ± 3.3) but the interaction was more pronounced in individuals with 'B1B1' genotype, while in those with 'B1B2' genotype, the interaction was not observed. A prospective cohort study of 603 men with T2D in the USA (96% of whom were white) [13] on the other hand reported that a higher intake of total fat (>33.5% from total energy intake), animal fat (>19.9% from total energy intake), SFA (>11.47% from total energy intake) and MUFA (>12.75% from total energy intake) was associated with lower HDL in participants with 'B1B1' genotype compared to those with 'B2B2' genotype (mean HDL (mg/dl) for low total fat intake (≤ 33.5% of energy) vs high total fat intake (>33.5% of energy): 40.0 ± 0.03 vs 36.2 ± 0.02 for 'B1B1', 41.5 ± 0.03 vs 44.9 ± 0.03 for 'B2B2', $P_{\text{interaction}} = 0.003$; mean HDL (mg/dl) for low animal fat intake (≤ 19.9% of energy) vs high animal fat intake (>19.9% of energy): 39.7 ± 0.02 vs 36.2 ± 0.03 for 'B1B1', 42.2 ± 0.04 vs 43.5 ± 0.03 for 'B2B2', $P_{\text{interaction}}$

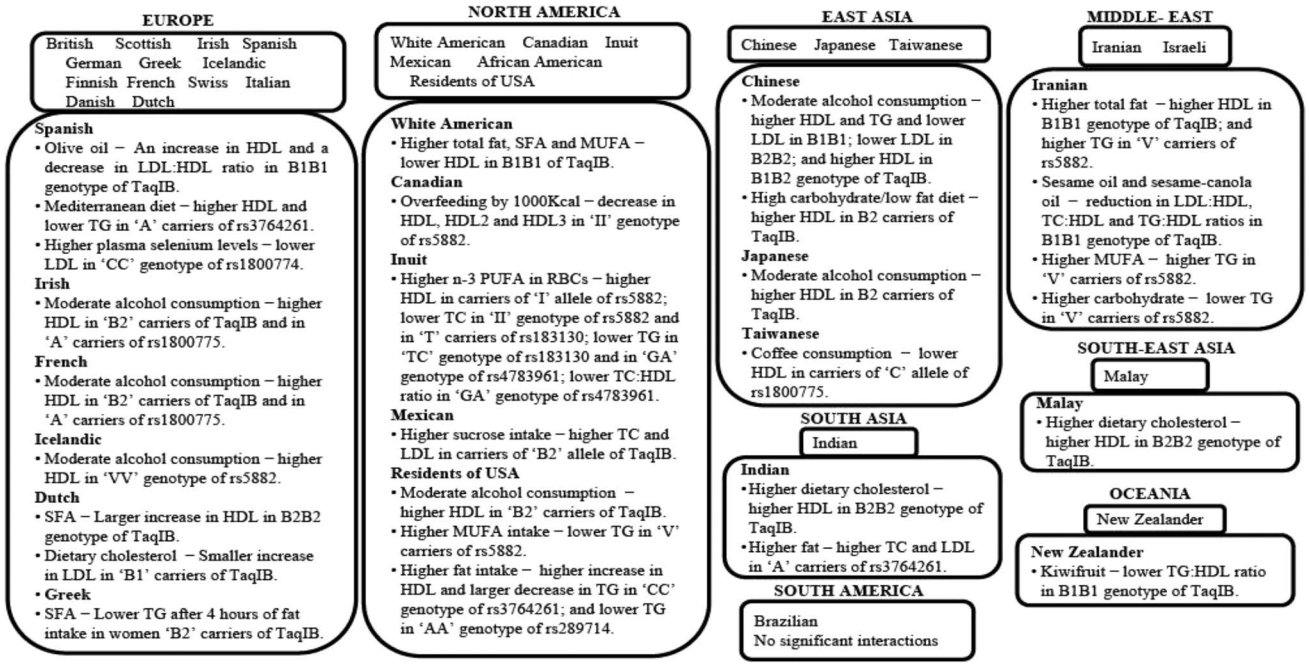

Fig. 3 *CETP*–diet interaction studies and the interaction findings in multiple ethnicities

= 0.02; mean HDL (mg/dl) for low SFA intake (≤ 11.47% of energy) vs high SFA intake (>11.47% of energy): 39.8 ± 0.02 vs 36.2 ± 0.03 for 'B1B1', 42.2 ± 0.04 vs 43.8 ± 0.03 for 'B2B2', $P_{\text{interaction}}$ = 0.02; mean HDL (mg/dl) for low MUFA intake (≤ 12.75% of energy) vs high MUFA intake (>12.75% of energy): 39.3 ± 0.03 vs 36.5 ± 0.02 for 'B1B1', 41.9 ± 0.03 vs 44.2 ± 0.03 for 'B2B2', $P_{\text{interaction}}$ = 0.04). The difference in the findings might be due to the type of fat consumed since the Iranian study only considered total fat intake while the American study investigated types of fat. Furthermore, the variation in frequency of the TaqIB SNP might also contribute to the difference in the findings. In the Iranian study [15], only 8 out of 127 normolipidemic individuals had the 'B1B1' genotype, but in the American study [13] 192 out of 603 participants had the 'B1B1' genotype. Thus, while these two studies were both conducted in patients with T2D, there is a wide variation in frequency of the 'B1B1' genotype between the two studies and this affects the interpretation of the findings. In an animal study performed in feral adult male St. Kitts vervet monkeys (*Cercopithecus aethiops sabeus*) [44], SFA was shown to increase CETP activity, thereby reducing HDL levels which might explain the findings of the study in the American population [13]. However, in the animal study [44], the effect of SFA on CETP activity was only observed when cholesterol was added to the diet. SFA has also been shown to lower the number of LDL receptors in the liver, which slows the removal of apolipoprotein B (ApoB)–containing lipoproteins [45], with the resulting effect of a decrease in HDL levels. It has also been demonstrated that the effect of dietary fat on *CETP* expression is not dependent solely on the composition of fat, but also on the amount of fat [46], although the mechanisms under which total fat affects *CETP* expression are still unclear [15]. A cross-sectional study of 2858 Chinese participants, 761 Malay participants and 588 Asian Indian participants [17] demonstrated that participants with 'B2B2' genotype had a significantly higher increase in HDL in response to a higher intake of dietary cholesterol compared to those with 'B1B1' and 'B1B2' genotypes, but the interaction was only significant in Asian Indians ($P_{\text{interaction}}$ = 0.0230) and Malays ($P_{\text{interaction}}$ = 0.0460). A cross-sectional study of 215 Mexican-Mestizos [47] also showed that a higher sucrose intake (≥ 5% of total energy per day) was linked to increased levels of total cholesterol and LDL in individuals with 'B1B2'/'B2B2' genotype compared to those with 'B1B1' genotype (mean total cholesterol (mg/dl) (95% confidence interval): 200.19 (184.79–215.60) vs 165.55(142.21–188.89), $P_{\text{interaction}}$ = 0.0340; mean LDL (mg/dl) (95% confidence interval): 128.64 (113.59–143.69) vs 99.29 (75.52–123.05), $P_{\text{interaction}}$ = 0.0370). As this study [47] was the only one which investigated sucrose intake, and considering that the sample size was 215, further studies are needed to corroborate these findings.

Several studies have investigated the interaction between alcohol intake and TaqIB genotype on HDL, LDL and TG [48–51]. In a cross-sectional study of 758 healthy Chinese participants [48], individuals with 'B1B1' genotype who consumed any amount of alcohol

had higher HDL (mean HDL (mmol/l): 2.09 ± 0.46 vs 1.94 ± 0.38; $P_{interaction} < 0.01$), higher TG (mean TG (mmol/l): 1.42 ± 2.71 vs 0.94 ± 0.36; $P_{interaction} < 0.05$) and lower LDL (mean LDL (mmol/l): 2.24 ± 0.65 vs 2.65 ± 3.01; $P_{interaction} < 0.01$) compared to those with 'B1B1' genotype who did not drink alcohol. Those with 'B1B2' genotype who consumed any amount of alcohol also had higher HDL (mean HDL (mmol/l): 2.17 ± 0.55 vs 2.02 ± 0.50; $P_{interaction}<0.05$) compared to individuals with 'B1B2' genotype who did not drink alcohol; and lower TG (mean TG (mmol/l): 1.01 ± 0.86 vs 1.42 ± 2.71; $P_{interaction}<0.05$) compared to those with 'B1B1' who consumed any amount of alcohol. There were no significant interactions between alcohol intake and TG or HDL in participants with 'B2B2' genotype. This study also observed that 'B2B2' individuals who drank any amount of alcohol had lower LDL than 'B2B2' participants who did not drink alcohol (mean LDL in mmol/l: 2.20 ± 0.52 vs 2.41 ± 0.86; $P_{interaction} < 0.0500$), while there were no significant interactions between alcohol intake and LDL in those with 'B1B2' genotype. Similar findings were reported in a nested case-control study involving 505 patients with coronary heart disease (CHD) and 1010 healthy controls from different ethnicities in the US population [49] in which it was observed that, among healthy individuals, a higher intake of alcohol (≥ 15g/day) was linked to higher HDL in participants carrying the 'B2' allele compared to those with 'B1B1' genotype, with 'B2B2' individuals having the highest HDL ($P_{interaction} < 0.0100$). These findings are consistent with the results of a case-control study consisting of 608 Irish and French men with myocardial infarction (MI) and 742 healthy controls [51], which reported that, among individuals with a higher alcohol intake (≥ 75g/day), those carrying the 'B2' allele had higher mean plasma HDL (30% higher for 'B2B2' and 13% higher for 'B1B2') than those with the 'B1B1' genotype ($P_{interaction} < 0.0001$). Likewise, a cross-sectional study of 1729 Japanese participants [50] reported that, among women who consumed any amount of alcohol, those with 'B2B2' genotype had higher HDL than those with 'B1B1' or 'B1B2' genotype (mean HDL (mmol/l): 1.57 ± 0.03 for 'B1B1'; 1.57 ± 0.03 for 'B1B2'; 1.79 ± 0.06 for 'B2B2'; $P_{interaction} = 0.0220$); while in men who consumed ≥ 2 drinks/day, those carrying the 'B2' allele had higher HDL than those with 'B1B1' genotype (mean HDL (mmol/l): 1.37 ± 0.03 for 'B1B1', 1.44 ± 0.03 for 'B1B2', 1.49 ± 0.05 for 'B2B2'; $P_{interaction} = 0.0490$). These findings suggest that alcohol intake could alter lipid profiles by increasing HDL in both 'B1' and 'B2' carriers; however, the underlying mechanism is unclear and considering that alcohol intake has been linked to other health issues such as liver cirrhosis, the overall benefit needs to be carefully considered. Moreover, interaction between alcohol intake and TaqIB genotype on blood lipids has been investigated by 12 studies and eight of the studies have not found significant interactions [13, 15, 52–57].

Six out of fourteen dietary intervention studies found significant interactions between TaqIB genotype, dietary factors and blood lipids. Three of the interactions were observed in participants carrying the 'B2' allele while the remaining three were reported in those with the 'B1B1' genotype. A 6-day dietary intervention study [58], using high carbohydrate/low-fat diet in 56 healthy Chinese individuals, showed that those carrying the 'B2' allele had higher HDL concentrations (mean HDL (mg/dl): 56.14 ± 10.69 after washout diet vs 59.77 ± 10.62 after high carbohydrate/low-fat diet; $P_{interaction} < 0.0500$) but the interaction was not observed in individuals with 'B1B1' genotype. As the duration of this intervention was only 6 days, intervention studies with longer duration are required to confirm the effect of carbohydrate on HDL in individuals carrying the 'B2' allele. In a meta-analysis of 26 dietary interventions using SFA, trans fat, dietary cholesterol and the coffee diterpene cafestol in 405 healthy Dutch participants over a 20-year period [59], participants with 'B2B2' genotype had a larger increase in HDL in response to SFA compared to those with 'B1B1' or 'B1B2' genotypes (mean change in HDL (mmol/l): 0.08 ± 0.02 for 'B2B2', 0.03 ± 0.01 for 'B1B2', 0.04 ± 0.02 for 'B1B1' genotype; $P = 0.0400$), while participants carrying the 'B1' allele had a smaller increase in LDL in response to dietary cholesterol than those with the 'B2B2' genotype (mean change in LDL (mmol/l): 0.27 ± 0.14 for 'B1B1', 0.35 ± 0.08 for 'B1B2', 0.75 ± 0.15 for 'B2B2'; 'B1B1' vs 'B2B2', $P = 0.0300$; 'B1B2' vs 'B2B2', $P = 0.0100$). In an oral fat tolerance test performed in 80 Greek participants who were heterozygous for familial hypercholesterolemia (HFH) and 11 control participants [60], it was demonstrated that, among participants in the HFH group who showed an abnormal postprandial TG response (TG concentration of >220 mg/dl), men with the 'B2' allele had higher levels of TG than women with the 'B2' allele after 4 hours of fat intake (279 ± 95 vs 239 ± 65 mg/dl, $P = 0.0300$) but there were no reports of significant interactions in participants with 'B1B1' genotype.

Statistically significant interactions between carriers of the 'B1' allele and dietary factors were reported by three dietary intervention studies [43, 61, 62]. In a randomised triple-blind crossover trial performed in 95 Iranian patients with T2D and 73 healthy controls using three diets: sesame oil, canola oil and sesame-canola oil [61], it was demonstrated that, in the T2D group, those with 'B1B1' genotype had a significant reduction in lipid ratios after consuming sesame oil and sesame-canola oil (change in LDL:HDL (mg/dl): −1.29, $P_{interaction} = 0.0270$; change in TC:HDL (mg/dl): −2.82, $P_{interaction} = 0.0240$; and change in TG:HDL (mg/dl): −7.00, $P_{interaction} = 0.0250$) but there were no reports of

significant reductions in lipid ratios in participants carrying the 'B2' allele. Another randomised controlled trial (RCT) performed in 85 New Zealander men with hypercholesterolemia, involving a 4-week healthy diet vs healthy diet plus two kiwi fruits per day [62], also showed that, among participants with 'B1B1' genotype, consumption of kiwi fruit resulted in lower TG:HDL ratio than the control diet (mean change in TG:HDL (mmol/l): −0.14 ± 0.51 for kiwifruit vs 0.09 ± 0.56 for control diet, $P = 0.03$; $P_{\text{interaction}} < 0.05$), while in individuals carrying the 'B2' allele, the interaction was not observed. Similar results were also observed in a crossover intervention conducted in Spanish prepubertal children with mild hypercholesterolemia, consisting of consumption of cow's skim milk vs cow's skim milk enriched with virgin olive oil for two periods of 6 weeks [43]. It was observed that intake of olive oil–enriched skim milk resulted in a larger increase in HDL and a decrease in LDL:HDL ratio in participants with 'B1B1' genotype compared to those carrying the 'B2' allele (mean change in HDL (mmol/l) (95% confidence interval): 0.179 (0.096 to 0.262) for 'B1B1' vs 0.089 (0.032 to 0.146) for carriers of 'B2', $P_{\text{interaction}} < 0.0010$; mean change in LDL:HDL ratio (mmol/l) (95% confidence interval): −0.470 (−0.729 to 0.211) for 'B1B1' vs −0.097 (−0.275 to 0.081) for carriers of 'B2', $P_{\text{interaction}} < 0.0010$). While these studies show that individuals with the 'B1B1' genotype could benefit from consuming these diets, the interactions were reported only in those with either T2D [61] or hypercholesterolemia [43, 62] indicating that these results may not apply to healthy participants and hence, this limits the wider application of the findings.

The TaqIB, located in intron 1 of the *CETP* gene, is considered to be non-functional and is believed to serve as a marker for functional SNPs in the promoter region [13, 17, 63]. The 'B1' allele differs from the 'B2' allele by the presence of a restriction site for TaqI endonuclease [17]. The 'B1' allele is believed to be associated with higher CETP activity, resulting in lower HDL and higher serum TG, and is considered a risk factor for dyslipidaemia [47]. This is supported by some of the studies as participants with the 'B1B1' genotype tended to have lower HDL [15, 17, 49, 56]. Nonetheless, the results suggest that people with this genotype can increase their HDL and modify their genetic risk by consuming sesame oil, canola oil, olive oil and kiwi fruit among others, although larger studies covering different ethnicities are warranted to tailor nutritional advice based on ethnicity and genetic profile.

SNP rs5882 (I405V G > A)

The SNP rs5882 (I405V) results in a substitution of valine (V) for isoleucine (I); hence, the 'G' allele is also called the 'V' allele while the 'A' allele is also known as the 'I' allele. The frequency of the 'V' allele is 34% globally but in Africans it is 58%, while in Asians it is 48% and in Europeans it is 32% [64]. Six out of eight observational studies found statistically significant interactions between this SNP and dietary factors on blood lipids. A cross-sectional analysis of 101 individuals from different ethnicities in the US population [10•] showed that a higher MUFA intake (>31g/day) was associated with lower TG in participants carrying the minor allele ('V') ($P_{\text{interaction}} = 0.0060$) but there were no reports of significant interactions in individuals with 'II' genotype. A longitudinal study of 4700 Iranian participants over 3.6 years [65] reported that a higher MUFA intake was linked to increased levels of TG in participants carrying the 'V' allele (mean changes in TG (mg/dl) across quartiles of MUFA intake: −3.03, 1.73, 8.06, 8.85; $P_{\text{interaction}} = 0.0010$), but the interaction was not observed in those with 'II' genotype. This study also observed that a higher intake of total fat correlated with increased levels of TG in those carrying the 'V' allele (mean changes in TG (mg/dl) across quartiles of total fat intake: −1.90, 2.6, 6.06, 8.88; $P_{\text{interaction}} = 0.0010$) but the interaction was not significant in those with 'II' genotype. A higher carbohydrate intake was also found to be associated with decreased levels of TG in 'V' allele carriers (mean changes in TG (mg/dl) across quartiles of carbohydrate intake: 6.65, 7.29, 4.42, −3.28; $P_{\text{interaction}} = 0.0100$) but the interaction was not significant in individuals with 'II' genotype [65]. Interactions with MUFA were also reported in a nested case-control of 441 Iranian participants with metabolic syndrome and 844 healthy controls [66] wherein carriers of the 'V' allele had a reduced risk of low HDL with a low intake of MUFA (<8.4% of energy) and an increased risk of low HDL with a higher intake of MUFA (9.6–11% of total energy intake) compared to those with 'II' genotype (odds ratio for low HDL across quartiles of MUFA intake: 0.49, 0.66, 0.88, 0.66 for carriers of 'V' allele vs 1, 0.61, 0.62, 0.68 for 'II' genotype; $P_{\text{interaction}} = 0.0200$). The findings of these studies suggest that the SNP rs5882 (I405V) may modify the link between fat intake and blood lipids. A higher intake of MUFA and total fat appears to be unfavourable in Iranian participants carrying the 'V' allele by leading to an increase in TG levels and the risk of low HDL while carbohydrate intake seems to be beneficial in reducing TG levels in these 'V' allele carriers [65, 66]. Conversely, the study in the US population [10•] implies MUFA is beneficial in individuals carrying the 'V' allele. As this study [10•] was performed in participants from different ethnicities, it is difficult to confirm ethnicity as a reason for the differential response to MUFA. Moreover, the study was performed in participants with overweight and obesity which could influence the findings since obesity is known to alter the interaction between diet and genotype

on lipids [10•]. Nonetheless, the Iranian case-control study [66] also involved participants with metabolic syndrome as well as healthy controls; but, the study did not report the findings for healthy controls. It has been demonstrated that *CETP* transgenic mice fed with MUFA had improved LDL receptor activity with a corresponding increase in the uptake of ApoB-containing lipoproteins by the liver [67], which could explain the reduction in TG levels associated with a high MUFA diet. The lipid-lowering effect of MUFA has also been linked to a decrease in expression of the transcription factor liver X receptor α (LXRα) which is involved in CETP activation [68]. Moreover, it has been argued that animal-based sources of MUFA also contain substantial amounts of SFA which could mask the effects of MUFA [69], implying that the source of MUFA needs to be taken into account when assessing the impact of MUFA on lipid-related outcomes.

In a cross-sectional study of Icelandic participants (152 men and 166 women) [70], alcohol intake was found to be associated with higher HDL in men with 'VV' genotype (13.7% higher HDL than 'II' genotype) compared to men with 'II' or 'IV' genotype ($P_{interaction} < 0.0200$) but the interaction was not statistically significant in women. Interactions with HDL were also observed in a cross-sectional study of 553 Inuit participants [71] in which higher levels of omega 3 polyunsaturated fatty acids (n-3 PUFA) in red blood cells (RBCs) was associated with higher HDL in participants carrying the major allele ('I') compared to those with 'VV' genotype (β (mmol/l) = 0.0263 ± 0.0115 for 'IV' genotype, β (mmol/l) = 0.0017 ± 0.0131 for 'II' genotype; $P_{interaction}$ = 0.0271). The study also found that n-3 PUFA in RBCs had a negative correlation with total cholesterol in participants with 'II' genotype compared to those with 'VV' or 'IV' genotype (β (mmol/l) = −0.0290 ± 0.0307; $P_{interaction}$ = 0.0334). In another cross-sectional study of 553 Inuit participants [16], individuals with 'II' genotype had a greater increase in total cholesterol with a higher intake of total fat than those with 'VV' or 'IV' genotype (β (mmol/l) = 0·0024 ± 0·0026; $P_{interaction}$ = 0.0460). These findings imply that while n-3 PUFA intake was beneficial for Inuit participants carrying the 'I' allele [71], higher total fat intake was not favourable for these participants [16]. PUFA is believed to promote the synthesis of LDL receptors which has the effect of increasing hepatic uptake of ApoB-containing lipoproteins [72], thereby raising the levels of HDL. To understand how PUFA affects regulation of the *CETP* gene, a study [73] was conducted in *CETP* transgenic mice which demonstrated that n-3 PUFA resulted in elevated *CETP* messenger RNA (mRNA) and protein levels, possibly by being a ligand for peroxisome proliferator–activated receptors α (PPARα), which is involved in the regulation of lipid-related genes [73]. However, increased *CETP* activity is known to have an inverse effect on HDL levels and does not explain the beneficial effect on HDL observed in the Inuit study. This raises the question of whether particular *CETP* SNPs dictate the response of the CETP protein to n-3 PUFA.

Only one of the six dietary intervention studies reported significant interactions between the I405V SNP and dietary factors on blood lipids. In this study [74], Canadian monozygotic twins (12 pairs) who were overfed by 1000 kcal per day for a period of 100 days showed a significant decrease in HDL, HDL_2 and HDL_3 in those with 'II' genotype compared to individuals with 'VV' genotype (mean change in HDL (mmol/l): −0.12 ± 0.04 vs 0.02 ± 0.04, $P = 0.02$; mean change in HDL_2 (mmol/l): −0.08 ± 0.03 vs 0.03 ± 0.03, $P = 0.04$; mean change in HDL_3 (mmol/l): −0.04 ± 0.02 vs −0.004 ± 0.02, $P = 0.0020$), but there were no reports of significant interactions in individuals with 'IV' genotype. The 'II' genotype of SNP rs5882 is believed to affect the ability of the CETP protein to mediate the exchange of cholesteryl esters for TG, resulting in increased TG concentrations [66], although this SNP has not been reported by any of the 32 GWASs to impact on lipids.

It has also been shown that the 'VV' genotype of the SNP rs5882 is associated with lower plasma CETP levels and increased HDL concentration [75]; however, baseline HDL data for participants with the 'VV' genotype was not available for all the studies because there were not enough participants with the 'VV' genotype in the two Iranian studies [65, 66]. Also, in the two Inuit studies [16, 71], baseline HDL data was not recorded separately for 'VV', 'IV' or 'II' genotype. However, in the Icelandic study [70], those with the 'VV' genotype had higher baseline HDL levels. Overall, the findings indicate that the SNP rs5882 may modify dietary response to lipids, but further studies are needed to clarify the differences in the results of some of the studies.

SNP rs3764261 (C > A)

Significant interactions between dietary factors and SNP rs3764261 on blood lipids were observed in two out of four observational studies. In a longitudinal study of 4700 Iranian participants over 3.6 years [65], it was reported that a higher fish intake was associated with a larger decrease in total cholesterol (TC) in participants carrying the minor allele ('A') (mean changes in TC (mg/dl) with quartiles of fish intake: 8.02, 6.93, 6.54, 5.58) compared to those carrying two copies of the major allele ('C') (mean changes in TC (mg/dl) with quartiles of fish intake: 3.65, 6.62, 4.57, 8.93) ($P_{interaction}$ = 0.02). Interactions with fat intake were also observed in a cross-sectional study of 3342 Indian participants [76] in which a high dietary fat intake (≥ 76.98g/day) was associated with increased levels of TC (β (mmol/l) = 0.097 ± 0.041; $P_{interaction}$ = 0.018) and LDL (β (mmol/l) = 0.085 ± 0.041; $P_{interaction}$ = 0.0420) in participants carrying the 'A' allele but there were no reports of interactions in

those with 'CC' genotype. A high-fat diet has been demonstrated to increase CETP activity in transgenic mice [77] which has the effect of increasing TC and LDL and could account for the findings reported. Moreover, the SNP rs3764261 (C > A) is located in the 5^1 region of the *CETP* gene and has been shown to regulate expression of the gene, the 'C' allele being associated with increased *CETP* expression and reduced HDL levels [78].

Two dietary intervention studies reported statistically significant interactions between the SNP rs3764261 and dietary factors on blood lipids. In a prospective, randomized, single-blind controlled dietary intervention trial carried out in 424 Spanish patients who had acute coronary syndrome (ACS) or CHD and also had metabolic syndrome [14], wherein participants consumed either a Mediterranean diet or a low-fat diet, it was observed that, after 1 year, consumption of Mediterranean diet was associated with higher HDL and lower TG in participants carrying the 'A' allele compared to those with 'CC' genotype (mean HDL (mg/dl): 41 vs 38, $P_{\text{interaction}} = 0.0060$; mean TG (mg/dl): 130 vs 146, $P_{\text{interaction}} = 0.0400$). This finding indicates that Mediterranean diet might be beneficial in increasing HDL in Spanish participants with ACS or CHD who carry the 'A' allele [14]; however, this finding might not be applicable to healthy individuals. In another study which was performed on participants from different ethnicities and involved a 2-year randomised weight loss trial, consisting of low-fat diet (20% fat) vs high-fat diet (40% fat), and a 2-year RCT consisting of low-fat diet (30% fat) vs low carbohydrate (high-fat) diet [46], the combined results of the two interventions showed that, among participants with 'CC' genotype, those in the high-fat diet group had a higher increase in HDL (11.7 vs 4.5%; $P_{\text{interaction}} = 0.01$) and a larger decrease in TG (−25.1 vs −11.7%; $P_{\text{interaction}} = 0.0007$) than those in the low-fat diet group, but there were no significant interactions in participants with 'CA' or 'AA' genotype. These results suggest that a high-fat diet (40% fat) in individuals from different ethnicities who have the 'CC' genotype might contribute to increased HDL and reduced TG levels [46] although the findings are not in agreement with the study performed in *CETP* transgenic mice [77] in which a high-fat diet resulted in increased CETP activity which lowered HDL levels. Considering that this was a weight loss intervention, it is unclear whether the changes in lipid levels were due to the high-fat diet or the loss of weight or both since physical activity has been shown to interact with genetic risk score and impact on waist-hip ratio [79]. Moreover, the 'C' allele of the SNP rs3764261 is regarded as a significant risk factor for low HDL [78, 80] although it has been demonstrated that this risk can be overcome by weight gain prevention [78]. The SNP rs3764261 has also been shown by GWASs to influence HDL levels in Asian Indians [19, 28], Japanese [26, 31], African-American [29], Chinese [20], Lebanese [21] and Finnish [35] but the evidence indicates that this SNP has not been extensively studied by gene–diet interaction studies. Therefore, further studies in different ethnicities are required to confirm the effect of the SNP in modifying dietary response to lipids.

C-629A (SNP rs1800775 C > A)

The SNP rs1800775 has been shown to be associated with HDL in seven of the nineteen GWASs [19, 22, 24, 31, 34, 35, 37]. Two out of five observational studies reported significant interactions between dietary factors and the SNP rs1800775 (C-629A) on blood lipids. In a cross-sectional study of 9075 Taiwanese participants [81], consumption of coffee was found to be associated with lower HDL in women carrying the minor allele ('C') compared to women with 'AA' genotype (β (mg/dl) = −1.8095 for 'AC' genotype, β (mg/dl) = −2.8151 for 'CC' genotype; $P_{\text{interaction}}<0.0001$), and in men carrying the 'C' allele compared to men with the 'AA' genotype (β (mg/dl) = −1.9623 for 'AC' genotype, β (mg/dl) = −2.7154 for 'CC' genotype; $P_{\text{interaction}}<0.0001$). A case-control study consisting of 568 Irish and French men with MI and 668 healthy controls [82] showed that, among individuals carrying the major allele ('A'), alcohol consumption was associated with higher HDL in healthy participants ($P_{\text{interaction}}<0.0020$) and in patients who were not treated with lipid-lowering medication ($P_{\text{interaction}}<0.0010$), while in individuals with 'CC' genotype, there was no association between alcohol intake and HDL. The results suggest that dietary factors other than fat intake may also play a role in modulating lipid levels, but these interactions need to be explored further to allow for comparison of results across multiple ethnic groups. The SNP rs1800775 (C-629A) is located in the promoter region of the *CETP* gene and the 'A' allele is associated with reduced *CETP* expression and higher HDL levels [17]. The 'A' allele of SNP rs1800775 (C-629A) is in a high degree of linkage disequilibrium with the 'B2' allele of SNP TaqIB and it is believed that this association is responsible for the protective effect of the 'B2' allele [17]. However, some are of the view that there might be other functional SNPs that are in linkage disequilibrium with TaqIB apart from SNP rs1800775 (C-629A) but it is unclear what these SNPs are [13, 63]. Moreover, despite the SNP rs1800775 (C-629A) being reported by several GWASs to be associated with blood lipids, this SNP has not been extensively studied in gene–diet interaction studies. To date, only one dietary intervention study [83] investigated the SNP rs1800775 (C-629A) which also failed to demonstrate any significant SNP–diet interactions on lipids. This study was an RCT performed in 490 participants from different ethnicities in the UK population and involved a reference diet (~18% SFA, 12% MUFA, 38% total fat, 45% carbohydrate (CHO)) for 4 weeks, followed by 1 of three

diets: a MUFA diet (~10% SFA, 20% MUFA, 38% total fat, 45% CHO); a low-fat diet (~10% SFA, 11% MUFA, 28% total fat, 55% CHO); or the reference diet for 24 weeks. The findings overall indicate that further large studies are needed to confirm the effect of the SNP rs1800775 in altering lipid profiles in response to diet.

Other SNPs

Other *CETP* SNPs which have been reported to interact with dietary factors and influence blood lipids are SNPs rs183130 (C-4502T), rs4783961 (G-971A), rs289714 (C>T) and rs1800774 (C > A). In the cross-sectional study of 553 Inuit participants [84], higher levels of n-3 PUFA in RBCs was linked to lower TC levels in participants carrying the minor allele ('T') of the SNP rs183130 (C-4502T) compared to those with 'CC' genotype (β (mmol/l) = −0.0632 ± 0.0241 for 'CT' genotype, β (mmol/l) = −0.0421 ± 0.0343 for 'TT' genotype; $P_{\text{interaction}} = 0.0326$); and lower TG levels in those with the 'TC' genotype of the SNP rs183130 (C-4502T) compared to individuals with 'TT' genotype (β (mmol/l) = −0.0095 ± 0.0051 vs β (mmol/l) = 0.0073 ± 0.0073; $P_{\text{interaction}} = 0.0300$), while there were no reports of significant interactions between n-3 PUFA in RBCs and TG in participants with 'CC' genotype. This study also reported that individuals with the 'GA' genotype of the SNP rs4783961 (G-971A) who had higher levels of n-3 PUFA in RBCs had lower TG levels (β (mmol/l) = −0.0106 ± 0.0057; $P_{\text{interaction}} = 0.0032$) and lower TC:HDL ratio (β (mmol/l) = −0.0055 ± 0.0033; $P_{\text{interaction}} = 0.0483$) compared to participants with 2 copies of the minor allele ('A') of the SNP rs4783961 (G-971A). These findings point to a beneficial role of PUFA in Inuit participants carrying the 'T' allele of the SNP rs183130(C-4502T) and the 'G' allele of the SNP rs4783961 (G-971A). PUFA is believed to improve the breakdown of ApoB-containing particles, thereby reducing TG concentrations [66], which is consistent with this finding. However, in a cross-sectional study of 821 participants who were normal glucose tolerant and 861 participants with T2D, involving the transcription factor 7-like 2 (*TCF7L2*) gene [85], higher PUFA intake (mean PUFA intake of 29g/day) was linked to 1.64 mg/dl lower HDL while lower PUFA intake (mean PUFA intake of 9g/day) was associated with 1.96 mg/dl higher HDL in Asian Indian participants carrying the 'T' allele of the *TCF7L2* SNP rs12255372 compared to those with the 'GG' genotype ($P_{\text{interaction}}$<0.0001). In another cross-sectional study involving 101 participants of different ethnicities in the US population [10•], it was reported that, among participants with two copies of the major allele ('A') of the SNP rs289714, those who consumed >92 g of total fat per day had lower TG levels (103 ± 63 mg/dl) than those who consumed <31 g of total fat per day (135 ± 15 mg/dl) ($P_{\text{interaction}} = 0.0010$). The interaction was significant for both the dominant and recessive modes of inheritance ($P_{\text{interaction}} = 0.0010$ and $P_{\text{interaction}} = 0.0230$ respectively), but there were no reports of significant interactions in individuals with 'GG' genotype. In another cross-sectional study of 1315 Spanish participants [86], higher plasma selenium levels were found to be associated with elevated LDL levels in all the three genotypes of the SNP rs1800774 but participants with two copies of the major allele ('C') had lower LDL compared to those with 'CT' and 'TT' genotypes (odds ratio per an interquartile range increase in plasma selenium (95% confidence interval): 0.97 (0.74 to 1.27) for 'CC', 1.76 (1.38 to 2.25) for 'CT', 3.20 (1.93 to 5.28) for 'TT' genotype; $P_{\text{interaction}} = 0.0002$). Selenium was also reported to be associated with lipid levels in a systematic review and meta-analysis [87], but it was shown to be linked to significant improvement in the levels of TC and TG and had no significant effect on LDL levels. A systematic review published in 2017, in which the results of 23 gene–diet interaction studies involving *CETP* were analysed [88], concluded that SNPs in the *CETP* gene may influence the effect of dietary factors on metabolic traits but that the findings from these studies were inconsistent and suggest that multiple factors might be involved.

Conclusion

In summary, this review has identified statistically significant interactions between 17 dietary factors and 8 SNPs in the *CETP* gene on blood lipids in the following populations: Mexican, Iranian, Spanish, White American, Chinese, Malay, Indian, Irish, French, Japanese, New Zealander, Dutch, Greek, Icelandic, Inuit, Canadian, Taiwanese and residents of the USA. The SNPs showing significant interactions with dietary factors (such as total fat intake, MUFA, n-3 PUFA, Mediterranean diet, olive oil and sesame-canola oil) were TaqIB (rs708272 G > A); rs5882 (I405V); rs3764261 (C > A); rs1800775 (C-629A); rs183130(C-4502T); rs4783961 (G-971A); rs289714 (C>T) and rs1800774 (C > A). The macronutrient investigated by majority of the studies was dietary fat, comprising of total fat, SFA, MUFA and PUFA. Total fat intake accounted for majority of the interactions across different SNPs, being associated with unfavourable lipid outcomes in some individuals but not others.

Studies reporting significant interactions in individuals with the B1B1 genotype of the SNP TaqIB (rs708272) have been performed in participants with either T2D or hypercholesterolemia. Similarly, those reporting significant interactions in individuals carrying the 'V' allele of the SNP rs5882 have been conducted in participants with overweight and obesity or metabolic syndrome. Moreover, some of the significant interactions involving the SNP rs3764261 have also been reported in patients with ACS or CHD, suggesting that some of the findings of these studies may not apply to healthy participants.

Overall, the findings suggest that *CETP* SNPs might alter blood lipid profiles by modifying responses to diet, but further large studies in multiple ethnic groups are warranted to identify individuals at risk of adverse lipid response to diet which is essential in developing dietary guidelines that are tailored to specific groups of people. Information on the underlying genetic factors for dyslipidaemia will also contribute to improved understanding of the mechanisms involved, which is central to the development of effective preventative strategies as well as identifying areas for further research.

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Author Contribution RW extracted and interpreted *CETP* genetic variants related to gene–diet interactions on lipids and drafted the manuscript, and this was double-checked by KSV and AAW. KSV conceived and designed the review and interpreted the results. All authors were involved in drafting the manuscript and revising it critically for intellectual content. All authors have approved the final version of the manuscript.

Declarations

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Higher Intake of Dairy Is Associated with Lower Cardiometabolic Risks and Metabolic Syndrome in Asian Indians

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Abstract: There is conflicting evidence about the association between dairy products and cardiometabolic risk (CMR). We aimed to assess the association of total dairy intake with CMR factors and to investigate the association of unfermented and fermented dairy intake with CMR in Asian Indians who are known to have greater susceptibility to type 2 diabetes and cardiovascular diseases compared to white Europeans. The study comprised 1033 Asian Indian adults with normal glucose tolerance chosen from the Chennai Urban Rural Epidemiological Study (CURES). Dietary intake was assessed using a validated open-ended semi-quantitative food frequency questionnaire. Metabolic syndrome (MS) was diagnosed based on the new harmonising criteria using central obesity, dyslipidaemia [low high-density lipoprotein cholesterol (HDL) and increased serum triglycerides (TG)], hypertension and glucose intolerance. Increased consumption of dairy (≥5 cups per day of total, ≥4 cups per day of unfermented or ≥2 cups per day of fermented dairy) was associated with a lower risk of high fasting plasma glucose (FPG) [hazards ratio (HR), 95% confidence interval (CI): 0.68, 0.48–0.96 for total dairy; 0.57, 0.34–0.94 for unfermented dairy; and 0.64, 0.46–0.90 for fermented dairy; $p < 0.05$ for all] compared to a low dairy intake (≤1.4 cups per day of total dairy; ≤1 cup per day of unfermented dairy; and ≤0.1 cup per day of fermented dairy). A total dairy intake of ≥5 cups per day was also protective against high blood pressure (BP) (HR: 0.65, 95% CI: 0.43–0.99, $p < 0.05$), low HDL (HR: 0.63, 95% CI: 0.43–0.92, $p < 0.05$) and MS (HR: 0.71, 95% CI: 0.51–0.98, $p < 0.05$) compared to an intake of ≤1.4 cups per day. A high unfermented dairy intake (≥4 cups per day) was also associated with a lower risk of high body mass index (BMI) (HR: 0.52, 95% CI: 0.31–0.88, $p < 0.05$) compared to a low intake (≤1 cup per day), while a reduced risk of MS was observed with a fermented dairy intake of ≥2 cups per day (HR: 0.71, 95% CI: 0.51–0.98, $p < 0.05$) compared to an intake of ≤0.1 cup per day. In summary, increased consumption of dairy was associated with a lower risk of MS and components of CMR.

Keywords: metabolic syndrome; Asian Indians; dairy intake; fermented dairy; unfermented dairy; CURES

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1. Introduction

Asian Indians have been shown to have distinct biochemical and clinical characteristics that put them at risk of type 2 diabetes (T2D) and cardiovascular diseases (CVDs) [1–4]. The distinct features include central obesity, dyslipidaemia, insulin resistance, increased levels

of visceral fat, total fat, and propensity to beta cell dysfunction [1–4]. The components of the 'Asian Indian Phenotype' are included in the metabolic syndrome (MS), which refers to a group of interconnected risk factors that make an individual susceptible to CVDs and T2D [5]. According to a systematic review and meta-analysis involving 133,926 participants from 111 studies [6], MS affects 1 in 3 adults in India, and the prevalence is higher among people in urban areas (32%) than those living in rural areas (22%). MS is associated with increased CVDs and all-cause mortality [7,8], warranting studies in Asian Indians who are known to have a predisposition to MS.

The existence of an entity called MS is surrounded by controversies, partly due to variations in the definition of MS [9–12]. However, it is generally agreed that the risk factors of central obesity, high blood pressure (BP), elevated levels of triglycerides (TG), low concentration of high-density lipoprotein cholesterol (HDL) and elevated fasting plasma glucose (FPG) tend to co-exist and are important indicators of an individual's risk of CVDs and T2D [9–13]. The increasing prevalence of these risk factors has been linked to genetic and environmental factors [1,14–17], and there is growing interest in the role of different types of food in the development of MS [1,5,16,17]. Several studies have reported a protective effect of dairy consumption on the risk of MS [5,18–21]. Consumption of at least two servings of dairy per day compared to no dairy intake, has been linked to a lower prevalence of MS [5]. Increased consumption of dairy (>7 times per week) was also found to be associated with a reduced risk of MS and central obesity compared to no dairy intake [21]. However, one study [22] reported that participants who did not consume milk had a lower risk of insulin resistance and MS compared to those who drank milk, making the findings inconsistent. Moreover, it has been suggested that fermented dairy might confer greater anti-inflammatory and cardiometabolic benefits than unfermented dairy [23,24]. Possible mechanisms for the proposed benefits of fermented dairy include the action of microbial cultures on gut microbiota, changes in lipid and glyceride profiles and the release of more bioactive compounds involved in regulating several metabolic and immune pathway genes [23–25].

Furthermore, consumption of dairy is high among Asian Indians [26–28] who also have a high prevalence of MS [6,29,30]. An examination of the dietary profile of 2042 Asian Indian participants [26] showed that, dairy intake was within the national recommendation of 300 g/day (g/day) [31]. However, despite dairy consumption being linked to lower risk of MS [5,18–20], few studies have examined the impact of dairy intake on the risk of MS in Asian Indians. Hence, the present study sought to investigate the association of total dairy consumption with MS and components of cardiometabolic risk (CMR) in Asian Indians. We also aimed to determine the association of fermented and unfermented dairy products with MS and components of CMR.

2. Methods

2.1. Study Population

The current study consisted of 1033 adults with normal glucose tolerance chosen from the Chennai Urban Rural Epidemiological Study (CURES), and details of the study design have been given in previous publications [1,15,32–34]. In brief, a total of 26,001 adults were recruited between 2001 to 2003 from the urban part of Chennai in Southern India through systematic random sampling, and the follow-up study was conducted between 2012 and 2013 and consisted of 2410 participants. The sample for the current study was chosen from the follow-up cohort as shown in Supplementary Figure S1. Approval was obtained from the Institutional Ethics Committee, and written informed consent obtained from all the study participants.

2.2. Data Collection

Demographic (including medical history and physical activity), anthropometric, biochemical and dietary data were collected both at baseline (2001–2003) and after 10 years (2012–2013) using a structured, pretested, and validated interviewer-administered ques-

tionnaire [35]. Family history of diabetes was considered as positive if either parents or sibling/s had diabetes. Smokers were defined as those who were currently smoking, and alcohol use was defined as current alcohol consumption.

Height, weight, waist circumference (WC) and BP were measured using standardised techniques [32], and body-mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared (m^2). Biochemical analyses, including fasting plasma glucose (FPG) and lipids, were performed in all individuals; in addition, plasma glucose estimation 2 h after a 75 g oral glucose load was performed in individuals without diabetes [32]. Biochemical analyses were performed in a laboratory certified by the National Accreditation Board for Testing and Calibration Laboratories and the College of American Pathologists on a Hitachi 912 autoanalyzer (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Basel, Switzerland) for estimation of plasma glucose (GOD-POD method).

2.2.1. Outcome Ascertainment

General Obesity

General obesity was defined as BMI $\geq$ 25 kg/m^2 and overweight as BMI $\geq$ 22.9 kg/m^2 in accordance with the Asia Pacific guidelines [36].

Metabolic Syndrome

MS was diagnosed based on the new harmonising criteria [37]. Individuals with any three of the following abnormalities viz. high WC (Asia Pacific cut-off $\geq$80 cm for female, $\geq$90 cm for male), hypertriglyceridemia [serum TG $\geq$ 1.70 mmol/L ($\geq$150 mg/dL)], low HDL [male participants $\leq$ 1.04 mmol/L ($\leq$40 mg/dL); female participants $\leq$ 1.30 mmol/L ($\leq$50 mg/dL)], abnormal glucose metabolism [defined as FPG $\geq$ 5.6 mmol/L ($\geq$100 mg/dL)] and elevated BP [systolic BP (SBP) $\geq$ 130 mmHg or diastolic BP (DBP) $\geq$ 85 mmHg] were considered to have MS.

The term "cardiometabolic risk" was first employed by the American Diabetes Association as an umbrella term to include all the risk factors for diabetes and CVD [38]. The components of CMR given in the present analysis are central and general obesity; elevated levels of triglycerides, total cholesterol and LDL and reduced HDL concentration; hyperglycaemia; hypertension; and insulin resistance.

2.2.2. Dietary Assessment

Dietary intake was assessed by trained dietitians using a validated open-ended semi-quantitative 222-item food frequency questionnaire (FFQ) both at baseline and follow-up. The FFQ was designed to estimate the usual dietary intake of participants, the development and validation of which have been described elsewhere [35]. The FFQ included both the frequency as well as the servings of food items consumed by the individuals which was then converted to standardised portion sizes. However, any new food item reported (new market foods over 10-year period) during the follow-up period was updated in the in-house Nutritional Epidemiology ('EpiNu') software. Dairy intake was estimated from the FFQ using the 'EpiNu' software. Total dairy intake consists of unfermented plain milk and milk included in tea and coffee; Indian milk sweets and desserts; and fermented milk, which consists of Indian yoghurt (curd) and buttermilk. The 'EpiNu' software which contains information on the nutritional composition of food that is mainly consumed in the Chennai area was developed for the local population using recipes from a wide range of sources, including fast-food and home-made. Details of the development of the 'EpiNu' software are available in a previous publication [35].

2.3. Statistical Analyses

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). All food groups and nutrients were energy adjusted by the residual method [39]. As nutrients and food groups were not normally distributed, estimates were

expressed in median and interquartile range (IQR). The Mann-Kruskal Wallis test was used to compare differences between the medians of continuous variables, and the chi-squared test was used to test differences in proportions. The lowest, medium and highest intakes of total dairy, unfermented and fermented dairy were derived by stratifying the data into deciles and regrouping as lowest (quartile 1(Q1)–quartile 4 (Q4)), medium (Q5–Q8) and highest intake (Q9–Q10) to test the association with CMR using the regression model. The hazard ratio (HR) for incidence of CMR and MS in each group of dairy intake (lowest intake, medium intake and highest intake) and its subdivision (fermented and unfermented) was calculated using Cox proportional hazards analysis. Potential confounders were identified by the univariate analysis and entered simultaneously into the multiple Poisson regression model with p-value < 0.2. The model was adjusted for age, sex, BMI, income, smoking, alcohol, major cooking oil, total poly unsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level (PAL), total energy (kcal) and tea and coffee intake. The linear trend across the lowest, medium and highest dairy intake and incidence of CMR and MS were tested with the regression model [40]. Difference between the dairy product and its subdivisions was assessed using the Kruskal-Wallis test for all the continuous variables. The p values were tested for statistical significance at <0.05 level.

3. Results

3.1. Characteristics of the Study Participants

The median age of the study participants was 36 (IQR: 15) years. As shown in Table 1, smoking and alcohol consumption were reported by 16% and 23% of participants, respectively. Nearly half of the participants (44%) had a family history of diabetes. The median SBP (113 mmHg), DBP (72 mmHg), FPG (84 mg/dL) and postprandial glucose (106 mg/dL) were within the normal ranges. Consumption of tea and coffee was the main source of dairy (80%) as shown in Figure 1a and Table 2. The medians of the lowest, medium, and the highest total dairy intake were 208, 411 and 755 g/day (1.4, 3 and 5 cups per day), respectively.

Table 1. Baseline Characteristics of the Study Population (n = 1033).

Variables	Overall Median (Interquartile Range)/*n* (%)
Age (years)	36 (15)
Gender n (%)	
Men *n* (%)	433 (42)
Women *n* (%)	600 (58)
Smoking (yes) *n* (%)	160 (15)
Alcohol (yes) *n* (%)	242 (23)
Income per month n (%)	
INR. < 2000	24 (2)
INR. 2000–5000	197 (19)
INR. 5000–10,000	415 (40)
INR. > 10,000	397 (39)
Family history of diabetes (yes) *n* (%)	449 (43)
Weight (kg)	58 (17)
BMI (kg/m^2)	23.2 (6.2)
Waist circumference (cm)	84 (16)
Systolic BP (mmHg)	113 (19)
Diastolic BP (mmHg)	72 (13)
Fasting blood glucose (mg/dL)	84 (12)
Postprandial blood glucose (mg/dL)	106 (33)
Total Cholesterol (mg/dL)	175 (47)
Triglyceride (mg/dL)	96 (65)
High density lipoprotein (mg/dL)	42 (13)
Low density lipoprotein (mg/dL)	109 (39)

Data presented as median (interquartile range) for continuous variables; and as number (n) (%) for categorical variables. INR—Indian rupees; BMI—body mass index; BP—blood pressure.

Table 2. Consumption of Dairy and its Products (g/day).

Dairy and Its Products (g/Day)	Median (Interquartile Range)		
	Lowest Intake **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**
Total dairy products	208 (116)	411 (144)	755 (228)
Fermented dairy products (curd and buttermilk)	32 (66)	75 (119)	167 (215)
Milk	10 (39)	37 (94)	74 (148)
Tea and coffee (contribution by milk)	118 (118)	235 (176)	471 (353)
Milk sweets and desserts (milk sweets, ice cream, milk shake and other milk beverages)	2 (8)	3 (10)	5 (22)

3.2. Association of Total Dairy Consumption and Components of CMR

A total dairy intake of ≥5 cups compared to ≤1.4 cups per day was associated with a decreased risk of three of the components of CMR [high BP, FPG and low HDL] and MS as shown in Table 3 and Figure 1b, respectively. A decreased incidence of two of the components of CMR (high FPG and low HDL) was also observed among individuals in the medium total dairy intake group (≥3 cups per day) compared to those in the low total dairy intake group (≤1.4 cups per day) (Table 3). There was no association between total dairy intake and insulin resistance as shown in Supplementary Figure S2.

Table 3. Total Dairy Consumption and its Association with Components of Cardiometabolic Risk.

	Hazards Ratio (95% Confidence Interval)		
	Lowest Intake **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**
Total Dairy Products (g/Day)	***208* (*116*)** **1.4 Cups**	***411* (*144*)** **3 Cups**	***755* (*228*)** **5 Cups**
Blood pressure (mmHg) ≥ 140/90	1 (ref)	0.82 (0.63–1.08)	0.65 (0.43–0.99) *
BMI (kg/m^2) ≥ 22.9	1 (ref)	0.84 (0.66–1.08)	0.78 (0.53–1.15)
Waist circumference (cm) (>80: F; >90: M)	1 (ref)	0.87 (0.7–1.09)	0.87 (0.62–1.24)
Total cholesterol (>200 mg/dL)	1 (ref)	0.72 (0.51–1.01)	0.70 (0.42–1.18)
Triglyceride (>150 mg/dL)	1 (ref)	1.05 (0.76–1.44)	0.74 (0.45–1.22)
High-density lipoprotein (mg/dL) (≤40: F; ≤50: M)	1 (ref)	0.74 (0.59–0.93) *	0.63 (0.43–0.92) *
Low-density lipoprotein (>100 mg/dL)	1 (ref)	0.95 (0.77–1.17)	0.83 (0.61–1.12)
Fasting plasma glucose (>100 mg/dL)	1 (ref)	0.75 (0.6–0.95) *	0.68 (0.48–0.96) *

Data presented as median (interquartile range). * p-value < 0.05 considered as significant. Adjusted variables are age, sex, BMI, income, smoking, alcohol, major cooking oil, total poly unsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level, total energy (kcal) and tea and coffee intake (g/day).

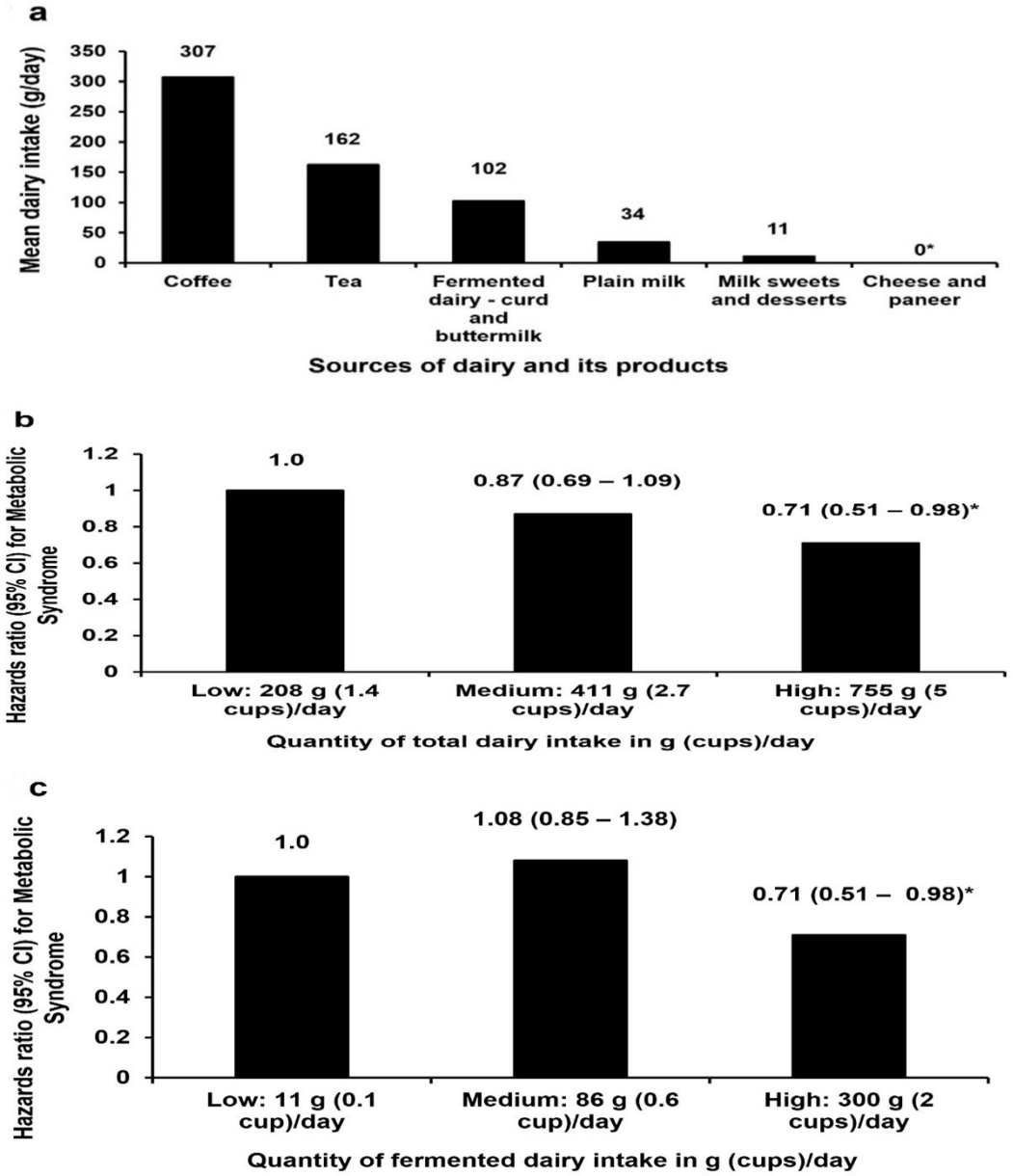

Figure 1. (**a**) **The sources of dairy and its products among the Chennai urban adults**. Milk sweets and desserts include Indian milk sweets, ice cream, milk shakes and other milk beverages. * Cheese and paneer intake was reported by only three individuals in the sample, and this resulted in a median value of 0. (**b**) **Total dairy consumption and its association with metabolic syndrome**. Data presented as median. * p-value < 0.05 considered as significant. Adjusted variables are age (years), sex, BMI, income, smoking, alcohol, major cooking oil, total poly unsaturated fatty acids (PUFA) (g), added sugar (g), total energy (kcal) and tea and coffee intake. (**c**) **Fermented dairy consumption and its association with metabolic syndrome.** Data presented as median. * p-value < 0.05 considered as significant. Adjusted variables are age (years), sex, BMI, income, smoking, alcohol, major cooking oil, PUFA (g), added sugar (g), physical activity level, total energy (kcal) and tea and coffee intake.

3.3. Association of Unfermented Dairy Consumption and Components of CMR

Consumption of 4 cups per day or more of unfermented dairy was associated with a lower incidence of high BMI and FPG (Table 4) compared to an intake of ≤1 cup per day of unfermented dairy. There was no significant association between unfermented dairy intake and MS (Supplementary Figure S2).

3.4. Association of Fermented Dairy Consumption and Components of CMR

Consumption of 2 cups per day or more of fermented dairy was associated with a lower incidence of high FPG (Table 4) compared to an intake of ≤0.1 cups per day. A high fermented dairy intake (≥2 cups per day) was also associated with a lower risk of MS compared to a low fermented dairy intake (≤0.1 cups per day) (hazards ratio (HR): 0.71, 95% confidence interval (CI): 0.51–0.98, $p < 0.05$) as shown in Figure 1c.

Table 4. Fermented and Unfermented Dairy Consumption and its Association with Components of Cardiometabolic Risk.

	Hazards Ratio (95% Confidence Interval)					
	Unfermented Dairy Products (g/Day)			**Fermented Dairy Products (g/Day)**		
	Lowest Intake **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**	***Lowest Intake*** **Q1–Q4**	***Medium Intake*** **Q5–Q8**	***Highest Intake*** **Q9–Q10**
Dairy Product (g/Day)	***138 (86)*** **1 Cup**	***290 (103)*** **2 Cups**	***581 (175)*** **4 Cups**	***11 (23)*** **0.1 Cup**	***86 (54)*** **0.6 Cup**	***300 (116)*** **2 Cups**
Blood pressure (mmHg) ≥ 140/90	1 (ref)	1.01 (0.73–1.41)	0.75 (0.45–1.27)	1 (ref)	0.83 (0.63–1.10)	0.71 (0.49–1.03)
BMI (kg/m^2) ≥ 22.9	1 (ref)	0.70 (0.50–0.99)	0.52 (0.31–0.88) *	1 (ref)	0.83 (0.63–1.10)	0.71 (0.49–1.03)
WC (cm) (>80: F; >90: M)	1 (ref)	0.91 (0.71–1.15)	0.89 (0.62–1.26)	1 (ref)	1.12 (0.92–1.37)	1.03 (0.81–1.34)
Total cholesterol (>200 mg/dL)	1 (ref)	0.78 (0.5–1.22)	0.59 (0.3–1.16)	1 (ref)	10 (0.72–1.39)	0.83 (0.54–1.28)
Triglyceride (>150 mg/dL)	1 (ref)	0.83 (0.57–1.2)	0.68 (0.38–1.22)	1 (ref)	1.14 (0.84–1.53)	0.98 (0.69–1.4)
HDL (mg/dL) (≤40: F; ≤50: M)	1 (ref)	1.02 (0.77–1.34)	0.93 (0.63–1.37)	1 (ref)	0.86 (0.69–1.06)	0.76 (0.57–1.01)
LDL (>100 mg/dL)	1 (ref)	0.92 (0.71–1.19)	0.77 (0.53–1.13)	1 (ref)	1.09 (0.9–1.33)	0.88 (0.69–1.13)
Fasting plasma glucose (>100 mg/dL)	1 (ref)	0.62 (0.44–0.88)	0.57 (0.34–0.94) *	1 (ref)	0.96 (0.74–1.24)	0.64 (0.46–0.90) *

Data presented as median (interquartile range). * p-value < 0.05 considered as significant. Adjusted variables are age, sex, BMI, income, smoking, alcohol, major cooking oil, total polyunsaturated fatty acids (PUFA) (g), added sugar (g), physical activity level (PAL), total energy (kcal) and tea and coffee intake. HDL—high-density lipoprotein cholesterol; LDL—low-density lipoprotein cholesterol; BMI—body mass index; WC—waist circumference.

4. Discussion

The present study has found evidence of a protective effect of dairy consumption against CMR factors in Asian Indians. We found a reduced risk with an increased intake of dairy products, where consumption of ≥5 cups per day of total, ≥4 cups per day of unfermented or ≥2 cups per day of fermented dairy was associated with a reduced risk of high FPG. A total dairy intake of ≥5 cups per was also associated with a lower risk of high BP, low HDL and MS. Consumption of ≥4 cups per day of unfermented dairy was also associated with a decreased incidence of high BMI; while an intake of ≥2 cups per day of fermented dairy was also associated with a lower risk of MS. Given that Asian Indians have high prevalence of CVDs and T2D [1–3,26], these findings are of public health importance. India is the largest producer of milk and it is commonly consumed by all classes of income groups, providing value for money and nutrients [27]. The results indicate that increasing the consumption of dairy products might help to reduce the risk of MS and its individual components in Asian Indians.

At baseline, the most widely consumed dairy products were reported to be tea and coffee with milk [26], and the same trend continued in the follow-up period after 10 years. In the Chennai area, a large quantity of milk is typically used in the preparation of tea and coffee, hence milk added to tea and coffee is a main source of dairy in the study population. Given that tea and coffee intake may independently influence the risk of CVDs (Supplementary Table S1), we adjusted for tea and coffee intake in our analysis. Our findings are consistent with previous studies in which dairy consumption showed a protective effect against MS [5,18–21]. In the Prospective Urban Rural Epidemiology (PURE) study [5], a large, multinational cohort study involving 112,922 individuals from

21 countries with a median follow-up of 9.1 years, a higher total dairy intake (≥2 servings per day) compared with no intake, was associated with a decreased prevalence of MS [odds ratio (OR), 0.76; 95% CI, 0.71–0.80; $p_{trend} < 0.0001$]. Similarly, the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), which involved 9835 participants [18], observed that total dairy intake was inversely associated with metabolic risk score (Beta = −0.04 ± 0.01, $p = 0.009$). The French Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) [20], a cohort study of 3435 participants also observed a negative association between consumption of dairy products, except cheese, and incidence of MS (OR, 0.88; 95% CI, 0.79–0.97; $p = 0.01$) and impaired fasting glycaemia/T2D (OR, 0.85; 95% CI 0.76–0.94; $p = 0.001$). A prospective study of 7240 Koreans [21] also reported that, a high consumption of dairy (≥7 times a week) was associated with a decreased risk of MS (HR, 0.72; 95% CI, 0.62–0.84; $p_{trend} < 0.001$) compared to no consumption of dairy. Overall, these findings indicate that consumption of dairy might be beneficial in reducing the risk of MS in different ethnic groups, but large dietary intervention studies will help to corroborate the findings.

The inverse association between dairy consumption and the risk of individual components of CMR observed in our study is also consistent with previous studies. In the PURE study [5], a higher total dairy intake (≥2 servings per day) compared to no intake, was associated with a decreased incidence of hypertension (HR, 0.89; 95% CI, 0.82–0.97; $p_{trend} = 0.02$) and T2D (HR 0.88; 95% CI, 0.76–1.02, $p_{trend} = 0.01$). The Caerphilly Prospective Study of 2512 men [41] also reported that participants in the highest milk consumption group had a 10.4 mmHg lower SBP ($p_{trend} = 0.023$) than those who did not consume milk after a 22.8 year follow-up. This study [41] also observed lower levels of glucose ($p_{trend} = 0.032$) with increasing intake of milk and dairy products. Furthermore, a cross-sectional study of 205 Indian participants with MS [42] showed that, consumption of milk and milk products (>4 servings/day) was associated with a lower risk of hypertension (OR, 0.54 95% CI, 0.18–1.67). A study involving 133 Indian women with gestational diabetes [43] also found an inverse association between consumption of dairy products and adverse neonatal outcomes (OR, 0.14, 95% CI, 0.02–0.8; $p = 0.03$). Moreover, a systematic review of randomised controlled trials [44] reported that dairy intake had a beneficial effect on body weight. All in all, the findings call for large, randomised trials to confirm the effect of dairy products on BP, BMI and blood glucose levels.

Our finding of a positive association between dairy intake and high HDL is also supported by a cohort study of 11,377 Norwegian participants (The Tromsø Study) [45] where consumption of cheese was positively associated with HDL concentration (Beta = 0.02 mmol/L, 95% CI, 0.01–0.03)). However, this association was only observed for total dairy intake in our study. The study [45] also reported that, a high intake of fermented dairy (250 g/day) was associated with lower TG concentration (Beta = −1.11, 95% CI, −1.96 to −0.24; $p = 0.01$) than a low intake, but this was not observed in our study. One possible explanation is that, cheese was a main part of fermented dairy in the Norwegian study [45] while in our study, the median intake of cheese was zero. On the whole, the findings indicate a need for large scale randomised trials to confirm the association of dairy products with blood lipids.

The average intake of SFA (% of energy) for this study population, Chennai urban area was 9% of total energy intake (TEI), which is within the recommended daily allowance of <10% of TEI [46]. Dairy is known to contain high amounts of SFA which is linked to elevated LDL concentration and high risk of CVDs leading to concerns about the health benefits of dairy, with some people resorting to low-fat dairy alternatives [17,47]. However, it has been noted that, SFAs are a large group of fatty acids, and their effects may vary depending on the type of food [17]. Moreover, a large multinational cohort study of 136,384 individuals from 21 countries (PURE) [17] observed no significant association between higher intake of SFA from dairy sources and total mortality or major CVD. Furthermore, odd chain fatty acids are the major SFAs in milk and they have been associated with better CVD outcomes with regards to lipids [48,49]. The association of dairy intake with favourable lipid levels

has also been linked to the presence of oleic acid, a monounsaturated fatty acid (MUFA) in dairy products [45] which is known to increase the concentration of HDL and lower the levels of LDL and TG [50–52]. Fatty acids derived from milk have also been associated with a decrease in the number of small dense LDL particles, which is linked to a favourable lipid profile since small dense LDL is negatively associated with HDL and positively associated with TG and fasting insulin levels [53]. Milk is a rich source of different nutrients [17,47], and it has been suggested that the protective effect of dairy consumption on the risk of MS is dependent on the individual as well as joint effect of the different nutrients [54,55]. Milk protein is believed to suppress angiotensin I-converting enzyme, which is involved in BP regulation [56]. Milk is also a rich source of potassium, which helps in regulating BP [57]. Whey protein derived from milk has also been reported to influence glucose levels through its involvement in the regulation of gastrointestinal hormones [55]. Fermented dairy is believed to confer greater anti-inflammatory and cardiometabolic benefits than unfermented dairy [23,24], but intake of fermented dairy was relatively low in this study, and this could have influenced our findings of fewer associations between fermented dairy and CMR. It has also been suggested that, the associations of dairy with blood lipids may be impacted by dairy matrix and fat content [45]. Moreover, findings from a large mendelian randomisation analysis of 1,904,220 individuals from three population-based studies [58] indicate that, genetic variants linked to milk consumption, might also influence BMI and lipid levels, suggesting that multiple factors are involved in the association of dairy intake with reduced risk of MS.

The strength of our study is the large sample size and the use of validated instruments in a well-characterised population. This study is one of few studies which have examined the association of total, unfermented and fermented dairy with the risk of MS in Asian Indians. Our study has some limitations. Comparing the benefits of fermented and unfermented dairy intake was not possible due to the relatively low intake of fermented dairy compared to unfermented dairy. Additionally, we did not investigate the effect of individual dairy products on the risk of MS. Furthermore, the fat content of the dairy products was not analysed in our study. Coffee and tea might also influence CVD risk independently as shown in Supplementary Table S1, but data on intake of caffeine and phenolic compounds was not available. However, we adjusted for coffee and tea intake in the regression model. Moreover, evidence from nutrigenetic studies shows that genetic variants might be involved in modifying responses to diet, which is outside the scope of this study. Nonetheless, our findings support previous work and add to the evidence linking dairy consumption to lower risk of MS and components of CMR.

5. Conclusions

We found that increased consumption of dairy ($\geq$5 cups per day of total, $\geq$4 cups per day of unfermented or $\geq$2 cups per day of fermented dairy) was associated with a lower risk of high FPG. A total dairy intake of $\geq$5 cups per day was also protective against high BP, low HDL and MS. A high unfermented dairy intake ($\geq$4 cups per day) was also associated with a lower risk of high BMI, while a reduced risk of MS was observed with a fermented dairy intake of $\geq$2 cups per day. The findings indicate that increasing the consumption of dairy might help to reduce CMR factors (high BP, BMI, FPG and low HDL) and MS in Asian Indians. Larger studies are needed to confirm our findings. Once our findings are confirmed, dietary guidelines focusing on increasing the consumption of dairy might be effective in reducing the risk of MS and components of CMR in Asian Indians.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14183699/s1, Figure S1: Study Design; Table S1: Tea and coffee consumption and its association with components of cardiometabolic risk; Figure S2: (a) total dairy intake and insulin resistance, (b) unfermented dairy intake and metabolic syndrome.

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investigation, R.W., K.S.V. and E.F.V.; resources, all authors; data curation, N.L., S.S., K.A., R.U. and K.K.; writing—original draft preparation, R.W. and K.S.V.; writing—review and editing, R.W., K.S.V., V.S., V.M. and R.M.A.; visualisation, V.M., K.S.V. and R.W.; supervision, K.S.V., V.M. and R.M.A.; project administration, V.M., K.S.V. and V.S.; funding acquisition, K.S.V., V.M. and R.M.A. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to [ethical reasons].

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Interaction between genetic risk score and dietary fat intake on lipid-related traits in Brazilian young adults

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Abstract

The occurrence of dyslipidaemia, which is an established risk factor for cardiovascular diseases, has been attributed to multiple factors including genetic and environmental factors. We used a genetic risk score (GRS) to assess the interactions between genetic variants and dietary factors on lipid-related traits in a cross-sectional study of 190 Brazilians (mean age: 21 ± 2 years). Dietary intake was assessed by a trained nutritionist using three 24-h dietary recalls. The high GRS was significantly associated with increased concentration of TAG (beta = 0·10 mg/dl, 95 % CI 0·05–0·16; $P < 0·001$), LDL-cholesterol (beta = 0·07 mg/dl, 95 % CI 0·04, 0·11; $P < 0·0001$), total cholesterol (beta = 0·05 mg/dl, 95 % CI: 0·03, 0·07; $P < 0·0001$) and the ratio of TAG to HDL-cholesterol (beta = 0·09 mg/dl, 95 % CI: 0·03, 0·15; $P = 0·002$). Significant interactions were found between the high GRS and total fat intake on TAG:HDL-cholesterol ratio ($P_{interaction} = 0·03$) and between the high GRS and SFA intake on TAG:HDL-cholesterol ratio ($P_{interaction} = 0·03$). A high intake of total fat (>31·5 % of energy) and SFA (>8·6 % of energy) was associated with higher TAG:HDL-cholesterol ratio in individuals with the high GRS (beta = 0·14, 95 % CI: 0·06, 0·23; $P < 0·001$ for total fat intake; beta = 0·13, 95 % CI: 0·05, 0·22; $P = 0·003$ for SFA intake). Our study provides evidence that the genetic risk of high TAG:HDL-cholesterol ratio might be modulated by dietary fat intake in Brazilians, and these individuals might benefit from limiting their intake of total fat and SFA.

Keywords: **Genetic risk score: Brazil: TAG to HDL-cholesterol ratio: Fat intake: SFA**

CVD are a top cause of mortality globally, accounting for 32 % of all deaths worldwide in 2019[1]. Over three-quarters of mortality from CVD has been reported to occur in low- and middle-income countries[1], highlighting the enormous impact of CVD in these countries. In Brazil, ischaemic heart disease and stroke accounted for most deaths in 2019, with a percentage increase of 18 and 14 %, respectively, from 2009[2]. An analysis of the factors contributing to death in Brazil using data from the Global Burden of Disease 2019 study[3] indicated that, more than 80 % of deaths from CVD is attributable to cardiovascular risk factors. Among the risk factors for CVD is an altered blood lipid profile (dyslipidaemia), which is evidenced by a rise in the concentration of triacylglycerol (TAG) or LDL-cholesterol and a reduction in the concentration of HDL-cholesterol[4,5].

The occurrence of dyslipidaemia has been attributed to multiple factors including genetic and environmental factors[6–11]. Dietary fatty acids are involved in modulating the metabolism of lipids and lipoproteins[12,13], and dietary recommendations to reduce CVD risk advocate for a reduction in SFA and total fat intake[14]. A high SFA intake has been associated with a rise in TAG-rich lipoproteins, which is associated with increased risk of myocardial infarction, ischaemic stroke, and other CVD[15–17]. Consumption of SFA has also been linked to a rise in circulating levels of inflammatory biomarkers[18,19] which contributes to the development of cardiometabolic diseases, including CVD[20–22]. A meta-analysis involving a total of forty-nine prospective studies[23] identified that higher concentration of circulating SFA was associated with a 50 % increased risk of CVD, 63 % increased

Abbreviations: APOA1, apolipoprotein A1; ATP2B1, ATPase plasma membrane Ca2+ transporting 1; BOLD, Obesity, Lifestyle and Diabetes in Brazil; CETP, cholesteryl ester transfer protein; GCKR, glucokinase regulator; GeNuIne, gene–nutrient interactions; GRS, genetic risk score; LIPC, hepatic lipase; LIPG, endothelial lipase; SORT1, sortilin 1; TC, total cholesterol; TEI, total energy intake.

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risk of CHD and 38 % increased risk of stroke. In a cross-sectional study of 282 Brazilian adults[24], consumption of SFA was found to be higher than the recommended intake in 79·7 % of the participants. The fat content of processed foods in Brazil was also found to be composed of high amounts of SFA, ranging from 9·3 to 12 g per 100 g of food products[25].

Evidence from genome-wide association studies has implicated several genetic loci for the development of dyslipidaemia[26–30], but these variants account for a small proportion of variability in blood lipid concentrations, and there is growing evidence that an interaction between genetic variants and environmental factors is responsible for part of the missing heritability[31–36]. Single variants often have small effect sizes and an effective approach to assessing the genetic contribution to complex traits is the use of a genetic risk score (GRS), which allows the combined effect of multiple variants to be analysed[37,38]. Single nucleotide polymorphisms (SNP) of lipid-pathway genes have been reported to contribute to variations in blood lipid concentrations[7,39–41], and the proteins encoded by these genes include cholesteryl ester transfer protein (CETP), which regulates HDL-cholesterol concentration and particle size by promoting the transfer of cholesteryl esters and TAG between lipoproteins[42]; apolipoprotein A1 (APOA1), which is the main component of HDL-cholesterol and is involved in the maturation of HDL-cholesterol[43]; glucokinase regulatory protein, which regulates the activity of glucokinase[44,45]; sortilin, which regulates plasma LDL-cholesterol by facilitating hepatic uptake of ApoB100-containing lipoproteins[46] and hepatic lipase (LIPC) and endothelial lipase (LIPG) which hydrolyse lipoproteins to release free fatty acids[47,48]. Only a few studies have utilised a GRS to assess the interactions between dietary intake and genetic variants on CVD traits in Brazilians[37,49,50], with even fewer studies focusing on young adults. Two of the studies[37,49] used data from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) cross-sectional study and involved 187 and 200 participants aged 19–24 years, respectively. Significant GRS–diet interactions were found in relation to vitamin D and glycaemic traits, respectively. The third study[50], which was also a cross-sectional study, consisted of 228 adults (19–60 years) and significant GRS–diet interactions on dyslipidaemia were reported. Hence, the aim of this study was to assess the genetic associations and the interaction of the GRS with dietary factors on lipid-related traits in Brazilian young adults.

Methods

Study participants

The study consisted of 190 young adults aged 19–24 years from the BOLD cross-sectional study[34,37]. Participants were recruited between March and June 2019 from the Federal University of Goiás. The study was performed as part of the gene–nutrient interactions (GeNuIne) collaboration, which is aimed at investigating how genetic and lifestyle factors interact to influence chronic diseases in diverse ethnic groups, with the goal of preventing and managing chronic diseases through personalised nutrition[6,51–53]. Details of the study design are published elsewhere[37,49]. In brief, a total of 416 individuals expressed interest in the study, but 207 individuals were found to be eligible. Participants were excluded if they were using lipid-lowering medication, vitamins or mineral supplements; had undergone dietary interventions in the past 6 months or undertaking vigorous physical activity or had a diagnosis of any chronic disease such as type 2 diabetes, dyslipidaemia or hypertension. Out of the 207 eligible participants, 200 completed the study; however, 190 participants were included in the present analysis after excluding participants with missing data for genetic and phenotypic measurements. The selection of the participants is shown in online Supplementary Fig. S1.

The study was approved by the Ethics Committee of the Federal University of Goiás (protocol number 3·007·456, 08/11/2018), and written informed consent was obtained from all the study participants. The study was performed in accordance with the ethical principles in the Declaration of Helsinki.

Anthropometric and biochemical measurements

Measurement of anthropometric parameters was done by trained staff from the Nutritional Genomics research group of The Federal University of Goiás, Brazil. A Tanita® (Tanita Corporation) portable electronic scale, which has a maximum capacity of 150 kg, was used to weigh participants. For height, a stadiometer with a movable rod was used, and the volunteers were asked to keep upright with heels, calves, shoulder blades and shoulders pressed against the wall, knees straight, feet together and arms extended along the body; the head raised (making a 90º angle with the ground), with the eyes looking at a horizontal plane ahead, in accordance with the Frankfurt plane. Weight and height were used to calculate the BMI using the formula: weight (kg)/the square of the height (m^2). Waist circumference was measured using an inelastic measuring tape at the midpoint between the lowest rib margin and the iliac crest[54].

Blood pressure was measured when the patient was seated, positioning the arm at heart level. Three measurements were taken, with 5-min intervals between them. At the end, the average of the three measurements was considered, as proposed by the American Heart Association[55] and approved by the VI Brazilian Guideline on Hypertension[54].

Approximately 10 ml of venous blood was collected from the medial cubital vein following a 12-h fasting period. The blood collection procedure was performed by a trained healthcare professional using single-use materials. Participants were instructed to abstain from consuming alcohol for 72 h and avoid engaging in strenuous physical activity for 24 h prior to the blood collection. The samples were processed immediately after collection at the Romulo Rocha Laboratory (Goiânia, Brazil). The levels of TAG, total cholesterol (TC) and HDL-cholesterol were assessed using direct enzymatic colorimetry. LDL-cholesterol levels were calculated using the Friedewald, Levy, and Fredrickson equation (1972)[56].

Dietary assessment

Dietary intake was assessed by a trained nutritionist using three 24-h dietary recalls consisting of non-consecutive days, including one weekend[57]. The nutritionist conducted the first interview in person according to multiple-pass method[58], and

the following two interviews were conducted via phone calls. To assist in estimating portion sizes of various foods, participants were provided with measuring equipment such as measuring cups and spoons. Intake of nutrients and energy was determined from the dietary recalls using the Avanutri Online® diet calculation software (Avanutri Informática Ltda) with three Brazilian food composition databases, Brazilian Institute of Geography and Statistics, 2011[59], food composition table-support for nutritional decision making (2016)[60] and food studies and research centre-Brazilian food composition table (2011)[61]. For processed or ultra-processed foods that were not in the databases, the information in the label was manually added.

Single nucleotide polymorphism selection and genotyping

A total of seven SNP representing seven loci were selected for this study based on their association with lipid-related traits at a genome-wide significance level ($P < 5 \times 10^{-8}$): *CETP* SNP rs3764261[26,62–66], glucokinase regulator (*GCKR*) SNP rs1260326[26,41,65,67–70], endothelial lipase (*LIPG*) SNP rs7241918[26,71–73], sortilin 1 (*SORT1*) SNP rs629301[26,71,72], hepatic lipase (*LIPC*) SNP rs1532085[26,65,70,74], apolipoprotein A1 (*APOA1*) SNP rs964184[26,27,68,75–79] and ATPase plasma membrane Ca2+ transporting 1 (*ATP2B1*) SNP rs2681472[80–83]. Table 1 shows the SNP, effect sizes, *P*-values and the genome-wide association studies. A review by our team[7] indicated that the *CETP* gene had the highest number of reported associations with lipid traits, and it was concluded that SNP of the *CETP* gene could potentially alter blood lipid profiles by interacting with diet. The *GCKR* gene was chosen as it has been reported to influence alterations in blood lipid profiles[90–95]. The *LIPG* gene, another key lipid metabolism gene has been reported to play a role in inflammation and could influence the risk of CVD[48,96,97]. Furthermore, the *SORT1* gene is considered the strongest genome-wide LDL-cholesterol associated locus[27,62,98–101] and the *LIPC* gene is also a main lipid-pathway gene which has been associated with abnormal lipid profiles[26,65,72,74,88]. Additionally, the *APOA1* gene has been widely studied and has been linked with variations in blood lipid levels[26,28,76,78,85] and the risk of CVD[102–105]. Similarly, the *ATP2B1* gene has been reported to influence the risk of developing CVD[80,81,83,89,104]. Six of the SNP included in our GRS (rs3764261, rs1260326, rs7241918, rs629301, rs1532085, rs964184) had previously been included in a GRS by a genetic association study involving 6358 participants from the Multi-Ethnic Study of Atherosclerosis Classic cohort[106] which observed significant associations between the GRS and lipid traits. The genotyping procedure has been previously published[49]. Briefly, blood samples (3 ml each) for genotyping were collected in BD Vacutainer® ethylenediamine tetraacetic acid (EDTA) tubes and kept at a controlled temperature of –80°C during transportation by the World Courier Company. Genotyping was performed by LGC Genomics, London, UK (http://www.lgcgroup.com/services/genotyping), using the competitive allele-specific PCR-KASP® assay.

Construction of genetic risk score

To construct the GRS, each SNP was first tested for independent association with the lipid-related traits using linear regression analysis, adjusted for age, sex and BMI. An unweighted GRS was then constructed by summing the number of risk alleles across all the seven SNP (*CETP* rs3764261, *GCKR* rs1260326, *LIPG* rs7241918, *SORT1* rs629301, *LIPC* rs1532085, *APOA1* rs964184 and *ATP2B1* rs2681472) for each participant. For each SNP, a score of 0, 1 or 2 was assigned depending on whether the participant carried no risk alleles (homozygous for the non-risk allele), one risk allele (heterozygote) or two risk alleles (homozygous for the risk allele). The scores for the seven SNP were then added up to create the GRS. The effect sizes of the SNP were not considered and the GRS for each participant represented the total number of risk alleles they carried from the seven SNP. An unweighted GRS was used because although we selected SNP which have shown associations with lipid-related traits, the studies were not conducted in the Brazilian population, and it has been reported that effect sizes may vary across populations and data from a genome-wide association study conducted in one population may not apply to another population[31,107]. Moreover, assigning weights to risk alleles has been shown to have minimal effect[108]. The risk alleles were defined as alleles previously reported to be associated with increased concentration of TAG, LDL-cholesterol or TC; or reduced concentration of HDL-cholesterol; or increased risk of coronary artery disease or myocardial infarction. The GRS ranged from 1 to 10, and the median GRS (6 risk alleles) was used as a cut-off point for grouping participants as low risk (GRS < 6 risk alleles) or high risk (GRS ≥ 6 risk alleles).

Statistical analysis

An independent sample t test was used to compare the means of continuous variables between men and women. The results for descriptive statistics are presented as means and SD. To test for normality, the Shapiro–Wilk test was used and all the biochemical, anthropometric and dietary variables, except total fat, carbohydrate, and MUFA intake (percentages of total energy intake (TEI)), were log-transformed prior to the analysis. Allele frequencies were determined by gene counting and Hardy–Weinberg equilibrium was calculated using the Chi-square test. All the seven SNP were in Hardy–Weinberg equilibrium ($P > 0{\cdot}05$) (online Supplementary Table S1), and the alleles had a frequency >5 %.

Linear regression was used to test the association of the GRS with lipid levels and blood pressure, with adjustment for age, sex and BMI. To determine interactions between the GRS and dietary factors on the outcome variables (TAG, TAG:HDL-cholesterol ratio, HDL-cholesterol, LDL-cholesterol, TC, systolic blood pressure (SBP), and diastolic blood pressure (DBP)), the interaction term was included in the regression model. The dietary factors examined were the intakes of fat, carbohydrate, and protein. Statistically significant GRS–diet interactions ($P < 0{\cdot}05$) were investigated further by stratifying participants according to the quantity of dietary intake. A significant

Table 1. SNP used to construct the GRS and the reported traits by genome-wide association studies

Gene and SNP	Effect allele	Lipid trait and effect size in mg/dl (*P* value)								Population and sample size	GWA Study
		HDL-cholesterol		LDL-cholesterol		TAG		TC			
CETP rs3764261	A	+0·24	1×10^{-769}	−0·05	2×10^{-34}	−0·04	2×10^{-25}	+0·05	4×10^{-31}	European ancestry (UK, Finland, Sweden, USA, Italy, Greece, Germany, Estonia, Norway) *n* 94 595	Willer *et al.* (2013)[72]
	A	+3·39	7×10^{-380}			−2·88	1×10^{-12}	+1·67	7×10^{-14}	European ancestry (Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) *n* 99 900 for HDL *n* 96 598 for TAG *n* 100 184 for TC	Teslovich *et al.* (2010)[26]
	A	+3·48	7×10^{-29}							Northern Finnish Founder *n* 4763	Sabatti *et al.* (2009)[65]
	A	+0·20*	9×10^{-18}							African American *n* 7813	Lettre *et al.* 2011[63]
	A	+3·18*	7×10^{-43}							Indian *n* 1036	Khushdeep *et al.* 2019[66]
CETP rs3764261	A	+6·20	3×10^{-12}							Japanese *n* 900	Hiura *et al.* 2009[64]
LIPG rs7241918	G	−1·31	3×10^{-49}							European ancestry (Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) *n* 99 900	Teslovich *et al.* (2010)[26]
	A							−1·94	2×10^{-19}	European ancestry (Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) *n* 100 184	Teslovich *et al.* (2010)[26]
	G	−0·09*	1×10^{-44}					−0·06*	4×10^{-18}	European ancestry (UK, Finland, Sweden, USA, Italy, Greece, Germany, Estonia, Norway) *n* 94 595	Willer *et al.* (2013)[72]
LIPG rs7241918	G	−0·08*	4×10^{-55}	−0·02*	1×10^{-8}					European ancestry *n* 115 082	Richardson *et al.* (2022)[84]
	A	+0·02*	3×10^{-27}							Multi-ancestry (African: *n* 23 761; Asian: *n* 13 171; European: *n* 90 272; Hispanic or Latin American: *n* 6620)	Bentley *et al.* 2019[71]
GCKR rs1260326	T					+8·76	6×10^{-133}	+1·91	7×10^{-27}	European ancestry (Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) *n* 96 598 for TAG *n* 100 184 for TC	Teslovich *et al.* (2010)[26]
	T					+0·12	2×10^{-239}	+0·05*	3×10^{-42}	European ancestry (UK, Finland, Sweden, USA, Italy, Greece, Germany, Estonia, Norway) *n* 94 595	Willer *et al.* (2013)[72]
GCKR rs1260326	T					+0·12*	2×10^{-31}			European (UK, Finland, Sweden, USA, Italy, France) *n* 19 840	Kathiresan *et al.* (2009)[28]

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Table 1. (*Continued*)

Gene and SNP	Effect allele	Lipid trait and effect size in mg/dl (*P* value) HDL-cholesterol	LDL-cholesterol	TAG	TC	Population and sample size	GWA Study
	T			+0·12* 5×10^{-88}	+0·05* 3×10^{-13}	European (UK, Finland, Sweden, Iceland, Netherlands, Germany, Estonia) *n* 62 166	Surakka *et al.* (2015)[85]
	T		+0·03* 6×10^{-60}			European ancestry *n* 440 546	Richardson *et al.* (2020)[73]
	T			1·41† 2×10^{-13}		Mexican *n* 2240	Weissglas-Volkov *et al.* (2013)[41]
	T		+0·03* 7×10^{-10}			Multi-ancestry (European: *n* 76 627; Hispanic: *n* 7795; East Asian: *n* 6855; African American: *n* 2958; South Asian: *n* 439)	Hoffman *et al.* 2018[86]
SORT1 rs629301	G		–5·65 1×10^{-170}		–5·41 6×10^{-131}	European ancestry (UK, Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, Croatia, Switzerland, Austria, France, Denmark) *n* 100 184 for TC *N* 95 454 for LDL-C	Teslovich *et al.* (2010)[26]
	G		–0·17* 5×10^{-241}		–0·13* 2×10^{-170}	European ancestry (UK, Finland, Sweden, USA, Italy, Greece, Germany, Estonia, Norway) *n* 94 595	Willer *et al.* (2013)[72]
	G	+0·04* 4×10^{-15}			–0·14* 7×10^{-135}	Multi-ancestry (European: *n* 76 627; Hispanic: *n* 7795; East Asian: *n* 6855; African American: *n* 2958; South Asian: *n* 439)	Hoffman *et al.* 2018[86]
	T		+4·46* 1×10^{-128}			Multi-ancestry (African: *n* 23 761; Asian: *n* 13 171; European: *n* 90 272; Hispanic or Latin American: *n* 6620)	Bentley *et al.* 2019[71]
SORT1 rs629301	G		–6·03* 2×10^{-72}		–5·80* 2×10^{-57}	European *n* 29 902	Kulminski *et al.* (2020)[87]
	T		+0·11* 2×10^{-31}			Japanese *n* 72 866	Sakaue *et al.* (2021)[83]
LIPC rs1532085	A	+0·11* 1×10^{-188}			+0·05* 7×10^{-47}	European ancestry (UK, Finland, Sweden, USA, Italy, Greece, Germany, Estonia, Norway) *n* 94 595	Willer *et al.* (2013)[72]
	A	+0·11* 1×10^{-213}				Multi-ancestry European: *n* 187 167; East Asian (China, Japan, Republic of Korea, Philippines, Singapore, Taiwan): *n* 34 930	Spracklen *et al.* (2017)[88]
LIPC rs1532085	G	–0·13* 1×10^{-35}				European ancestry (UK, Finland, Sweden, Australia, Italy, Netherlands, Germany, Croatia, Norway, Denmark) *n* 21 412	Aulchenko *et al.* 2009[74]
	G			+2·99 2×10^{-13}		European ancestry (Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, UK, Croatia, Switzerland, Austria, France, Denmark) *n* 96 598	Teslovich *et al.* (2010)[26]
	A	+1·90 2×10^{-10}				Northern Finnish Founder *n* 4763	Sabatti *et al.* 2009[65]
APOA1 rs964184	G		+2·85 1×10^{-26}	+16·95 7×10^{-240}		European ancestry (UK, Finland, Sweden, USA, Australia, Iceland, Italy, Netherlands, Germany, Croatia, Switzerland, Austria, France, Denmark)	Teslovich *et al.* (2010)[26]

Table 1. (*Continued*)

Gene and SNP	Effect allele	Lipid trait and effect size in mg/dl (*P* value) HDL-cholesterol	LDL-cholesterol	TAG	TC	Population and sample size	GWA Study
APOA1 rs964184	G			+0·24* 2×10^{-157}		*n* 96 598 for TAG; *n* 95 454 for LDL-cholesterol European (UK, Finland, Sweden, Iceland, Netherlands, Germany, Estonia)	Surakka *et al.* (2015)[85]
	G	–0·03* 2×10^{-11}				*n* 62 166 European (UK, Finland, Italy, Switzerland)	Waterworth *et al.* 2010[76]
	G	–0·05* 3×10^{-12}		+0·16* 4×10^{-33}		*n* 17 723 African American: *n* 7601, Hispanic: *n* 3335 for TAG; African American: *n* 7917, Hispanic: *n* 3506 for HDL-cholesterol	Coram *et al.* 2013[78]
	G	–0·17 1×10^{-12}		+0·30* 4×10^{-62}		European ancestry (UK, Finland, Sweden, USA, Italy, France) *n* 19 840	Kathiresan *et al.* (2009)[28]
		CAD	**MI**				
ATP2B1 rs2681472	G	1·07† 8×10^{-11}				European *n* 63 731	Nelson *et al.* 2017[81]
ATP2B1 rs2681472	G		+0·07* 1×10^{-11}			European (UK, Finland): *n* 461 823; Japanese: *n* 161 206	Sakaue *et al.* (2021)[83]
	G		1·08† 6×10^{-9}			European: *n* 126630, Hispanic or Latin American (USA): *n* 3615, Middle Eastern, North African or Persian: *n* 754, African American or Afro-Caribbean (USA): *n* 2908, South Asian (India, UK, Pakistan): *n* 23 156; East Asian (Republic of Korea, China): *n* 9396	Nikpay *et al.* (2015)[80]
	G		1·07† 1×10^{-12}			European *n* ~472 000	Hartiala *et al.* (2021)[89]

SNP, single nucleotide polymorphism; GRS, genetic risk score; TC, total cholesterol; GWA, genome-wide association.
* Effect sizes are in units of SD.
† OR.

Table 2. Characteristics of study participants by sex

	All (*n* 190)		Women	(*n* 141)	Men	(*n* 49)	
	Mean	SD	Mean	SD	Mean	SD	*P* Value
Age (years)	21	2	21	2	22	2	0·17
BMI (kg/m^2)	23	1	23	1	24	1	**0·01**
WC (cm)	72	1	69	1	83	1	**<0·001**
TAG (mg/dl)	76	2	76	2	75	2	0·81
TAG:HDL ratio	2	2	1	2	2	2	**0·01**
HDL-cholesterol (mg/dl)	55	1	59	1	46	1	**<0·0001**
LDL-cholesterol (mg/dl)	99	1	100	1	99	1	0·80
TC (mg/dl)	174	1	178	1	163	1	**0·01**
SBP (mmHg)	107	1	105	1	114	1	**<0·0001**
DBP (mmHg)	64	1	63	1	67	1	**<0·001**
Energy (kcal/day)	1735	1	1668	1	1944	1	**0·003**
Total fat (% of energy)	32	6	32	6	31	6	0·14
SFA (% of energy)	9	1	9	1	9	1	0·84
MUFA (% of energy)	8	3	8	3	8	3	0·07
PUFA (% of energy)	5	2	5	2	5	2	0·08
Carbohydrate (% of energy)	51	7	51	7	51	8	0·88
Protein (% of energy)	17	1	16	1	18	1	**0·04**

WC, waist circumference; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
P values for the differences in means between men and women were calculated using independent sample *t* test.

interaction between the GRS and total fat intake was explored further by analysing the effects of subtypes of fat (SFA, MUFA and PUFA). The median intake of total fat, SFA, MUFA and PUFA was used as a cut-off point to place participants into groups: 'low' (for participants with an intake lower than or equal to the median) and 'high' (for those with an intake higher than the median); and the effect of the GRS on the outcome was examined for participants in each group. The Bonferroni adjusted *P*-value for association was 0·007 (1GRS * 7 outcome variables = 7 tests; 0·05/7 = 0·007), and for interaction, it was 0·002 (1GRS * 7 outcome variables*3 dietary factors = 21 tests; 0·05/21 = 0·002). The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA). Additionally, the GRS was scaled by converting the scores to units of standard deviation from the mean[109] and the association of the GRS as a continuous variable with the lipid-related traits was tested by linear regression using the R software version 4·3·1[110].

Power and sample size calculation. Power calculation was performed using the QUANTO software, version 1·2·4 (May 2009)[111] in the form of minimum detectable effect at 80 % power and a significance level of 5 %. For an SNP with a minor allele frequency of 5 %, the minimum detectable effect at 80 % power was 6·6 mg/dl for TC, LDL-cholesterol and TAG. For an SNP with a minor allele frequency of 50 %, the minimum detectable effect at 80 % power was 2·9 mg/dl for TC, LDL-cholesterol and TAG.

Results

Characteristics of the study participants

The demographic and clinical characteristics of the participants in this study are summarised in Table 2. The mean age of the sample was 21 ± 2 years, and men had higher BMI and waist circumference than women ($P = 0·01$ and $P < 0·001$, respectively). Women, however, had higher concentrations of HDL-cholesterol ($P < 0·0001$) and TC ($P = 0·01$) but lower TAG:HDL-cholesterol ratio ($P = 0·006$), SBP ($P < 0·0001$), and DBP ($P < 0·001$) than men. Intakes of total energy and protein were higher in men than in women ($P = 0·003$ and $P = 0·04$, respectively), but consumption of total fat, SFA, MUFA, PUFA and carbohydrate did not differ significantly between men and women. Table 3 shows the characteristics of the study participants according to GRS. Participants with a high GRS had a significantly lower intake of energy ($P = 0·02$) than those with a low GRS. No other significant differences were observed between participants in the two groups. The distribution of the GRS across deciles of TC, LDL-cholesterol, TAG and TAG:HDL ratio is presented in online Supplementary Fig. S2.

Association of the genetic risk score with blood lipids

Four significant associations were identified between the GRS and lipid traits where individuals carrying six or more risk alleles had significantly higher TAG, LDL-cholesterol and TC concentrations, as well as higher TAG:HDL-cholesterol ratio compared with participants with less than six risk alleles (Table 3). When the GRS was tested as a continuous variable, each standard deviation increase in the GRS was associated with a 1·05 mg/dl increase (95 % CI 1·02, 1·07) in the concentration of TC ($P = 0·002$); 1·07 mg/dl increase (95 % CI 1·03, 1·12) in the concentration of LDL-cholesterol ($P < 0·001$); 1·14 mg/dl increase (95 % CI 1·07, 1·21) in the concentration of TAG ($P < 0·0001$) and a 1·16 mg/dl increase (95 % CI 1·09, 1·24) in TAG:HDL-cholesterol ratio ($P < 0·0001$). All the associations remained significant after Bonferroni correction for multiple testing. The distribution of the lipid-related traits across deciles of the GRS is presented in Fig. 1. As the decile of the GRS increased, the concentration of TC, TAG, LDL-cholesterol and TAG:HDL also increased.

Table 3. Association of GRS with blood lipids and blood pressure and the characteristics of the participants stratified by GRS

	GRS < 6 (*n* 92)		GRS ≥ 6 (*n* 98)		
Trait	Mean	SE	Mean	SE	*P* value
TAG (mg/dl)	67·3	1·0	84·9	1·0	**<0·001**
TAG:HDL-cholesterol ratio	1·2	1·0	1·5	1·0	**0·002**
HDL-cholesterol (mg/dl)	54·5	1·0	55·5	1·0	0·56
LDL-cholesterol (mg/dl)	91·4	1·0	107·6	1·0	**<0·0001**
TC (mg/dl)	164·1	1·0	183·7	1·0	**<0·0001**
SBP (mmHg)	106·9	1·0	107·2	1·0	0·69
DBP (mmHg)	63·2	1·0	64·1	1·0	0·48
	GRS < 6 (*n* 92)		GRS ≥ 6 (*n* 98)		
Characteristic	Mean	SD	Mean	SD	*P* value*
Age (years)	21	2	21	2	0·28
Sex (W/M)	67/27	–	78/26	–	0·56
BMI (kg/m^2)	23	1	23	1	0·97
WC (cm)	73	1	72	1	0·59
Energy (kcal/day)	1827	1	1648	1	**0·02**
Total fat (% of energy)	32	6	32	6	0·99
SFA (% of energy)	9	1	9	1	0·45
MUFA (% of energy)	8	2	8	3	0·27
PUFA (% of energy)	5	1	4	2	0·12
Carbohydrate (% of energy)	51	7	50	7	0·68
Protein (% of energy)	17	1	17	1	0·84

GRS, genetic risk score; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; W, women; M, men.
P values were obtained from linear regression analysis with adjustment for age, sex and BMI. Log-transformed variables were used for the analysis and values in bold represent significant associations.
* *P* values for the differences in means between participants with low GRS and those with high GRS were obtained using independent sample *t* test. The distribution of sex in the two groups was compared using the χ^2 test.

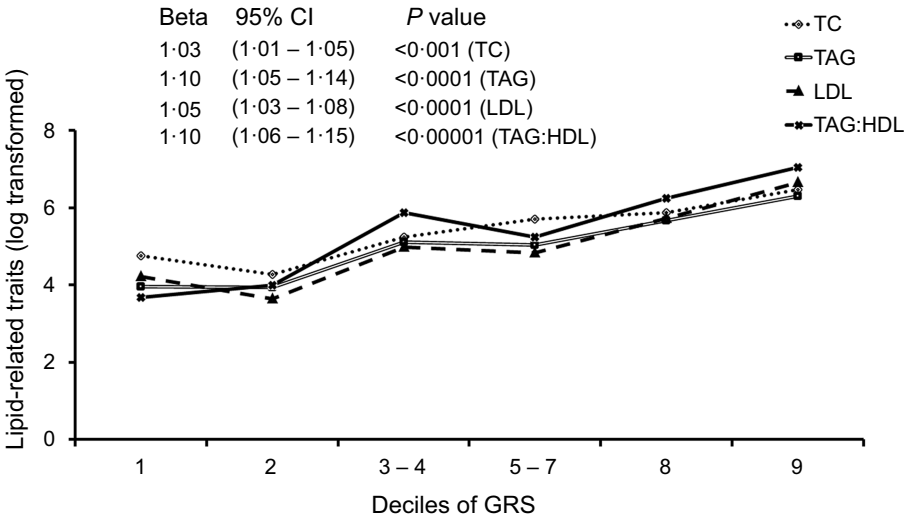

Fig. 1. Distribution of lipid-related traits across deciles of GRS (genetic risk score). TC (total cholesterol), LDL-cholesterol (low-density lipoprotein cholesterol), TAG (triacylglycerol), TAG:HDL-cholesterol (TAG to high-density lipoprotein cholesterol ratio). GRS, genetic risk score; TC, total cholesterol.

Interaction between genetic risk score and dietary factors on blood lipids

There was a significant interaction between GRS and total fat intake on TAG:HDL-cholesterol ratio ($P_{interaction} = 0·03$) as shown in Table 4. In the high total fat intake group (>31·5 % of TEI), participants carrying six or more risk alleles had a higher TAG:HDL-cholesterol ratio compared with those carrying less than six risk alleles (beta = 0·14, 95 % CI: 0·06, 0·23; $P < 0·001$) (Fig. 2(a)). No significant difference in TAG:HDL-cholesterol ratio was found between participants with a high GRS (≥6 risk alleles) and those with a low GRS (<6 risk alleles) in the low total fat intake group (≤31·5 % of TEI). When subtypes of fat were investigated, a significant interaction was found between GRS and SFA intake on TAG:HDL-cholesterol ratio ($P_{interaction} = 0·03$) (Fig. 2(b)), where a high SFA intake (>8·6 % of TEI) was associated with a higher TAG:HDL-cholesterol ratio in

Table 4. Interaction between GRS and dietary factors on blood lipids and blood pressure

	GRS * Protein (% of energy)			GRS * Fat (% of energy)			GRS * Carbohydrate (% of energy)		
Trait	Beta coefficient	SE	$P_{interaction}$	Beta coefficient	SE	$P_{interaction}$	Beta coefficient	SE	$P_{interaction}$
TAG (mg/dl)	0·33	0·30	0·27	0·01	0·01	0·26	–0·004	0·004	0·30
TAG:HDL-cholesterol ratio	0·28	0·32	0·39	0·01	0·01	**0·03**	–0·01	0·004	0·06
HDL-cholesterol (mg/dl)	0·06	0·14	0·70	–0·01	0·002	**0·007**	0·004	0·002	0·05
LDL-cholesterol (mg/dl)	0·29	0·18	0·12	–0·001	0·003	0·75	0·001	0·002	0·69
TC (mg/dl)	0·22	0·13	0·10	–0·002	0·002	0·35	0·001	0·002	0·46
SBP (mmHg)	0·002	0·05	0·96	–0·0002	0·001	0·83	–0·001	0·001	0·17
DBP (mmHg)	–0·03	0·08	0·71	0·00004	0·001	0·98	–0·001	0·001	0·31

GRS, genetic risk score; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
P values were obtained from linear regression analysis with adjustment for age, sex and BMI. Log-transformed variables were used for the analysis and values in bold represent significant interactions.

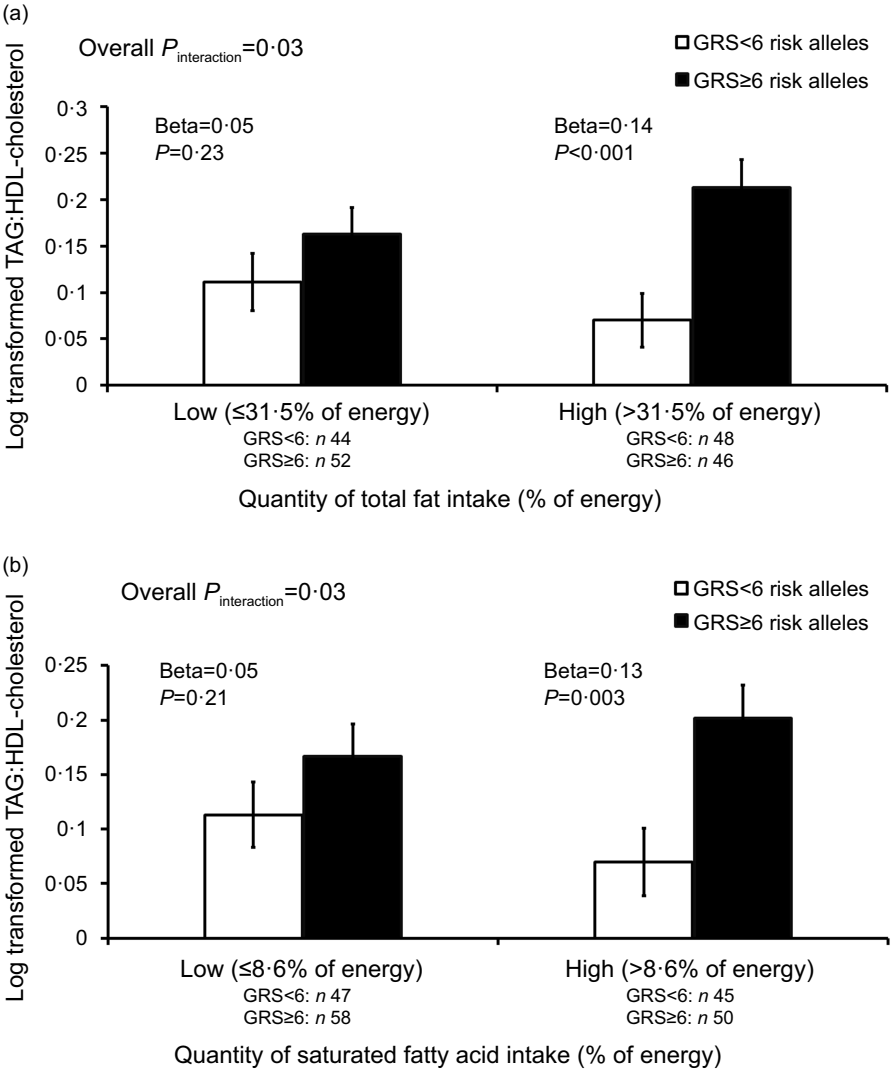

Fig. 2. **(a)** Interaction between GRS (genetic risk score) and total fat intake on TAG:HDL-cholesterol (TAG to high-density lipoprotein cholesterol) ratio. Low refers to total fat intake lower or equal to the median and high refers to total fat intake above the median. In the high total fat intake group, participants with a high GRS (≥6 risk alleles) had higher TAG:HDL-cholesterol ratio than those with a low GRS (<6 risk alleles). There was no significant difference in TAG:HDL-cholesterol ratio in the low total fat intake group. **(b)** Interaction between GRS (genetic risk score) and SFA intake on TAG:HDL-cholesterol (TAG to HDL-cholesterol ratio). Low refers to SFA intake lower or equal to the median and high refers to SFA intake above the median. A high intake of SFA was associated with higher TAG:HDL-cholesterol in participants with a high GRS compared with those with a low GRS, but no significant difference in TAG:HDL-cholesterol was observed when SFA intake was low. GRS, genetic risk score.

participants with a high GRS compared with those with a low GRS (beta = 0·13, 95 % CI: 0·05, 0·22; $P = 0·003$), but there was no significant difference in TAG:HDL-cholesterol ratio when SFA intake was low (≤8·6 % of TEI). A significant interaction was also observed between GRS and total fat intake on HDL-cholesterol concentration ($P_{interaction} = 0·007$). However, when individuals were stratified according to quantity of total fat intake, there was no significant association between the GRS and HDL-cholesterol concentration. The interactions did not pass the Bonferroni threshold.

Discussion

Our findings provide evidence that the genetic risk for disturbances in blood lipids concentration might be modulated by dietary fat intake. Significant interactions were found between the GRS and total fat intake on TAG:HDL-cholesterol ratio and between the GRS and SFA intake on TAG:HDL-cholesterol ratio. Increased consumption of total fat (>31·5 % of energy) and SFA (>8·6 % of energy) was associated with higher TAG:HDL-cholesterol ratio in participants carrying ≥6 risk alleles compared with those with <6 risk alleles. The results suggest that the TAG:HDL ratio in Brazilian young adults with a high genetic risk for disturbances in lipid-related traits maybe responsive to dietary fat intake; hence, interventions targeting a reduction in total fat and SFA intake could potentially benefit these individuals. Although the interactions did not pass the Bonferroni threshold, three of the SNP included in our GRS (*CETP* rs3764261, *APOA1* rs964184 and *GCKR* rs1260326) have previously been reported to interact with dietary fat intake and influence lipid-related traits. In a study involving two trials (a 2-year randomised weight loss trial (POUNDS LOST) consisting of 732 overweight/obese adults and a replication in 171 overweight/obese adults from an independent 2-year randomised weight loss trial (DIRECT))[112], significant interactions were observed between the *CETP* SNP rs3764261 and dietary fat intake on changes in the concentration of HDL-cholesterol and TAG (pooled $P_{interaction} < 0·01$). Similarly, a prospective, randomised, single-blind controlled dietary intervention trial (Coronary Diet Intervention With Olive Oil and Cardiovascular Prevention) involving 424 Spanish individuals with metabolic syndrome[113] found significant interactions between the *CETP* SNP rs3764261 and Mediterranean diet on the concentration of HDL-cholesterol ($P_{interaction} = 0·006$) and TAG ($P_{interaction} = 0·04$). In another study consisting of 734 overweight/obese adults from the POUNDS LOST trial[114], the *APOA1* SNP rs964184 was also found to interact with dietary fat intake in relation to changes in the concentration of HDL-cholesterol, LDL-cholesterol and total cholesterol ($P_{interaction} = 0·006$, 0·02 and 0·007, respectively). Additionally, a cross-sectional study of 3342 individuals (1671 sib pairs) in India[115] found a significant interaction between the *APOA1* SNP rs964184 and dietary fat intake on the concentration of TAG ($P = 0·04$). This study[115] also observed significant interactions between the *CETP* SNP rs3764261 and dietary fat intake on the concentrations of total cholesterol ($P = 0·02$) and LDL-cholesterol ($P = 0·04$). Furthermore, an interaction between the *GCKR* SNP rs1260326 and MUFA intake on HDL-cholesterol concentration was reported in a cross-sectional study of 101 participants of different ethnicities in the USA population ($P_{interaction} = 0·02$)[116]. Therefore, the interactions in our study cannot be ruled out completely; hence, a replication is warranted.

The ratio of TAG:HDL-cholesterol has been identified as an independent predictor of CHD, mortality from CVD and insulin resistance[16,17,117,118]. Hence, our findings have significant public health implications in terms of prevention and management of dyslipidaemia in individuals with a high genetic risk. Our data support the recommendations of the WHO[14] to reduce the intake of total fat and SFA to less than 30 % and 10 % of energy intake, respectively, to help prevent cardiometabolic diseases. Our findings are also in agreement with the dietary guidelines for Brazilians which recommend decreasing the intake of food rich in solid fat and added sugar and limiting the daily energy intake from total fat to less than 30 %[119,120].

In the current study, the GRS was positively associated with the concentration of TAG, LDL-cholesterol and TC and the ratio of TAG:HDL-cholesterol. Our findings are consistent with those of a study involving 8526 participants from two Danish cohorts[121] (a randomised nonpharmacological intervention study (Inter99), *n* 5961; and a population-based epidemiological study (Health2006), *n* 2565), in which a positive association was identified between lipid-GRS and the concentration of TAG (beta = 1·4 % mmol/l, $P < 0·0001$); LDL-cholesterol (beta = 0·024 mmol/l, $P < 0·0001$) and TC (beta = 0·027 mmol/l, $P < 0·0001$). Similarly, a prospective study of 3495 Swedish participants[122] reported significant associations between lipid-GRS and changes in the concentration of TC and TAG after a 10-year follow up (beta = 0·02 mmol/l per effect allele, $P < 0·0001$ for TC; beta = 0·02 mmol/l per effect allele, $P < 0·0001$ for TAG). The European Prospective Investigation of Cancer-Norfolk cohort study, consisting of 20 074 participants[123], also found a positive association between a lipid-GRS and the concentration of TAG (beta = 0·25 mmol/l, 95 % CI 0·22, 0·27 per allele change; $P < 0·001$), indicating the role of genetic polymorphisms in predicting variability in blood lipid concentration.

A systematic review and meta-analysis of six prospective studies including 10 222 participants[16] reported that, in patients with CHD, those with elevated TAG:HDL-cholesterol ratio had increased risk of all-cause mortality (hazard ratio = 2·92, 95 % CI 1·75, 4·86; $P < 0·05$) and major adverse cardiovascular events (hazard ratio = 1·56, 95 % CI 1·11, 2·18; $P < 0·05$) compared with those with lower TAG:HDL-cholesterol ratio. In line with our findings, a study conducted in 228 Brazilian adults[50] reported a significant interaction between a GRS based on lipid metabolism genes and intake of solid fat, alcoholic beverages and added sugar on the risk of dyslipidaemia ($P_{interaction} < 0·001$), where participants with a high GRS had a lower risk of dyslipidaemia when their intake of solid fat, alcoholic beverages and added sugar was below the median. Similarly, a prospective randomised controlled trial involving 523 Spanish patients with coronary artery disease from the Coronary Diet Intervention With Olive Oil and Cardiovascular Prevention study[124] reported that, carriers of the risk allele ('G' allele) of *APOA1* SNP rs964184 who consumed a low-fat diet (containing <30 % of total fat) had reduced post-prandial TAG concentrations after 3 years, while

'G' allele carriers on a Mediterranean diet (containing a minimum of 35 % of total fat) continued to have higher post-prandial TAG concentrations. Along these lines, a fat response genetic score based on SNP showing a positive interaction with dietary fat in relation to LDL-cholesterol was found to predict a 1-year change in LDL-cholesterol in a sample of 422 Black and Hispanic participants from the Women's Health Initiative cohort[125]. A significant interaction was identified between the dietary modification trial arm and fat response genetic score for LDL-cholesterol concentration ($P = 0{\cdot}002$), where participants in the control arm showed a trend towards minimal reductions in LDL-cholesterol concentrations at higher fat response genetic scores, while the opposite trend was observed in participants following a low-fat diet[125]. Taking together, these findings suggest that the genetic susceptibility to dyslipidaemia could be modulated by dietary fat intake in different populations.

A nationwide dietary survey involving 32 749 Brazilian individuals (≥10 years old)[126] highlighted a change in dietary pattern in Brazil which is characterised by increased consumption of processed foods rich in fat and simple sugars. An increase in the consumption of ultra-processed food among Brazilians aged ≥10 years was also reported in a study using food consumption data from 2008–2009 (*n* 34 003) to 2017–2018 (*n* 46 164) Household Budget Surveys[127]. Similarly, an assessment of the diet quality of Brazilians using data from the national survey[119] showed that, in 60 % of the population, the mean SFA intake was 10·7 % of TEI, which exceeds the WHO's recommendation of <10 % of TEI[14]. The study[119] also reported that solid fat and added sugar contributed more than 45 % of TEI. In the present study, the median intake of total fat was 31·5 % of TEI which is more than the recommended intake of <30 %[14]; however, the median intake of SFA (8·6 % TEI) was within the recommended level[14]. This suggests that individuals who have a genetic predisposition to dyslipidaemia may find greater benefit from adhering to dietary recommendations.

The mechanisms through which dietary fat intake affects blood lipid concentration have been examined by several studies[12,128–131]. Dietary fatty acids affect lipid metabolism through the activation of several transcription factors and nuclear receptors including PPAR and liver X receptors[128,131]. PPAR regulate the expression of different genes involved in lipid and lipoprotein metabolism, and the activation of PPAR is positively correlated with the chain length and degree of unsaturation of fatty acids[12,128,131]. SFA are also believed to decrease LDL-cholesterol receptor activity which slows the clearance of TAG-rich lipoproteins[128], and this could explain the increased TAG:HDL-cholesterol ratio observed among participants in the high SFA intake group. Consumption of SFA has also been shown to suppress the expression of genes involved in fatty acid oxidation and synthesis of TAG[12] and promote the expression of inflammatory genes[132]. However, SFA of different chain lengths and from different food sources have been reported to exert different effects on cardiometabolic traits[133,134].

The main strength of our study is the use of a GRS based on established lipid metabolism genes. Our study is one of few studies which have utilised this approach to explore CVD traits in Brazilian young adults, considering the increased prevalence of CVD in young people aged 15–49 years in Brazil in 2019[135]. The GRS approach is more effective in assessing the genetic contribution to complex traits such as blood lipid concentration since single variants often have moderate effect sizes and hence less likely to accurately predict the genetic risk of multifactorial traits[11,35,136]. Another strength is the use of validated techniques and trained personnel to assess biochemical, anthropometric and dietary variables, which enhances the accuracy of the assessments. However, our study has some limitations. The small sample size could have influenced our findings since large sample sizes improve the power to detect interactions with small effects[137,138]. Given that we did not have access to another Brazilian young adult cohort, we were not able to replicate our study findings. However, we were able to replicate previously reported associations and interactions. Another limitation is the use of self-reported dietary recalls that can introduce bias through overestimation and underestimation of dietary intake[139,140]. Moreover, we did not investigate types or food sources of SFA, which have been reported to have different effects on CVD traits[133,141]. Additionally, the cross-sectional design means that causality between dietary fat intake and TAG:HDL-cholesterol ratio cannot be established[31].

In conclusion, our study provides evidence that the genetic risk of increased TAG:HDL-cholesterol ratio might be modulated by dietary fat intake. The findings indicate that Brazilian young adults with a high genetic risk for dyslipidaemia might benefit from limiting their intake of total fat and SFA. Our results support the dietary guidelines of the WHO which recommend reducing total fat and SFA to help prevent cardiometabolic diseases. The findings suggest that personalised nutrition strategies based on GRS might be effective for the prevention and management of dyslipidaemia but confirmation in dietary intervention studies with large sample sizes is required.

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The authors' contributions are as follows: K. S. V. conceived the study; R. W. and K. S. V. performed the statistical analyses, interpreted the data and wrote the manuscript; R. W., K. S. V., M. A. H., N. R. D. S., N. T. C., H. A., S. A. and G. C. C. K. participated in data curation, reviewing and editing; K. S. V. and M. A. H. were responsible for project administration and funding acquisition; K. S. V., M. A. H. and G. C. C. K. supervised the study. All authors have read and agreed to the final version of the manuscript.

The authors declare that they have no conflict of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524001594

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Interactions between genetic and lifestyle factors on cardiometabolic disease-related outcomes in Latin American and Caribbean populations: A systematic review

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Introduction: The prevalence of cardiometabolic diseases has increased in Latin American and the Caribbean populations (LACP). To identify gene-lifestyle interactions that modify the risk of cardiometabolic diseases in LACP, a systematic search using 11 search engines was conducted up to May 2022.

Methods: Eligible studies were observational and interventional studies in either English, Spanish, or Portuguese. A total of 26,171 publications were screened for title and abstract; of these, 101 potential studies were evaluated for eligibility, and 74 articles were included in this study following full-text screening and risk of bias assessment. The Appraisal tool for Cross-Sectional Studies (AXIS) and the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) assessment tool were used to assess the methodological quality and risk of bias of the included studies.

Results: We identified 122 significant interactions between genetic and lifestyle factors on cardiometabolic traits and the vast majority of studies come from Brazil (29), Mexico (15) and Costa Rica (12) with FTO, APOE, and TCF7L2 being the most studied genes. The results of the gene-lifestyle interactions suggest effects which are population-, gender-, and ethnic-specific. Most of the gene-lifestyle interactions were conducted once, necessitating replication to reinforce these results.

Discussion: The findings of this review indicate that 27 out of 33 LACP have not conducted gene-lifestyle interaction studies and only five studies have been undertaken in low-socioeconomic settings. Most of the studies were cross-sectional, indicating a need for longitudinal/prospective studies. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and

the built environment. The protocol has been registered on PROSPERO, number CRD42022308488.

Systematic review registration: https://clinicaltrials.gov, identifier CRD42022308488.

KEYWORDS

systematic review, nutrigenetics, Latin American and Caribbean, genetics, gene-lifestyle interaction, dietary intake, physical activity

1. Introduction

Cardiometabolic diseases such as hypertension and type 2 diabetes (T2D) are accountable for most non-communicable disease (NCD) deaths and impose an economic burden on low- and middle-income countries (1). In Latin American and the Caribbean populations (LACP), the prevalence of hypertension, T2D and obesity is 47, 22, and above 20%, respectively (2, 3). The etiology of cardiometabolic diseases is multifactorial where studies have demonstrated an interaction between the environment, genetic, behavioral, physiological, and socioeconomic factors (4–9). These intertwined mechanisms interact, modifying the risk of developing cardiometabolic diseases. Genetic variations or single nucleotide polymorphisms (SNPs) may modify the susceptibility to cardiometabolic diseases conditioned by the exposure to lifestyle factors (4, 5). Genome-wide association studies have identified several genetic loci associated with cardiometabolic traits but most of these studies have been performed in Caucasian populations (10–15). Similarly, majority of nutrigenetic studies have been performed in Western countries and the findings might not be applicable to low-income countries due to variations in allele frequencies, dietary pattern, and environmental factors (5, 16).

Factors such as changes in patterns of food consumption, the process of urbanization, increased health and socioeconomic disparities, underfinanced healthcare systems, lower levels of income and productivity, and the rise in sedentary lifestyle have led to an increase in NCDs (17–21). Moreover, studies have shown that metabolic responses to lifestyle factors such as diet and physical activity vary between ethnicities due to genetic heterogeneity (4, 5, 22, 23), and hence we sought to determine which lifestyle factors are interacting with genetic variants in different LACP with regards to cardiometabolic disease traits. The discovery of gene-lifestyle interactions in LACP will help to identify population subgroups that will respond to lifestyle interventions.

The influence of gene-lifestyle interactions on obesity, T2D and cardiovascular diseases (CVDs) has been broadly studied, and there is evidence that the genetic risk of cardiometabolic traits can be modified (4, 5, 24–27). However, to our knowledge, no previous systematic reviews have been conducted regarding the interactions of genetic and lifestyle factors on cardiometabolic disease traits in LACP. Thus, the objective of this systematic review was to identify studies examining the interactions between genetic variants and lifestyle factors such as diet, nutrient intake, nutritional status, physical activity, socioeconomic factors, and the built environment on obesity, CVDs, and T2D-related traits in LACP.

2. Methods

2.1. Inclusion and exclusion criteria

Eligible for inclusion were articles that explored the interaction between genetic variations and lifestyle factors on cardiometabolic disease traits in LACP. All cardiometabolic diseases and traits were considered including CVDs, cerebrovascular diseases such as stroke, blood lipid levels, obesity-related traits such as body mass index (BMI) and T2D-related traits such as fasting glucose. The eligible articles included observational and dietary intervention studies and were in either English, Spanish, or Portuguese. Articles that did not explore gene-lifestyle interactions or were not based on LACP were excluded.

2.2. Information sources and search strategy

A literature search was conducted in MEDLINE (*via* PubMed and EBSCO Host), Web of Science, ScienceDirect, SciELO, SCOPUS, Taylor & Francis Online, Cochrane library, LILACS (Latin American and Caribbean Health Sciences Literature), IBECS, Google Scholar, and ERIC (Education Resources Information Center *via* EBSCO Host) search engines until the 25th of May 2022. To reach literature saturation, the researchers conducted independent search strings (**Supplementary Table 1**), and the included publications were searched through to identify potential articles in reference lists. We followed the Peer Review of Electronic Search Strategies (PRESS) guideline (28) and the literature search was limited to human participants and had no dates of publication restrictions. The protocol was registered on PROSPERO, number CRD42022308488.

2.3. Study selection, synthesis methods, effect measures, and data collection process

Duplicate articles were removed using Rayyan software (29), titles and abstracts were blindly screened to assess against the pre-established inclusion criteria, followed by full-text screening and discussion until consensus between E.F.V. and R.W. All the data required to assess the eligibility of the studies was available, hence study investigators were not contacted to obtain or confirm the data. The reviewers ensured consistency across the data that needed to

be extracted, and a narrative synthesis was conducted to collate the data, including populations, lifestyle factors, study designs, genetic variations, cardiometabolic disease traits, and *P*-values for gene-lifestyle interactions on obesity, diabetes and CVD traits. *P*-values for gene-lifestyle interactions were used as indicators of the relationship between the exposure (genetic and lifestyle factors) and the outcome (cardiometabolic traits). *P*-values < 0.05 were considered statistically significant. $P_{interaction}$ refers to the *P*-value for the interaction between the genetic variant and dietary/lifestyle factors on cardiometabolic traits. To synthesize the findings, we categorized the outcomes into four categories: obesity, diabetes, CVD, and overall cardiometabolic risk. We then coded the exposures considering major themes; proteins, carbohydrates, fats, and fiber as well as plasma fatty acids, polyunsaturated fatty acids (PUFA), saturated fatty acids (SFA), breastfeeding, smoking, alcohol, coffee, and lifestyle (if the exposure was multiple, including factors embracing diet, physical activity, smoking, and/or socioeconomic status, education), macronutrients (when the exposures included at least proteins, carbohydrates, fats, and fiber), and micronutrients (when the exposure referred to minerals or vitamins). The final graphical representation of the interaction between the genetic variations, and the coded lifestyle factors on the clustered outcomes was a heat map, where the intensity of the color corresponds to the *P*-values of the gene-lifestyle interactions (**Figures 1–4**). All heat maps were produced using the ggplot2 package (30) in R software with RStudio environment (31). A meta-analysis could not be conducted due to the wide range of dietary factors, genetic variants and cardiometabolic traits investigated by the included studies, in addition to heterogeneity in the methods used.

2.4. Data items

Data was extracted in **Table 1** and the main outcomes were diabetes, obesity, CVD, and their related traits including lipid levels, blood pressure and anthropometric measurements.

2.5. Risk of bias and certainty of assessment

To evaluate the methodological quality and risk of bias (RoB) of cross-sectional studies we used the Appraisal tool for Cross-Sectional Studies (AXIS) (32) (**Supplementary Tables 2, 3**). Cohort studies, case-control studies, and non-randomized trials were assessed by using the RoB in Non-randomized Studies—of Interventions (ROBINS-I) assessment tool (32, 33) (**Supplementary Table 4**). Risk of bias due to missing results was assessed using the AXIS RoB (questions 12–14) and the ROBINS-I assessment [part 5 (questions 5.1–5.4)]. The current article adheres to the recommendations of the Synthesis without Meta-analysis (SWiM) in Systematic Reviews: Reporting Guideline (34).

3. Results

3.1. Study selection and characteristics

The search string results had an output of 29,092 articles and from these, 101 articles were identified as potential studies. After the full-text screening, 27 articles were excluded for the following reasons: six studies were not based on LACP (35–40), five studies aimed to identify the effect of genomic ancestry (41–45), six studies focused only on genetic associations (46–51), eight studies did not include cardiometabolic diseases (52–59), and two studies investigated gene x phenotype interactions (60, 61) as shown in **Figure 5**. Finally, after excluding the irrelevant articles based on the exclusion criteria, 74 studies were included in this systematic review as shown in **Table 1**.

3.2. Gene-lifestyle interactions in LACP

The 74 studies conducted in LACP encompass ethnicities from Argentina, Colombia, Chile, Costa Rica, Mexico, Brazil, and LACP diaspora, including Dominicans, Puerto Ricans, Mexicans, and other Hispanic ethnicities residing in the United States of America (USA). Most of the studies are focused on four countries: Brazil (29), Mexico (15), Costa Rica (12), and Puerto Ricans in Boston (10). The studies have identified 122 significant gene-lifestyle interactions on cardiometabolic traits ($p < 0.05$), as shown in **Table 1**. The results are stratified by country to enable identification of ethnic-specific gene-lifestyle interactions and to present a structured mapping of the research gaps for a multidisciplinary audience.

3.3. Gene x lifestyle interactions in Brazilians

3.3.1. Interaction between dietary fat intake and genetic variants on CVD traits

Interaction between dietary fat intake and genetic variants on CVD-related traits was examined by five Brazilian studies (62–66). In a cross-sectional study of 567 participants (62), a significant interaction was reported between olive oil intake and Apolipoprotein E (*APOE*) genotype on low-density lipoprotein cholesterol (LDL) ($P_{interaction} = 0.028$), where a high intake of olive oil ($\geq$ once a week) was associated with lower LDL levels in men carrying the "ε*2*" allele but had no effect in men without the "ε*2*" allele. In this study (62), a high polyunsaturated fatty acid (PUFA) intake (> twice a week) was associated with increased LDL levels in carriers of the "ε*4*" allele, but this was not observed in participants without the "ε*4*" allele ($P_{interaction} = 0.04$). A reduction in triglyceride levels in response to a high PUFA intake was also observed in carriers of the "ε*2*" allele but not in participants without the "ε*2*" allele ($P_{interaction} = 0.04$). A high PUFA intake was also associated with increased high-density lipoprotein cholesterol (HDL) concentration in participants without the "ε*4*" allele and reduced HDL levels in carriers of the "ε*4*" allele ($P_{interaction} = 0.018$) (62). In contrast, a cross-sectional study of 252 Brazilian women (63) observed increased triglyceride and very-low density lipoprotein cholesterol (VLDL) in response to a low PUFA or a high fat diet intake in carriers of the "ε*4*" allele of *APOE*, but not in non-carriers ($P_{interaction} < 0.05$ for both). The findings of the first study (62) indicate that, PUFA intake might be beneficial in increasing HDL levels in individuals without the "ε*4*" allele, while in those with the "ε*4*" allele, PUFA intake might contribute to a rise in triglyceride and LDL levels which is associated with higher risk of CVDs (67). Nonetheless, the findings of the second study (63) suggest a detrimental effect of low PUFA intake in carriers of the "ε*4*"

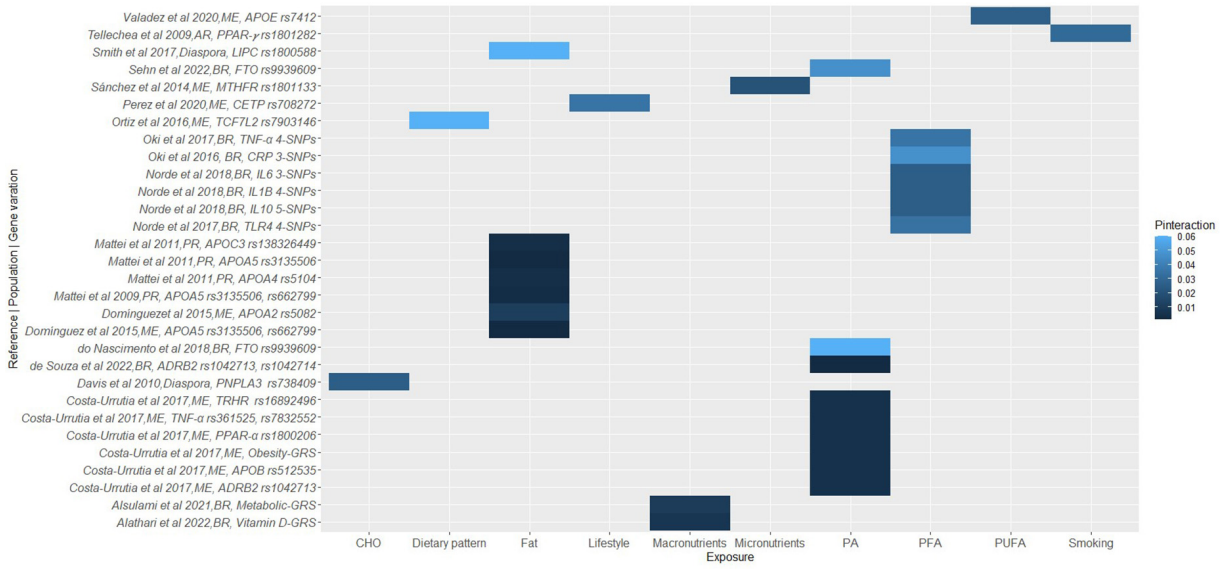

FIGURE 1
A heat map showing the findings for gene-lifestyle interactions on overall cardiometabolic disease risk. Alsulami et al. (72), Metabolic-GRS = *TCF7L2 (rs12255372, rs7903146); MC4R (rs17782313, rs2229616); PPAR γ (rs1801282); FTO (rs8050136); CDKN2A/2B (rs10811661); KCNQ1 (rs2237892); CAPN10 (rs5030952);* Alathari et al. (73), Vitamin D-GRS = *VDR (rs2228570, rs7975232), DHCR7 (rs12785878), CYP2R1(rs12794714), CYP24A1(rs6013897), GC (rs2282679), FTO (rs8050136, rs10163409), TCF7L2 (rs12255372, rs7903146), MC4R (rs17782313), KCNQ1 (rs2237895, rs2237892), CDKN2A (rs10811661), PPAR γ (rs1801282), CAPN10 (rs5030952);* Costa-Urrutia et al. (118), Obesity-GRS = *ABCA1 (rs2230806, rs9282541); ADIPOQ (rs2241766); ADRB2 (rs1042713); AGT (rs699); APOA4 (rs675); APOB (rs512535); APOE (rs405509); CAPN10 (rs2975760, rs2975762, rs3792267); FTO (rs1121980, rs9939609); HNF4 (rs745975); LIPC (rs1800588); LPL (rs320); PPAR-α (rs1800206); PPAR-γ (rs1801282); SCARB1 (rs1084674); TCF7L2 (rs7903146); TNF (rs361525); TRHR (rs1689249, rs7832552)*; Norde et al. (79), 5-SNPs = *IL10 rs1554286, rs1800871, rs1800872, rs1800890, rs3024490*; Oki et al. (78), 4-SNPs = *TNF-α rs1799724, rs1800629, rs361525, rs1799964;* Norde et al. (76), 4-SNPs = *TLR4 rs11536889, rs4986790, rs4986791, rs5030728;* Oki et al. (77), 3-SNPs = *CRP rs1205, rs1417938, rs2808630;* Norde et al. (79), 4-SNPs = *IL1B rs16944, rs1143623, rs1143627, rs1143643; 3-SNPs = rs1800795, rs1800796, rs1800797;* BR, Brazilian; ME, Mexican; PR, Puerto Rican; AR, Argentinian.

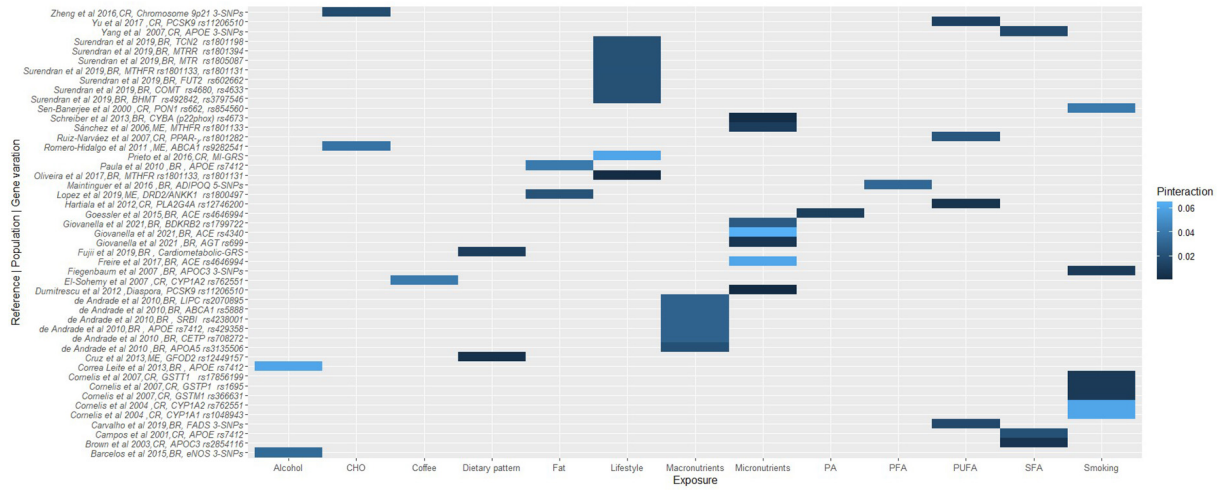

FIGURE 2
A heat map showing the findings for gene-lifestyle interactions on cardiovascular disease traits. Sotos-Prieto et al. (144), MI-GRS = *CDKN2A/2B (rs4977574, rs10757274, rs2383206, rs1333049); CELSR2-PSRC1-SORT1 (rs646776, rs599839); CXCL12(rs501120, rs1746048); HNF1A, C12orf43 (rs2259816); MRAS (rs9818870); SLC22A3 (rs2048327); LPAL2 (rs3127599); LPA (rs7767084, rs10755578);* Fujii et al. (64), Cardiometabolic-GRS = *APOA5 (rs662799); APOB (rs693, rs1367117); LDLR (rs688, rs5925); LIPC (rs2070895, rs1800588);* Brown et al. (125), 3-SNPs = *APOE rs7412, rs449647, rs429358*; Fiegenbaum et al. (92), 3-SNPs = APOC3 rs2854116, rs2854117, rs5128; Maintinguer Norde et al. (75), 5-SNPs = ADIPOQ rs2241766, rs16861209, rs17300539, rs266729, rs1501299; Carvalho et al. (65), 3-SNPs = FADS rs174575, rs174561, rs3834458; Barcelos et al. (88), 3-SNPs = eNOS rs2070744, rs1799983, rs61722009; Zheng et al. (135), 3-SNPs = Chromosome 9p21 rs4977574, rs2383206, rs1333049. BR, Brazilian; CR, Costa Rican.

allele. The differences in the findings could be attributed to the small sample sizes and the fact that, the second study (63) was conducted in women unlike the first study (62). PUFA is a ligand for peroxisome proliferator-activated receptors (PPARs) which are involved in regulating several lipid-pathway genes and it has been suggested that, increased consumption of PUFA might promote the expression of APOE and hepatic uptake of "ε*4*"-containing VLDL particles (68, 69).

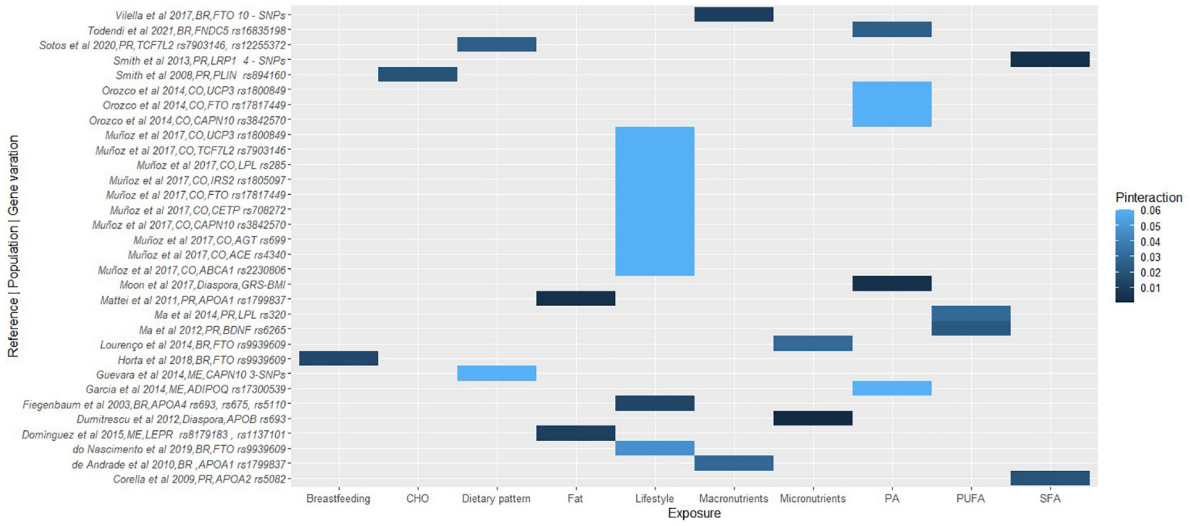

FIGURE 3
A heat map showing the findings for gene-lifestyle interactions on obesity traits. Vilella et al. (80), 10-SNPs = *FTO rs79149291, rs62048379, rs115530394, rs75066479, rs2003583, rs115662052, rs114019148, rs62034079, rs1123817, rs16952663;* Smith et al. (146), 4-SNPs = *LRP1 rs1799986, rs1799986, rs1800191, rs715948*; Cao et al. (107), 3-SNPs = *CAPN10 rs5030952, rs3792267, rs2975762*. BR, Brazilian; PR, Puerto Rican; ME, Mexican; CO, Colombian.

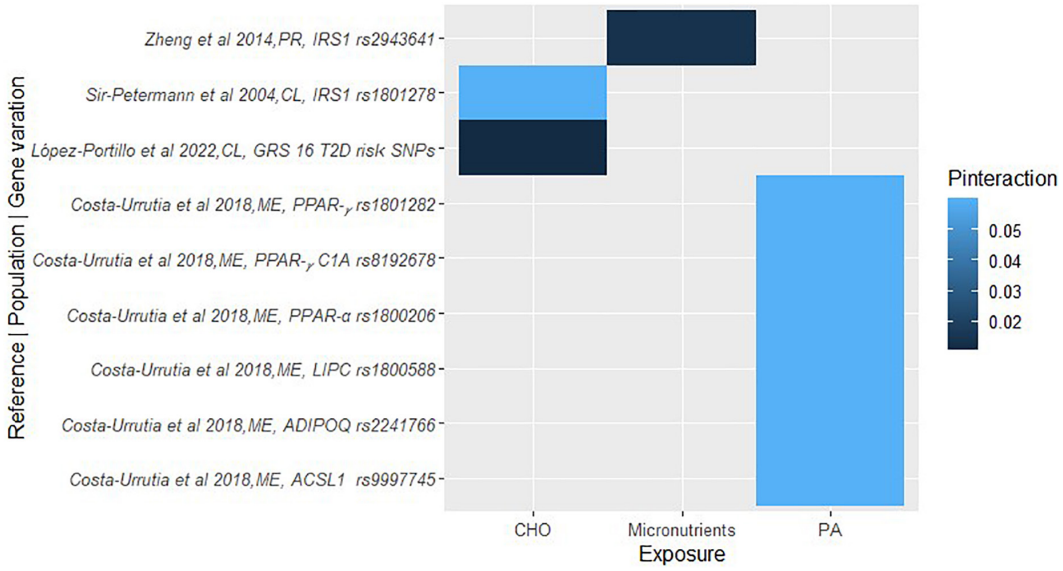

FIGURE 4
A heat map showing the findings for gene-lifestyle interactions on diabetes traits. López-Portillo et al. (161), GRS-16 Type 2 Diabetes (T2D) risk SNPs = *MTNR1B (rs10830963); TCF7L2 (rs7903146); CDKAL1 (rs7756992); ADCY5 (rs11717195); ANK1 (rs516946); BCAR1 (rs7202877); CDC123 (rs11257655); DUSP9 (rs5945326); GRB14 (rs3923113); RASGRP1 (rs7403531); TLE4 (rs17791513); TLE1 (rs2796441); ZBED3 (rs6878122).*

Furthermore, a cross-sectional study of 228 Brazilian participants from the Health Survey of São Paulo (HS-SP) (64) observed significant interactions between a GRS based on seven SNPs (**Table 1**) and the Brazilian Healthy Eating Index Revised (BHEI-R) on the risk of dyslipidaemia. Participants with a higher GRS (5–8) had a lower odds ratio for dyslipidaemia with an intake of BHEI-R oil component above the median ($P_{\text{interaction}} = 0.019$); while those with a GRS > 9 had a lower odds ratio for dyslipidaemia with an intake of BHEI-R solid fats, alcoholic beverages and added sugars (SoFAAS) component below the median ($P_{\text{interaction}} < 0.001$). Similarly, a cross-sectional study involving 250 pregnant women (65) observed significant interactions between fatty acid desaturase (*FADS*) SNPs (rs174561 and rs3834458) and dietary α-linolenic acid (ALA) and linoleic/α-linolenic acid ratio (LA/ALA) on plasma concentrations of omega-3 (n-3) PUFAs. It was reported that, in women with high ALA intake, plasma ALA concentrations were higher in homozygotes for the minor allele ($p < 0.05$), compared to carriers of the major allele (MM and Mm) of rs174561 and rs3834458. However, the *P*-values given in the study ($p = 0.004$ for rs174561 and $p = 0.028$ for rs3834458) seem to represent associations stratified by genotype, instead of interactions. FADS are involved in the synthesis of PUFA and their activation is linked to inflammation and coronary artery disease (70, 71), and these findings suggest that SNPs which alter the activation of FADS might affect plasma concentration of PUFA. In

another cross-sectional study of 113 adolescents from the Obesity, Lifestyle and Diabetes in Brazil (BOLD) study (66), no significant interactions were reported between seven genes involved in the one-carbon metabolism pathway (**Table 1**) and fat intake on lipid-related traits.

3.3.2. Interaction between dietary fat intake and genetic variants on glycemic traits

Interaction between dietary fat intake and genetic variants on glycemic traits was investigated by two cross-sectional studies (72, 73) using data from the BOLD study. In the first study which consisted of 200 participants (72), a high total fat intake [37.98% of total energy intake (TEI)/day] was shown to interact with a 10-SNP metabolic-GRS (**Table 1**), where individuals with 5 or more risk alleles had increased homeostasis model assessment estimate of insulin secretion (HOMA-B) ($P_{interaction} = 0.016$), fasting insulin ($P_{interaction} = 0.017$), body fat mass ($P_{interaction} = 0.009$), and decreased insulin:glucose ratio ($P_{interaction} = 0.01$), but the interaction did not influence homeostasis model assessment estimate of insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c), or waist circumference (WC). Similarly, the second BOLD study (73) which also examined the interaction between dietary fat intake and a 10-SNP metabolic-GRS did not find significant interactions between the GRS and dietary fat intake on fasting glucose, fasting insulin or HbA1c (**Table 1**). The mechanisms through which dietary fat intake influence glycemic traits are unclear, although a sustained increase in blood glucose levels following a high fat meal has been reported (74).

3.3.3. Interaction between plasma fatty acid profile and genetic variants on systemic inflammation

Five Brazilian cross-sectional studies (75–79) investigated the interaction between plasma fatty acids and genetic variants on systemic inflammation, using data from the HS-SP. The first study (75) consisted of 262 adults, and significant interactions were identified between plasma n-3 and adiponectin (*ADIPOQ*) SNP rs2241766 ($P_{interaction} = 0.019$); arachidonic acid and *ADIPOQ* rs16861209 ($P_{interaction} = 0.044$); docosapentaenoic acid and *ADIPOQ* rs16861209 ($P_{interaction} = 0.037$); and SFA and *ADIPOQ* rs17300539 ($P_{interaction} = 0.019$) on the risk of systemic inflammation. Carriers of the "G" allele of rs2241766 had a reduced odds ratio of having inflammatory biomarkers when plasma n-3 levels were above the median, while participants with the "CC" genotype of rs16861209 had a lower odds ratio of having inflammatory biomarkers in the 50th percentile of plasma arachidonic acid and docosapentaenoic acid. Moreover, carriers of the "A" allele of rs17300539 had a higher odds ratio of having inflammatory biomarkers in the upper 50th percentile of plasma SFA compared to those with the "GG" genotype (75). In the second study (76), which consisted of 262 participants, an interaction was also observed between plasma arachidonic acid/eicosapentaenoic acid ratio and toll-like receptor 4 (*TLR4*) SNP rs11536889, in which individuals with the "C" allele had an increased odds ratio of having inflammatory biomarkers at the higher percentile of arachidonic acid/eicosapentaenoic acid ratio ($P_{interaction} = 0.034$). Similarly, the third study consisting of 262 participants (77) identified a significant interaction between plasma palmitoleic acid and C-reactive protein (*CRP*) SNP rs1417938, where individuals with the "AA" genotype had a higher odds ratio of having inflammatory biomarkers with a plasma palmitoleic acid above the median ($P_{interaction} = 0.047$).

In line with these findings, an increasing risk of having inflammatory biomarkers in response to increasing plasma SFA was observed in carriers of the "A" allele of tumor necrosis factor-α (*TNF*-α) SNP rs180062 (−308G/A) ($P_{interaction} = 0.041$); while a decreasing risk with increasing plasma stearic acid was found in participants with the "GG" genotype ($P_{interaction} = 0.046$), in a sample of 281 participants from the HS-SP (78). Furthermore, a decreasing risk of metabolic syndrome (MetS) was observed in response to increasing plasma stearic acid levels in "A" allele carriers of interleukin 1 beta (*IL1B*) SNP rs16944 ($P_{interaction} = 0.043$), and in response to increasing plasma arachidonic acid levels in those with the "GG" genotype of interleukin 10 (*IL10*) SNP rs1800896 ($P_{interaction} = 0.007$), in a sample of 301 participants from the HS-SP (79). However, no significant interactions were identified between total SFA, myristic acid, palmitic acid, stearic acid and *ADIPOQ* SNPs rs1501299 and rs266729; *TLR4* SNPs rs11536889 and rs5030728; and *CRP* SNP rs1205 on inflammatory biomarkers in three of the studies (75, 78, 79). Plasma fatty acid profile is considered an indicator of dietary fatty acid intake (75) and these findings suggest that plasma fatty acid profile can interact with SNPs of several genes and modify the risk of systemic inflammation which is linked to cardiometabolic diseases such as type 2 diabetes and CVDs (75).

3.3.4. Interaction between carbohydrate intake and genetic variants on cardiometabolic traits

Three Brazilian cross-sectional studies (66, 72, 73) investigated the interactions between carbohydrate intake and genetic variants on cardiometabolic traits, using data from the BOLD study. In the first study which consisted of 113 participants (66), a total carbohydrate intake of 47.7% TEI was associated with a significantly increased homocysteine concentration ($P_{interaction} = 0.031$) in carriers of the "*AA*" genotype of fucosyltransferase 2 (*FUT2*) SNP rs602662. Carbohydrate intake also interacted with Catechol-O-Methyltransferase (*COMT*) SNP rs4680, increasing oxidized-LDL more in carriers of "AA" than "GG" genotype ($P_{interaction} = 0.005$) (66). Notwithstanding, after applying Bonferroni correction for multiple testing, none of the interactions were considered significant (66). Moreover, the other two studies (72) which consisted of 200 participants and (73) which consisted of 187 participants, from the BOLD study, did not identify significant interactions between carbohydrate intake and a metabolic-GRS based on 10 SNPs (**Table 1**) on cardiometabolic traits.

3.3.5. Interaction between protein intake and genetic variants on cardiometabolic traits

Three studies (66, 73, 80) investigated the interaction between protein intake and genetic variants on cardiometabolic traits, two of which (66, 73) used data from the BOLD study. A cross-sectional study of 1191 overweight and normal weight children (80) observed a significantly increased BMI ($p = 0.01$) among participants carrying the "*T*" allele of *FTO* SNP rs79149291 with a protein intake above 12.7% TEI/day (80). Similarly, in the BOLD study discussed above (66), those with a protein intake of 16.99% TEI who were carriers of the "*AA*" genotype of *FUT2* SNP rs602662 ($P_{interaction} = 0.007$) had increased homocysteine levels (66). However, in the other BOLD study (73), there were no interactions between protein intake and a GRS based on 10 SNPs (**Table 1**) on obesity or diabetes traits.

TABLE 1 Summary table of gene-lifestyle interactions and study characteristics.

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
FTO						
rs9939609	Brazilian $n = 1,088$	LS	Plasma vitamin D	BMI	0.02–0.04	Lourenço et al. (84)
rs9939609	Brazilian $n = 1,215$	C-S	Screen time	Cardiometabolic risk score	0.047	Sehn et al. (96)
rs9939609	Brazilian $n = 432$	C-C	Physical activity intervention	TC, HDL, LDL, TG, glucose, insulin, HOMA-IR, QUICKI	NS	do Nascimento et al. (98)
rs9939609	Brazilian $n = 3,701$	P-C	Breastfeeding	BMI, overweight, fat mass, lean mass, WC, visceral, and subcutaneous abdominal fat thickness	0.01–0.02	Horta et al. (102)
rs9939609	Brazilian $n = 434$	C-C	hypocaloric diet, physical exercise program	BMI, WC, AC	0.047	do Nascimento et al. (99)
rs17817449	Colombian $n = 212/212$	C-C	Physical activity	BMI	NS	Orozco et al. (163)
rs17817449	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
rs79149291, rs62048379, rs115530394, rs75066479, rs2003583, rs115662052, rs114019148, rs62034079, rs1123817, rs16952663	Brazilian $n = 1,191$	C-S	Carbohydrate, protein, total fat, MUFA, PUFA:SFA intake	Overweight/ obesity	0.01	Vilella et al. (80)
APOE						
rs7412, rs429358	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)
rs7412	Brazilian $n = 252$	C-S	Total fat, PUFA: SFA	LDL, TG, VLDL	<0.05	Paula et al. (63)
rs7412	Brazilian $n = 851$	P-C	Alcohol intake	SBP, DBP	NS	Correa Leite et al. (89)
rs7412	Mexican $n = 224$	C-S	MUFA intake, n-3:n-6	TC, Non-HDL, LDL, HbA1c	0.016–0.035	Torres-Valadez et al. (103)
rs7412	Costa Rican $n = 420$	C-S	SFA	TG, TC, VLDL, LDL, HDL, Apo A1, Apo B, LDL particle size	0.02–0.03	Campos et al. (124)
rs7412, rs429358, rs449647	Costa Rican $n = 1,927/1,927$	C-C	SFA	TC, HDL, LDL, TG, MI	0.0157	Yang et al. (125)
APOA5						
rs3135506	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)
rs3135506, rs662799	Mexican $n = 100/100$	C-C	SFA, total fat	TC, TG, LDL, HDL, obesity	0.001–0.02	Domínguez-Reyes et al. (105)
rs3135506, rs662799	Puerto Rican $n = 802$	LS	Total fat	WC, serum glucose, SBP, DBP, HDL, LDL, TC, VLDL	0.002–0.032	Mattei et al. (152)
APOA5						
rs3135506	Puerto Rican $n = 821$	LS	Total fat	WC, SBP, DBP	0.001–0.005	Mattei et al. (147)
MTHFR						
rs1801133, rs1801131	Brazilian $n = 3,803$	C-S	Physical activity, alcohol intake, and blood folate	Homocysteine	<0.001–0.002	Oliveira et al. (85)
rs1801133, rs1801131	Brazilian $n = 113$	C-S	Fat, protein, carbohydrate intake, physical activity	Vitamin B12, homocysteine, folic acid, HDL, LDL, TG, oxidized LDL	0.005–0.034	Surendran et al. (66)

(Continued)

TABLE 1 (Continued)

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
rs1801133	Mexican $n = 996$ (women); 231 (new-borns)	P-C	Folate and Vitamin B12	Weight, length and BMI of new-born	0.02	Torres-Sánchez et al. (115)
rs1801133	Mexican $n = 130$	C-S	Vitamin B12, alcohol intake	Plasma Folate, total homocysteine	0.01	Torres-Sánchez et al. (116)
ACE						
rs4340	Brazilian $n = 335$	C-S	Sodium, potassium, calcium, magnesium	SBP, DBP	0.004–0.009	Giovanella et al. (81)
rs4340	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
rs4646994	Brazilian $n = 234$	C-C	Sodium	Hypertension	NS	Freire et al. (82)
ACE						
rs4646994	Brazilian $n = 34$	RCT	Physical activity	SBP, DBP	0.02 –0.002	Goessler et al. (97)
TCF7L2						
rs7903146	Mexican $n = 137$	P-LS	Two diets: Nopal tortilla and whole grain bread	Weight, BMI, WC, HC, WHR, glucose, HbA1c, TG, TC, HDL, LDL, insulin, HOMA-B, HOMA-IR, GLP-1	NS	López-Ortiz et al. (185)
rs7903146	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
rs7903146, rs12255372, rs7903146, rs12255372	Puerto Rican $n = 1,120$	C-S	Mediterranean diet score	BMI, WC, weight	0.014–0.036	Sotos-Prieto et al. (150)
ABCA1						
rs5888	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)
rs9282541	Mexican $n = 3,591$	C-S	Carbohydrate	HDL	0.037	Romero-Hidalgo et al. (112)
rs2230806	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
LIPC						
rs2070895	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)
rs1800588	Mexican $n = 167/398$	C-C	Maximal oxygen consumption (VO2 max), muscle endurance (ME)	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. (119)
rs1800588	Dominican/Puerto Rican, other Caribbean Hispanics $n = 41$	RCT	High fat diet	HDL, LDL, TC, TG, glucose	NS	Smith et al. (153)
APOC3						
rs2854116, rs2854117, rs5128	Brazilian $n = 673$	C-S	Smoking	TG	0.009	Fiegenbaum et al. (92)
rs2854116, T-625del	Costa Rican $n = 336$	C-S	SFA	TG, TC, LDL, HDL, Apo B, LDL diameter	0.0004 –0.01	Brown et al. (126)
rs138326449	Puerto Rican $n = 821$	LS	Total fat	WC, SBP, DBP	0.001–0.005	Mattei et al. (147)
CETP						
rs708272	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)

(Continued)

TABLE 1 (Continued)

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
rs708272	Mexican $n = 215$	C-S	Sucrose intake, physical activity	TC, LDL, TG, HDL, TG:HDL, BMI, WC	0.033–0.037	Campos-Perez et al. (113)
CETP						
rs708272	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
ADIPOQ						
rs2241766, rs16861209, rs17300539, rs266729, rs1501299	Brazilian $n = 262$	C-S	Plasma fatty acids (14:0, 16:0, 16:1 n-7, 18:0, 18:1, 18:2 n-6, 18:3 n-3, 20:3 n-6, AA, EPA, DPA, DHA, SFA, MUFA, n-6, n-3, PUFA, n-3 HUFA, SCD-16, SCD-18, D5D, D6D)	Systemic Inflammation	0.019–0.044	Maintinguer Norde et al. (75)
rs17300539	Mexican $n = 394$	C-S	MUFA, physical activity	adiponectin level	NS	Garcia-Garcia et al. (120)
rs2241766	Mexican $n = 167/398$	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. (119)
PPAR-γ						
rs1801282	Mexican $n = 167/398$	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. (119)
rs1801282	Costa Rican $n = 1,805/1,805$	C-C	PUFA intake	MI, PUFA in adipose tissue	0.016 –0.03	Ruiz-Narváez et al. (127)
PPAR-γ						
rs1801282	Argentina $n = 572$	C-S	Smoking status	MetS, fasting plasma glucose, SBP, DBP, WC, HDL, TG, fasting insulin, loginsulin, HOMA-IR, LogHOMA-IR, QUICKI	0.031	Tellechea et al. (165)
PPAR-γ C1A						
rs8192678	Mexican $n = 167/398$	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. (119)
PPAR-α						
rs1800206	Mexican $n = 167/398$	C-C	VO2 max, ME	pre-diabetes (fasting glucose concentrations)	NS	Costa-Urrutia et al. (119)
rs1800206	Mexican $n = 608$	C-C	VO2 max, ME	BMI, WC, fat mass, pre-DM	0.001–0.007	Costa-Urrutia et al. (118)
APOA4						
rs693, rs675, rs5110	Brazilian $n = 391$	C-S	Smoking, alcohol intake, physical activity	BMI, WC	0.007–0.02	Fiegenbaum et al. (91)
rs5104	Puerto Rican $n = 821$	LS	Total fat	WC, SBP, DBP	0.001–0.005	Mattei et al. (147)
IRS1						
rs2943641	Puerto Rican $n = 1,144$	LS	25(OH)D	HOMA-IR	0.004–0.023	Zheng et al. (159)
rs1801278	Chile $n = 243$	NRCT	3-day unrestricted diet containing 300 g/d of carbohydrate, an overnight fast of 10 h and 75 g glucose	Fasting glucose, fasting insulin, fasting HOMA-IR, insulinogenic index, insulin sensitivity index composite	NS	Sir-Petermann et al. (162)
IRS2						
rs1805097	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)

(Continued)

TABLE 1 (Continued)

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
PON1						
rs662	Mexican $n = 206$	C-S	Urinary 1-hydroxypyrene	Serum asymmetric dimethylarginine (ADMA)	0.02	Ochoa-Martínez et al. (121)
rs662	Mexican $n = 185$	C-S	Urinary arsenic levels	ADMA, fatty acid-binding protein 4, micro-RNAs	< 0.001 – < 0.010	Ochoa-Martínez et al. (122)
rs662, rs854560	Costa Rican $n = 492/518$	C-C	Smoking status	MI	0.04	Sen-Banerjee et al. (138)
AGT						
rs699	Brazilian $n = 335$	C-S	Sodium, potassium, calcium, magnesium	SBP, DBP	0.004–0.009	Giovanella et al. (81)
rs699	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
ADRB2						
rs1042713, rs1042714	Brazilian $n = 197$	P-C	Physical exercise intervention	Body fat, AC, BMI, DBP, SBP, TC, HDL, LDL, TG, glucose, insulin, HOMA-IR, QUICK, TG-glucose index	0.001	de Souza et al. (94)
rs1042713	Mexican $n = 608$	C-C	VO2 max, ME	BMI, WC, fat mass, pre-DM	0.001–0.007	Costa-Urrutia et al. (118)
TNF-α						
rs1799724, rs1800629, rs361525, rs1799964	Brazilian $n = 281$	C-S	Plasma fatty acids (C14:0, C16:0, C18:0, C16:1, C18:1, n-6, C18:2, C20:3, C20:4, n-3, C18:3, C20:5, C22:5, C22:6, n-3 HUFA, SCD-16, SCD-18, D5D, D6D, n-6:n-3, SFA, MUFA, PUFA)	Systemic inflammation	0.026 –0.044	Oki et al. (78)
TNF-α						
rs361525, rs7832552	Mexican $n = 608$	C-C	VO2 max, ME	BMI, WC, fat mass, pre-diabetes	0.001–0.007	Costa-Urrutia et al. (118)
CAPN10						
rs5030952, rs3792267, rs2975762	Mexican $n = 31$	P-C	Low SFA diet, soy protein, soluble fiber	TC, TG, HDL, LDL	NS	Guevara-Cruz et al. (107)
rs3842570	Colombian $n = 212/212$	C-C	Physical activity	BMI	NS	Orozco et al. (163)
rs3842570	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
PCSK9						
rs11206510	Costa Rican $n = 1,932/2,055$	C-C	LC n-3 PUFA, EPA, DPA, DHA	MI	0.012	Yu et al. (128)
rs11206510	Mexican American $n = 1,734$	C-S	Serum Vitamin A	LDL	7.65×10^{-5}	Dumitrescu et al. (158)
CYP1A2						
rs762551	Costa Rican $n = 2,014/2,014$	C-C	Coffee intake	MI	0.04	El-Sohemy et al. (136)
rs762551	Costa Rican $n = 873/932$	C-C	Smoking	MI	NS	Cornelis et al. (139)
CYP1A1						
rs1048943	Costa Rican $n = 873/932$	C-C	Smoking	MI	NS	Cornelis et al. (139)

(Continued)

TABLE 1 (Continued)

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
APOA2						
rs5082	Mexican $n = 100/100$	C-C	SFA, total fat	TC, TG, LDL, HDL, obesity	0.001–0.02	Domínguez-Reyes et al. (105)
rs5082	Puerto Rican $n = 930$	C-S	SFA	BMI	0.02	Corella et al. (145)
APOA1						
rs1799837	Puerto Rican $n = 821$	LS	Total fat	WC, SBP, DBP	0.001–0.005	Mattei et al. (147)
rs1799837	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)
APOB						
rs512535	Mexican $n = 608$	C-C	VO2 max, ME	BMI, WC, fat mass, pre-DM	0.001–0.007	Costa-Urrutia et al. (118)
rs693	Mexican American $n = 1,734$	C-S	Serum Vitamin E	LDL	8.94×10^{-7}	Dumitrescu et al. (158)
LPL						
rs320	Puerto Rican $n = 1,171$	LS	Low PUFA, n-3 PUFA, n-6 PUFA intake	BMI, WC	0.02–0.04	Ma et al. (148)
rs285	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
UCP3						
rs1800849	Colombian $n = 212/212$	C-C	Physical activity	BMI	NS	Orozco et al. (163)
rs1800849	Colombian $n = 1,081$	C-S	Socioeconomic stratum, maternal education year, maternal breastfeeding	BMI	NS	Muñoz et al. (164)
TLR4 *rs11536889, rs4986790, rs4986791, rs5030728*	Brazilian $n = 262$	C-S	Systemic Inflammation	0.034	Norde et al. (76)	Systemic inflammation
BDKRB2 *rs1799722*	Brazilian $n = 335$	C-S	Sodium, potassium, calcium, magnesium	SBP, DBP	0.004–0.009	Giovanella et al. (81)
FADS *rs174575, rs174561, rs3834458*	Brazilian $n = 250$	C-S	α-linolenic acid, linoleic:α-linolenic acid ratio.	Plasma concentration of PUFA	0.004–0.028	Carvalho et al. (65)
CYBA (p22phox) *rs4673*	Brazilian $n = 1,298$	C-S	Urinary sodium	SBP, DBP, hypertension	<0.001–0.004	Schreiber et al. (83)
eNOS *rs2070744, rs1799983, rs61722009*	Brazilian $n = 113$	C-S	Alcohol intake	SBP, DBP, nitrite levels in plasma	0.033	Barcelos et al. (88)
FNDC5 *rs16835198*	Brazilian $n = 1,701$	C-S	Cardiorespiratory fitness, lower limb strength	WC, BMI	0.007–0.044	Todendi et al. (95)
LEPR rs8179183, rs1137101	Mexican $n = 100/100$	C-C	SFA, total fat intake	TC, TG, LDL, HDL, obesity	0.001–0.02	Domínguez-Reyes et al. (105)
ACSL1 rs9997745	Mexican $n = 167/398$	C-C	VO2 max, ME	pre-diabetes	NS	Costa-Urrutia et al. (119)
TRHR rs16892496	Mexican $n = 608$	C-C	VO2 max, ME	BMI, WC, fat mass, pre-diabetes	0.001–0.007	Costa-Urrutia et al. (118)
DRD2/ANKK1 rs1800497	Mexican $n = 175$	C-S	Maltose, total fat, MUFA, dietary cholesterol	**TG**	0.001 –0.041	Ramos-Lopez et al. (104)
GFOD2 rs12449157	Mexican $n = 41$	P-C	Low SFA diet, soy protein and soluble fiber	TC, LDL, HDL, TG	0.002–0.006	Guevara-Cruz et al. (106)
PLA2G4A *rs12746200*	Costa Rican $n = 1,936/2,035$	C-C	n-6 PUFA intake	MI	0.005	Hartiala et al. (129)

(Continued)

TABLE 1 (Continued)

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
CRP *rs1205, rs1417938, rs2808630*	Brazilian $n = 262$	C-S	Plasma fatty acids (Myristic acid, Palmitic acid, Stearic acid, C16:1, C18:1, n-6, C18:2, C20:3, C20:4, n-3, C18:3, C20:5, C22:5, C22:6, n-3 HUFA, SFA, MUFA, PUFA, SCD-16, SCD-18, D5D, D6D, n-6/n-3)	Systemic Inflammation	0.047	Oki et al. (77)
GSTM1 *rs366631* ***GSTP1*** *rs1695* ***GSTT1*** *rs17856199*	Costa Rican $n = 2,042/2,042$	C-C	Cruciferous vegetables, smoking	MI	0.008	Cornelis et al. (137)
IL1B *rs16944, rs1143623, rs1143627, rs1143643* ***IL6*** *rs1800795, rs1800796, rs1800797* ***IL10*** *rs1554286, rs1800871, rs1800872, rs1800890, rs3024490*	Brazilian $n = 301$	C-S	Plasma fatty acid (C14:0, C16:0, C16:1 n-9, C18:0, C18:1 n-9, C18:2 n-6, C18:3 n-3, AA, EPA, DHA, n-6, n-3); desaturates activity (SCD-16, SCD-18, D6D, D5D)	MetS	0.007–0.043	Norde et al. (79)
MTR *rs1805087* ***MTRR*** *rs1801394* ***TCN2*** *rs1801198* ***COMT*** *rs4680, rs4633* ***BHMT*** *rs492842, rs3797546* ***FUT2*** *rs602662*	Brazilian $n = 113$	C-S	Fat, protein, carbohydrate intake, physical activity	Vitamin B12, homocysteine, folic acid, HDL, LDL, triglycerides, oxidized LDL	0.005–0.034	Surendran et al. (66)
GSTM1 *rs366631* ***GSTP1*** *rs1695* ***GSTT1*** *rs17856199*	Costa Rican $n = 2,042/2,042$	C-C	Cruciferous vegetables, smoking	MI	0.008	Cornelis et al. (137)
LRP1 *rs1799986, rs1799986, rs1800191, rs715948*	Puerto Rican $n = 676$	P-C	SFA, palmitic acid (C16:0), stearic acid (C18:0), butyric acid (C4:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0), lauric acid (C12:0), myristic acid (C14:0)	BMI, WC, HC	0.002–0.004	Smith et al. (146)
PLIN *rs894160*	Puerto Rican $n = 920$	LS	Complex carbohydrate, total carbohydrate, simple sugars	WC, HC, BMI	0.004–0.035	Smith et al. (155)
Chromosome 9p21 *rs4977574, rs4977574, rs2383206, rs1333049*	Costa Rican $n = 1,560/1,751$	C-C	Sugar sweetened beverages, fruit juice	MI	0.005–0.03	Zheng et al. (135)
BDNF *rs6265*	Puerto Rican $n = 1,340$	LS	PUFA, n-3: n-6, food intake	BMI, WC, HC	0.002–0.043	Ma et al. (149)
PNPLA3 *rs738409*	Hispanic ancestry $n = 153$	C-S	Carbohydrate, sugar	Hepatic fat	0.01–0.04	Davis et al. (156)
SRBI *rs4238001*	Brazilian $n = 567$	C-S	Olive oil, PUFA, sucrose, soluble and insoluble fiber	LDL, TG, TC	0.018–0.04	de Andrade et al. (62)
GRS*:TCF7L2 (rs12255372, rs7903146); MC4R (rs17782313, rs2229616); PPARγ (rs1801282); FTO (rs8050136); CDKN2A/2B (rs10811661); KCNQ1 (rs2237892); CAPN10 (rs5030952)*	Brazilian $n = 200$	C-S	Total fat, SFA, PUFA, MUFA, carbohydrate, protein	HbA1c, HOMA-IR, HOMA-B, fasting glucose, fasting insulin, insulin:glucose, body fat mass, BMI, WC	0.002–0.017	Alsulami et al. (72)
GRS: *VDR (rs2228570, rs7975232), DHCR7 (rs12785878), CYP2R1(rs12794714), CYP24A1(rs6013897), GC (rs2282679), FTO (rs8050136, rs10163409), TCF7L2 (rs12255372, rs7903146), MC4R (rs17782313), KCNQ1 (rs2237895, rs2237892), CDKN2A (rs10811661), PPARγ (rs1801282), CAPN10 (rs5030952)*	Brazilian $n = 187$	C-S	Carbohydrate, protein, fat and fiber	BMI, WC, body fat, glucose, HbA1c, fasting insulin	0.006	Alathari et al. (73)

(Continued)

TABLE 1 (Continued)

Gene and SNP	Population and sample size	Study design	Dietary/lifestyle factor	Outcome	$P_{interaction}$*	References
GRS: *ABCA1 (rs2230806, rs9282541); ADIPOQ (rs2241766); ADRB2 (rs1042713); AGT (rs699); APOA4 (rs675); APOB (rs512535); APOE (rs405509); CAPN10 (rs2975760, rs2975762, rs3792267); FTO (rs1121980, rs9939609); HNF4 (rs745975); LIPC (rs1800588); LPL (rs320); PPAR-α (rs1800206); PPAR-γ (rs1801282); SCARB1 (rs1084674); TCF7L2 (rs7903146); TNF (rs361525); TRHR (rs1689249, rs7832552)*	Mexican $n = 608$	C-C	VO2 max, ME	BMI, WC, fat mass, pre-diabetes	0.001–0.007	Costa-Urrutia et al. (118)
GRS: *CDKN2A/2B (rs4977574, rs10757274, rs2383206, rs1333049); CELSR2-PSRC1-SORT1 (rs646776, rs599839); CXCL12(rs501120, rs1746048); HNF1A, C12orf43 (rs2259816); MRAS (rs9818870); SLC22A3 (rs2048327); LPAL2 (rs3127599); LPA (rs7767084, rs10755578)*	Costa Rican $n = 1{,}534/1{,}534$	C-C	Lifestyle cardiovascular risk score (unhealthy diet, physical inactivity, smoking, elevated waist:hip ratio, high alcohol intake, low socioeconomic status.)	MI	NS	Sotos-Prieto et al. (144)
GRS based on 97 BMI associated SNPs	Puerto Rican, Mexicans, Dominicans, Cuban, Central American, South American $n = 9{,}645$	P-C	Total physical activity, physical activity at a moderate to vigorous intensity, sedentary behavior	BMI, fat mass, fat mass index, fat percentage, WC Fat-free mass	0.001 –0.005	Moon et al. (160)
GRS: *MTNR1B* (*rs10830963*); *TCF7L2* (*rs7903146*); *CDKAL1* (*rs7756992*); *ADCY5* (*rs11717195*); *ANK1* (*rs516946*); *BCAR1* (*rs7202877*); *CDC123* (*rs11257655*); *DUSP9* (*rs5945326*); *GRB14* (*rs3923113*); *RASGRP1* (*rs7403531*); *TLE4* (*rs17791513*); *TLE1* (*rs2796441*); *ZBED3* (*rs6878122*)	Chile $n = 2{,}828$	P-C	Sugar sweetened beverages intake	Fasting glucose	0.001–0.02	López-Portillo et al. (161)
GRS: *APOA5 (rs662799); APOB (rs693, rs1367117); LDLR (rs688, rs5925); LIPC (rs2070895, rs1800588)*	Brazilian $n = 228$	C-S	Brazilian Healthy Eating Index Revised	Dyslipidaemia	0.001 –0.019	Fujii et al. (64)

APOE, Apolipoprotein E; *APOA*, Apolipoprotein A; *ApoB*, Apolipoprotein B; *SRBI*, scavenger receptor class B member 1; *ABCA1*, ATP binding cassette subfamily A member 1; *CETP*, cholesteryl ester transfer protein; *APOC3*, Apolipoprotein C; *ADIPOQ*, adiponectin; *TLR4*, toll like receptor 4; *FTO*, alpha-ketoglutarate dependent dioxygenase; *CRP*, C-reactive protein; GRS, genetic risk score; *MTHFR*, methylenetetrahydrofolate reductase; *FADS*, fatty acid desaturase; *TNF*, tumor necrosis factor; *ADRB*, adrenoceptor beta; *ACE*, angiotensin I converting enzyme; *AGT*, angiotensinogen; *BDKRB*, bradykinin receptor; *eNOS*, endothelial nitric oxide synthase; *CYBA*, cytochrome B-245 alpha chain; *IL*, interleukin; *FNDC5*, fibronectin type III domain containing 5; GRS, genetic risk score; *VDR*, vitamin D receptor; *DHCR7*, 7-dehydrocholesterol reductase; *CYP2R1*, cytochrome P450 family 2 subfamily R member 1; *CYP24A1*, cytochrome P450 family 24 subfamily A member 1; *GC*, group-specific component; *TCF7L2*, transcription factor 7 like 2; *MC4R*, melanocortin-4-receptor; *KCNQ1*, potassium voltage-gated channel subfamily Q member 1; *CDKN*, cyclin dependent kinase inhibitor; *PPAR*, peroxisome proliferator activated receptor; *CAPN*, Calpain; *MTR*, methionine synthase; *MTRR*, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; *TCN2*, transcobalamin 2; *COMT*, catechol-O-methyltransferase; *BHMT*, betaine-homocysteine S-methyltransferase; *FUT2* fucosyltransferase 2; *LEPR*, leptin receptor; *TRHR*, thyrotropin releasing hormone receptor; *LIPC*, hepatic lipase; *ACSL*, acyl-CoA synthetase long chain family member 1; *GFOD2*, Glucose-Fructose Oxidoreductase Domain Containing 2; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *PON1* Paraoxonase 1; *CYP1A2*, cytochrome P450 family 1 subfamily A member 2; *PLA2G4A*, phospholipase A2 group IVA; *GSTM1*, glutathione S-transferase Mu 1; *GSTP1*, glutathione S-transferase Pi 1; *GSTT1*, glutathione S-transferase theta 1; *CYP1A1*, cytochrome P450 family 1 subfamily A member 1; *CELSR2*, Cadherin EGF LAG seven-pass G-type receptor 2; *PSRC1*, proline and serine rich coiled-coil 1; *SORT1*, sortilin 1; *CXCL12*, C-X-C motif chemokine ligand 12; *HNF1A*, hepatocyte nuclear factor 1; *MRAS*, muscle RAS oncogene homolog; *SLC22A3*, solute carrier family 22 member 3; *LPAL2*, lipoprotein(A) like 2, pseudogene; *LPA*, lipoprotein(A); *IRS*, insulin receptor substrate; *MTNR1B*, melatonin receptor 1B; *CDKAL1*, CDK5 regulatory subunit-associated protein 1-like 1; *ADCY5*, adenylyl cyclase type V; *ANK1*, ankyrin-1; *BCAR1*, breast cancer anti-estrogen resistance protein 1; *CDC123*, cell division cycle 123; *DUSP9*, dual specificity phosphatase 9; *GRB14*, growth factor receptor bound protein 14; *RASGRP1*, RAS guanyl-releasing protein 1; *TLE*, transducin-like enhancer protein; *ZBED3*, zinc finger BED-Type containing 3; *UCP3*, uncoupling protein 3; *LPL*, lipoprotein lipase; MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; TG, triglycerides. HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment estimate of insulin resistance; QUICKI, quantitative insulin-sensitivity check index; AUC, area under the curve; TC, total cholesterol; VLDL, very-low density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol. MI, myocardial infarction; PUFA, polyunsaturated fatty acid. MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; n-3, omega-3; LC, long-chain; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid; C-S, C-S, cross-sectional; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; P-C, prospective cohort; LS, longitudinal study; C-C, case-control; NS, not significant. *Only significant $P_{interaction}$ values are given.

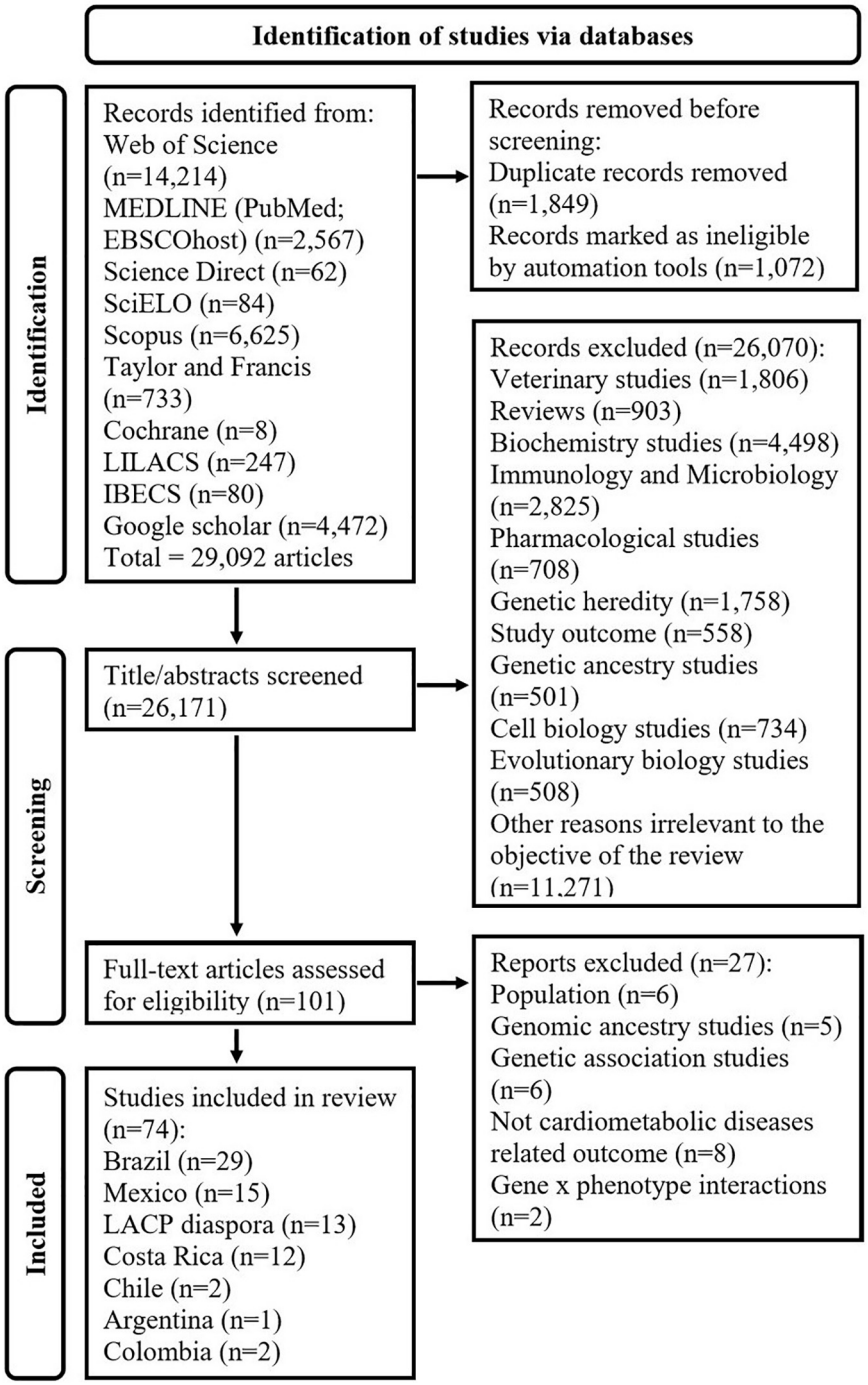

FIGURE 5
Flow chart showing the exclusion criteria and selection of studies. Literature search was conducted in MEDLINE (*via* PubMed and EBSCO Host), Web of Science, ScienceDirect, SciELO, SCOPUS, Taylor & Francis Online, Cochrane library, LILACS (Latin American and Caribbean Health Sciences Literature), IBECS, Google Scholar, and ERIC (Education Resources Information Center *via* EBSCO Host) search engines until the 25th of May 2022.

3.3.6. Interactions between micronutrients and genetic variants on cardiometabolic traits

The interaction between micronutrients and genetic variants on cardiometabolic traits was examined by five Brazilian studies (81–85). A cross-sectional study of 335 healthy young adults (81), observed a pronounced increase in systolic blood pressure (SBP) ($P_{\text{interaction}} = 0.016$) among carriers of the "*G*" allele of Angiotensinogen (*AGT*) SNP rs699 with a higher plasma magnesium (209.3 mg). Similarly, among those with a high calcium intake (573.3 mg), carriers of the "*T*" allele of Bradykinin Receptor B2 (*BDKRB2*) SNP rs1799722 had significantly higher SBP ($P_{\text{interaction}} = 0.015$) and diastolic BP (DBP) ($P_{\text{interaction}} = 0.014$) than carriers of the "*CC*" genotype (81). In line with these findings, a case-control study of 234 elderly people (82) reported an interaction between sodium intake and angiotensin-converting enzyme (*ACE*) SNP rs4646994 on the risk of hypertension, where carriers of the "*I/I*" genotype with a high sodium intake (>2 g/day) had an increased risk of hypertension ($P_{\text{interaction}} = 0.007$). Furthermore, in

a cross-sectional study of 1298 healthy adults (83), those carrying the "*T*" allele of Cytochrome B-245 Alpha Chain (*CYBA*) (*p22phox*) with more than 86.5 mEq sodium per 12 h of urine collection, had increased SBP ($P_{interaction} < 0.001$) and DBP ($P_{interaction} = 0.011$). Sodium is known to increase BP by reducing vasodilation (86), while dietary calcium is believed to stabilize intracellular calcium in smooth muscles, thereby reducing vasoconstriction and BP (87). Additionally, the "*A*" allele of *AGT* SNP rs699 is thought to be a risk factor for elevated SBP, possibly due to its association with a rise in plasma AGT levels (60, 81), and the findings of the study discussed above (81) indicate that, the protective effect of the "*G*" allele might be lost in the presence of higher plasma magnesium.

Similarly, in a longitudinal study of 1088 children with a follow up of 4.6 years (84), those with a deficit of plasma vitamin D (<75 nmol/L) and carriers of the risk allele ("*A*") of *FTO* SNP rs9939609 had increased BMI ($P_{interaction} = 0.033$). However, a cross-sectional study examining folate intake in 5914 healthy adults (85) did not identify interactions between folate intake and *MTHFR* SNP rs1801133 on homocysteine concentrations.

3.3.7. Interactions between alcohol intake and genetic variants on cardiometabolic traits

Three Brazilian studies (85, 88, 89) examined the interaction between alcohol intake and genetic variants on cardiometabolic traits. In a cross-sectional study of 113 participants (88), a significant interaction was observed between alcohol intake and endothelial nitric oxide synthase (*eNOS*) SNP rs2070744 (−786 T/C) on plasma nitrite levels. Individuals carrying the "C" allele who consumed alcohol had lower plasma nitrite levels ($P_{interaction} = 0.033$). However, there were no significant interactions between alcohol intake and rs2070744 on BP (88). Similarly, in a cross-sectional study of 3,803 participants from the Pelotas Birth Cohort (85), an interaction was identified between alcohol intake and *MTHFR* SNP rs1801133 (C677T), in which men with the "677TT" genotype who consumed ≥ 15 g of alcohol per day had the highest homocysteine concentration ($P_{interaction} = 0.002$); but the interaction was not observed in women. Moreover, a prospective cohort study of 964 postmenopausal women (89), reported no interactions between alcohol intake and *APOE* genotype on lipid traits. A rise in homocysteine concentration is attributed to a deficiency in B vitamins and folate, and SNPs of *MTHFR* might affect homocysteine concentration by impairing folate metabolism (90). However, it is unclear how alcohol intake modifies the activity of MTHFR, and the finding of the study (85) suggests a sex-specific response.

3.3.8. Interactions between smoking and genetic variants on cardiometabolic traits

Two studies (91, 92) investigated the interaction between smoking and genetic variants on cardiometabolic traits in Brazilians. In a cross-sectional study of 391 participants (91), smoking interacted with *APOA-IV* SNPs rs693 (*Xba*I), rs675 (Thr347Ser) and rs5110 (Gln360His), increasing BMI in individuals with the "X*2" ($P_{interaction} = 0.007$) and "347Ser" ($P_{interaction} = 0.02$) alleles. However, men with the "360His" allele who were non-smokers had a larger WC than homozygotes for the "Gln" allele ($P_{interaction} = 0.018$) (91). Similarly, in a cross-sectional study of 673 overweight adults (403 women and 270 men) (92), carriers of the "S2" allele of *APOC3* SNP rs5128 had increased triglycerides and the effect was more pronounced in women who smoked than in non-smokers ($P_{interaction} = 0.009$). Serum APOC3 concentration has been shown to be positively associated with triglyceride levels, and smoking has been reported to lower the concentration of APOC3 but only in women without central obesity (93), indicating a sex-specific response which is influenced by obesity traits.

3.3.9. Interactions between physical activity and genetic variants on cardiometabolic traits

Interactions between physical activity and genetic variants on cardiometabolic traits were investigated by nine Brazilian studies (66, 85, 91, 94–99). In a longitudinal study of 197 overweight or obese children (94), a physical exercise program (3 sessions/week for 12 weeks) interacted with adrenoceptor beta 2 (*ADRB2*) SNP rs1042714, decreasing triglyceride levels and triglyceride-glucose index ($P_{interaction} = 0.001$ for both) more in carriers of the "Glu27Glu" genotype than those carrying the "Gln27" allele. A cross-sectional study of 1701 children and adolescents (95) also reported higher BMI and WC in individuals with the "TT" genotype of fibronectin type III domain containing 5 (*FNDC5*) SNP rs16835198 compared to carriers of the "G" allele only in those with lower levels of cardiorespiratory fitness (CRF) ($P_{interaction} = 0.038$ and $P_{interaction} = 0.007$ for WC and BMI, respectively); and lower limb strength ($P_{interaction} = 0.040$ and $P_{interaction} = 0.044$ for WC and BMI, respectively). Physical activity has been proposed to alter the expression of certain genes (100), and the findings of these studies indicate that, the effect of physical activity on lipid, glycemic and anthropometric traits might be influenced by SNPs of *ADRB2* and *FNDC5* genes.

Similarly, a sedentary behavior (a screen time of > 378 min/day) was shown to increase cardiometabolic risk score in carriers of "AA" genotype of *FTO* SNP rs9939609 with a low CRF but not in those with a high CRF in a cross-sectional study of 1,215 children and adolescents ($P_{interaction} = 0.047$) (96). Along this line, a randomized controlled trial of 34 participants (97) reported that, a 45-min walk on a treadmill at moderate intensity resulted in a reduction in SBP ($P_{interaction} = 0.02$) and DBP ($P_{interaction} < 0.01$) in carriers of the "I" allele of *ACE* SNP rs4646994 compared with a non-exercise control session, but the reduction was not observed in participants with "DD" genotype. However, five studies (66, 85, 91, 98, 99) did not identify significant interactions between physical activity and genetic variants on cardiometabolic traits as shown in **Table 1**.

3.3.10. Other gene-diet interactions in Brazilians

In the BOLD study consisting of 113 participants (66), a total fat intake of 25.36% TEI interacted with Betaine-Homocysteine S-Methyltransferase (*BHMT*) SNP rs492842, increasing vitamin B12 concentrations ($P_{interaction} = 0.034$) in participants with the "TT" genotype. A case-control interventional study of 126 obese women (101) also reported that, a hypocaloric diet (< 600 kcal/day) for 7 weeks was associated with a decreased abdominal circumference ($P_{interaction} = 0.04$) among carriers of the "*A*" allele of *FTO* SNP rs9939609. Furthermore, in a prospective cohort study of 3,701 women, breastfeeding (> 6 months duration) interacted with *FTO* SNP rs9939609, decreasing BMI ($P_{interaction} = 0.03$), fat mass ($P_{interactin} = 0.03$), and WC ($P_{interaction} = 0.04$) in carriers of the "*A*" allele (102).

In summary, research in Brazil stands out in comparison to the rest of the gene-lifestyle research in LACP for being the most abundant; twenty-nine studies investigated gene x lifestyle interactions in the Brazilian population as shown in **Table 1**, covering

a wide range of cardiometabolic traits. Dietary fat intake and plasma fatty acid profile were the most frequently investigated dietary factors examined by seven and five studies, respectively, although all the studies examining plasma fatty acid profile used data from the HS-SP. Carbohydrate intake was examined by only three studies, all of which used data from the BOLD study. Similarly, protein intake was investigated by only three studies, two of which used data from the BOLD study. Physical activity was the most frequently examined lifestyle factor, followed by smoking and alcohol intake. Breastfeeding was examined by only one study (102), and lifestyle factors such as socioeconomic status, level of education, and the effect of rural and urban environments were not investigated. Only one study was conducted in rural settings (88), but it was not focused on interaction of the rural environment with genetic variants. The *FTO* SNP *rs9939609* was the most studied, being explored by five studies (84, 85, 96, 98, 99). Overall, the findings call for further research into lifestyle factors such as socioeconomic status, level of education and the effect of rural and urban environments as well as other dietary factors such as fruit and vegetable intake.

3.4. Gene x lifestyle interaction in Mexicans

3.4.1. Interaction between dietary fat intake and genetic variants on CVD traits

The interaction between dietary fat intake and genetic variants on CVD-related traits was examined by five Mexican studies (103–107). In a cross-sectional study of 224 participants with T2D (103), interactions between monounsaturated fatty acid (MUFA) intake and *APOE* genotype on blood lipid concentrations were reported. A low MUFA intake (< 10–15% TEI) was found to be associated with higher total cholesterol (TC) ($P_{interaction}$ = 0.016), non-HDL ($P_{interaction}$ = 0.024) and LDL ($P_{interaction}$ = 0.030) only in carriers of the "ε2" allele of *APOE* SNP rs7412. Similarly, interactions between MUFA intake ($P_{interaction}$ = 0.001), total fat intake ($P_{interaction}$ = 0.001), dietary cholesterol intake ($P_{interaction}$ = 0.019) and Dopamine Receptor D2/Ankyrin Repeat and Kinase Domain Containing 1 (*DRD2/ANKK1*) SNP rs1800497, increasing triglyceride levels in carriers of the "A2A2" genotype were observed in a cross-sectional study of 175 Mexican adults with T2D (104). MUFA intake has been linked to decreased triglyceride concentration (108) which is consistent with the findings of the first study (103). However, the findings of the second study (104) imply that MUFA intake might not be beneficial for individuals with the "A2A2" genotype of rs1800497. Both studies were conducted in participants with T2D which is known to affect lipid metabolism (109). Moreover, as highlighted by the authors of the second study (104), the effect of dietary fat intake on triglycerides concentration may be influenced by other factors including physical activity and the level of insulin resistance.

A Mexican case-control study consisting of 100 participants with normal weight and 100 participants with obesity (105) also found significant interactions between SFA intake and leptin receptor (*LEPR*) SNP rs1137101 on TC ($P_{interaction}$ = 0.002) and triglyceride ($P_{interaction}$ = 0.02) levels. It was reported that, a SFA intake of ≥ 12 g/day was associated with a 3.8 times higher risk of hypercholesteroleamia and a 2.4 times higher risk of hypertriglycerideamia compared to an intake of < 12 g/day in participants carrying the "G" allele of rs1137101 (105). An interaction between total fat intake with *LEPR* SNP rs1137101 on TC ($P_{interaction}$ = 0.001) was also reported in this study (105), where a high intake of total fat (≥83 g/d) was associated with a 4.1 times higher risk of hypercholesteroleamia in carriers of the "G" allele of rs1137101. Similarly, in a prospective cohort study involving a dietary intervention in 41 participants with hypercholesterolemia (106), interactions were observed between consumption of a diet low in SFA (<6% TEI/day) in addition to another diet containing 15 g of soluble fiber and 25 g of soy protein for 2 months and Glucose-Fructose Oxidoreductase Domain Containing 2 (*GFOD2*) SNP rs12449157 on TC ($P_{interaction}$ = 0.006) and LDL ($P_{interaction}$ = 0.025). Participants carrying the "G" allele had a larger decrease in TC and LDL in response to the dietary intervention compared to subjects with the "AA" genotype of rs12449157 (106). In this study (106), baseline LDL and TC levels were higher in carriers of the "G" allele, but they responded better to the dietary intervention, which indicates that the genetic risk of dyslipidaemia can be modified by a dietary intervention. However, in another study of 31 Mexican participants with dyslipidaemia (107) from the same cohort as above (106), using the same dietary intervention, no significant interactions were identified between the diet and Calpain 10 (*CAPN10*) SNPs rs5030952, rs2975762, and rs3792267 on lipid traits. It has been reported that SFA of different types and from different food sources might have different effects on cardiometabolic traits (110, 111), however, both studies (106, 107) used the same dietary intervention. Nonetheless, factors such as physical activity have also been reported to influence the effect of dietary fat intake on cardiometabolic traits (104), which could explain the differences in the findings.

3.4.2. Interaction between carbohydrate intake and genetic variants on cardiometabolic traits

Interactions between carbohydrate intake and genetic variants on cardiometabolic traits were examined by three Mexican studies (104, 112, 113). In a cross-sectional study of 3591 adults (112), carbohydrate intake was negatively associated with HDL concentrations in premenopausal women carrying the risk allele ("C") of ATP Binding Cassette Subfamily A Member 1 (*ABCA1*) SNP rs9282541 (*R230C*), but not in those carrying the "R" allele ($P_{interaction}$ = 0.037). In another cross-sectional study of 215 healthy adults (113), a high sucrose intake (>5% TEI) significantly increased TC ($P_{interaction}$ = 0.034) and LDL ($P_{interaction}$ = 0.037) more in participants with "B1B2/B2B2" genotype than those with "B1B1" genotype of cholesteryl ester transfer protein (*CETP)* SNP rs708272. However, the interaction did not influence triglycerides, HDL, BMI nor waist circumference (113). In contrast, the cross-sectional study discussed above (104), reported that the intake of maltose (0.68 ± 0.42 g/day) significantly decreased triglycerides ($P_{interaction}$ = 0.023) in carriers of the "A1"allele of *DRD2/ANKK1* SNP rs1800497. These findings indicate that carbohydrate intake might modulate lipid levels in Mexicans with certain genetic variants, but the mechanism through which carbohydrates affect lipid levels are unclear. Moreover, it has been reported that, the effect of carbohydrates on lipids might be dependent on glycemic index or glycemic load, and highly processed carbohydrates are linked to unfavorable lipid profiles (114).

3.4.3. Interaction between micronutrients and genetic variants on cardiometabolic traits

Two cross-sectional studies examined the interaction between micronutrients and genetic variants on cardiometabolic traits (115,

116). In the first study which consisted of 231 healthy new-borns (115), a deficient maternal vitamin B12 (<2.0 mcg/d) was found to be associated with a smaller size baby at birth in mothers with the "TT" genotype of *MTHFR* SNP rs1801133 ($P_{interaction} = 0.02$) but a deficient maternal folate (<400 mcg/d) was not associated with anthropometric parameters (weight, length or BMI) of new-borns (115). A low vitamin B12 intake (<2.0 mcg/d) was also associated with increased homocysteine levels ($P_{interaction} = 0.01$) in carriers of the "TT" genotype of *MTHFR* SNP rs1801133 in a cross-sectional study of 130 healthy women (116). The "TT" genotype of *MTHFR* is associated with decreased enzymatic activity and increased homocysteine concentration (117) and the findings of these studies suggest that increasing the intake of vitamin B12 might improve fetal development in Mexican women with the "TT" genotype.

3.4.4. Interaction between alcohol intake and genetic variants on cardiometabolic traits

The cross-sectional study of 130 healthy women discussed above (116), was the only study which examined alcohol intake and no interaction was found between alcohol intake and *MTHFR* SNP rs1801133 on homocysteine levels which could be due to the fact that 80% of the studied population consumed less than 1 cup/week of alcohol (116).

3.4.5. Interaction between physical activity and genetic variants on cardiometabolic traits

Interactions between physical activity and genetic variants on cardiometabolic traits were investigated by four Mexican studies (113, 118–120). In the cross-sectional study discussed above (113), increased concentration of TC ($P_{interaction} = 0.033$) was observed in individuals carrying the "B2" allele of *CETP* SNP rs708272 who did not perform physical activity, compared to those with the "B1B1" genotype. However, there were no interactions on TG, HDL, TG:HDL ratio, LDL, BMI or WC (113). Similarly, interactions between physical fitness measured by muscular endurance (ME) and aerobic capacity with genetic variants were observed in a case-control study of 608 physically active adults (118), where higher levels of ME and aerobic capacity were associated with a lower WC in individuals with a high GRS based on 23 SNPs (**Table 1**) ($P_{interaction} = 0.0001$ for both). In this study (118), a higher risk of obesity was found in older participants (≥ 40 years) with the "AA" genotypes of *APOB* SNP rs512535 ($P_{interaction} = 0.004$) and tumor necrosis factor (*TNFA*) SNP rs361525 ($P_{interaction} = 0.007$) with low levels of ME. However, another cross-sectional study of 565 physically active participants (119) did not find significant interactions between physical fitness and six SNPs (*ADIPOQ* rs2241766, *ACSL1* rs9997745, *LIPC* rs1800588, *PPARA* rs1800206, *PPARG* rs1801282 and *PPARGC1A* rs8192678) on glycemic traits. Moreover, the fourth cross-sectional study which consisted of 394 participants (120), did not identify interactions between physical activity and *ADIPOQ* SNP –11391G/A on adiponectin levels.

3.4.6. Other gene-lifestyle interactions in Mexicans

In a cross-sectional study of 206 Mexican women (121), an interaction between polycyclic aromatic hydrocarbons (PAHs) and Paraoxonase 1 (*PON1*) SNP rs661 (Q192R) on serum asymmetric dimethylarginine (ADMA) was observed, where individuals carrying the "R" allele had higher ADMA levels compared to those with the "QQ" genotype in response to higher levels of urinary 1-hydroxypyrene ($P_{interaction} = 0.02$). Increased levels of ADMA ($p < 0.01$) and fatty acid-binding protein 4 ($p < 0.001$) were also identified in individuals with the "RR" genotype of *PON1* SNP rs661 with higher urinary arsenic levels (>45.0 μg/g of creatinine) in comparison with participants with the "QQ" genotype in a sample of 185 Mexican women (122). The mechanisms of the interaction may be shared in the case of exposure to PAHs as these are also involved in the generation of reactive oxygen species (123).

Overall, different cardiometabolic traits have been investigated in Mexico, where eleven out of fifteen studies found significant gene x lifestyle interactions (103–106, 112, 113, 115, 116, 118, 121, 122) as shown in **Table 1**. Dietary fat intake was the most frequently examined dietary factor, being investigated by five studies (103–107); followed by carbohydrate intake, which was examined by three studies (104, 112, 113). Physical activity was the most frequently examined lifestyle factor, while alcohol intake was investigated by only one study. Lifestyle factors such as smoking, socioeconomic status, level of education and the impact of rural and urban environments were not investigated. Moreover, dietary factors such as consumption of protein, complex carbohydrates, and fruits and vegetables have not been investigated, highlighting a need for further research.

3.5. Gene x lifestyle interaction in Costa Ricans

3.5.1. Interactions between dietary fat intake and genetic variants on CVD-related traits

The interaction between dietary fat intake and genetic variants on CVD-related traits was examined by six Costa Rican studies (124–129). In a cross-sectional study of 420 participants (124), SFA intake interacted with *APOE* genotype and influenced blood lipid concentrations. A higher SFA intake (13.5% energy) was associated with higher levels of very-low density lipoprotein cholesterol (VLDL) ($P_{interaction} = 0.03$) and lower concentration of HDL ($P_{interaction} = 0.02$) in carriers of the "ε*2*" allele. However, no significant interactions were identified between SFA intake and *APOE* genotype on lipids in a case-control study involving 1,927 participants with myocardial infarction (MI) and 1,927 matched controls (125). In another cross-sectional study of 336 participants (126), SFA intake was found to interact with *APOC3* genotype and impact on the concentration of TC ($P_{interaction} = 0.0004$) and LDL ($P_{interaction} = 0.01$). Homozygotes for the *APOC3-455T-625T* alleles had a 13% increase in TC and a 20% increase in LDL with a high SFA intake (>11% of energy intake), but the interaction was not significant in individuals with the *APOC3-455C-625del* allele (126). In the case-control study discussed above (125), a significant interaction between SFA intake and *APOE* genotype on the risk of MI ($P_{interaction} = 0.0157$) was also reported, in which carriers of the "ε*4*" allele had a 49% increased risk of MI compared to a 2.2 fold increased risk in those with the "ε*2*" allele in response to a high SFA intake (>11.8% of energy intake).

APOE plays a key role in lipid metabolism, being a main component of triglyceride-rich lipoproteins and HDL, and a ligand for LDL receptor (124, 130) and it is believed that the metabolism of fatty acids is impaired in carriers of the "ε*4*" allele which is considered a risk factor for CVDs (131). However, the above findings indicate that, a high SFA intake is more detrimental to carriers of the "ε*2*" allele

than those carrying the "ε*4*" allele, highlighting the potential role of SFA intake in modifying genetic risk.

In accordance with the findings above, a case-control study of 1805 participants with a first non-fatal MI and 1,805 matched controls (127), reported an interaction between PUFA intake and *PPARγ* SNP rs1801282, influencing the risk of MI ($P_{interaction} = 0.03$). Individuals with the "Pro12/Pro12" genotype had a 34% reduced risk of MI per 5% increment in energy from PUFA compared to a 7% decreased risk in those carrying the "*Ala12*" allele (127). Similarly, a case-control study of 1932 participants with a first non-fatal MI and 2,055 matched controls (128), reported a significant interaction between long-chain omega-3 (LC n-3) PUFA intake and Proprotein Convertase Subtilisin/Kexin Type 9 (*PCSK9*) SNP rs11206510 on the risk of MI ($P_{interaction} = 0.012$), where carriers of the "C" allele had an odds ratio for MI of 0.84 per 0.1% increase in total energy from LC n-3 PUFA, compared to an odds ratio of 1.02 in participants without the "C" allele (128). Along similar lines, a case-control study of 1936 participants with a first non-fatal MI and 2,035 matched controls (129) reported a significant interaction between omega-6 (n-6) PUFA intake and Phospholipase A2 Group IVA (*PLA2G4A*) SNP rs12746200 on the risk of MI ($P_{interaction} = 0.005$), in which participants with the "G" allele had a reduced risk of MI with an intake of n-6 PUFA above the median compared to those with the "AA" genotype. However, there were no significant interactions with n-3 PUFA intake (129).

These findings indicate that the beneficial effect of PUFA intake reported by some studies (101, 132) might be limited in individuals with certain genetic variants. PPARγ is a nuclear receptor which is involved in adipogenesis and plays a role in the metabolism of glucose and fatty acids (133, 134), and the "*Ala12*" allele of PPARγ SNP rs1801282 has been reported to slow down the release of PUFA from adipocytes, which could explain the smaller reduction in the risk of MI in comparison with carriers of the "Pro12/Pro12" genotype (127).

3.5.2. Interaction between other dietary factors and genetic variants on the risk of MI

Interactions between other dietary factors and genetic variants on the risk of MI were examined by three Costa Rican studies (135–137). In a case-control study of 1,560 incident cases of non-fatal MI and 1,751 matched controls (135), sugar sweetened beverage (SSB) intake interacted with a GRS based on 3 SNPs of chromosome 9p21 (rs4977574, rs2383206 and rs1333049), increasing the risk of MI ($P_{interaction} = 0.03$). SSB intake also interacted with rs4977574, increasing the risk of MI in carriers of the "G" allele ($P_{interaction} = 0.005$), but there was no interaction with fruit juice intake (135). In another case-control study of 2,014 participants with a first acute non-fatal MI and 2,014 matched controls (136), an increased risk of MI with increasing coffee intake was observed in carriers of the "C" allele (also known as "slow metabolizers of caffeine") of Cytochrome P450 Family 1 Subfamily A Member 2 (*CYP1A2*) SNP rs762551 compared to carriers of the "AA" genotype ($P_{interaction} = 0.04$). Similarly, in a case-control study consisting of 2,042 participants with a first non-fatal MI and 2042 control subjects (137), cruciferous vegetable intake (0.86 servings/day of half a cup) interacted with Glutathione S-Transferase Theta 1 (*GSTT1*) SNP rs17856199, lowering the risk of MI in carriers of the "*1" allele, but not in individuals with the "*0*0" genotype ($P_{interaction} = 0.006$). These findings indicate that, dietary factors other than fat intake, might also influence the risk of MI in Costa-Ricans with certain genetic variants.

3.5.3. Interaction between smoking and genetic variants on the risk of MI

Interaction between smoking and genetic variants on the risk of MI was investigated by three Costa Rican case-control studies (137–139), two of which found significant interactions (137, 138). In a case-control study of 492 participants with a first non-fatal MI and 518 matched controls (138), an interaction was observed between smoking status and Paraoxonase 1 ($PON1_{192}$) SNP rs661 on the risk of MI ($P_{interaction} = 0.04$), where the $PON1_{192Arg}$ allele was associated with an increased risk of MI only in non-smokers. Similarly, in the case-control study discussed above (137), the combined intake of cruciferous vegetables (>5 servings/day) and smoking (1–10 cigarettes/day) in carriers of the "*1" allele of rs17856199, lowered the risk of MI ($P_{interaction} = 0.008$). However, there were no significant interactions with *GSTM1* or *GSTP1* genotype on the risk of MI (137). Moreover, in the third Costa Rican case-control study which involved 873 participants with a first non-fatal MI and 932 control subjects (139), no significant interactions were observed between smoking and *CYP1A1* SNP rs1048943 or *CYP1A2* SNP rs762551 on the risk of MI. Smoking has been linked to increased risk of MI (140, 141) although the mechanisms are unclear. Smoking is also believed to impair the activity of PON1, which is linked to increased risk of CVDs (142, 143), but this is not supported by the findings of the studies above, suggesting that Costa Ricans with certain genetic variants might respond differently to smoking.

3.5.4. Other gene-lifestyle interactions in Costa Ricans

One case-control study consisting of 1534 participants with a first non-fatal MI and 1,534 matched controls (144), investigated the interaction between a lifestyle cardiovascular risk score comprising of physical activity, smoking, alcohol consumption, waist-to-hip ratio, and socioeconomic status; and a GRS based on 14 SNPs (**Table 1**) on the risk of MI, and no significant interactions were identified.

The research in Costa Rica has mainly focused on CVD traits in adults, with an emphasis on the risk of MI, and dietary fat intake has been the most frequently examined exposure. Socioeconomic status was examined by one study (144), and lifestyle factors such as educational level, the effect of rural and urban environments as well as dietary factors such as consumption of protein, fiber and complex carbohydrates have not been explored, highlighting a need for further research.

3.6. Gene x lifestyle interaction in LACP diaspora

3.6.1. Interaction between dietary fat intake and genetic variants on anthropometric traits

Interaction between dietary fat intake and genetic variants on anthropometric traits were investigated by six studies (145–150), all of which used data from the Boston Puerto Rican Health Study (BPRHS). In a cross-sectional study of 930 Puerto Ricans from the BPRHS (145), a high intake of SFA (≥22 g/day) was associated with a 7.9% higher BMI in individuals with the "CC" genotype of *APOA2* SNP rs5082 than those carrying the "T" allele ($P_{interaction} = 0.003$); but the SNP had no effect on BMI when SFA intake was low (<22 g/day). This study also observed that, among individuals with a high SFA intake (≥22 g/d), those with the "CC" genotype had a

higher risk of obesity than participants carrying the "T" allele of the SNP rs5082 [Odds ratio (OR) = 1.84; 95% confidence interval (CI) = 1.38–2.47; $P < 0.0001$). A similar finding was reported in a prospective cohort study of 920 participants from the BPRHS (146), where a high intake of SFA (≥ 9.3% of total energy) was linked to higher BMI ($P_{interaction} = 0.006$), WC ($P_{interaction} = 0.02$), and hip circumference (HC) ($P_{interaction} = 0.002$) in participants carrying the minor allele ("T") of LDL receptor related protein 1 (*LRP1*) SNP rs1799986 compared to individuals with the "CC" genotype; but the SNP had no effect on anthropometric traits when SFA intake was low (<9.3% of total energy). The "CC" genotype of *APOA2* rs5082 is believed to affect body fat distribution by lowering plasma concentration of APOA2 and these findings indicate that, a low SFA intake might attenuate this genetic risk (145, 151).

An interaction of total fat intake with *APOA1*-75 on WC was also reported in a longitudinal study of 821 participants of the BPRHS (147), in which individuals carrying two copies of the major allele had a lower WC with a low total fat intake than those carrying the minor allele ($P_{interaction} = 0.005$). A longitudinal study performed in 1,171 participants (333 men and 838 women) of the BPRHS (148) also observed that, women with the "TT" genotype of lipoprotein lipase (*LPL)* SNP rs320 had lower BMI ($P_{interaction} = 0.002$) and WC ($P_{interaction} = 0.001$) with a high intake of PUFA but this was not observed in minor allele ("G") carriers and there were no significant interactions in men. In contrast, another longitudinal study of 1,340 participants (395 men and 945 women) of the BPRHS (149) found that, men with the "GG" genotype of brain derived neurotrophic factor (*BDNF)* SNP rs6265 had higher BMI ($P_{interaction} = 0.042$), WC ($P_{interaction} = 0.018$), and HC ($P_{interaction} = 0.009$) with a low PUFA intake (<8.76% of energy) than those carrying the "A" allele but no difference was observed when PUFA intake was high (≥8.76% of energy) and the interaction was not observed in women. Interaction between Mediterranean diet with *TCF7L2* SNP rs7903146 on obesity-related traits was also observed in a cross-section study of 1,120 Puerto Ricans of the BPRHS (150), where carriers of the "T" allele had lower WC (99.2 ± 0.9 vs. 102.2 ± 0.9 cm; $P_{interaction} = 0.026$) and weight (77.3 ± 1.0 vs. 80.9 ± 1.0 kg; $P_{interaction} = 0.024$) with a high Mediterranean diet score than individuals with "CC" genotype. However, there were no significant differences between the genotypes when the Mediterranean diet score was low. The findings suggest that a high intake of PUFA and Mediterranean diet might be beneficial in reducing the genetic risk of obesity-related traits in a sex-specific manner and call for further research into the mechanisms involved.

3.6.2. Interaction between dietary fat intake and genetic variants on CVD traits

Interaction between total fat intake and genetic variants on CVD traits were reported by three studies (147, 152, 153). In a longitudinal study of 802 participants of the BPRHS (152), a significant interaction was observed between total fat intake and *APOA5* SNP -1131T < C on plasma triglycerides ($P_{interaction} = 0.032$), where a high total fat intake (≥31% of total energy) was associated with a higher plasma triglyceride concentration in individuals with the "1131C" allele, although no difference between the genotypes was observed when total fat intake was low. This study (152) also observed an interaction between *APOA5* SNP S19W with total fat intake on SBP ($P_{interaction} = 0.002$) and DBP ($P_{interaction} = 0.007$), where participants with the minor allele ("G") had a higher SBP with a low total fat intake (< 31% of total energy), and a lower SBP with a high total fat intake in comparison with individuals with the "CC" genotype. The study on 821 participants of the BPRHS discussed above (147), also reported significant interactions between total fat intake and *APOC3* -640 on DBP ($P_{interaction} = 0.003$), *APOA4* N147S and *APOA5* S19W on SBP ($P_{interaction} = 0.001$ and $P_{interaction} = 0.002$, respectively). It was observed that, homozygous for the major allele of *APOA1*-75, *APOA4* N147S and *APOA5* S19W had lower SBP with a low intake of total fat (< 31% of total energy) than those carrying the minor allele; while heterozygous for *APOC3* -640 had lower DBP with a high total fat intake (≥ 31% from energy) (147). However, a randomized crossover trial involving 41 adults from Dominican, Puerto Rican and other Caribbean Hispanic origins (153), did not find significant interactions between a high fat diet and hepatic lipase (*LIPC*) SNP rs1800588 on HDL, LDL, TC or plasma glucose concentrations. A high intake of total fat has been associated with an unfavorable lipid profile and high blood pressure (154) and the above findings indicate that, this association might be influenced by variants of several genes.

3.6.3. Interaction between carbohydrate intake and genetic variants on cardiometabolic traits

Two studies investigated the interaction between carbohydrate intake and genetic variants on cardiometabolic traits (155, 156). In a longitudinal study involving 920 participants of the BPRHS (155), a significant interaction was observed between Perilipin 1 (*PLIN 1*) SNP 1,482 G > A and complex carbohydrate intake on WC ($P_{interaction} = 0.002$), where individuals carrying the "A" allele had a higher WC with a low intake of complex carbohydrate (<144 g/day) and a lower WC with a high intake of complex carbohydrate (≥144 g/day) than those with the "GG" genotype. Similarly, a cross-sectional study of 153 children descendent from Hispanic ancestry (156), identified significant interaction between carbohydrate intake (211.4 g/day) and total sugar intake (96.1 g/day), increasing hepatic fat fraction in carriers of the "GG" genotype of Patatin like phospholipase domain containing 3 (*PNPLA3*) SNP rs738409 ($P_{interaction} = 0.04$ and $P_{interaction} = 0.01$, respectively), but the interaction was not observed in individuals carrying the "C" allele. It has been reported that, body weight might be influenced by the type of carbohydrate consumed (157) which is supported by the findings of these studies, but the results also indicate that genetic variants might also play a role.

3.6.4. Interaction between micronutrient intake and genetic variants on cardiometabolic traits

The interaction between micronutrient intake and genetic variants on cardiometabolic traits was investigated by two studies (158, 159). A cross-sectional study involving 1,734 Mexican Americans (158) reported a significant interaction between vitamin E and *APOB* SNP rs693 on LDL ($P_{interaction} = 8.94 \times 10\text{-}7$), and between vitamin A and *PCSK9* SNP rs11206510 on LDL ($P_{interaction} = 7.65 \times 10\text{-}5$), but the direction of the interactions is unclear. Similarly, in the longitudinal study of 1,144 Puerto Ricans of the BPRHS discussed above (159), a significant interaction between vitamin D status and *IRS1* rs2943641 on the risk of T2D was identified in women in which minor allele homozygotes ("TT") had a lower risk of T2D compared with "C" allele carriers only when 25(OH)D was higher than the median [>17 ng/mL (42.4

nmol/L)] ($P_{interaction}$ = 0.007), but the interaction was not observed in men. The findings of these studies indicate that micronutrients might modulate the association between genetic variants and lipid and glycemic traits, but further studies are needed to replicate and elucidate the mechanisms involved.

3.6.5. Interaction between physical activity and genetic variants on cardiometabolic traits

Only one study (160) examined the interaction between physical activity and genetic variants on cardiometabolic traits. This study (160) was a prospective cohort study of 9,645 adult Puerto Ricans, Mexicans, Dominicans, Cuban, Central American, and South American from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) cohort, USA, and a positive association was observed between a GRS based on 97 SNPs (**Table 1**) and BMI, but the effect of the GRS was stronger in the first tertile of moderate to vigorous physical activity compared to the third tertile ($P_{interaction}$ = 0.005). Significant interactions following the same pattern were observed for fat mass ($P_{interaction}$ = 0.003), fat percentage ($P_{interaction}$ = 0.003) and fat mass index ($P_{interaction}$ = 0.002) (160).

In summary, research in LACP diaspora has mainly focused on Puerto Ricans residing in USA and most of this evidence (10 out of 13 studies) comes from the same study (BPRHS). Dietary fat intake has been the most frequently studied, with carbohydrate intake being examined by only two studies. Similarly, physical activity was investigated by only one study and lifestyle factors such as socioeconomic status, level of education, and the effect of rural and urban environments have not been explored.

3.7. Gene x lifestyle interactions in Chileans

3.7.1. Interaction between carbohydrate intake and genetic variants on glycemic traits

Two gene-diet interaction studies were reported in Chileans (161, 162). The first study (161) was a cross-sectional study of 2828 healthy Chilean adults, and a significant interaction was observed between consumption of SSB and a weighted genetic risk score (wGRS) based on 16 T2D risk SNPs (**Table 1**) on log-fasting glucose ($P_{interaction}$ = 0.02), where the strongest effect was observed between the highest SSB intake (≥2 servings/day of 330 ml) and the highest wGRS. In this study (161), SSB intake also interacted with additive effects of Transcription Factor 7 Like 2 (*TCF7L2*) SNP rs7903146 ($P_{interaction}$ = 0.002) and with the "G/G" genotype of Melatonin Receptor 1B (*MTNR1B*) SNP rs10830963 ($P_{interaction}$ = 0.001), increasing log-fasting glucose levels. The second Chilean study (162) was a non-randomized controlled trial performed in 97 healthy women and 147 women with polycystic ovary syndrome, and there were no reported interactions between a high glycemic carbohydrate intake (75 g of glucose) during an oral glucose tolerance test and Insulin Receptor Substrate 1 (*IRS-1*) SNP rs1801278 on glycemic traits. In Chile, research has been limited to diabetes traits as outcomes and simple carbohydrates as exposure, reflecting a need for further research into other dietary and lifestyle factors such as socioeconomic status, level of education and the effect of rural and urban environments.

3.8. Gene x lifestyle interactions in Colombians

Two gene-lifestyle interaction studies were conducted in Colombians (163, 164). The first study (163) was a case-control study involving 212 normal weight, 112 overweight and 100 obese teenagers and no significant interactions were observed between physical activity and three SNPs (Uncoupling Protein 3 (*UCP3*) rs1800849, *FTO* rs17817449, and *CAPN10* rs3842570) on excess weight. However, sub-group analysis showed that, a sedentary lifestyle was associated with an increased risk of excess weight only in those with the "GG" or 'TT' genotype of *FTO* rs17817449 (p = 0.0005); and 'CC' genotype of *UCP3* rs1800849 (p = 0.0032) (163). It was also observed that, even with an active lifestyle [1.6–1.9 metabolic equivalent task (MET) minute/day], individuals with the "II" genotype of *CAPN10* rs3842570 had a higher risk of excess body weight compared to those carrying the "D" allele (p = 0.0212) (163). The second study which was also a cross-sectional study involved 1,081 Colombian teenagers (164), and there were no interactions between lifestyle factors (socioeconomic stratum, level of education and maternal breastfeeding) and ten SNPs on BMI (**Table 1**). As both studies (163, 164) were conducted in teenagers and focused on obesity traits, there is a need for further research into other cardiometabolic traits in the wider Colombian population.

3.9. Gene x lifestyle interactions in Argentinians

Only one study (165) was conducted in Argentinians, and this was a cross-sectional study consisting of 572 healthy Argentinian men. This study (165) reported a significant interaction between smoking status and *PPARγ* SNP rs1801282 on the risk of MetS ($P_{interaction}$ = 0.031) where among the non-smokers, carriers of the "*Pro/Ala*" genotype (p = 0.0059) and the "*Ala12*" allele (p = 0.009) had a higher risk of MetS than non-carriers. It is unclear whether there were significant interactions between smoking status and rs1801282 genotype on the other outcomes investigated in the study (165) (**Table 1**), since the p-values given are for associations stratified by smoking status. The study adjusted for BMI and age only, but the pathophysiological mechanism of MetS is multifactorial (166), and hence other factors should be considered simultaneously. There have been no studies in Argentina examining the interactions of genetic variants with dietary factors, physical activity, or other lifestyle factors apart from smoking status.

4. Summary of the findings of commonly investigated interactions across the countries

The most commonly investigated interactions in LACP related to dietary fat intake and genetic variants on blood lipids. A high intake of olive oil was associated with lower LDL in Brazilian men with the "ε*2*" allele of *APOE* (62), while a low MUFA intake was linked to higher TC, non-HDL and LDL in Mexicans carrying the "ε*2*" allele of *APOE* (103). In contrast, increased TG concentration in response to a high MUFA intake was observed in Mexicans who were homozygotes

for the A2 allele of *DRD2/ANKK1* SNP rs1800497. A high PUFA intake was also associated with increased concentration of LDL in Brazilian carriers of the "ε*4*" allele, and reduced concentration of TG in those carrying the "ε*2*" allele of *APOE* (62). However, a low PUFA intake was linked to increased TG and VLDL concentration in Brazilian women with the "ε*4*" allele of *APOE* (63).

Furthermore, a high SFA intake was associated with higher VLDL and lower HDL concentrations in Costa Rican carriers of the "ε*2*" allele of *APOE* (124), but no significant interactions were identified between SFA intake and *APOE* genotype on blood lipids in a Costa-Rican case-control study involving participants with MI (125). However, a high SFA intake was linked to increased concentrations of TC and LDL in Costa Ricans who were homozygotes for the *APOC3-455T-625T* alleles (126). Similarly, a high SFA intake was associated with increased TC and TG concentrations in Mexicans with the "G" allele of *LEPR* SNP rs1137101 (105); while a low SFA intake was linked to a decrease in TC and LDL concentrations in Mexicans with the "G" allele of *GFOD2* SNP rs12449157 (106).

The inconsistencies in the findings of the above studies call for further research into the interaction between sub-types of fat and genetic variants on blood lipids. The sources of dietary fat also need to be considered since SFA from different food sources have been reported to have different effects on cardiometabolic traits (111).

5. Discussion

This is the first systematic review to investigate gene-lifestyle interactions on cardiometabolic diseases in LACP, highlighting several gene-lifestyle interactions with effects being significant in Brazilians, Mexicans, Costa Ricans, Chileans, Argentinians, Colombians and LACP diaspora. The most frequently studied genes have been *FTO*, examined in Colombians, Mexicans, and Brazilians, *APOE* explored in Costa Ricans, Mexicans, and Brazilians, and *TCF7L2* investigated in Chileans, Mexicans, Brazilians and LACP diaspora. The concentration of blood lipids such as HDL and LDL was the most widely investigated trait, followed by BMI and WC; MI was examined by 11 studies and one study looked at hepatic fat accumulation, while diseases such as stroke and liver cirrhosis were not investigated. Research has identified gene-lifestyle interactions that describe effects which are population-, gender-, and ethnic-specific. The findings of this review indicate that most of the gene x lifestyle interactions were conducted once, necessitating replication to strengthen the evidence.

Another issue that could affect the results is the accuracy of the methods used to measure exposure variables such as dietary intake and physical activity (167, 168). Some studies used 24-h recall questionnaires and self-reporting methods (64, 77, 81, 112, 144, 158), which might have induced recall bias, inadequate estimations, daily variation bias, and over and underreporting of values (169, 170). Measurement of dietary intake is a crucial part of gene-diet interaction studies as under or overestimation of dietary intake can weaken or reverse the association between dietary factors and cardiometabolic traits (170, 171). Moreover, other studies used food frequency questionnaires with no information on whether they were tested for validity. Genotyping errors can also affect the results of gene-diet interactions by leading to deviations from the true genotype (172, 173).

Sample size has also been highlighted as a key methodological issue in gene-lifestyle interaction studies (167, 168). For complex traits where the main effects of genetic variants are often modest, a large sample size is required to detect small interaction effects (167, 174). Thus, it is important that studies are adequately powered to detect true interactions (168). Nonetheless, most of the studies had small sample sizes and only a few included information on statistical power to detect interactions. There is also the risk of false-positive finding when there is no correction for multiple comparisons (173, 175), but only a few of the studies provided information on correction for multiple comparisons.

Overall, the included studies are majorly cross-sectional, indicating a need for longitudinal/prospective studies. The findings reflect gaps in covering the genetic risks and the socioeconomic variables to which the LACP are exposed; 27 out of 33 LACP have not conducted gene-lifestyle interaction studies yet. Only five studies have been conducted in contexts of low socioeconomic status, and from these, only two studies investigated gene-socioeconomic status interactions (144, 164). Moreover, no studies have examined the impact of rural and urban environments on the genetic predisposition to cardiometabolic diseases, highlighting a gap in knowledge in LACP. The higher number of nutrigenetic studies in Brazil compared to the other countries could be attributed to several factors including existing data on genetic studies (176–181), GWAS done mainly in Brazil (182–184), increased awareness on nutrigenetics in Brazil or more research facilities available in Brazil compared to other LACP. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and the built environment. Moreover, the molecular mechanisms that underlie the gene-lifestyle interactions identified by this systematic review need to be explored. The strength of this review is the comprehensive search strategy and the inclusion of all dietary/lifestyle exposures and cardiometabolic traits. Another strength is the use of standardized tools to assess the quality of the studies. However, the study has some limitations.

In conclusion, this systematic review has identified several gene-lifestyle interactions on cardiometabolic disease traits in Brazilians, Mexicans, Costa Ricans, Chileans, Argentinians, Colombians and LACP diaspora, highlighting effects which are population-, gender-, and ethnic-specific. However, the lack of replication of most of the gene-lifestyle interactions made it difficult to evaluate the evidence. Moreover, most of the studies were cross-sectional meaning that they preclude causal assumptions hence a temporal relationship cannot be established. Future gene-lifestyle interaction studies will need to replicate primary research of already studied genetic variants to enable comparison, and to explore the interactions between genetic and other lifestyle factors such as those conditioned by socioeconomic factors and the built environment. Moreover, the molecular mechanisms that underlie the gene-lifestyle interactions identified by this systematic review need to be explored.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

KV: conceptualization, supervision, and project administration. EV, KV, and RW: methodology, validation, investigation, writing—original draft preparation, and resources. EV and RW: software, formal analysis, data curation, and visualization. AS and KV: funding acquisition. All authors contributed to writing—review and editing and read and agreed to the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1067033/full#supplementary-material

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Impact of Lipid Genetic Risk Score and Saturated Fatty Acid Intake on Central Obesity in an Asian Indian Population

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Abstract: Abnormalities in lipid metabolism have been linked to the development of obesity. We used a nutrigenetic approach to establish a link between lipids and obesity in Asian Indians, who are known to have a high prevalence of central obesity and dyslipidaemia. A sample of 497 Asian Indian individuals (260 with type 2 diabetes and 237 with normal glucose tolerance) (mean age: 44 ± 10 years) were randomly chosen from the Chennai Urban Rural Epidemiological Study (CURES). Dietary intake was assessed using a previously validated questionnaire. A genetic risk score (GRS) was constructed based on cholesteryl ester transfer protein (*CETP*) and lipoprotein lipase (*LPL*) genetic variants. There was a significant interaction between GRS and saturated fatty acid (SFA) intake on waist circumference (WC) ($P_{interaction}$ = 0.006). Individuals with a low SFA intake (≤23.2 g/day), despite carrying ≥2 risk alleles, had a smaller WC compared to individuals carrying <2 risk alleles (Beta = −0.01 cm; p = 0.03). For those individuals carrying ≥2 risk alleles, a high SFA intake (>23.2 g/day) was significantly associated with a larger WC than a low SFA intake (≤23.2 g/day) (Beta = 0.02 cm, p = 0.02). There were no significant interactions between GRS and other dietary factors on any of the measured outcomes. We conclude that a diet low in SFA might help reduce the genetic risk of central obesity confirmed by *CETP* and *LPL* genetic variants. Conversely, a high SFA diet increases the genetic risk of central obesity in Asian Indians.

Keywords: genetic risk score; Asian Indians; lipids; central obesity; fat intake; gene-diet interaction; saturated fatty acid

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1. Introduction

Asian Indians are more prone to developing type 2 diabetes (T2D) and cardiovascular diseases (CVDs) at a lower body mass index (BMI) than Caucasians, due to the 'Asian Indian phenotype', which is characterised by central obesity, dyslipidaemia, and increased levels of total fat, visceral fat, insulin resistance and faster decline in beta cell function [1–3]. The location of body fat is thought to be more important in predicting

adverse cardiovascular events [4–6]. Central obesity has been linked to several conditions, including insulin resistance and increased mortality from CVDs [7–10], necessitating studies to fully understand the underlying mechanisms for the development of central obesity in Asian Indians.

Abnormalities in lipid metabolism have been linked to the development of obesity, and lipoprotein lipase (LPL), a key enzyme in lipid metabolism, contributes to the development of obesity through its role in the partitioning of lipids to different tissues [10–12]. Cholesteryl ester transfer protein (CETP), mainly expressed in adipose tissue, is also a major enzyme in lipid metabolism, which mediates the transport of cholesteryl esters and triglycerides (TG) between high-density lipoprotein cholesterol (HDL) and apolipoprotein B (ApoB)–containing lipoproteins such as very-low-density lipoprotein (VLDL) [13]. Increased CETP activity results in lower HDL concentration, which is associated with higher risk of CVDs [14]. Consumption of a high saturated fatty acid (SFA) diet has also been shown to contribute to obesity by decreasing cholesterol efflux due to reduced expression of peroxisome proliferator-activated receptors involved in lipid metabolism [15–17]. Genome-wide association (GWA) and candidate gene studies have demonstrated that lipid levels are influenced by single nucleotide polymorphisms (SNPs) in lipid-pathway genes [18–23]. SNPs of the *CETP* gene have been associated with HDL concentrations [21,24–28], while SNPs of the *LPL* gene have been associated with both HDL and TG levels [21,29–31]. A recent review of GWA studies of lipids [32] showed that *CETP* SNPs had the highest number of associations with lipids, followed by *LPL* SNPs. *CETP* and *LPL* SNPs have also been associated with obesity-related traits [33,34].

Several studies have shown significant interactions between genetic variants and lifestyle factors regarding the association between lipid profile and obesity-related traits [1,19,33,35,36], but the findings have been inconsistent. Moreover, it has been shown that the effect size of individual SNPs is modest and less likely to accurately predict the risk of complex diseases, and a more effective approach involves combining several risk alleles to generate a genetic risk score (GRS) [35,37]. Nonetheless, studies investigating interactions between GRS and dietary factors on lipid and obesity-related traits have not been adequately performed in Asian Indians. Hence, the aim of this study was to examine the effect of a GRS and its interaction with dietary factors on lipid and obesity-related traits in Asian Indian adults with and without T2D.

2. Methods

2.1. Study Participants

A sample of 497 individuals (260 with T2D and 237 with normal glucose tolerance (NGT)) were randomly chosen from an epidemiological study called the Chennai Urban Rural Epidemiological Study (CURES), details of which have been given in previous publications [1,19,33,35,38–43]. Briefly, a total of 26,001 adults residing in the urban part of Chennai in Southern India were recruited by systematic random sampling between 2001 to 2003, and those who reported having T2D (1529 individuals) were tested to confirm their diagnosis [1,40]. The follow-up study was conducted between 2012 to 2013 and consisted of 2410 participants (Figure 1). The sample for the current study was selected from the follow-up cohort. Participants were excluded if they were taking lipid-lowering medication such as statins and fibrates. Ethical approval was granted by the Madras Diabetes Research Foundation Institutional Ethics Committee and written informed consent was obtained from study participants [1].

2.2. Anthropometric and Biochemical Measurements

Anthropometric measurements including height, weight, waist circumference (WC), hip circumference, and waist–hip ratio (WHR) were obtained using standardized techniques. BMI was calculated as weight in kilograms (kg) divided by the square of the height in meters (m). Individuals with BMI < 25 kg/m^2 were classified as non-obese and those with BMI ≥ 25 kg/m^2 were classified as obese, in accordance with the World

Health Organisation Asia Pacific Guidelines [44]. Biochemical analyses were conducted using Hitachi-912 Auto Analyzer (Hitachi, Mannheim, Germany) with kits supplied by Roche Diagnostics (Mannheim, Germany). Serum total cholesterol was measured by cholesterol oxidase-phenol-4-amino-antipyrene peroxidase method and HDL by direct method-polyethylene glycol-pretreated enzymes. Serum TG was measured by glycerol phosphatase oxidase-phenol-4-amino-antipyrene peroxidase method, and low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula [45]. Serum insulin concentration was estimated using an enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark), fasting plasma glucose (FPG) by glucose oxidase-peroxidase method, and glycated haemoglobin (HbA1c) by high-performance liquid chromatography using a Variant™ machine (Bio-Rad, Hercules, CA, USA).

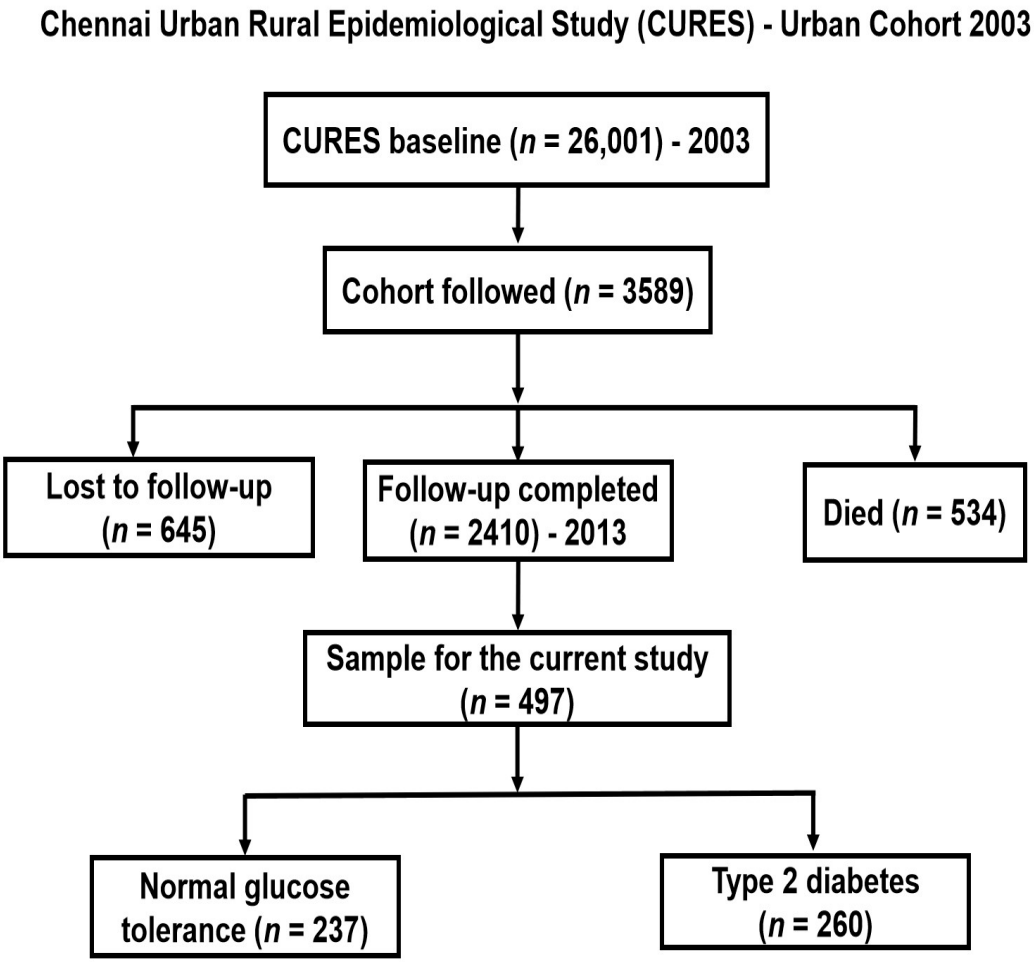

Figure 1. A flow chart showing the selection of participants from the CURES.

2.3. Dietary Assessment

Dietary intake was assessed by an interviewer using a previously validated semi-quantitative food frequency questionnaire (FFQ) containing 222 items [46]. Participants were asked to estimate how much and how often they consumed various food items in the FFQ (number of times per day, week, month, year or never). The FFQ was designed to estimate the usual dietary intake of participants on a meal-by-meal basis. Open-ended questions were used to enable participants to estimate the frequency of their usual dietary intake. To help in estimating portion sizes, participants were shown common household measures such as spoons and cups and pictures of different sizes of fruits. The data were analysed using the Nutritional Epidemiology ('EpiNu') software to estimate average daily intake of macronutrients and total energy. Consumption of SFA, polyunsaturated fatty acid

(PUFA), monounsaturated fatty acid (MUFA) and other macronutrients was estimated from the FFQ using the 'EpiNu' software which contains information on the nutritional content of commonly consumed food in the Chennai area. The 'EpiNu' software was developed for the local population using recipes from various sources including home-made and fast-food. Details of the development of the FFQ and the 'EpiNu' software are published elsewhere [46].

2.4. SNP Selection and Genotyping

Five SNPs (*CETP* SNP: rs4783961; and *LPL* SNPs: rs327, rs3200218, rs1800590 and rs268) were selected for this study based on their association with lipid-related traits in different ethnic groups, including Asian Indians [21–23,33,47–50]. Two SNPs (rs268 and rs1800590) had a minor allele frequency < 5% (Supplementary Table S1), and hence, they were excluded. The remaining three SNPs (rs327, rs3200218 and rs4783961) were included in the current analysis. The genotyping methodology has been previously published [19]. Briefly, the DNA was extracted from whole blood using the phenol–chloroform method, and the SNPs were genotyped by the polymerase chain reaction-restriction fragment length polymorphism method.

2.5. Construction of GRS

An additive model was used to construct an unweighted GRS by adding the number of risk alleles across the three SNPs (rs327, rs3200218 and rs4783961) for each participant. The risk alleles were defined as alleles previously reported to be associated with dyslipidaemia or obesity-related traits. The risk alleles were not weighed due to limited available information on effect sizes of the SNPs for the Asian Indian population. Moreover, it has been demonstrated that assigning weights to risk alleles only has minimal effect [37], and hence, we used an unweighted GRS. The 3-SNP GRS ranged from 0 to 5, and based on the median GRS (2 risk alleles), participants were placed into two groups: low-risk group (for individuals with a GRS < 2 risk alleles) and high-risk group (for individuals with a GRS $\geq$ 2 risk alleles).

2.6. Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 28; SPSS Inc., Chicago, IL, USA). Normality test was performed by Shapiro–Wilk test, and all biochemical and anthropometric variables were log-transformed before the analysis. Results of descriptive statistics for continuous variables are presented as means and standard deviation (SD) and categorical variables as percentages [1]. Allele frequencies were determined by gene counting and a goodness-of-fit Chi-square test was performed to examine if the observed genotype counts were in Hardy-Weinberg equilibrium (HWE) (Supplementary Table S1). The three SNPs were all in HWE ($p > 0.05$), and the alleles had a frequency greater than 5%. An independent sample t test was used to compare the means of the quantitative variables between individuals with low GRS (<2 risk alleles) and those with high GRS ($\geq$2 risk alleles). A Chi-square test was performed to compare categorical variables such as smoking status between individuals in the low (GRS < 2 risk alleles) and high-risk (GRS $\geq$ 2 risk alleles) groups.

Linear and logistic regression analyses were used to examine the association of the 3-SNP GRS with continuous and categorical outcomes, with adjustment for age, sex, BMI, T2D, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake wherever appropriate. Interactions between GRS and dietary factors were analysed by adding the interaction term in the regression models. For GRS–diet interactions, total energy was adjusted for, in addition to the other covariates. The dietary factors investigated in this study were consumption of fat, carbohydrate, protein, and dietary fibre. GRS–diet interactions reaching statistical significance ($p < 0.05$) were investigated further by stratifying individuals based on the quantity of dietary intake. A significant interaction of GRS with total fat was explored further to include subtypes of fats (SFA, PUFA and MUFA).

A median intake of total fat, SFA, MUFA, and PUFA was used to classify individuals into two groups, 'low' (lower than median) and 'high' (higher than median) group, and association between GRS and the outcome was then analysed for each group.

3. Results

3.1. Characteristics of the Study Participants

The mean age of the study participants was 44 ± 10 (Table 1). At baseline, there were no significant differences in anthropometric traits (BMI, WC and WHR), lipid sub-fractions (HDL, LDL, TG, and total cholesterol), systolic blood pressure (SBP) and diastolic blood pressure (DBP), or glycaemic traits (FPG, fasting serum insulin, insulin resistance and HbA1c) between participants with low GRS (<2 risk alleles) and those with high GRS (≥2 risk alleles). Furthermore, consumption of macronutrients did not differ significantly between participants with low GRS (<2 risk alleles) and those with high GRS (≥2 risk alleles) as shown in Table 1. Smoking was higher among individuals with high GRS (≥2 risk alleles) compared to those with low GRS (<2 risk alleles) (p = 0.03). The baseline HDL concentration was significantly higher in women than in men (43.5 ± 1.3 vs. 38.7 ± 1.3 mg/dL; $p = 2.3 \times 10^{-8}$).

Table 1. Characteristics of the study participants.

	All Participants (n = 497)	**GRS < 2 (n = 239)**	**GRS ≥ 2 (n = 258)**	***p* Value ***
Age (years)	44 ± 10	45 ± 10	44 ± 9	0.34
Sex [Men (%), Women (%)]	225 (45), 272 (55)	106 (47), 133 (49)	119 (53), 139 (51)	0.69
BMI (kg/m^2)	24.6 ± 4.5	24.7 ± 4.7	24.4 ± 4.3	0.41
WC (cm)	87 ± 11	88 ± 12	87 ± 11	0.39
WHR	0.92 ± 0.08	0.92 ± 0.09	0.91 ± 0.08	0.57
Obese cases (%)	209 (42)	109 (52)	100 (48)	0.12
HDL (mg/dL)	42 ± 10	42 ± 10	42 ± 10	0.79
LDL (mg/dL)	119 ± 32	118 ± 32	119 ± 32	0.81
TG (mg/dL)	165 ± 150	166 ± 120	164 ± 173	0.87
Total cholesterol (mg/dL)	191 ± 40	192 ± 42	190 ± 38	0.64
Systolic BP (mmHg)	122 ± 20	123 ± 22	120 ± 18	0.15
Diastolic BP (mmHg)	76 ± 11	76 ± 12	75 ± 11	0.60
Fasting plasma glucose (mg/dL)	126 ± 65	126 ± 64	127 ± 67	0.79
Fasting serum insulin (μIU/mL)	9 ± 6	9 ± 6	9 ± 7	0.89
Insulin resistance	3 ± 2	3 ± 2	2 ± 2	0.44
HbA1c (%)	7 ± 2	7 ± 2	7 ± 2	0.91
Fat (g)	67 ± 27	67 ± 26	67 ± 27	0.83
Carbohydrate (g)	410 ± 136	410 ± 134	411 ± 138	0.92
Protein (g)	72 ± 24	73 ± 24	72 ± 23	0.63
Dietary fibre (g)	32 ± 12	32 ± 12	32 ± 11	0.77
Energy (kcal/day)	2560 ± 822	2560 ± 809	2559 ± 834	0.99
Total SFA (g)	25 ± 11	25 ± 11	25 ± 11	0.91
Total MUFA (g)	20 ± 8	20 ± 8	21 ± 9	0.79
Total PUFA (g)	19 ± 9	18 ± 9	19 ± 10	0.77
Plant protein (g/day)	41 ± 14	40 ± 13	42 ± 14	0.23
Animal protein (g/day)	23 ± 13	23 ± 12	22 ± 13	0.75
Smokers (%)	88 (18)	33 (38)	55 (63)	0.03
Alcohol drinkers (%)	123 (25)	52 (42)	71 (58)	0.14
T2D cases (%)	260 (52)	131 (50.4)	129 (49.6)	0.28

Data are mean ± standard deviation or frequencies where appropriate. * p values for the differences in means/frequencies between participants with low GRS and those with high GRS. p values were calculated using independent sample t test for continuous variables and Chi-square test for categorical variables. BMI—body mass index; WC—waist circumference; WHR—waist hip ratio; HDL—high-density lipoprotein cholesterol; LDL—low-density lipoprotein cholesterol; TG—triglycerides; HbA1c—glycated haemoglobin; SFA—saturated fatty acids; MUFA—monounsaturated fatty acids; PUFA—polyunsaturated fatty acids.

3.2. Association of GRS with Lipid and Obesity-Related Traits

There was no significant association between GRS and any of the outcomes measured (HDL, LDL, TG, total cholesterol, SBP, DBP, BMI, WC, WHR and obesity) after adjusting for the confounding factors, age, sex, BMI, T2D, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake where appropriate (Supplementary Tables S2 and S3).

3.3. Interaction of GRS with Dietary Factors on Lipid and Obesity Related Traits

A significant interaction was observed between GRS and total fat intake on WC ($P_{interaction}$ = 0.03) after adjusting for age, sex, T2D, duration of diabetes, anti-diabetic medication, smoking status, alcohol intake, and total energy intake (Table 2). When individuals were stratified based on the median intake of total fat, there were no significant associations between GRS and total fat intake on WC, and when sub-types of fat were investigated (Figure 2), there was a significant interaction of GRS with SFA intake on WC ($P_{interaction}$ = 0.006) and MUFA intake on WC ($P_{interaction}$ = 0.004). In the low SFA intake group (≤23.2 g/day), individuals carrying ≥2 risk alleles had a smaller WC compared to those carrying <2 risk alleles (Beta = −0.01 cm, p = 0.03), while in the high SFA intake group (>23.2 g/day), there was no significant difference in WC between participants carrying ≥2 risk alleles and those carrying <2 risk alleles. For those individuals carrying ≥2 risk alleles, a high SFA intake (>23.2 g/day) was significantly associated with a larger WC than a low SFA intake (≤23.2 g/day) (Beta = 0.02 cm, p = 0.02). When individuals were grouped based on the median MUFA intake, there was no association between GRS and MUFA intake on WC. To examine whether the interactions of GRS with fat intake and SFA intake on WC were mediated by lipids, we included the four lipid subfractions (HDL, LDL, TG and total cholesterol) as confounding factors in addition to other confounding factors and found that the interaction was no longer significant for total fat intake ($P_{interaction}$ = 0.08), but it remained significant for SFA intake ($P_{interaction}$ = 0.02).

Table 2. Interaction of GRS with dietary factors on blood lipids, blood pressure, obesity-related traits, and obesity.

Trait	GRS ∗ Fat (g)	GRS ∗ Carbohydrate (g)	GRS ∗ Protein (g)	GRS ∗ Dietary Fibre (g)
	Beta Coefficient ± SE ($P_{interaction}$)	**Beta Coefficient ± SE ($P_{interaction}$)**	**Beta Coefficient ± SE ($P_{interaction}$)**	**Beta Coefficient ± SE ($P_{interaction}$)**
BMI (kg/m^2)	0.05 ± 0.04 (0.21) [a]	0.04 ± 0.05 (0.36) [a]	0.04 ± 0.05 (0.35) [a]	−0.01 ± 0.04 (0.77) [a]
WC (cm)	0.06 ± 0.03 (**0.03**) [a]	0.05 ± 0.03 (0.18) [a]	0.07 ± 0.04 (0.07) [a]	0.00 ± 0.03 (0.93) [a]
Waist hip ratio	0.01 ± 0.02 (0.52) [b]	0.00 ± 0.02 (0.98) [b]	0.01 ± 0.02 (0.58) [b]	−0.01 ± 0.02 (0.62) [b]
Common obesity	−1.76 ± 1.14 (0.12) [a]	0.10 ± 0.08 (0.20) [a]	−2.52 ± 1.41 (0.08) [a]	−0.35 ± 1.26 (0.78) [a]
HDL (mg/dL)	−0.04 ± 0.05 (0.42) [b]	−0.07 ± 0.06 (0.23) [b]	−0.07 ± 0.06 (0.21) [b]	−0.04 ± 0.05 (0.47) [b]
LDL (mg/dL)	0.02 ± 0.06 (0.82) [b]	0.02 ± 0.08 (0.79) [b]	−0.01 ± 0.08 (0.90) [b]	−0.02 ± 0.07 (0.81) [b]
TG (mg/dL)	0.10 ± 0.12 (0.39) [b]	−0.01 ± 0.15 (0.97) [b]	−0.02 ± 0.15 (0.89) [b]	0.08 ± 0.13 (0.57) [b]
Total cholesterol (mg/dL)	0.02 ± 0.04 (0.70) [b]	−0.00 ± 0.06 (0.98) [b]	−0.02 ± 0.06 (0.65) [b]	−0.00 ± 0.05 (0.98) [b]
Systolic BP (mmHg)	0.03 ± 0.03 (0.35) [b]	0.03 ± 0.04 (0.49) [b]	0.03 ± 0.04 (0.48) [b]	0.04 ± 0.03 (0.25) [b]
Diastolic BP (mmHg)	0.02 ± 0.03 (0.50) [b]	0.01 ± 0.04 (0.87) [b]	0.03 ± 0.04 (0.51) [b]	0.01 ± 0.04 (0.72) [b]

GRS—genetic risk score; BMI—body mass index; WC—waist circumference; HDL—high-density lipoprotein cholesterol; LDL—low-density lipoprotein cholesterol; TG—triglycerides. p values were obtained from linear regression analysis for continuous traits and logistic regression analysis for obesity. [a] p values adjusted for age, sex, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, alcohol intake, and total energy intake. [b] p values adjusted for age, sex, BMI, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, alcohol intake, and total energy intake. Log-transformed variables were used for the analysis. p-value in bold represents statistically significant interaction.

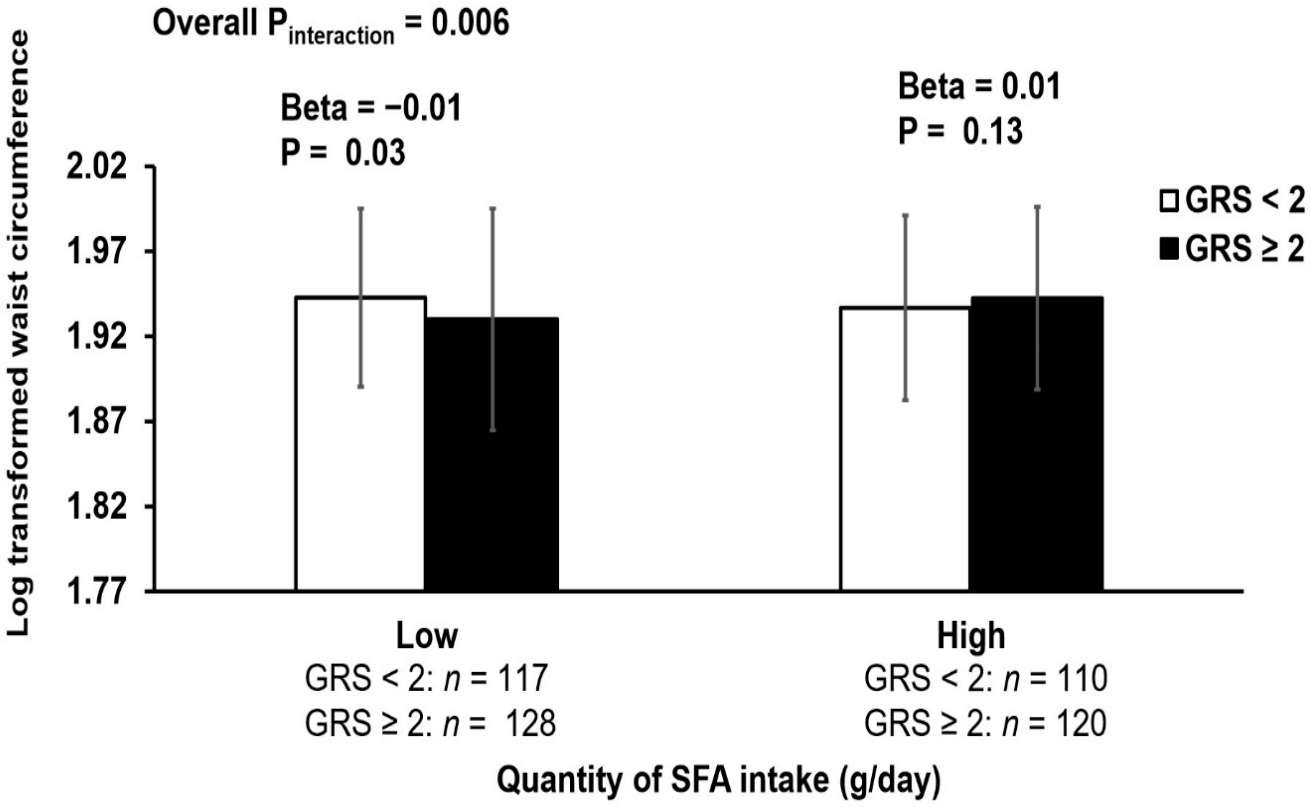

Figure 2. Interaction of GRS with SFA intake on log-transformed waist circumference. *p* values adjusted for age, sex, type 2 diabetes, duration of diabetes, anti-diabetic medication, smoking status, and alcohol intake. Low (≤23.2) and high (>23.2) refer to lower or equal to median and higher than median intake of SFA (g/day) respectively. In the low SFA intake group (≤23.2 g/day), individuals carrying 2 or more risk alleles had a smaller waist circumference compared to those carrying less than 2 risk alleles (Beta = −0.01, $p = 0.03$), and in the high SFA intake group (>23.2 g/day), there was no significant difference in waist circumference between participants carrying 2 or more risk alleles and those carrying less than 2 risk alleles.

4. Discussion

Our study has shown that SFA intake may modify the effect of lipid-pathway genes on central obesity in Asian Indians. Our findings indicate that the combined effect of *LPL* and *CETP* SNPs (rs327, rs3200218 and rs4783961) on obesity traits may be altered by SFA intake, where consumption of high amounts of SFA may increase the combined genetic risk of central obesity posed by *LPL* and *CETP* SNPs while a low intake of SFA may help to reduce this risk. These findings are of public health importance considering the burden of central obesity in Asian Indians [2,51–54]. Our results suggest that Asian Indians with a higher genetic risk for central obesity are responsive to SFA intake and could benefit from dietary modifications to help prevent central obesity in Asian Indians.

An examination of the fatty acid profile of commonly consumed foods in India showed that milk and milk products were the main source of SFA and the median intake of SFA was 8.7% of total energy intake per day [55]. However, some of the commonly consumed food, such as potato chips, contained high amounts of palmitic acid, which could be attributed to the type of cooking oil used in their preparation [55]. The WHO's dietary guidelines [56] state that SFA consumption should be less than 10% of total energy intake, and the National Dietary Guidelines Consensus Group [57] recommends that for Asian Indians who have higher LDL concentration (≥100 mg/dL), SFA intake should be <7% of total energy intake per day. Moreover, intake of SFA at 8.6% of total energy was found to be associated with increased risk of T2D in Indians [55]. In the present study, the median intake of SFA was 8.5% of total energy intake, which is within the WHO's dietary guidelines [56], but as

Indians are predisposed to dyslipidaemia, reducing SFA even further as recommended by the National Dietary Guidelines Consensus Group [57] might help to prevent central obesity in individuals with a high genetic risk.

Abnormalities in lipid metabolism have been linked to the development of obesity [16,58]. We used a nutrigenetic approach to see if dietary intake can modify this link by employing a GRS from the two lipid pathway genes, *CETP* and *LPL*, which have been shown to have the strongest effect on lipid concentrations [21,24,25,27–29,32,59]. To account for the effect of T2D on lipid levels, we adjusted for T2D status, anti-diabetic medication, and duration of T2D in our analysis. We found significant interactions between GRS and total fat, SFA and MUFA intake on WC, where a low intake of SFA (≤23.2 g/day) was found to be associated with a smaller WC in individuals with a higher genetic risk compared to those with a lower genetic risk. We also found that a high SFA intake (>23.2 g/day) was significantly associated with a larger WC than a low SFA intake (≤23.2 g/day) in individuals with a high genetic risk. Our findings are in agreement with the results of a double-blind, randomized, crossover, controlled-feeding trial performed in 101 participants from Canada and the United States [16] where consumption of a diet low in SFA and high in unsaturated fatty acids resulted in increased serum-mediated cholesterol efflux which showed a negative association with WC (Beta = −0.25, $p = 0.01$) and abdominal adiposity (Beta = −0.33, $p = 0.02$). A parallel controlled-feeding trial performed in 20 individuals who were centrally overweight [15] also showed that consumption of a high SFA diet resulted in an increase in the expression of inflammatory genes in adipose tissue and a decrease in the expression of genes involved in fatty acid β-oxidation and synthesis of triglycerides, which could explain the increase in WC with a high SFA intake observed in our study. *LPL* was chosen as one of the candidate genes for the present nutrigenetic study, given that significant associations between *LPL* SNPs and obesity traits have been reported by previous studies in addition to their association with lipid traits. In a case-control study of 944 Koreans [48], the *LPL* SNP rs3200218, which is in the 3′-UTR, was shown to be associated with WHR ($p = 0.009$), and in a previous study in CURES participants [33], carriers of the minor allele (G) of *LPL* SNP rs1800590 had a larger WC ($p = 0.03$) and higher BMI ($p = 0.003$) compared to those carrying two copies of the major allele (T). Increased risk of common obesity (2.73-fold increase) among carriers of the minor allele of *LPL* rs1800590 was also observed in Northern Indians [47]. Furthermore, LPL is a rate-restricting enzyme for the hydrolysis of TG in chylomicrons and VLDL [11], and it has been suggested that the level of LPL activity in muscle relative to that in adipose tissue determines body mass composition and contributes to obesity by influencing the rate at which fatty acids derived from TG are used or stored [10]. This suggests that SNPs that alter LPL activity in muscle and adipose tissue could affect obesity related traits. It has also been shown that SFAs are associated with a lower postprandial oxidation rate [60] and decreased energy expenditure [61] than MUFA.

Another important candidate gene for the study is *CETP*, the SNPs in which have been reported to influence obesity and lipid-related traits. The 'A' allele of the SNP rs4783961 has been shown to influence the concentration of CETP mass in plasma by producing binding motifs for transcription factor SP3, which modulates *CETP* promoter activity [62,63], but studies examining the association of rs4783961 with obesity traits are limited. However, the 'A' allele of rs4783961 has been linked to higher HDL concentration in Taiwanese [64] (an increase of 1.71 mg/dL per allele, standard error (SE) = 0.52; $p = 0.001$) and African Americans [22] (Beta = 4.6, SE = 1.3; $p = 0.0009$). A study involving 10,366 African American, 26,647 European American, 1410 Hispanics and 717 Chinese American participants from nine cohorts [65] also reported that the 'A' allele of rs4783961 was associated with increased HDL concentration in all the cohorts, but the effect size was larger in African Americans (0.17 to 0.24) than in European Americans (0.09 to 0.15) ($p = 2 \times 10^{-10}$). The mechanism under which rs4783961 affects obesity traits are unclear, although it has been proposed that *CETP* SNPs might affect deposition of fat in visceral adipose tissue by being in linkage with SNPs of other genes [65]. Nonetheless, association of other *CETP* SNPs with obesity traits

have been previously reported. A cross-sectional study of 1005 Spanish individuals who were obese [66] reported that participants carrying the 'A' allele of *CETP* SNP rs1800777 compared to non-carriers had higher WC (Delta: 5.6 ± 2.1 cm; $p = 0.02$), WHR (Delta: 0.04 ± 0.01 cm; $p = 0.01$) and fat mass (Delta: 4.4 ± 1.1 kg; $p = 0.04$). Similarly, a study performed in 571 Chinese individuals [34] observed that participants with the 'GT' genotype of *CETP* SNP rs3764261 had a reduced risk of central obesity (Odds ratio (OR) = 0.631, 95% confidence interval (CI) = 0.460–0.865; $p = 0.004$), and a study involving 3575 Dutch participants [67] reported that the minor allele of *CETP* SNP rs5882 was associated with a decreased prevalence of central obesity (OR = 0.90, 95% CI = 0.83–0.97; $p = 0.007$).

Our findings of significant interactions between GRS and dietary fat intake on WC are consistent with a previous study [58]. This study [58], which consisted of 199 overweight/obese Spanish adolescents and involved a weight loss intervention, showed that each minor allele of *CETP* SNP rs1800777 was associated with a −1.4 kg decrease in body weight after 10 weeks ($p = 1.5 \times 10^{-4}$). Studies examining CETP and obesity have mainly focused on the impact of body weight on CETP mass and activity [68–70]. A study involving 21 morbidly obese female participants (BMI > 40 kg/m^2) [68] who underwent a weight loss procedure concluded that weight loss was associated with a marked decrease in CETP mass and activity. Another study involving 51 normal weight individuals [70] also reported that participants with a body weight of around 46 kg had 15% lower serum CETP compared to those with a body weight of about 55 kg. However, an anti-adipogenic effect of CETP in the presence of apolipoprotein CIII (apoCIII) was reported by an animal study involving *CETP* and *apoCIII* transgenic mice [71], where obesity induced by a high-fat diet was reversed by the expression of *CETP*. As this study did not look at *CETP* SNPs, it is unclear whether different *CETP* SNPs will have the same effect. Individually, the SNPs in our study did not show any significant interaction with dietary factors. The discrepancies in findings between our study and others could be because of allele frequencies and effect sizes which differ between populations [1,32]. Another plausible explanation is differences in dietary pattern and the methods used to assess dietary intake [1]. Moreover, a systematic review of observational studies [72] concluded that SFAs were not linked to CVDs, and an analysis of data from randomized controlled trials [73] indicated that replacing SFA with linoleic acid was effective in lowering total cholesterol but there was no benefit in terms of lower risk of CVDs or death. However, large cohort studies [74,75] have indicated that the effect of SFA is dependent on the type and food sources of SFA. The European Prospective Investigation into Cancer and Nutrition—Netherlands (EPIC—NL) cohort study of 37,421 participants [74] observed that total dietary SFA had no association with T2D, but SFA derived from cheese and long-chain SFAs were negatively associated with T2D. The EPIC-InterAct case-cohort study of 27,296 participants [75] also reported that even-chain SFAs including palmitic acid and myristic acid had a positive association with T2D, while odd-chain and longer-chain SFAs had a negative association with T2D.

The strength of our study is the use of a GRS based on two established lipid pathway genes in a well characterised population. Our study is the first of its kind to investigate the link between lipids and obesity from a nutrigenetic perspective. Another strength is the use of validated questionnaires and the robust sensitivity analysis incorporating conventional risk factors including alcohol consumption and smoking as confounding factors. Nonetheless, our study has several limitations. The small sample size could have influenced the lack of association between GRS and the measured outcomes (lipids and obesity). Another limitation is that we did not investigate different types or sources of SFAs. As this is a cross-sectional study, it is not possible to determine causality between fat intake and WC. Despite our robust sensitivity analysis, we cannot rule out residual confounding from unidentified factors [1]. However, we were able to replicate previously reported interactions between GRS and fat intake on WC.

5. Conclusions

Our findings suggest that dietary fatty acid intake may modify the effect of SNPs in lipid-pathway genes on central obesity in Asian Indians. The results indicate that a diet low in SFA might help to reduce the genetic risk of central obesity while a high SFA diet might increase the genetic risk of central obesity in Asian Indians. These findings support the WHO's dietary guidelines for preventing unhealthy weight gain by limiting SFA intake to less than 10% of total energy intake, and they indicate that personalised nutrition based on GRS might be an effective strategy for the management of central obesity in Asian Indians who have a high genetic risk, but additional studies with large sample sizes are needed to confirm our findings.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14132713/s1, Table S1: Allele Frequencies and Hardy–Weinberg Equilibrium *p* value, Table S2: Association of GRS with blood lipids, blood pressure and obesity-related traits, Table S3: Association of GRS with obesity.

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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

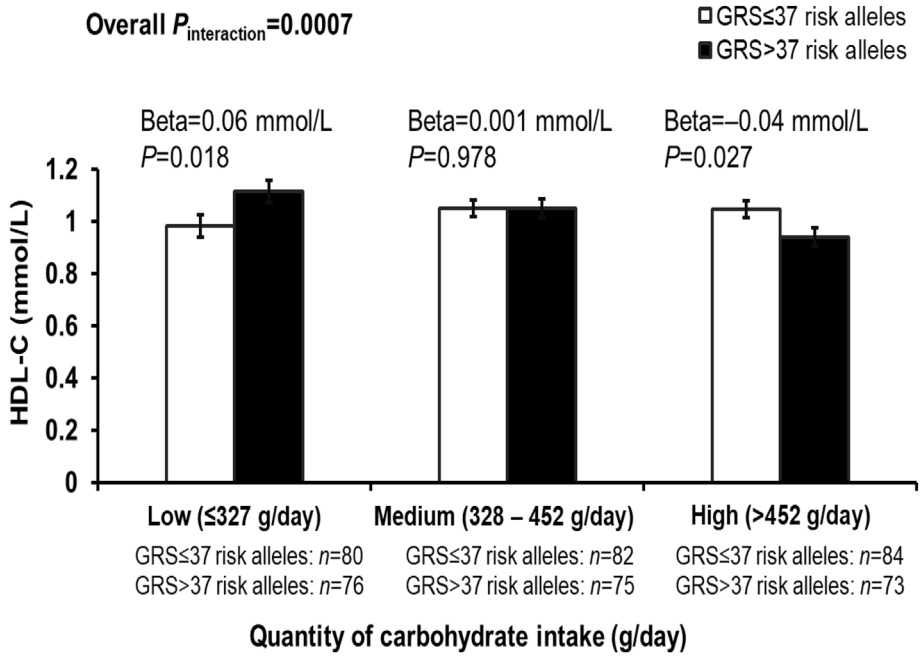

Fig. 1. Interaction of GRS and carbohydrate intake on HDL-C concentration. In the first tertile of carbohydrate intake (≤327 g/day), participants with a high GRS (>37 risk alleles) had higher HDL-C concentration than those with a low GRS (≤37 risk alleles). However, in the third tertile of carbohydrate 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.

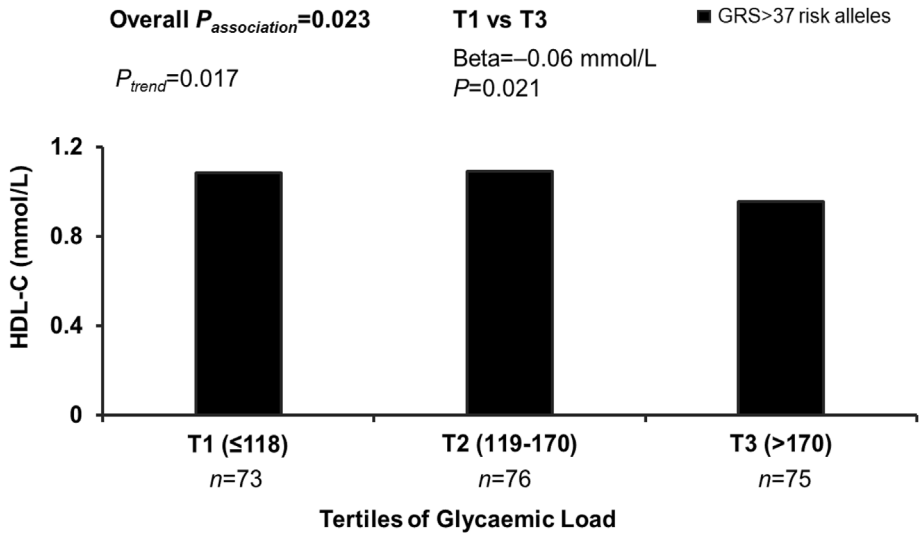

Fig. 2. Association of glycaemic load (GL) with HDL-C concentration in individuals with a high GRS. The concentration of HDL-C was lower across tertiles of GL. The analysis was adjusted for sex, BMI, family history of diabetes, smoking status, physical activity level and total energy intake.

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.

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Barriers in Translating Existing Nutrigenetics Insights to Precision Nutrition for Cardiometabolic Health in Ethnically Diverse Populations

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Abstract
Background: Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of cardiovascular disease mortality (more than three-quarters) occurring in low- and middle-income countries. There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors. Despite the remarkable progress, several factors need to be considered before the translation of nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations. Some of these factors include variations in genetic predispositions, cultural and lifestyle factors as well as socio-economic factors. ***Summary:*** This review aimed to explore the factors that need to be considered in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities. Several factors might influence variations among individuals with regard to dietary exposures and metabolic responses, and these include genetic diversity, cultural and lifestyle factors as well as socio-economic factors. A multi-omics approach involving disciplines such as metabolomics, epigenetics, and the gut microbiome might contribute to improved understanding of the underlying mechanisms of gene-diet interactions and the implementation of precision nutrition although more research is needed to confirm the practicality and effectiveness of this approach. Conducting gene-diet interaction studies in diverse populations is essential and studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention studies will be required to further strengthen the evidence and facilitate their application in clinical practice. ***Key Messages:*** Nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. Conducting gene-diet interaction studies in diverse populations is essential giving the genetic diversity and variations in dietary patterns. Integrating data from disciplines such as metabolomics, epigenetics, and the gut microbiome could help in early identification of individuals at risk of cardiometabolic diseases as well as the implementation of precise dietary interventions for preventing and managing cardiometabolic diseases.

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Introduction

Cardiometabolic diseases pose a significant threat to global public health, with a substantial majority of cardiovascular disease (CVD) mortality (more than three-quarters) occurring in low- and middle-income countries (LMICs) [1]. According to the Centres for Disease Control and Prevention [2], individuals in LMICs are often affected by cardiometabolic diseases during the peak of their productivity, which coupled with huge healthcare expenses and limited employment opportunities worsens the financial burden of cardiometabolic diseases in these countries. Thus, cardiometabolic diseases present severe health and economic consequences for individuals, families, and communities [1], necessitating further research into the prevention and management of these conditions. Risk factors such as dyslipidaemia, hypertension, and obesity have been shown to be influenced by genetic factors [3–7]. However, unlike monogenic disorders like sickle cell anaemia which are usually caused by mutations in a single gene [8], most cardiometabolic diseases, such as CVDs, are influenced by numerous genes and are also impacted by environmental factors [9–13].

There have been remarkable advances in recent years in identifying genetic variants that alter disease susceptibility by interacting with dietary factors [9, 11, 14–17]. Thus, a genetic variant might not always pose a higher risk of a disease as its effects might be modulated by the environmental factors that interact with it [18]. Defined as the scientific field that investigates the impact of genetic variability on individual responses to diet [19], nutrigenetics focuses on understanding gene-diet interactions that predispose to specific diseases, offering the potential to design personalised dietary guidelines for preventing and managing cardiometabolic diseases [20, 21].

Gene-diet interaction studies have been extended to cover previously under-represented populations [22–27], although there is still limited research in some areas [28, 29] and most studies have not been replicated [28, 30]. Despite the remarkable progress in nutrigenetics research, several factors need to be considered before the translation of existing nutrigenetics insights to personalised and precision nutrition in ethnically diverse populations [31, 32]. Ethnic diversity covers a broad range of factors including variations in genetic predispositions, cultural and lifestyle factors which can hinder the worldwide application of nutrigenetics findings [33]. Therefore, this review aimed to explore the potential barriers and challenges in bridging the gap between existing nutrigenetics insights and the implementation of personalised and precision nutrition across diverse ethnicities.

Genetic Diversity

One of the main challenges (shown in Fig. 1) in translating existing nutrigenetics insights to personalised and precision nutrition in various ethnic groups is the genetic diversity that exists among populations. Numerous studies have shown that individuals of different ethnic backgrounds have distinct genetic variations that impact how their bodies metabolise certain nutrients [10, 19, 34–36]. Therefore, research covering populations that represent different ethnicities is required to gain a better understanding of the genetic variations and specific nutritional requirements within these groups. Research by the gene-nutrient interaction (GeNuIne) collaboration identified that the genetic influence on obesity in different Asian populations was influenced by different dietary factors [19, 34, 37–42]. Using a genetic risk score (GRS), it was observed that South Asians with a higher GRS had a greater susceptibility to obesity when consuming a high-carbohydrate diet, whereas South East and Western Asian populations with a higher GRS displayed an increased risk of central obesity in response to a high-protein diet [19]. Similarly, research by the Diabetes Heart Study [43–45] indicates that African Americans have elevated levels of circulating arachidonic acid (AA) in comparison with individuals of European ancestry. Notable differences were also observed in allele frequencies of various SNPs within the fatty acid desaturase (*FADS*) gene cluster which have been shown to play a significant role in determining circulating levels of fatty acids. In particular, the "GG" genotype of the SNP rs174537, which is linked to elevated AA levels, was present in 81% of African Americans compared to 46% of European Americans [45]. Thus, while research conducted on individuals of European descent suggests that only a small fraction of dietary linoleic acid is converted to AA in humans, this minimal conversion rate may not be consistent across all populations [43–45]. Given that AA and its metabolites play crucial roles in immune responses and inflammation, thereby influencing the onset and advancement of various diseases including diabetes and CVDs [46, 47], tailored dietary recommendations regarding the intake of PUFA might be beneficial for this population.

One of the most widely studied genes in relation to cardiometabolic diseases is the apolipoprotein E (*ApoE*) gene [48–53], and variations in the frequency of the E4

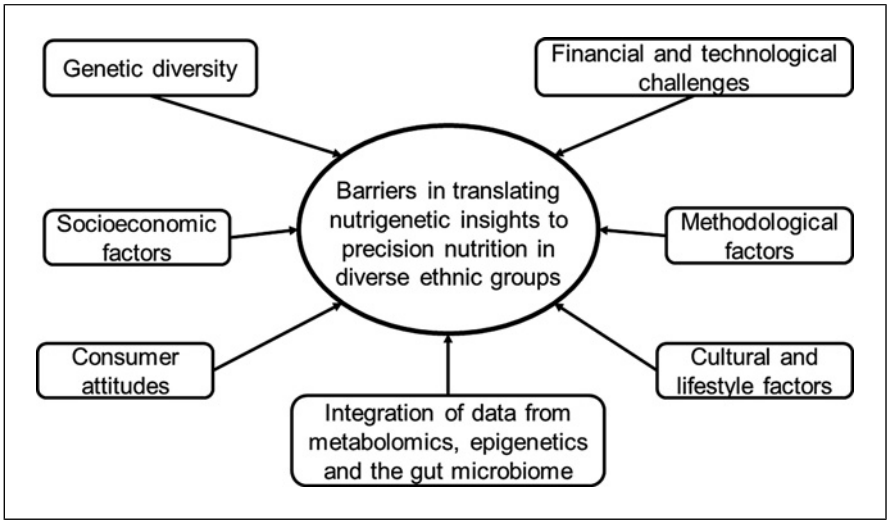

Fig. 1. Barriers affecting the translation of existing nutrigenetics insights to precision nutrition in ethnically diverse populations.

isoform of the gene, which is associated with increased risk of CVDs, have been reported [54, 55]. African and Asian populations tend to have higher frequencies of the E4 isoform (29–40% in Central Africa) compared to Caucasians [54, 55] which could contribute to differences in susceptibility to certain diseases among these populations. Furthermore, within Europe there are regional variations in the frequency of the E4 isoform, ranging from 5 to 10% in Spain, Portugal, Italy, and Greece; up to 16% in France, Belgium, and Germany; and further rising to up to 23% in the Scandinavian peninsula, with the Saami population of Finland showing frequencies as high as 31% [54, 55]. However, the link between the E4 isoform and increased low-density lipoprotein cholesterol levels is more pronounced in populations with diets high in saturated fat and cholesterol compared to other groups [56, 57], suggesting that interventions targeting a reduction in saturated fatty acid (SFA) intake could be effective for CVD prevention and management in populations with a high frequency of the E4 isoform.

The use of a GRS has been shown to be effective in assessing the genetic contribution to complex traits such as dyslipidaemia since it allows the combined effects of multiple genetic variants to be analysed [58–60]. A weighted GRS, which takes into account the effect sizes of the risk alleles, is used by some studies [61–63]. However, most of the published data on effective sizes come from GWA studies which have been conducted in populations of European ancestry and it has been reported that effective sizes may vary across populations [37, 63], suggesting that using a weighted GRS might not be ideal for populations which are under-represented in GWA studies. In a study by the National Heart, Lung, and Blood Institute's Candidate Gene Association Resource (CARe), consisting of 10,366 African American, 26,647 European American, 1,410 Hispanic, and 717 Chinese American individuals from nine cohorts [64], there were marked differences in effect sizes across the ethnic groups for some of the SNPs, and this has also been reported in a review of nutrigenetic studies [35]. The effect size of the cholesteryl ester transfer protein (*CETP*) SNP rs4783961, the "A" allele of which is associated with higher concentration of high-density lipoprotein cholesterol, was uniformly larger in African American cohorts (0.17 to 0.24) compared to European Americans (0.09 to 0.15) [64]. In contrast, another high-density lipoprotein cholesterol-associated SNP, rs17231506, also in *CETP*, had larger effect sizes in European Americans and Hispanics (0.21 to 0.28) compared to African Americans (0.06 to 0.26). A potential reason for this finding as explained by the authors [64] is that African Americans and European Americans possess the same underlying causal variant within a gene, yet because of ethnicity-specific variations in the frequencies of major and minor alleles, a SNP might have varying degrees of correlation with the underlying variant, resulting in varying effect sizes and degrees of association.

Methodological Factors

Aside genetic diversity, another barrier that affects the translation of nutrigenetics is the lack of replication in most gene-diet interaction studies [30, 36, 65]. Conducting replication studies, especially in diverse populations, is vital in enhancing the reliability of findings

and facilitating their application in clinical practice [18]. In a systemic review of gene-diet interaction studies in relation to CVDs [30], it was observed that many of the studies that identified significant interactions had not been replicated, with only a small number of studies examining the same dietary and genetic factors. Similarly, a lack of replication was reported in a systemic review of gene-lifestyle interaction studies conducted by our team [36] in which it was identified that most of the studies were conducted only once. Furthermore, a systematic review of nutrigenetic studies focusing on omega-3 fatty acid and plasma lipid, lipoprotein, and apolipoproteins [65] highlighted a lack of replication of previously identified interactions. To strengthen the evidence and enhance comparability across studies, it is important for studies to be replicated in independent samples [30, 36].

In addition to the lack of replication, sample size has been cited as a methodological issue that affects the quality of the evidence generated by gene-diet interaction studies [30, 35, 36, 65]. A large sample size improves the power to detect interactions with minimal effect sizes, and this is especially important for multifactorial traits where the main effects of genetic variants are often subtle [30, 66, 67]. Moreover, there is a scarcity of genotype-based dietary intervention studies [19]. It has been highlighted that dietary intervention studies can help raise the evidence level of gene-diet interactions identified in observational studies once they have been replicated [18]. In a 12-week randomised controlled trial involving 145 participants with overweight or obesity, participants were first identified as being responsive to fat or carbohydrate based on a GRS, before being randomised to a high-fat or high-carbohydrate diet [68]. Although no differences in weight loss were observed between participants who were randomised to the appropriate diet based on their genotype and those who were not [68], studies utilising this approach could help determine the effectiveness of dietary interventions based on genotypes and facilitate the translation of nutrigenetics into precision nutrition.

Cultural and Lifestyle Factors

Cultural and lifestyle factors also need to be considered in translating nutrigenetics and implementing precision nutrition. Ethnic groups often have long-standing dietary traditions, specific food preferences, and cooking practices that have been passed down through generations, making them a fundamental part of their cultural identity [69, 70]. Therefore, incorporating precision nutrition based on nutrigenetics into these cultural practices without compromising their valued traditions might be challenging. A systematic review of 20 qualitative studies revealed that the food preferences of individuals of Asian, African, and other minority ethnic communities were impacted by social and cultural elements besides nutritional and health considerations [70]. It was observed that individuals from African, Asian, and other minority ethnic backgrounds place significant value on traditional foods, viewing them as symbols of their ethnic identity and belonging [70]. Similarly, in African Americans, despite a disproportionate prevalence of cardiometabolic diseases in comparison with white Americans [71, 72], adherence to dietary guidelines has been found to be influenced by a preference for a dietary intake that reflects a cultural tradition known as "soul food" [72]. This diet often consists of fatty meats, added fat, sugar, and salt and involves methods of cooking such as deep frying and others that raise the amount of calories and sodium in the diet [72]. Accordingly, African Caribbean individuals living in Britain were found to prioritise spending on traditional foods such as yams over potatoes, thereby preserving their cultural food preferences [73]. Moreover, specific practices such as adhering to a vegetarian diet, avoiding pork and beef, and following certain cooking procedures are considered valuable to people of Asian and African backgrounds [70, 74]. Moreover, the concept of "local food" has attracted a lot of attention in recent years, with many consumers preferring products that have travelled short distances or been directly marketed by producers [75–77]. However, the extent to which individuals adhere to their traditional dietary practices is influenced by several factors, with younger individuals more likely to adopt new dietary habits [69, 78].

With regard to diet and cardiometabolic diseases, examining the overall dietary pattern is believed to offer several advantages since foods and the nutrients they contain often have synergistic effects, which can make it difficult to identify the influence of a single food or nutrient [79]. Moreover, it has been shown that it is not specific nutrients but rather the overall dietary pattern that exerts the most significant impact on cardiometabolic diseases [79–81]. Dietary pattern is defined as the regular consumption of various foods, drinks, and nutrients in specific quantities and combinations, including the frequency at which they are consumed [82]. Recognising a dietary pattern could lead to a stronger correlation with a specific health indicator and provide a broader and more inclusive understanding of how nutrients and other bioactive compounds in our food are

consumed, as well as how patterns of consumption affect health outcomes [82, 83]. In a study involving South Asian Surinamese, African Surinamese, and Dutch participants in the Netherlands [84], three dietary patterns, categorised as "noodle/rice and white meat," "red meat, snacks, and sweets," and "vegetables, fruits, and nuts," were identified. In contrast to Dutch participants, those of Surinamese origin had a stronger adherence to the "noodle/rice and white meat" pattern, which reflected the dietary preferences typical of the traditional Surinamese diet. Dutch participants on the other hand showed a higher level of adherence to the "red meat, snacks, and sweets" and "vegetables, fruits, and nuts" patterns [85]. Variations in dietary consumption and factors shaping dietary behaviours across different ethnic groups were also observed in a systematic review of 49 studies [86]. Consumption of fruits and vegetables was found to be low in populations of African ancestry and higher in Hispanic and Latino populations, while fish consumption was low in white and Hispanic populations. In contrast, white and Asian populations were found to have the highest dairy intake (2.17 and 1.3 servings per day, respectively) compared to populations of African ancestry (0.58 servings per day) [86]. These findings indicate a low tendency towards fruit and vegetable consumption as well as reduced intake of dairy in African ancestry populations in comparison with the other ethnic groups, highlighting a need for ethnic-specific initiatives. It should be noted that within the same ethnic group, there are variations in dietary pattern depending on whether they are living in developed countries or in their native countries [85], indicating that public health priorities with regard to diet and disease prevention might differ based on geographic location.

Traditional diets for certain ethnic groups have often been associated with health benefits [87]. The traditional South Asian diet in particular is composed mainly of fresh fruits and vegetables along with beans, legumes, nuts, and spices [87]. However, a rise in type 2 diabetes (T2D) and CVDs has been seen in South Asians [19, 37] and this has partly been linked to unhealthy modifications to the traditional diet, shifting from nutrient-rich fresh produce to refined products and the use of large amounts of saturated cooking oils [87]. Similarly, the traditional African diet is enriched with fresh vegetables such as okra, spinach, and other green leafy vegetables [88, 89]. Nonetheless, a shift away from traditional meals towards processed foods and soft drinks has been reported across African countries [90]. Hence, understanding cultural and lifestyle factors that shape food preferences and dietary habits is vital in translating existing nutrigenetic insights to various ethnic groups.

Socio-Economic Factors

Socio-economic and geographical disparities are also important factors to consider in the translation of nutrigenetics to precision nutrition. Ethnic populations may experience disparities in access to healthcare, technologies, and resources required for implementing precision nutrition effectively. The allocation of money to healthcare has been reported to vary across countries depending on their level of economic development, with high-income countries allocating on average, USD 3,000 per person towards healthcare, while low-income countries only spend around USD 30 per person [91]. Similarly, a report by the World Health Organization [92] indicated that healthcare costs in low-income countries were mainly covered by individuals paying directly (44%) and aid from external sources (29%), while government funding played a predominant role in high-income countries (70%). Moreover, socio-economic and political factors also influence the distribution of food, adjustments in food composition, or the implementation of optional taxes on unhealthy food products as well as the adoption of dietary guidelines promoting the consumption of healthy options such as fruits and vegetables [93, 94].

Aside cost and infrastructure, the knowledge and attitudes of healthcare providers, including dietitians, towards nutrigenetics, are crucial for its integration into clinical practice, which may also be influenced by socio-economic-related educational opportunities [95]. Healthcare professionals need to understand genetic influences on public health, evaluate the clinical relevance and utility of genetic tests as well as analyse the individual's background in order to recommend genetic assessments, screening or lifestyle adjustments [96]. It has been highlighted that nutritional genetics has emerged as a relatively new field over the past two decades, with much of its scientific knowledge not integrated into healthcare education [97]. Consequently, healthcare professionals lack the essential foundation to provide effective nutrigenetic counselling [97]. Available evidence on knowledge and attitudes of healthcare professionals towards nutrigenetics mainly comes from studies conducted in high-income countries, and the findings indicate a general lack of awareness among healthcare professionals [98–101]. In a survey of 390 dietitians in the UK [98], it was observed that, despite being involved in the management of polygenic conditions such as diabetes, obesity, and CVDs which are influenced by both genetic and dietary factors, majority of the participants were not engaged in activities related to genetics or nutrigenetics

and expressed low confidence in undertaking such activities. Similarly, a survey involving 1,844 dietitians from Australia (390), the USA (461), and the UK (993) [99] revealed that the participants had limited knowledge, engagement, and confidence in nutrigenetics. Giving the lack of resources in LMICs, knowledge and awareness of nutrigenetics are likely to be even lower. In this regard, initiatives such as the GeNuIne collaboration are required [34]. Through funding from the British Nutrition Foundation (BNF), the GeNuIne collaboration was started at the University of Reading in 2013, and it has been instrumental not only in conducting nutrigenetics studies in diverse ethnic groups, but also in facilitating training and resource development to improve the ability of professionals and policymakers in low-income countries to effectively apply nutrigenetics findings within their domains [19, 34, 36, 41, 95, 102].

Financial and Technological Challenges

Funding from public bodies is vital for developing innovative approaches within nutrition programmes, promoting collaboration among scientists, facilitating the distribution of nutrigenetics information through modern virtual communication technologies as well as establishing a well-trained public health nutrition workforce [103]. Several studies have highlighted the necessity for enhancing capacity in public health nutrition across individual, organisational, and systemic levels [103–106]. However, global initiatives such as the Scaling Up Nutrition (SUN) movement which is focused on addressing the complex causes of malnutrition through the implementation of evidence-based, nutrition-specific interventions in developing countries face challenges due to financial constraints in most countries [107].

In a report by Sight and Life [108], it was noted that personalised nutrition appears not only feasible and rational but also cost-effective in terms of developing effective nutrition interventions to alleviate the burden of diseases and improve health outcomes in LMICs. However, several implementation challenges were highlighted including how to extend the application of personalised nutrition approaches to benefit a larger population giving the financial constraints, deciding which methods offer the greatest potential for successful adoption, what resources are necessary to expand the implementation of personalised nutrition, and whether there is sufficient support and interest in introducing personalised nutrition approaches to LMICs [108]. Moreover, it has been recognised that the integration of nutrigenetics into healthcare systems requires a multisystem approach that includes the gut microbiome and environmental factors [21], which poses a huge challenge in LMICs. According to Sight for Life [108], personalised nutrition approaches that are more specific are less readily available in LMICs and these include genetic and microbiome analysis and counselling, alongside tools for assessing metabolic markers such as glucose monitors and energy intake sensors.

Consumer Attitudes towards Nutrigenetics and Personalised Nutrition

There is a growing interest in nutrigenetics and personalised nutrition, although at present, accessibility is limited to a narrow group of highly motivated individuals with high socio-economic status [109]. Commercial companies offering nutrigenetic testing exist mostly in Europe and North America [110], with the aim of enabling consumers to identify their genetic susceptibility to diseases and offering personalised dietary recommendations to promote health [110, 111]. The growing interest in direct-to-consumer (DTC) genetic testing has been associated with social elements such as enhanced internet access to information and a cultural shift towards individuals taking greater responsibility for their health and lifestyle choices, while relying less on conventional expert guidance [112]. However, there are concerns about the accuracy and usefulness of the health-related data provided by DTC genetic testing companies as well as potential adverse outcomes if consumers or their healthcare providers misinterpret such information [113–116]. In a study of 1,648 participants [117], it was observed that before undertaking personalised DTC genetic testing, consumers were mostly interested in information about ancestry (73.7%), traits (72.2%), and disease risks (71.9%). In terms of susceptibility to disease, heart disease (68%), breast cancer (67%), and Alzheimer's disease (66%) attracted a high level of interest [117]. It should be noted that the participants were mostly women, Caucasian, and from a high socio-economic background [117]. Similarly, a survey of 1,048 customers of DTC genetic testing [112] indicated that the customers' individual circumstances and subjective understanding of disease susceptibility were linked to specific health-related behaviours they undertake upon receiving their test results. More specifically, various aspects of the participants' lives such as having a chronic condition, a family history of diseases tested by the DTC service, self-reported health issues, and regular visits to a doctor were significantly correlated with several health-related

behaviours individuals displayed following receipt of their results [112]. Along these lines, a survey of 2,037 customers of DTC services showed that the response to genetic testing was influenced by both the perceived severity and sense of control over the condition of interest. Higher perceived severity and lower perceived control were linked to increased, though not clinically significant, levels of anxiety and distress [118].

With regard to attitudes of the general public towards personalised nutrition, a survey of 9,381 participants across nine European countries (the UK, Germany, Ireland, Spain, Greece, Poland, Portugal, the Netherlands, and Norway) [119] indicated that the trust and preference consumers have for personalised nutrition services are key indicators of their likelihood to embrace such services. Variations in trust in the national health service as a regulatory body and source of information, as well as trust in dietitians and nutritionists as service providers, were observed across the countries, although in all the countries, family doctors emerged as the most relied-upon sources of information [119]. Similarly, a study conducted in the UK and Ireland by Food4Me [120] identified that there was a preference for government-led services delivered in person, which was believed to enhance trust, transparency, and overall value. In both countries, paying for nutritional advice was associated with heightened commitment and motivation to adhere to guidelines [120]. Furthermore, a study involving 438 Dutch participants [121] showed that consumers' acceptance of personalised nutrition was positively influenced by consensus among expert stakeholders, benefits for consumers or scientists, ease of implementation, and freedom of choice. In line with these findings, a study consisting of 1,425 Canadian participants [122] revealed that most of the participants (93.3%) regarded dietitians as the most suitable professionals to provide personalised dietary advice based on nutrigenetic testing. In this study [122], health and disease prevention were cited as the primary benefits for nutrigenetic testing and there were concerns regarding accessibility to genetic testing through telemarketing companies and spam as well as companies using personal genetic data to promote sales [122]. Although there are limited data on the attitudes of consumers in LMICs towards nutrigenetics, previous studies by our group indicated a reluctance to give blood samples for genetic testing. Hence, individuals from various sociodemographic backgrounds may have varying levels of trust in service providers, regulators, and online information delivery. Consequently, preferences regarding the manner and source of personalised nutrition services might vary across countries and cultural settings [119].

Integration of Data from Multiple Fields

Precision nutrition is centred around integrating data from multiple disciplines such as metabolomics, epigenetics, and the gut microbiome as this is argued to be important in enhancing the scientific understanding of inter-individual variability in response to dietary interventions, although the practicality and effectiveness of this process are still being explored [123, 124]. So far, progress has been made in the mechanistic understanding of dietary interventions through the integration of omics technologies such as metabolomics and the gut microbiome [125]. Metabolomics focuses on analysing small molecules (metabolites) found in biological samples to understand changes in metabolism under various conditions [123]. Metabolites are the direct products of dietary consumption and metabolism, enabling a more accurate assessment of biological and physiological pathways as well as the related biomarkers for diet or disease [125]. Metabolic profiles have been linked to variations in nutritional needs and responses to diet, which offers the potential to stratify populations with similar metabolic and phenotypic profiles, enabling the development of tailored dietary recommendations [126]. Moreover, an accurate assessment of dietary intake is essential in understanding the link between diet and diseases, and methods currently used to assess dietary intake such as food frequency questionnaires, weighed food diaries, and 24-h recalls are prone to errors including underestimation of energy intake [123]. By applying metabolomics, specific biomarkers associated with foods eaten can be obtained, and this involves participants consuming specific foods and the collection of biofluid samples over time [123]. These biomarkers could provide useful information to supplement self-reported dietary intake [126].

Using metabolomics, a possible explanation of the mechanisms underlying the health benefits of low glycaemic index diets was reported in a 6-month parallel randomised trial involving 122 adult participants with overweight and obesity [127]. An analysis of plasma metabolites revealed that a low glycaemic index diet resulted in higher levels of serine, lower levels of valine and leucine, and alterations in a group of two sphingomyelins, two lysophosphatidylcholines, and six phosphatidylcholines. These changes in plasma amino acids and lipid species were found to be correlated with changes in body weight, glucose levels, insulin, and certain inflammatory markers [127]. Similarly, a metabolomic study identified underlying risks for T2D, insulin resistance, and related comorbidities through analysis of

blood metabolites in participants who had normoglycaemia and no clinical symptoms [128]. In this study [128], metabolomic analysis was performed at baseline and after the implementation of a personalised lifestyle intervention for 100 days. By combining metabolites associated with specific disease risks and calculating risk scores, the baseline analysis showed that some of the participants had moderate to high risks for insulin resistance, T2D, and CVDs. However, when the analysis was repeated following the personalised lifestyle intervention, specific metabolites that were previously outside the normal range had returned to the normal range, thereby reducing potential health risks during the second time point [128].

The gut microbiome supports the host by interacting directly or indirectly with host cells through the production of bioactive molecules, and this interaction allows the gut microbiome to regulate various biological processes related to immunity and energy balance [129]. This ability to interact with the host depends on the types of bacteria present and their distribution within the gut microbial community [130]. The application of the gut microbiome in precision nutrition involves using the gut microbiome as a biomarker to predict how specific dietary components affect host health, and the use of this information to design precision dietary interventions aimed at promoting health [129]. It has been highlighted that the way individuals respond to certain dietary interventions may be influenced by the composition and function of the gut microbiota which differs among individuals with distinct metabolic profiles [130]. In a study involving 14 men with obesity [131], controlled diets supplemented with resistant starch or non-starch polysaccharide and a weight-loss diet were found to result in distinct changes in the microbiota composition. The resistant starch diet was linked to an increase in several Ruminococcaceae phylotypes, while the non-starch polysaccharide primarily resulted in an increase in Lachnospiraceae phylotypes, and the weight-loss diet significantly decreased *Bifidobacteria*. It was concluded that since the dietary response of an individual's microbiota varied significantly and was inversely related to its diversity, individuals could be classified as responders or non-responders based on the characteristics of their intestinal microbiota [131]. In another study involving a cohort of 800 participants with no previous diagnosis of T2D [132], variations in postprandial glycaemic responses to similar standardised meals were observed. A machine learning algorithm was then developed by integrating blood parameters, dietary habits, anthropometric data, physical activity, and gut microbiota information from the same cohort and was found to be effective in predicting personalised postprandial glycaemic responses to real-life meals. Subsequently, a blinded randomised controlled dietary intervention based on the algorithm resulted in significantly reduced postprandial responses and consistent changes in gut microbiota composition [132].

Epigenetics covers the molecular processes that can alter the activity of genes without changing the DNA sequence, and these processes include DNA methylation, histone modifications, and alterations in noncoding RNAs [133]. Epigenetic changes might explain individual differences in metabolic health and responses to diet, and have the potential to identify novel biomarkers for precision nutrition and targets for precise interventions [134]. Similarly, transcriptomics technologies have been applied in nutrition research to understand the molecular and signalling pathways associated with nutrients [135]. In an interventional study, a transcriptomic approach was used to assess the impact of a high-carbohydrate or high-protein diet on gene expression profiles in blood leukocytes [136]. The findings showed that the high-carbohydrate breakfast resulted in changes in the expression of genes related to glycogen metabolism, while the high-protein breakfast led to changes in the expression of genes associated with protein biosynthesis [136]. Another interventional study [137], utilising a transcriptomic approach to assess the postprandial effect of consuming different fatty acids on the gene expression profiles of peripheral blood mononuclear cells, reported that intake of PUFA was associated with a decrease in the expression of genes in liver X receptor signalling, while consumption of SFA led to an increase in the expression of these genes. Consumption of PUFA also resulted in an increase in the expression of genes linked to cellular stress responses, while MUFA had a moderate effect on several genes [137]. The findings suggest that data from multiple individuals undergoing postprandial gene expression profiling in peripheral blood mononuclear cells could enable the stratification of gene expression profiles as "healthy" or "unhealthy," as well as the identification of particular meals that could be categorised as healthy or unhealthy for such individuals [123].

With regard to obesity, a significant interaction was observed between SFA intake and the *APOA2* SNP rs5082 on the risk of obesity in a study of 3,462 participants from three populations in the USA (the Framingham Offspring Study [1,454 whites], the Genetics of Lipid Lowering Drugs and Diet Network Study [1,078 whites], and the Boston-Puerto Rican Centers on Population Health and Health Disparities Study [930 Hispanics of Caribbean

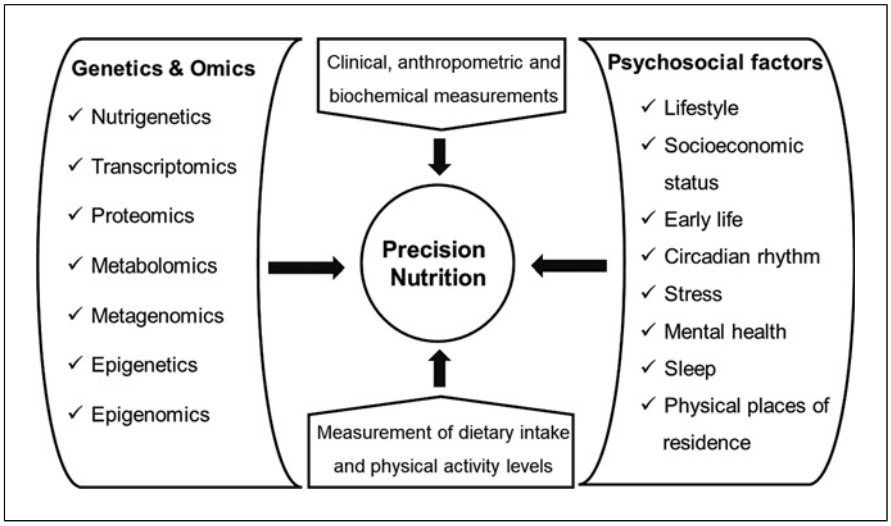

Fig. 2. List of factors that should be considered for the implementation of precision nutrition.

origin]) [22]. This finding was also replicated in Chinese, Asian Indians, and whites from the Valencia Region of Spain [138]. Individuals with the "CC" genotype had an increased risk of obesity compared to those with the "TT" or "TC" genotypes only when their SFA intake was high (≥22 g/day) [22, 138]. To explore the mechanisms underlying this interaction, the authors performed a multi-omics study involving methylome, transcription, and metabolomic analyses from three different populations (the Boston Puerto Rican Health Study, the Genetics of Lipid Lowering Drugs and Diet Network Study, and the Framingham Heart Study) [139]. The epigenetic state of the *APOA2* regulatory region was found to be linked to SFA intake and the rs5082 genotype, causing differences in *APOA2* expression between the "CC" and "TT" genotypes on a high-SFA diet and influencing branched-chain amino acid and tryptophan metabolism [139]. Therefore, integrating data from nutrigenetics, metabolomics, the gut microbiome, epigenetics, phenotypic traits, and lifestyle factors might help in designing personalised and precise nutrition interventions. Machine learning and artificial intelligence enable the integration of data from various fields by identifying patterns in large datasets and grouping similar data to create predictive models and algorithms [140]. A machine learning model utilising age, systolic blood pressure, routine blood and urine tests as well as dietary intake values has been reported to be effective in identifying young, asymptomatic individuals at higher risk of CVDs [141]. Similarly, integrating data on lifestyle factors, gut microbiome, clinical variables, subcutaneous adipose tissue gene expression, and metabolomics derived from serum, urine, and faeces were found to be effective in identifying biomarkers linked to insulin sensitivity [142]. Thus, integrating data from multiple disciplines could help in designing personalised and precise dietary interventions for the prevention and management of cardiometabolic diseases, although the effectiveness and practicality of this approach are still being explored (Fig. 2).

Conclusion

Nutrigenetics has a potential role to play in the prevention and management of cardiometabolic diseases. Several factors might influence variations among individuals with regard to dietary exposures and metabolic responses, and these include genetic diversity, cultural and lifestyle factors as well as socio-economic factors. A multi-omics approach involving disciplines such as metabolomics, epigenetics, and the gut microbiome might contribute to improved understanding of the underlying mechanisms of gene-diet interactions and the implementation of precision nutrition, although more research is needed to confirm the practicality and effectiveness of this approach. Therefore, conducting gene-diet interaction studies in diverse populations is essential to improve their clinical application worldwide. To bridge the gap between existing nutrigenetic insights and their application in clinical practice, it is vital for initial findings to be replicated in independent samples, followed by dietary intervention studies. Studies utilising large sample sizes are required as this improves the power to detect interactions with minimal effect sizes. Future studies should focus on replicating initial findings to enhance reliability and promote comparison across studies. Once findings have been replicated in independent samples, dietary intervention

studies will be required to further strengthen the evidence and facilitate their application in clinical practice. The issues discussed in this review are particularly important, given the current diverse climate, which poses significant risks to food security and diet quality, making vulnerable populations across the world susceptible to various forms of malnutrition [143].

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

K.S.V. conceived the study; R.W. and K.S.V. wrote the manuscript and approved the final version of the manuscript.

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