Roles of Functional Genetic Variants and Dietary Factors on MicroRNA-Mediated Gene Regulation of Cardiometabolic Traits

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Abstract

Background:
Dysregulation of metabolic traits and obesity are risk factors for cardiovascular disease (CVD) and other chronic diseases that accompany unhealthy aging. MicroRNAs (miRNAs) regulate gene expression via targeting mRNAs and represent an epigenetic mechanism that underlies human biology and diseases, including metabolic function and CVD. Previous research has identified functional genetic variants involved in miRNA-based gene regulation, suggesting that such genetic polymorphisms also modulate cardiometabolic traits through miRNAs. This leads to our interest in investigating the roles of genetic variants in miRNA-mediated regulation of blood lipids and their interactions with diet (gene × environment interactions). It has also been demonstrated that dietary factors can modulate miRNA levels. The underlying miRNA-based mechanisms related to the effect of dietary factors on cardiometabolic traits are not well-understood.

Aims:
To create a genome-wide miRNA-related single nucleotide polymorphism (SNP) database with a particular focus on genetic variants which potentially modulate miRNA-mediate gene regulation and affect blood lipids (*Aim 1a*) and to identify *miRNA-related genetic associations and their interactions with diet* for blood lipid concentrations (*Aim 1b*). Then to investigate *the effect of virgin olive oil intervention* on miRNA profiles in the context of cardiovascular disease biomarkers (*Aim 2*). We hypothesize that miRNAs affect the activity of genes regulating blood lipids, and miRNA function can be further modulated by genetic variants and dietary factors.

Methods:
We used miRNA target prediction algorithms, publicly available databases and bioinformatics tools to create a genome-wide miRNA-related SNP database (*Aim 1a*). We then performed functional genome-wide association studies (fGWAS) and genome-wide interaction studies (fGWIS) and meta-analyzed association and interaction data in 9 population-based cohort studies (n = ~21,000, European origin participants) from the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium for blood lipids using SNPs predicted to be functional via miRNA-related mechanisms. We evaluated interactions for dietary carbohydrate and saturated, monounsaturated and polyunsaturated fats *(Aim 1b)*. We conducted a two-armed, 3-month randomized controlled trial (RCT): 41 overweight/obese older participants (age: 72.0 ± 5.6 y; BMI: 28.8 ± 2.6 kg/m^2) were given virgin olive oil or control (soy oil/corn oil/butter) oil to replace substitutable oils/fats commonly used in participants' typical American diet. We quantified blood miRNAs using miRNA microarray and quantitative RT-PCR and used bioinformatics analyses to assess the effects of olive oil on cardiometabolic traits (*Aim 2*).

Results:
We created a miRNA-related SNP database, including 914,515 miRNA-related SNPs (*Aim 1a*). Using miRNA fGWAS and fGWIS approaches, we identified 19 loci associated with blood lipids and 17 novel loci potentially interacted with diet in determining blood lipids. Several of these key results such as miRNA-related SNPs in *CELSR2*, *NECTIN2* (also known as *PVRL2*), *FADS1*, *SH3YL1*, *ONECUT2* and *PPIL2* were supported by multiple functional annotation databases (*Aim 1b*). In the olive oil RCT, following a 3-month intervention, systolic blood pressure (SBP) was significantly reduced in the olive oil group (P = 0.004) but not in the control group. Individuals in the olive oil group had a significantly lower SBP (P = 0.04) compared with the control group at month 3. Change in hsa-miR-96-5p was correlated with changes in serum glucose and insulin levels in the olive oil group after 3 months. Furthermore, participants with impaired fasting glucose appeared to benefit from the olive oil intervention by improving fasting glucose and insulin (*Aim 2*).

Conclusions:
The comprehensive miRNA-related SNP database can be used to assess the genetic contribution of miRNA-mediated regulation on any traits of interest (*Aim 1a*). Our study of fGWAS and fGWIS generated miRNA-based hypotheses for previously known lipid-associated loci and identified novel genetic variants in response to dietary macronutrients for blood lipids. Replication, different analytic methods and follow-up functional studies are recommended for further investigation (*Aim 1b*). Our findings from the olive oil RCT suggested that hsa-miR-96-5p may be induced by olive oil intervention to regulate glycemic homeostasis. The regulation of miRNAs related to olive oil consumption contributing to health benefits requires further research (*Aim 2*). Further mechanistic examination and larger dietary intervention studies are needed to validate our findings, to advance the general field of miRNA regulation of blood lipids and to eventually develop personalized strategies/recommendations to reduce CVD risk.

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Chapter 1 Introduction

1.1 Literature Review

Elevated plasma triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) levels are considered clinically relevant risk factors for cardiovascular disease (CVD) [1, 2], a leading cause of morbidity and mortality in the US [3]. Regulation of expression of lipoprotein constituents, by genetic variants, dietary factors and their interrelationships, can have a profound impact on CVD onset and progression.

Human microRNAs (miRNAs), one type of short non-coding RNA, are predicted to regulate 30-60% of protein-coding genes [4-6] and have emerged as important epigenetic regulators and fine-tuners of biological processes and human diseases, including lipoprotein metabolism and CVD [7-18]. Previous studies have identified functional single nucleotide polymorphisms (SNPs) involved in miRNA-mediated gene repression [19-21], suggesting that such genetic variants also modulate lipoprotein metabolism through miRNAs. Additionally, the association of some SNPs with the disease can be modified by environmental factors [22, 23]. Such modifications or gene-environment (G×E) interactions are situations where the allele for disease risk shows its impact on risk when a given environmental factor, such as diet or lifestyle, passes a threshold. The importance of identifying gene-diet interactions is underscored by their ability to alter disease risk. However, the impact of genetic variation and dietary factors and their interactions in regulating blood lipids via miRNA-mediated gene regulation remains largely unknown. This research project aimed to elucidate the roles of genetic variants and dietary factors on miRNA-based gene regulation of CVD risk factors. We created a genome-wide miRNA SNP database to identify potential functional miRNA-related SNPs (*Aim 1a*) and to identify *miRNA-related genetic associations and their interactions with diet* for blood lipid concentrations (*Aim 1b*) and then to investigate *the effect of virgin olive oil intervention* on miRNA profiles in the context of cardiovascular disease biomarkers (*Aim 2*). We hypothesize that miRNAs affect the genes that regulate blood lipids, and miRNA function can be further modulated by genetic variants and dietary factors.

miRNA Genomic Organization, Function and Biogenesis

Over 85% of the human genome harbors actively transcribed non-coding RNAs [24]. MiRNAs are one class of non-coding RNAs (19~24 nucleotides, nts) which negatively regulate gene expression at the post-transcriptional level by binding to sites in the 3' untranslated region (3'UTR) of targeted messenger RNAs (mRNAs), leading to mRNA degradation or reducing protein translation. Besides, 5'UTR [25] and coding sequences [26] were also found to interact with miRNAs. MiRNAs are currently known to modulate a broad range of gene expression patterns in almost every level of regulation, biological processes and diseases, including development, the stress response, viral infection, and cancer [27-32]. Based on sequence conservation, the ability to fold into a hairpin

structure and experimental analyses, the human genome is predicted to encode thousands of miRNAs, which are estimated to regulate at least 30% to 60% of protein-coding genes [4-6]. MiRNAs also represent one of the largest gene families, accounting for ~2% of the whole human genome [33]. To date, 2,588 mature miRNAs have been annotated in the miRNA registry, miRBase (release 21) [34, 35]. A single miRNA is estimated to regulate on average over 200 genes, potentially providing simultaneous regulation of multiple genes involved in a physiological pathway. Around 36% of miRNAs are found in clusters (55 distinct clusters [36]), and 50% are associated with known transcription units in humans [37]. Furthermore, multiple miRNAs were demonstrated to target a single gene [38], suggesting that the miRNA-based gene regulation is a complex network of interactions between multiple miRNAs and mRNAs.

Biogenesis of miRNAs starts in the nucleus. Long immature pri-miRNAs are first transcribed from miRNA genes (located in introns of protein-coding genes or as intergenic or polycistronic genes) by RNA polymerase II or III, and RNase III Drosha-DGCR8 processes pri-miRNAs into ~70-100 nt long hairpin-shaped pre-miRNAs. Pre-miRNAs are then exported from the nucleus to the cytoplasm by the RAN-GTPase/exportin-5-dependent mechanism. RNase III Dicer and a helicase cleave pre-miRNAs to release single-stranded RNAs that are incorporated into the miRNA-induced silencing complex (miRISC), containing GEMIN3 and GEMIN4, and then the mature miRNA/miRISC complex binds to a target mRNA sequence. MiRNAs negatively regulate gene expression through two major mechanisms, mRNA destabilization and/or translational repression [27, 39-41]. MiRNAs exhibiting full complementarity to target mRNA are shown to prompt mRNA degradation. In case of non-perfect complementary binding to the target mRNA, miRISC may hinder protein translation by several different distinct mechanisms.

miRNA-Target: Principles and Prediction

Altered miRNA regulation can lead to a disease through different interactions between miRNAs and their targets, mRNA transcripts. Based on early experiments and analyses of sequences, many algorithms have been developed to predict miRNA targets. For example, TargetScan [42] is based on bases 2-8 from the 5'end of the miRNA and requires paring to conserved 3'UTR mRNA sequences, but functional miRNA target sites were reported not limited to be conserved across evolution [43]. Other contextual features have been identified through experimental and computational approaches to predict targets. Such features include a 6 nt seed match [6] with a complementary site at position 8 (7mer-m8), and/or an A opposite the miRNA position 1 (7mer-A1), or with an A opposite miRNA position 9 [44]. Various target prediction tools/algorithms have additionally incorporated tolerance of a G:U wobble [45-47], free energy binding of the miRNA-mRNA duplex, secondary structure accessibility, nucleotide content in and around the putative target site and position of seed complementary sites within the mRNA transcript [48]. Current prediction methods agree that: (1) Requiring conserved Watson-Crick pairing to the 5' region of the miRNA centered on nts 2-7 (miRNA "seed"); (2) Conserved pairing to the seed region alone can also be sufficient for

predicting conserved targets; (3) Highly conserved miRNAs have many conserved targets [27]. Despite advances in target prediction algorithms, the overlap of predicted targets between different platforms remains relatively small. Additionally, these *in silico* target prediction algorithms are not cell-type or context specific.

miRNAs Regulation of Lipid and Cholesterol Metabolism and Cardiovascular Disease Risk Factors

Research has shown that some miRNAs are important cellular regulators of lipoprotein and cholesterol metabolism [7-17, 49, 50] with potential implications for CVD risk. Among them, miR-122, miR-33, miR-148a, miR-128-1 miR-370, miR-378/378*, miR-335, miR-34a, miR-106b, miR-758, miR-302a, and miR-27b have been described to regulate lipid metabolism [51-54]. Specifically, miR-122 is highly expressed in liver, a major regulatory organ for cholesterol and lipoprotein metabolism. Silencing of miR-122 down-regulates genes involved in cholesterol biosynthesis and lipid metabolism leading to reduced plasma cholesterol [9, 10, 55, 56]. MiR-33, an intronic miRNA located in the gene encoding sterol-regulatory element-binding factor-2 (*SREBP-2*) has been shown to regulate numerous steps of the reverse cholesterol transport pathway by targeting the ATP-binding cassette transporters (*ABCA1*) for both HDL biogenesis in the liver and cellular cholesterol efflux from macrophages [11] and *CYP7A1* for bile acid synthesis and *ABCB11* and *ATP8B1* secretion. In addition to miR-33, *ABCA1* is highly regulated at the post-transcriptional level by many other miRNAs. HDL particles deliver cholesterol to the liver via the SRB1 receptor, which is also regulated by several miRNAs including miR-185, miR-223, miR-96. More importantly, inhibition of miR-33 was found to elevate HDL-C levels in mice on a Western diet [12] and increased HDL-C and decrease very-low-density lipoprotein (VLDL) associated TG levels in non-human primates [17].

The liver plays a key role in controlling plasma LDL-C levels by regulating VLDL secretion and LDL clearance via the LDL receptor (LDLR). VLDL secretion is regulated by microsomal transfer protein (MTP). MTP expression is controlled by miR-30c and miR-122. LDLR and LDLRAP1 hepatic levels are regulated by numerous miRNAs including miR-301b, miR-130b, miR-185, miR-128-1, miR-148a and miR-27a/b. Of particular importance for CVD, Inhibition of miR-148a may prove an important approach for improving dyslipidemia, as this has been shown to both raise plasma HDL levels and lower LDL levels in mice by targeting both *ABCA1* and *LDLR*, respectively.

In addition, miRNAs have also been reported to be transported by lipoproteins such as HDL and LDL [57-59]. This represents an emerging field and potential extracellular miRNA regulation in CVD progression and prevention. Nevertheless, the roles of genetic and dietary factors on miRNA-based regulation in lipid metabolism and cholesterol transport remain to be elucidated.

Gene-Environment Interaction (GxE) Studies

The effect of an environmental factor on a phenotype has been found to be variable due to individual's genetic background. Many loci have been identified contributing to the variation in cardiometabolic traits and incidence of cardiovascular disease (CVD) in response to diet (gene-by-diet interactions) from cross-sectional studies to large dietary intervention studies. The purpose of investigating G×E is multifold. First, understanding G×E (gene-by-diet) interactions improves our ability to mitigate genetic predisposition to chronic diseases by modifying lifestyle or dietary factors and eventually defining, tailoring and implementing the genetically informed recommendations [60-62]. One of the most validated examples of gene-by-diet interactions is apolipoprotein A2 (*APOA2*) gene interacting with dietary saturated fat (SFA) in determining obesity-related traits [63-67]. Second, G×E will provide a better understanding of the etiology of complex disease by detecting novel loci related to phenotypes to provide insight into biological pathways [68, 69]. Finally, G×E interactions are suggested to be a contributor to phenotypic variance and can help explain "missing heritability" [23].

G×E interactions have been investigated based on a candidate gene approach and then evolved to the genome-wide association studies (GWAS) signals and genome-wide interaction studies (GWIS) recently [70]. In our studies, we conducted a functional GWIS (fGWIS) using potentially functional miRNA-related genetic variants, which represent a targeted, hypothesis-driven approach comprehensive but more selective than traditional genome-wide scan.

Genetic Effects on miRNA-mediated Regulation

Genetic variants that affect gene expression levels (i.e., expression quantitative trait loci, eQTL) have been shown to be related with human diseases [71, 72]. Genetic alterations in the process of miRNA-mediated gene regulation have been also reported to be associated with disease-related phenotypes [19, 73], suggesting that dysregulation of miRNA-based gene regulation can be a potential mechanism of developing disease phenotypes, and thus genetic polymorphisms affecting miRNA-mediated regulation can modulate blood lipids. MiRNA-related SNPs, which can categorized as SNPs in miRNA processing machinery genes, in miRNA genes (pri- or pre-miRNA sequences) or at the miRNA binding sites (seed or regulatory regions) [74], can modulate miRNA and target gene expression to influence disease-related outcomes and disease development.

This class of functional genetic variants may change miRNA levels, their interactions with targets, or a combination of these two. A genetic polymorphism located in miRNA processing machinery genes or miRNA genes may affect the expression of many genes with a greater impact, whereas a genetic variant resided at or near a miRNA target site may be more target and/or pathway specific. These variants can be present in a variety of forms in human genomes, leading to loss or gain of a miRNA binding site/function. Examples of loss of miRNA target sites are the following: rs5186 in the 3'UTR (untranslated region) of the angiotensin receptor-1 (*AGTR1*) gene mediates allele specific targeting of miR-155 [20], and the 1166C allele of *AGTR1* has been shown to increase

the risk of hypertension and CVD [20]; ACAA insertion/deletion polymorphism in the 3'UTR of the IGF-II receptor (*IGF2R*) alters the interactions with miR-657 in type 2 diabetes [73]; in addition, researchers in our group have determined that rs8887 in the 3'UTR of perilipin 4 (*PLIN4*), associated with obesity-related traits, creates a seed site for miR-522 [21]. Other research groups have suggested associations of miRNA polymorphisms with disease progression and drug response [75-79]. Similarly, miRNA-related genetic polymorphisms may modulate the effects of diet on blood lipid concentrations. Our group found that rs13702 located in Lipoprotein Lipase (*LPL*) 3'UTR--minor allele disrupting a target site for human miR-410--was associated with TG and HDL-C, and a statistical interaction with dietary polyunsaturated fatty acids was significant on TG in the CHARGE Consortium [80].

Moreover, computational combinations of polymorphism data and miRNA target predictions have suggested potential SNPs in miRNAs and their targets on human disease susceptibility [75, 81-83]. A recent study investigated the roles of miRNA-related SNPs in cardiometabolic traits-associated GWAS results [84]. However, none of these studies have focused on the roles of potential genetic variants on blood lipids in response to dietary factors through this mechanism.

Dietary (Epigenetic) Effects on miRNA-mediated Regulation and Expression Profiling

MiRNA expression has been considered as one of several epigenetic mechanisms of gene expression regulation. Epigenetic alterations are potentially reversible and can thus be modified by the environment. Drugs and diet are environmental factors that have been hypothesized and shown to affect miRNA regulation in cancer research [85, 86] and much less known in atherosclerosis process. Interestingly, a previous study demonstrated that statins (a family of drugs used to lower cholesterol levels) could induce miR-33, which decreases expression of biliary transporters (ABCB11 and ATP8B1) as its functional targets, resulting in cholestasis. Silencing of miR-33 eliminated the toxic side effects from taking statins in an animal model [87]. Some studies have shown dietary nutrients [11, 15, 53, 88, 89] can potentially modulate miRNA function, and the effect of dietary factors on miRNA regulation remains to be investigated to understand the relationship with phenotypes. Therefore, our research project also aimed to elucidate the effects of diet on epigenetic (miRNAs-target interactions) alterations.

Dietary fat intake influences plasma fatty acid profile, and altered plasma fatty acid composition has been shown to be associated with several metabolic diseases [90-92]. Olive oil as part of the Mediterranean diet has been intensively studied and shown for its overall cardio-protective effects [93, 94]. The health effects of olive oil are linked mostly to its high proportion of oleic acid (C18:1, n9), phenolic compounds, and squalene [94-96]. Some nutrigenomic studies have been demonstrated to elucidate the mechanisms underlying the effect of olive oil consumption on metabolic traits [97-99]. However, to our knowledge, no intervention study has yet investigated the effect of olive oil intervention on miRNA expression profiles in older adults in humans.

1.2 Central Hypothesis and Specific Aims

The overall objectives of this thesis are 1) to identify SNPs, with potential biological effects on the miRNA-target gene interaction affecting the regulation of blood lipids, and 2) to investigate the miRNA-based regulation mediated by dietary factors on cardiometabolic traits.

The ***central hypothesis*** is that MiRNAs affect the activity of genes regulating blood lipids, and miRNA function can be further modulated by genetic variants and dietary factors. We tested our central hypotheses and accomplished the overall goals of this study by pursuing the following specific aims.

Aim 1a: To create a genome-wide miRNA-related SNP database with a particular focus on genetic variants that potentially modulate miRNA-mediate gene regulation and affect blood lipids.
Aim 1b: To identify miRNA-related genetic associations and their interactions with diet for blood lipid concentrations.
Hypothesis: Genetic variants could modulate miRNA repression on targeted genes involved in lipid metabolism through regulation of miRNA biogenesis and/or miRNA-mRNA interactions, and thus affect blood lipid levels.

Aim 2: To investigate the effect of virgin olive oil intervention on miRNA profiles in the context of cardiovascular disease biomarkers.
Hypothesis: Diet-induced changes in metabolic traits are associated with changes in miRNA levels.

1.3 Significance

Gaps in current knowledge illustrate the need to investigate the roles of genetic variants and dietary factors and their interactions on miRNA-mediated post-transcriptional gene regulation of cardiometabolic traits. More research is needed before miRNA and genetically-informed dietary recommendations can be applied [32]. Current evidence indicates that blood lipid levels are modulated by complex interactions between genetic and environmental factors [22, 100, 101], suggesting that gene-diet interaction should be investigated in the context of miRNA. In general, this dissertation research aimed to investigate miRNA-mediated gene regulation of cardiometabolic traits in two areas: roles of genetic variation and dietary factors.

This dissertation work is significant because successful identification of genetic and dietary effects on miRNA-mediated regulation of plasma lipids provides important evidence regarding the roles of miRNA on cardiometabolic traits and assist further efforts at translational research in CVD to develop preventative nutrition strategies. *This dissertation study is innovative* in applying a comprehensive approach – synthesizing data from bioinformatics and population studies – to identify miRNA-target pairs altered by genetic variants using meta-analyzed data in a consortium setting. Further identification of dietary sensitive genetic alleles or modifiable miRNAs will lead to a deeper understanding of metabolic regulation by diet to ameliorate genetic susceptibility to CVD. We also explored whether changes in miRNA profiles are biomarkers that reflect metabolic changes after a dietary intervention. From a public health perspective, results of gene-diet interactions provided us with information to develop personalized recommendations, such as dietary modification for subjects at high risk of CVD.

1.4 References

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Chapter 2 Roles of miRNA-Related SNPs on Plasma Lipids and Their Interactions with Dietary Factors

2.1 Identification of miRNA-Related Genetic Variants for Blood Lipids: A Functional Genome-Wide Association and Macronutrient Intake Interaction Study within CHARGE Consortium

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2.1.1 ABSTRACT

Background:
MicroRNAs (miRNAs) regulate gene expression via targeting mRNAs and represent an epigenetic mechanism that underlies human biology and diseases, including lipoprotein metabolism and cardiovascular disease. This leads to questions regarding roles of genetic variants in miRNA-mediated regulation of blood lipids and their interactions with diet (gene × environment interactions). Therefore, we investigated associations and dietary interactions for miRNA-related Single Nucleotide Polymorphisms (SNPs) for the outcomes of blood lipids.

Objective:
Using SNPs predicted to modify miRNA-target interactions, we aimed to identify those associated with blood lipids and those interacting with diet for blood lipid concentrations.

Design/Methods:
We created a genome-wide miRNA-related SNP database by integrating miRNA targeting prediction algorithms and databases. We then performed functional genome-wide association studies (fGWAS) and genome-wide interaction studies (fGWIS) for blood lipids (triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) using SNPs predicted to be functional via miRNA-related mechanisms. We evaluated interactions for dietary carbohydrate and saturated, monounsaturated and polyunsaturated fats. Finally, we meta-analyzed association and interaction data from > 21,000 European origin adults in CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) cohorts: ARIC, GOLDN, GOYA male, InCHIANTI, Inter99, Rotterdam Study and YFS. An *a priori P* value based on 25,000 SNPs predicted to affect miRNA-mediated regulation of gene expression was used.

Results:
We identified 19 loci associated with blood lipids and 17 novel loci potentially interacted with diet in determining blood lipids. Among these, some key results such as miRNA-related SNPs in *CELSR2*, *NECTIN2* (also known as *PVRL2*), *FADS1*, *SH3YL1*, *ONECUT2* and *PPIL2* were supported by multiple publicly available functional annotation databases.

Conclusions:
Our findings contribute to a better understanding of miRNA-mediated regulation, generating new hypotheses for identified signals and their relationships to dietary macronutrients (modifiable environmental factor) on blood lipids. This targeted, hypothesis-driven approach is more selective than traditional GWAS, thus lowering the multiple testing burden. However, the heterogeneity and small effect of SNP-by-diet interaction may limit the power for gene discovery. Replication, different analytic methods and follow-up functional studies are recommended for further investigation.

Trials related to this study were registered at clinicaltrials.gov as NCT00005131 (Atherosclerosis Risk in Communities), NCT00083369 (Genetic and Environmental Determinants of Triglycerides; GOLDN), and NCT01331512 (InCHIANTI Study) and NCT00289237 (Inter99).

KEYWORDS: miRNA, genetic variants, blood lipids, diet, macronutrients, gene-by-environment interaction, functional genome-wide interaction study, meta-analysis, CHARGE consortium.

ABBREVIATIONS

miRNA, microRNA; SNP, Single Nucleotide Polymorphism, GWAS, genome-wide association study; GWIS, genome-wide interaction study; G×E, gene-by-environment interaction; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CHO, carbohydrates, SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; eQTL, expression quantitative trait locus.

2.1.2 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death, accounting for almost a third of all deaths globally [1]. Abnormal blood lipid levels (high triglycerides (TG) [2], low high-density lipoprotein cholesterol (HDL-C) [3] and high low-density lipoprotein cholesterol (LDL-C) [4]) are intermediate biomarkers and significant risk factors for developing CVD. These complex traits can be determined by genetic and environmental factors and gene-by-environment (G×E) interactions.

Genome-wide association studies (GWAS) have identified genetic contributors to blood lipids, but understanding is still limited. The most recent GWAS for lipids have identified 157 loci [5, 6] in >188,000 European-ancestry individuals. However, the blood lipids variance explained by all these loci in the Framingham offspring was ~12-15% of heritability, much lower than that estimated from family studies (for example, ~48-59% at Framingham Heart Study Examination 1) [7]. Moreover, characterizing the functional significance of identified loci has been challenging.

Preceding and in parallel with genetic studies, environmental factors, such as diet and macronutrients (e.g., fat, carbohydrate and protein), have been investigated for decades for their impact on blood lipids [8-13]. Dietary recommendations have been developed to lower the risk of CVD, without consideration of the potential role of genetics. The intake of saturated fatty acids (SFA) has been shown to be positively correlated with LDL-C. However, dietary macronutrient composition alone has been inconsistently associated with intermediate biomarkers of CVD risk (blood lipids) and CVD events [13-19].

Incorporating dietary macronutrients into genetic studies to explore G×E interactions provides multiple potential advantages, such as reducing missing heritability [20, 21]. Further, investigating G×E interactions may reveal novel genetic loci and help us to understand the complex etiological mechanisms underlying human diseases, perhaps, more importantly, examining G×E interactions could identify population subgroups who are genetically susceptible to a disease and sensitive to the intensity of environmental exposures---a potential opportunity for personalized strategy in CVD prevention. Many research efforts have been made for the candidate gene-by-diet interaction studies. SFA, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA) and carbohydrate (CHO) are commonly evaluated for their roles of modification on genetic associated CVD risk factors [22-26].

Many identified genetic variants associated with blood lipids contribute to CVD risk [6, 27-29], however other gene-related factors such as epigenetic regulation may be equally important. Specifically, human microRNAs (miRNAs) are short non-coding RNA estimated to regulate up to 60% of genes [30-32] via binding to their targets mRNAs and have emerged as important epigenetic regulators of biological processes and human diseases, including lipid metabolism, cardio-metabolic traits and CVD [33-55]. Genetic variants involved in miRNA-mediated regulation have been shown to affect gene expression [56-58] thus contributing to phenotypic variation and disease. However, the role of genetic variation of miRNA-mediated regulation for CVD risk factors is largely

unidentified. Recent studies have identified functional single nucleotide polymorphisms (SNPs) that alter miRNA-mediated gene repression and may potentially alter CVD-related traits [24, 59-65]. To focus efforts on human SNPs likely to participate in miRNA targeting modification (e.g., functional SNPs), we first created a genome-wide miRNA-related SNP database by integrating miRNA targeting prediction algorithms and databases from various resources. This comprehensive database allows us to assess the genetic effect/contribution of miRNA-mediated regulation on the traits of interest.

We hypothesize that SNPs predicted to interfere with miRNA regulation (miRNA-related SNPs) are more likely to be functional and have phenotypic consequences. More specifically, miRNA-related SNPs may mediate blood lipids by altering miRNA-mRNA interactions to modulate the transcript level of a target gene. In addition, miRNA levels can be modulated by environmental factors [66, 67]; therefore, we further hypothesize that the association between miRNA-related SNPs and blood lipids can be modified by dietary factors. Moreover, we hypothesize that miRNA mediated gene repression is a mechanism through which environmental factors modulate genetic susceptibility to CVD. We conducted a functional GWAS (fGWAS, miRNA fGWAS) and functional genome-wide interaction studies (fGWIS, miRNA fGWIS) with dietary factors (SFA, MUFA, PUFA and CHO as a % of total energy intake) for the outcome of blood lipids using miRNA-related SNPs. The combined contributions of genetic variants and dietary factors on the roles of miRNAs in regulating blood lipids remain virtually unexplored, and are the major focus of the current study. We anticipate that better understanding of miRNA-mediated gene regulation induced by a genetic polymorphism and a modifiable dietary factor will generate preventative strategies to reduce CVD risk through improvement of dysregulated lipid metabolism.

2.1.3 METHODS

MiRSNP Database

The miRSNP database includes 914,515 genetic variants located in target regulatory regions/miRNA seed sites, miRNA genes and miRNA processing machinery. Building on our earlier miRNA target SNP database [68], we added human SNPs that are potentially involved in miRNA targeting regulation by using miRNA target prediction algorithms, such as TargetScan [32], TargetScanS, miRanda [69, 70], microRNA.org [71, 72], PITA [73], PicTar [74], mirsnpscore [75, 76] and dbSMR [77]. We downloaded the targets with genome coordinates and mapped to genomic positions according to GRCh37/hg19 using the LiftOver tool from the UCSC Genome Browser when needed and mapped to any db137 SNPs located in predicted target sites. We also collected SNPs from published miRNA SNP databases: PolymiRTS [78], PolymiRTS 2.0 [79], PolymiRTS 3.0 [80], Patrocles [81], PupaSuite 3.1 [82], miRdsnp [83], miRNASNP [84], MirSNP [85] miRcode [86] and other literature resources, including predicted and experimentally validated sites. As previous research suggested [87-90], the SNPs in this database are not limited to 3' untranslated region (UTR) of target genes; they can reside in any part of target transcripts. For SNPs located in miRNA genes, we used UCSC Genome Browser tract wgRna_sno/miRNA and limited results to miRNA precursor forms (miRBase release 15.0) followed by a search for any SNPs positioned within gene regions. For genetic variants affecting miRNA processing machinery, SNPs were identified that mapped within genes encoding these related enzymes/proteins.

A miRSNP confidence score (ranging from 1 to 30) was created for each SNP by counting the number of algorithms, datasets or tables supporting a genetic effect of miRNA-mediated regulation, in order to rank the likelihood of being miRNA regulatory SNPs (**Supplemental Figure 2.1.1**). After removing the SNPs with a score lower than 3 (low confidence miRSNPs), we collected all potential (predicted and experimentally validated) regulatory miRSNPs (ranged 3-30) to map to the GWAS or GWIS data.

Ethics Statement

Informed consent forms were signed by all participants. All cohort studies were conducted according to the principles outlined in the Declaration of Helsinki, and the study protocol was approved by local Institutional Review Boards and/or oversight committees of the participating cohorts.

Participating Cohorts

The samples for the cross-sectional meta-analyses included up to ~24,000 participants of European descent adults from 9 US and European cohort studies (**Table 2.1.1**) participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Nutrition Working Group: the Atherosclerosis Risk In Communities (ARIC) study, the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), the Genetics of Obesity in Young Adults (GOYA) study, the Invecchiare in Chianti, aging in the Chianti area (InCHIANTI), Inter99 Study, the Rotterdam Study baseline and extensions (RS-I, RS-II and RS-III) and the Cardiovascular Risk in Young Finns Study (YFS).

Within each cohort, non-European-descent (self-reported or identity-by-state [IBS] clustering of GWAS data) and subjects who were taking lipid-lowering medications at the time of blood lipids measurement were excluded from analyses. Individuals were also excluded if they had missing or non-fasting blood lipid measurements, TG levels > 1000 mg/dL, missing genotype, dietary or covariates data, had extreme phenotype outcomes or implausible energy intake and/or dietary values (cohort-specific). In general, each cohort could exclude any phenotype outcome or exposure value > upper quartile (Q3) + 1.5 × interquartile range (IQR) or < lower quartile (Q1) - 1.5 × IQR or using cohort-specific quality control (QC) criteria.

Measurement of Blood Lipid Outcomes and Covariates

Fasting plasma or serum concentrations of triglycerides (TG), HDL-C and LDL-C (mmol/L) were determined (**Supplemental Table 2.1.2**). GOLDN, RS-I and RS-III measured the LDL-C levels directly, while the other cohorts used the Friedewald equation to calculate LDL-C [91, 92]. The LDL-C values were designated as missing for subjects with TG levels > 400 mg/dL (4.52 mmol/L) or existing chylomicrons. If both TC and TG levels were elevated, a modified formula was used [93]. Natural logarithmic transformations were carried out for fasting TG to achieve normality before statistical analysis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and treated as a continuous variable. Diabetic status was dichotomous, and diabetes was defined by fasting plasma glucose concentration ≥ 7 mmol/L (≥ 126 mg/dL) or history of diabetes or use of insulin or other antidiabetic medication or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 11.1 mmol/L (≥ 200 mg/dL).

Assessment of Dietary Macronutrients

For all cohort studies, dietary intake was assessed using food-frequency questionnaires (FFQs), except for GOYA, which used food records (**Supplemental Table 2.1.3**). The type of FFQ used in each cohort differed slightly to capture the dietary habits of the population of interest. In the present study, we investigated four dietary macronutrients as the exposures in GWIS, carbohydrate (CHO), saturated fatty acid (SFA), monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) intakes (as a % of total energy). All dietary variables were modeled continuously. Extreme or implausible energy and dietary intake were excluded from analyses based on cohort-specific QC criteria.

GWA/Metabochip Genotyping and Imputation

Genome-wide genotyping was conducted using Affymetrix and Illumina platforms in 8 cohorts, and Cardio-MetaboChip was used in the Inter99 study, as described in **Supplemental Table 2.1.4**. Each study performed cohort-specific quality control (QC) for sample and genotyped single nucleotide polymorphisms (SNPs) using minor allele frequency (MAF), call rate and departure from Hardy-Weinberg equilibrium (HWE) before imputation. Phased haplotypes from HapMap II CEU were used to impute ~2.5 million autosomal SNPs by using a Hidden Markov model algorithm implemented in MACH except in Inter99 (**Supplemental Table 2.1.3**).

Cohort-level Statistical Analyses for GWAS and GWIS

All participating cohorts followed a standardized analysis plan to perform cohort-level GWAS and GWIS. All three lipid traits were analyzed as continuous dependent variables using linear regression or linear mixed-effects models for family data. For GWAS (main associations between SNPs and blood lipids), we evaluated the additive effect of each SNP on blood lipid levels (ln-TG, HDL-C and LDL-C) adjusting for cohort-specific covariates (study field center, population substructure [94] and familial relationship when applicable, shown in **Supplemental Table 2.1.4**), age and sex (basic model 1) and additional adjustment for BMI (model 2) and further adjustment for diabetic status (model 3). We conducted GWIS (interaction between SNPs and dietary macronutrients with respect to lipid traits) with 4 dietary macronutrients (CHO, SFA, MUFA and PUFA) for blood lipid outcomes (ln-TG, HDL-C and LDL-C) by including an interaction term (SNP × macronutrient) assuming an additive genetic model with additional adjustment for total energy intake. Sandwich (model-robust) standard errors (SE) were reported for GWIS [95, 96].

Pre-Meta-Analyses Quality Control

Each file of genome-wide per SNP and SNP×E (SNP × macronutrient interaction) summary statistics at the cohort-level underwent extensive SNP quality control before meta-analysis. Examination of file formatting, SNP information, data validity/plausibility and distributions of test statistics and quality measurements were performed at the study file-level and meta-level using an R package EasyQC (v9.2) [97]. Monomorphic SNPs, SNPs with low minor allele count (MAC, <= 6 for associations and <= 20 for interactions), low sample size (< 30 within cohort), low genotyping quality (call rate < 95% per SNP in a population; or Hardy–Weinberg equilibrium [HWE] $P < 1 \times 10^{-6}$ within a population; not in admixed population) or poor imputation quality (MACH: $R^{2\wedge} < 0.3$) were removed from the analysis.

Meta-analysis of Main Effects and Interaction Terms

We performed meta-analyses using fixed-effects inverse variance-weighted approach to determine an overall level of significance of SNP main effects (without interaction term) and SNP × macronutrient interaction terms (1 degree of freedom, 1DF, interaction) for 9 CHARGE participating studies for each blood lipid trait. METAL software (version 2011-03-25, University of Michigan, Center for Statistical Genetics; http://csg.sph.umich.edu/abecasis/metal) [98] was used. Cochran's Q statistic and I^2 index were used to assess heterogeneity across studies [99, 100]. I^2 in the range between 50-90% or greater than 75% were considered substantial or considerable heterogeneity [101]. To assess the results with substantial heterogeneity, we evaluated the results by using R package meta (v4.7-1) and function metagen for random-effects inverse variance-weighted meta-analyses. When results were similar to those from the fixed-effects meta-analyses, we only present the results of the fixed-effects meta-analyses.

We also conducted joint meta-analysis (JMA, 2 degrees of freedom, 2DF) method with fixed-effects [102] implemented in METAL (version 2010-02-08 with a patch source code) [98] to assess SNP effects when also taking interaction with macronutrient into account (2DF test of null hypothesis $\beta_{SNP} = 0$ and $\beta_{INT} = 0$). Cohort-level beta regression coefficients

(β), robust SE and robust covariance estimates between β_{SNP} and β_{INT} (obtained using QUICKTEST version 0.95 or newer (http://toby.freeshell.org/software/quicktest.shtml), ProbABEL version 0.1–3 or newer (http://mga.bionet.nsc.ru/~yurii/ABEL/) [103] or gee.test function in R package geepack) were combined to conduct 2DF JMA. Heterogeneity statistic was used to evaluate the heterogeneity.

To account for population stratification, the method of genomic control (λGC , inflation factors) was used to correct SE (GC corrected SE=SE/$\sqrt{\lambda}$GC)) if it was greater than 1 for GWAS main effects [104] and GWIS results. The first GC (GC1, at the cohort-level) and second GC (GC2, at the meta-level) were applied before and after meta-analyses, respectively. Study-specific and meta-level GC for all analyses ranged 0.92-1.07.

All meta-analyses were confirmed by two independent analysts. The final meta-analysis results excluded SNPs with low weighted average MAF (< 1%), low total sample size (< 5,000), low number of studies contributing to each analysis (< 4) or high heterogeneity ($P < 1\times10^{-6}$ or $I^2 > 75\%$). Additional sensitivity analyses were conducted by excluding one cohort study at a time, smaller cohorts (n < 1200) or cohorts with smaller MAC (<= 40) to validate our reported results. Some SNPs were excluded from the presentation as results because of the likelihood that they represented false positives based on low MAF, implausibly low *P* values, an I^2 heterogeneity measure of > 75% or results of sensitivity analyses.

Genome-wide significance was defined as a *P* value of $< 5 \times 10^{-8}$ after GC2, corresponding to a Bonferroni correction of 1 million independent tests [105]. For each miRNA fGWAS or fGWIS analysis, Bonferroni correction was used for adjusting for multiple testing (~25,000 SNPs), yielding a statistical significance threshold of $P = 2 \times 10^{-6}$. In exploratory analyses, SNPs with suggestive associations ($P < 2 \times 10^{-4}$) in the miRNA fGWAS meta-analyses (from the current data and publicly available data) were considered for miRNA fGWIS meta-analyses (**Figure 2.1.1**). All statistical significance thresholds were determined using Bonferroni correction.

We performed power calculations using Quanto (version 1.2.4, http://biostats.usc.edu/Quanto.html) [106]. The statistical power for detecting association with continuous and binary phenotypes was previously estimated for GWAS [107]. For an additive genetic model with marginal per-allele effect size ($\bar{\beta}_G$) of 0.03 interacting with a continuous exposure (SD=2) with marginal effect size ($\bar{\beta}_E$) of 0.03 in ~20,000 subjects, we had 80% power to detect interaction regression coefficients (β_{GE}) greater than ~0.007 mmol/L (α=0.05) on fasting lipid levels depending on the allele frequency.

The meta-analyses for the SNP-by-macronutrient interaction tests whether the SNP's association with a blood lipid level differed depending on the level of a macronutrient intake. The interpretation for interaction is based on: Lipid = $b_0 + b_1 \times$ SNP + $b_2 \times$ Diet + $b_3 \times$ SNP × Diet. We assume that we will evaluate the effect of 5% increments in a nutrient as % total energy. When β_{SNP} and β_{INT} showed the same direction, the SNP effect would be synergistic. In the case of both positive directions, the positive effect of a SNP on a lipid

level will be increased by greater macronutrient (such as SFA) intake. Carriers of 1 copy of the coded allele who consumed 5% more dietary SFA would be expected to have $b_3 \times 5$ stronger SNP effect compared to an individual with lower intake. When β_{SNP} and β_{INT} showed opposite directions, the magnitude of the SNP effect on a blood lipid would be weakened. In the case of positive β_{SNP} and negative β_{INT}, the positive effect of SNP on a lipid level will be weakened by higher dietary macronutrient (such as PUFA) intake. In other words, by carrying 1 copy of coded allele, an individual having 5 percent more dietary PUFA would be expected to have $b_3 \times 5$ weaker SNP effect compared to an individual with lower intake.

Publicly Available Data

The published GWAS meta-analysis data from the Global Lipid Genetics Consortium (GLGC 2013) for lipids traits (N > 173,000) were used to compare with the present study and serve as the discovery phase [6]. In exploratory analyses, SNPs showing suggestive significance ($P < 2 \times 10^{-5}$) in GLGC 2013 were evaluated for replication in CHARGE miRNA fGWAS meta-analyses (**Figure 2.1.1**).

Functional Annotation of Selected miRNA-Related SNPs

For the identified/selected miRSNPs (passing significance or suggestive thresholds), we extracted potential regulatory miRNAs depending on SNP alleles along with their miRSNP confidence score from our miRSNP database. We then investigated the evidence of gene expression of miRSNP host genes and regulatory miRNAs and their possible coexpression in relevant tissues. The association between miRSNPs and expression of their host genes (expression Quantitative Trait Loci (eQTL)) were examined in relevant tissues. We also searched for significant associations between expression of miRSNP host genes and miRSNP-associated lipid traits in an existing CHARGE meta-analysis dataset. Finally, we searched other potential functional features for the miRSNPs.

MiRSNP Host Gene and Regulatory MiRNA Expression

We searched for the evidence of miRSNP host gene expression and their predicted regulatory miRNA expression in relevant tissues (liver, adipose and small intestine) for blood lipid traits using publicly available mRNA expression database, such as Genotype-Tissue Expression (GTEx, https://gtexportal.org) [108] and BioGPS (http://biogps.org) [109] and published miRNA expression data [110-112] and database such as miRmine (http://guanlab.ccmb.med.umich.edu/mirmine) [113].

Expression Quantitative Trait Loci (eQTL) Analyses

Functional miRSNPs are expected to affect the expression levels of their target genes by altering miRNA binding. The GTEx Portal (Release V6p, dbGaP accession number phs000424.v6.p1, https://gtexportal.org, accessed on 07/28/2017) [108] was used to search for *cis*-eQTL data (in a +/- 1Mb window) in relevant tissues, such as liver, adipose tissue (subcutaneous and visceral), small intestine (terminal ileum) and whole blood. We set the significance threshold at $P < 0.0001$. We also searched eQTL data in adipose, skin, and lymphoblastoid cell lines (LCLs) from 856 healthy female twins participating in the Multiple Tissue Human Expression Resource (MuTHER) Study [114] and examined *cis*-eQTL evidence in whole blood collected from 5,311 individuals using the Gene Network

Blood eQTL database (http://genenetwork.nl/bloodeqtlbrowser/) [115]. The significance threshold was set at a false-discovery rate of 0.50. Other published *cis*-eQTL data in relevant tissue/cell types (liver [116-119], omental and subcutaneous adipose [116, 120] and whole blood samples [120, 121]) and the web annotation tool HaploReg (Version 4.1, http://archive.broadinstitute.org/mammals/haploreg/haploreg.php) [122] were also interrogated for associations between miRSNPs and their host gene transcript levels. The statistical criterion for significant SNP associations was study-specific. SNPs determined to exhibit a *cis*-effect on the expression levels of their host transcripts (increase or decrease) were suggested for further analyses.

Association between MiRSNP Host Gene Transcript Expression and Blood Lipid Levels

The meta-analyses of peripheral blood transcripts association with blood lipid levels (transcriptome-wide association study (TWAS)) were performed in 3 cohort studies, Framingham Heart Study (FHS), the RS and the InCHIANTI, participating in the CHARGE Consortium Gene Expression Working Group. The materials and methods used have been previously described in a similar study. [123]

Annotation of the Selected miRNA-Related SNPs to Regulatory Elements

To determine whether any of our identified/selected miRSNPs is functional through miRNA-mediated mechanisms and not potentially related to other molecular regulatory functions, we searched for other potential regulatory features. We first identified all variants within 1 Mb and in high linkage disequilibrium (LD) ($r^2 > 0.8$, 1000 Genomes Project EUR) with our lead miRSNPs. None of our lead variants were coding variants for any genes. For non-coding variants, web-based annotation tools, HaploReg (v4.1) [122] and RegulomeDB (Version 1.1, http://regulomedb.org/) [124] and the NCBI Roadmap Epigenomics Mapping Consortium reference human epigenomes data (http://www.roadmapepigenomics.org/; http://egg2.wustl.edu/roadmap/web_portal/), were used to explore conservation, chromatin states and epigenomic regulatory motifs.

2.1.4 RESULTS

The analysis flow chart of the current study is presented in **Figure 2.1.1**. Our overall aims were to perform miRNA fGWAS on blood lipid levels in CHARGE participating cohorts and in the latest published blood lipid GWAS data from the Global Lipids Genetics Consortium (GLGC 2013) [6] and to further carry out miRNA fGWIS (dietary interactions with miRNA-related SNPs) for blood lipids in the selected CHARGE cohorts.

Characteristics of the Participating Cohorts

The demographic, blood lipid outcomes and dietary characteristics of participants in 9 cohorts are shown in **Table 2.1.1**. Around 24,000 individuals from 9 studies contributed to the GWAS meta-analysis, and >21,000 participants of these 9 studies contributed to the GWIS meta-analysis. Mean ages ranged from 37.7 to 72.4 years, and females comprised 51–58.2% of participants in each cohort except for the GOYA study (all males). Across studies, mean TG concentrations ranged from 95 to 126 mg/dl, mean HDL-C concentrations ranged from 47 to 56 mg/dl, and mean LDL-C concentrations ranged from 117 to 163 mg/dl. Macronutrient intakes were similar across studies in general, but they differed slightly for different types of fats. The InCHIANTI had lowest and the RS-I reported the highest mean SFA intake (% energy). The GOYA had lowest and the InCHIANTI showed the highest mean MUFA intake (% energy). InCHIANTI had lowest and the GOLDN reported the highest mean PUFA intake (% energy. Mean BMI for all cohorts exceeded 25 kg/m^2. Detailed information about each participating cohort study, blood lipids and dietary measurements are described in **Supplemental Table 2.1.1, 2.1.2 and 2.1.3**. Information regarding study-specific genotyping, imputation, analysis tools and inflation factors for the individual GWAS and GWIS (range of 0.98–1.05) are shown in **Supplemental Table 2.1.4.**

MiRSNP Database and MiRNA Functional Genome-Wide Associations Using GLGC Published Lipid GWAS Data

The miRNA SNP confidence score (ranged from 1-30; mean: 2.79; Q1: 1; Q3: 4) for each SNP was created by counting the number of the supported algorithms, datasets or tables to rank the likelihood of being functional miRNA-related SNPs in our original miRSNP database (**Supplemental Figure 2.1.1**). We removed SNPs with a score lower than 3 (low confidence miRSNPs; 58%) arbitrarily, resulting in a trimmed miRSNP database with ~379,000 SNPs with a confidence score ranging from 3-30 (mean: 5.09; Q1: 4; Q3: 6) for screening in the present study.

Using GLGC 2013 published lipid GWAS data (TG, HDL-C and LDL-C) [6] to match our original miRSNP database by SNP, the confidence score of ~51,800 matched miRNA-related SNPs ranged from 1 to 29 (mean: 3.76; Q1: 1; Q3: 7). When the GLGC 2013 dataset was matched with trimmed miRSNP database (score ≥ 3), the confidence score of ~25,000 SNPs ranged from 3 to 29 (mean: 7.30; Q1: 5; Q3: 9). Here, we set a significance threshold ($P < 2 \times 10^{-6}$) using Bonferroni correction (N = 25,000) for miRNA fGWAS and fGWIS in the current study.

For miRNA fGWAS using GLGC 2013 data, 88 (31 independent signals, $r^2 > 0.8$) SNPs passed the threshold, and the miRNA confidence score ranged from 3-16 (mean: 7.58; Q1: 5; Q3: 10) for TG association; 110 (31 independent signals, $r^2 > 0.8$) SNPs passed the threshold, and the miRNA confidence score ranged from 3-20 (mean: 7.63; Q1: 5; Q3: 10) for HDL-C; 100 SNPs (26 independent signals, $r^2 > 0.8$) passed the threshold, and the miRNA confidence score ranged from 3-14 (mean: 7.61; Q1: 6; Q3: 10) for LDL-C. Manhattan and QQ plots of miRNA fGWAS for TG, HDL-C and LDL-C using GLGC 2013 data are presented in **Supplemental Figure 2.1.5**.

Meta-Analysis of MiRNA Functional Genome-Wide Associations on Blood Lipids Revealed Potential MiRNA-Related SNPs for Blood Lipids

We performed meta-analyses of the association between miRNA-related SNPs and blood lipid levels in 9 CHARGE participating cohorts. Meta-analysis of miRNA fGWAS identified SNPs associated with blood lipids via potential miRNA-mediated mechanisms using our pre-determined threshold at $P < 2 \times 10^{-6}$ (**Figure 2.1.2, Supplemental Figure 2.1.2**, **Table 2.1.2, Supplemental Figure 2.1.4**). Five, nine and seven individual loci ($r^2 > 0.8$) were identified for ln-TG and HDL-C and LDL-C respectively in the current study. (**Table 2.1.2**). A total of 19 individual signals were identified by previous large GWAS studies and remained significant after adjusting for BMI and diabetic status (model 2 and 3) in the current study (**Table 2.1.2, Supplemental Figure 2.1.4**). Some gene expression levels such as *RANBP10* (*RAN binding protein 10*), *NUP160* (*nucleoporin 160*), *NECTIN2* (*nectin cell adhesion molecule 2*, also known as *PVRL2*) and *LDLR* (*low density lipoprotein receptor*) were significantly associated with blood lipids (nominal *P* values) based on meta-analyses of TWAS for the association between gene expression in the blood cells and blood lipid levels (**Table 2.1.2**). The meta-analyses of complete GWAS (as opposed to the miRNA fGWAS) in the current CHARGE study were presented in **Supplemental Figure 2.1.3**.

To further confirm our findings, we present the miRNA-related SNPs for blood lipids replicated in the current study based on the following criteria -- $P < 2 \times 10^{-5}$ from the GLGC 2013 results and $P < 4 \times 10^{-4}$ using the current CHARGE miRNA fGWAS results using Bonferroni correction -- in **Supplemental Table 2.1.5 B**. A total of 39 individual signals (12, 24 and 11 ($r^2 > 0.8$) for ln-TG and HDL-C and LDL-C respectively) were selected.

Meta-Analysis of MiRNA Functional Genome-Wide Interactions with Dietary Macronutrients on Blood Lipids

In light of the limited understanding of how environmental factors interact with miRNA targeting sites to affect blood lipids, we evaluated the interactions between miRNA-related SNPs and dietary macronutrients (as environmental modulators). Two statistical meta-analysis methods were performed to analyze the cohort-level statistical interaction data. First, we used joint meta-analyses (JMA) of SNP main and interaction effects, i.e. 2 degree of freedom (2DF) test, to explore the association of each SNP with blood lipids (SNP association beta) in combination with its modulation by each dietary macronutrient (SNP-by-Diet interaction term beta). Second, we focused on meta-analyses of the interaction term (SNP-by-Diet; 1 degree of freedom (1DF)) alone to investigate the role of dietary modification on miRNA SNP main effects for blood lipid levels.

--MiRNA Functional Genome-Wide Joint Meta-Analysis of Main and Interaction Effects (2DF) Yielded Similar Loci for Blood Lipids

We aimed to discover novel loci associated with blood lipids by considering each SNP's interaction with a dietary macronutrient. The 2DF JMA method was previously demonstrated to provide greater statistical power than meta-analyses for SNP main and interactive effects alone when effects of SNP and interaction are both present [102]. Therefore, we performed a 2DF JMA test using miRNA-related SNP main effect and SNP-by-dietary macronutrient (CHO, SFA, MUFA or PUFA) interaction for each blood lipid level in 9 CHARGE cohorts. Our JMA of SNP and SNP-by-diet model 1 identified 13, 14 and 9 independent loci associated with LnTG, HDL-C and LDL-C respectively when using the pre-determined Bonferroni-corrected threshold of $P < 2 \times 10^{-6}$ (**Figure 2.1.3, Supplemental Figure 2.1.6**). Six of these loci were novel, to our knowledge, for association with blood lipids; however, they did not survive for models 2 and 3 or following sensitivity analyses. The remaining loci were all previously identified lipid loci. Beta coefficients (β) for SNP main effect were larger than those for interaction for most SNPs; thus, this may explain why most of these hits were significant for all 4 macronutrients for a blood lipid outcome, and not dependent on the interaction to drive significance. By jointly testing for SNP main effect and interaction with a macronutrient, we expected to observe a lower *P* value for the 2DF JMA test compared to its *P* value for SNP main effect alone (without interaction term), due to our expectation for increased power. However, our results did not reveal much difference between these two analyses. Among the SNPs showing lower *P* values in 2DF analyses than SNP main effect, we further removed SNPs showing inconsistent effect directions in interaction terms from 1DF and 2DF JMA. Three qualified SNPs are presented in **Table 2.1.3** and **Supplemental Figure 2.1.8**. Their corresponding *P* values for 1DF interaction were significant or marginally significant at the nominal significance level of 0.05. This observation suggests that the 2DF JMA could be more powerful when both SNP and interaction effects are present. The complete JMA (as opposed to the miRNA JMA fGWIS) in the current CHARGE study are presented in **Supplemental Figure 2.1.7**.

The strongest signal in 2DF JMA model 3 was the association between rs174546 (in *FADS1, fatty acid desaturase 1*) and fasting HDL-C (β_{SNP} ± SE: 0.024 mmol/l ± 0.021; β_{INT} ± SE: -0.0009 mmol/l ± 0.0004, $P_{JMA} = 7.49 \times 10^{-10}$) when considering the interaction with dietary CHO (**Table 2.1.3**). This suggests that the effect of HDL-C raising T (minor) allele can be attenuated by greater dietary CHO intake. By carrying 1 copy of T allele, an individual having 5 percent more dietary CHO would be expected to have 0.0047 mmol/l (0.18 mg/dl) weaker SNP effect on HDL-C compared to an individual with lower intake. An individual with 2 copies of T allele who consumes 5 percent more dietary CHO would be predicted to have 0.0094 mmol/l (0.36 mg/dl) weaker SNP effect on HDL-C compared to an individual with lower intake. In this example, the T (risk) allele was associated with lower HDL-C without interaction term (β_{SNP} ± SE: -0.020 mmol/l ± 0.003), and risk allele carriers may be deteriorated by consuming greater dietary CHO. This SNP is in strong LD with rs4246215 ($r^2 \sim 0.9$, based on 1000 Genomes Project CEU, phase 3).

In exploratory analyses, we also screened main effects [125] in CHARGE or GLGC 2013 before testing the interactions in our CHARGE cohorts (**Figure 2.1.1**). Two selection approaches are presented: (1) the SNPs that showed a suggestive or statistically significant association with blood lipid outcomes at $P < 2 \times 10^{-4}$ from the GLGC 2013 results were included in subsequent interaction analyses (**Supplemental Table 2.1.6 A**); (2) the SNPs that showed a suggestive or statistically significant association with blood lipid outcomes at $P < 2 \times 10^{-4}$ from the CHARGE miRNA fGWAS results (**Supplemental Table 2.1.5 A**) were further screened using the CHARGE miRNA fGWIS results (**Supplemental Table 2.1.6 B**). The new *P* value for significance was based on the Bonferroni correction. No SNPs passed the significance threshold based on 1DF interaction analyses using these two approaches.

--Meta-analysis of MiRNA SNPs Interactions with Dietary Macronutrients (1DF) Suggested Some New miRNA-Mediated Regulatory Mechanism

Meta-analyses of 1DF interaction analyses of miRNA fGWIS in 9 CHARGE cohorts did not identify any miRNA-related SNPs that reached our pre-determined Bonferroni-corrected threshold ($P_{INT} < 2 \times 10^{-6}$) (data not shown). We therefore explored our miRNA fGWIS results for suggestive hits using a $P_{INT} < 1 \times 10^{-4}$ (**Supplemental Table 2.1.7**). We identified 10, 11, 17 independent suggestive loci of G×E effects for LnTG, HDL-C and LDL-C respectively (**Supplemental Figure 2.1.9**). As we observed high heterogeneity across cohorts in interaction analyses, we removed SNPs showing a high level of evidence of heterogeneity ($I^2 > 75\%$ and *P* for *Q* statistic < 0.01) in model 3, and the remaining loci are presented in (**Table 2.1.4 and Supplemental Figure 2.1.11**). Since none of these interacting SNPs showed significant SNP main effects for lipids in the present study ($P > 0.05$), our interaction findings suggest that these loci are novel and possibly modified by diet. Some miRSNP host gene expression levels such as *TMEM33* (*transme mbrane protein 33*), *ANXA13* (*annexin A13*) and *TMEM2* (*transmembrane protein 2*) were found to be significantly associated with corresponding blood lipids (nominal *P* values) according to meta-analyses of the association between gene expression in the blood cells and blood lipid levels (**Table 2.1.4**). The meta-analyses of complete GWIS (as opposed to the miRNA fGWIS) in the current study are presented in **Supplemental Figure 2.1.10**.

The strongest signal from meta-analyses of interaction term in model 3 was between rs10009 (in *PPIL2, peptidylprolyl isomerase like 2*) and dietary CHO concerning fasting TG ($\beta_{INT} \pm$ SE: -0.003 ln-mmol/l ± 0.001, $P_{INT} = 3.35 \times 10^{-6}$) (**Table 2.1.4**). This SNP is in strong LD with another signal, rs1860 ($r^2 > 0.9$, based on 1000 Genomes Project CEU, phase 3) (**Table 2.1.4**). This interaction suggests that TG raising A allele carriers can be ameliorated by greater CHO intake. By carrying 1 copy of A allele, an individual having 5 percent more dietary CHO would be expected to have 0.015 ln-mmol/l weaker SNP effect compared to an individual with lower intake.

Annotation of Identified miRNA-Related Variants Generated Hypotheses for Future Studies

All miRNA-related SNPs listed in **Table 2.1.2**, **2.1.3** and **2.1.4** were annotated intensively for their biological function related to miRNA. We listed all potential (predicted and experimentally validated) regulatory miRNAs and their confidence scores from our in-

house miRSNP database for each identified SNP in **Table 2.1.5**. All miRNA-related SNPs were found to be located in the miRNA target regions, none of them were found in miRNA genes or genes involved in miRNA processing machinery. We also showed the eQTL evidence for these identified miRSNPs.

The summary of *cis*-eQTL evidence (with host genes only) for all identified/selected miRSNPs is listed in **Table 2.1.5** with notes for relevant tissues. The liver *cis*-eQTL evidence is described here. Based on GTEx Analysis Release V6p (dbGaP Accession phs000424.v6.p1), rs629301—host gene *CELSR2* (*cadherin EGF LAG seven-pass G-type receptor 2*) and rs1860—host gene *YPEL1* (*yippee like 1*) showed strong liver *cis*-eQTL. The rs629301—*CELSR2* in the liver is one of the strongest *cis*-eQTL associations (strongest is in skeletal muscle). The rs629301—*CELSR2* is also one of the strongest liver *cis*-eQTLs among nearby genes. The G (minor) allele of rs629301 was associated with higher *CELSR2* expression levels in liver ($\beta = 1.1 \pm 0.11$, $P = 2.5 \times 10^{-15}$) and lower LDL-C (**Table 2.1.2**). The G allele is predicted to provide a binding site for liver expressed hsa-miR-454-5p although the direction of allele differential gene expression was not expected (assuming such interaction suppressing the gene expression). The rs1860—host gene *YPEL1* in liver showed *cis*-eQTL association (strongest in esophagus mucosa). The rs1860—*YPEL1* is also one of the strongest liver *cis*-eQTLs among nearby genes. The G (major) allele of rs1860 was associated with higher *YPEL1* expression levels in liver ($\beta = 0.58 \pm 0.12$, $P = 3.8 \times 10^{-6}$) and a negative effect of SNP × CHO for ln-TG (**Table 2.1.4**). The function of this gene and predicted interaction with miRNAs are still unexplored in lipid metabolism.

We also found evidence for adipose *cis*-eQTL. The rs1051921—host gene *MLXIPL* (*MLX interacting protein like*) ($P = 8.6 \times 10^{-7}$), rs1109166—host gene *LCAT* (*lecithin-cholesterol acyltransferase*) ($P = 6.0 \times 10^{-6}$), rs9213—host gene *SH3YL1* (*SH3 and SYLF domain containing 1*) ($P = 2.1 \times 10^{-6}$), rs10009—host gene *PPIL2* ($P = 3.2 \times 10^{-5}$) showed subcutaneous adipose *cis*-eQTL. The rs1051921—*MLXIPL* ($P = 3.4 \times 10^{-6}$), rs9213—*SH3YL1* ($P = 2.3 \times 10^{-5}$), rs10009—*PPIL2* ($P = 4.6 \times 10^{-5}$) also showed visceral adipose *cis*-eQTL but slightly weaker than subcutaneous adipose. The rs4803—host gene *KRTCAP3* (*keratinocyte associated protein 3*) ($P = 2.2 \times 10^{-5}$) appeared in visceral but not subcutaneous adipose. The rs1051921—*MLXIPL* in adipose showed strong *cis*-eQTL associations (rs1051921—*MLXIPL* in esophagus mucosa being the strongest). The rs1051921—*MLXIPL* is also one of the strongest subcutaneous adipose *cis*-eQTLs among nearby genes. The A (minor) allele of rs1051921 was associated with higher transcription factor *MLXIPL* expression levels (but not in a linear manner) and lower ln-TG (**Table 2.1.2**). The A allele is predicted to offer a binding site for liver expressed hsa-miR-214, but how this miRNA could affect the gene and blood lipids still needs further investigation. The rs1109166—*LCAT* association was found significant in subcutaneous fat and whole blood (strongest in the sun-exposed skin from the lower leg). The rs1109166—*LCAT* is one of the strongest subcutaneous adipose *cis*-eQTLs among nearby genes. The C (minor) allele of rs1109166 was associated with higher transcription factor *LCAT* expression levels and higher HDL-C (**Table 2.1.2**). The T allele is predicted to offer a binding site for liver expressed hsa-miR-622 to lower gene expression and possibly HDL-C, but how this miRNA could affect the host gene expression and blood lipids still needs further

investigation. The rs9213—*SH3YL1* showed strong *cis*-eQTL associations in adipose, small intestine and whole blood (strongest rs9213—*SH3YL1* in esophagus mucosa). The rs9213—*SH3YL1* is also one of the strongest adipose and whole blood *cis*-eQTLs among nearby genes. The A (minor) allele of rs9213 was associated with higher *SH3YL1* expression levels in adipose, lower expression levels in the small intestine (terminal ileum) and whole blood and a negative effect of SNP × PUFA for LDL-C (**Table 2.1.4**). We hypothesize that the A allele provides the binding site for hsa-miR-155, which may be carried by LDL particles [126], to lower gene expression and its possible function on the signaling regulation close to the membrane. [127, 128] The expression of hsa-miR-155-3p was also previously shown to be decreased in white blood cells with a Mediterranean diet-based weight loss program. [129]

The rs6859—host gene *NECTIN2* showed whole blood *cis*-eQTL ($P = 8.4 \times 10^{-11}$, strongest across multiple tissues). The rs6859—*NECTIN2* is the strongest whole blood *cis*-eQTLs among nearby genes. The G (major) allele was associated with higher gene expression in whole blood and lower LDL-C. The A allele may provide binding sites for liver expressed hsa-miR-26b-3p and hsa-miR-218-5p (also found in adipose), that may decrease gene expression to modulate LDL-C.

Three SNPs in strong LD located in *ONECUT2* (*one cut homeobox 2*), which encodes a transcription factor, were found significantly interacting with PUFA for ln-TG (**Table 2.1.4**). These interactions suggest that TG raising A allele carriers might benefit from greater PUFA intake. By carrying 1 copy of the A allele, an individual having 5 percent more dietary PUFA would be expected to have 0.22 (2DF JMA)-0.25 (1DF) ln-mmol/l lower SNP effect compared to an individual consuming less PUFA. However, we did not find any significant related eQTL evidence for this SNP. The rs17831587 allele A (major) also provides a targeting site for liver expressed hsa-miR-627-3p that may affect the expression of *ONECUT2*, also shown overexpressed in the liver [130, 131], and its downstream binding genes. More studies are needed for validating this hypothesis.

2.1.5 DISCUSSION

We performed meta-analyses of fGWAS and fGWIS with macronutrients using miRNA-related SNPs (targeted subsets of the genome) for blood lipids in the CHARGE Consortium (9 studies, > 21,000 adults). Using meta-analyses of miRNA fGWAS and fGWIS, we aimed to identify SNPs that modify miRNA-target interactions affecting the regulation of blood lipid levels and to further identify SNPs that respond to an environmental factor (i.e., G×E, SNP-by-macronutrient) through the mechanism of miRNA regulation. In the current report, we suggested potential miRNA-related regulatory features for identified blood lipid-associated loci and provided supporting evidence for potential miRNA-related loci interacting with dietary macronutrients to improve our understanding of how miRSNPs affect blood lipid levels.

The current study identified fewer signals than the GLGC 2013 GWAS. One possible explanation is that our sample size is smaller than the GLGC 2013 GWAS. However, the current study offered lipid-associated SNPs with potential miRNA-mediated mechanisms to better inform functional understanding of SNPs (**Table 2.1.2**, **2.1.3** and **2.1.5** and **Supplemental Table 2.1.5 B** and **2.1.6**). More importantly, the current study yields SNPs that may be responsive to dietary macronutrients through miRNA-mediated mechanism to affect blood lipid levels (**Table 2.1.4** and **Supplemental Table 2.1.7**). Although further confirmation through experimental and epidemiological approaches are needed, these results may aid future characterization of the roles of miRNA or miRSNPs in CVD etiology and provide further insights into the biological mechanisms that underlie variation in lipid responses to diet.

Conducting genome-wide screening for genetic variants predicted to participate in a molecular mechanism would be expected to uncover functional loci associated with phenotypes of interest (fGWAS). Variants that respond to environmental factors to determine these phenotypes (fGWIS) are promising candidates for future functional studies. The miRNA-mediated regulation was selected to demonstrate these concepts in the present study. We searched meta-analysis results of GWAS and GWIS for blood lipids against our miRSNP database to identify potential allele-specific miRNA-mRNA interactions which may affect blood lipids. To our knowledge, this is the first miRNA fGWAS and fGWIS to investigate interactions between miRSNPs and dietary macronutrients for the outcome of blood lipids. We expected that our results would generate biological hypothesis and elucidate miRNA-phenotype or miRNA-environmental factor relationships. This genetically targeted (hypothesis-driven genome-wide) approach is more selective than traditional GWAS and is expected to lower the multiple testing burden by providing the hypothesis in a class of molecular regulation for blood lipids. However, we did not identify significant miRSNP-by-macronutrient interaction using the hypothesis-based significance threshold.

Several factors may have limited our ability to detect significant interactions. First, moderate to high levels of heterogeneity among study results created challenges to replicating and validating the results. Our participating cohorts were from the US and Europe. The characteristics of studies and participants were different genetically,

geographically and culturally. While the number of tested macronutrients (or percentage from the total energy) appeared similar across the studies, the foods through which macronutrients are supplied can be very different. We may expect food sources, dietary pattern, food preparation and meal eating times to vary across continents and cohorts (or even within cohorts). All of these factors and the non-macronutrient constituents of different foods may modify the effects of macronutrients on blood lipids. Dietary data are prone to measurement errors. In addition to the limitations of accurately measuring dietary intake, different assessment methods used in participating cohorts may introduce high levels of heterogeneity into meta-analysis results. Even though the measurement errors were minimized, the dietary exposures were measured at different time points, and the instruments were modified and implemented differently for each population. We investigated other modifying factors possibly contributing to the heterogeneity among studies, such as age, the time (year) during which the studies were conducted and geographical subgroups, but none of these led to clear explanations for heterogeneity. These modifying effects need further investigation.

Second, our statistical analyses for interaction test were under powered. The level of heterogeneity may increase with the number of populations/studies; therefore, analyzing GWIS in a larger number of studies, can still provide substantial challenges. Third, we did not evaluate the quality of each macronutrient and the modulation by protein intake. Different types of SFA, MUFA, PUFA and carbohydrates may have different metabolic effects and different associations with CVD. Our focus was to screen miRSNPs for interactions with macronutrients, so different energy replacement models (such as replacing SFA with PUFA) to evaluate the effect of a specific nutrient could be explored further in the future. Fourth, the observational studies cannot prove causality and can be subject to potential reverse causality. Fifth, the relationship between genetic variants associated with CVD risk factors (such as blood lipid biomarkers) and CVD is still unclear [27, 132, 133]. In the current study, we tested traditional single blood lipid biomarker, and the relevance of our findings to CVD events could be explored in the future studies.

Previous studies demonstrated that jointing SNP and SNP-by-environment interactions (2DF JMA) provided better power to identify novel complex traits associated loci that are missed when interaction terms are not considered [102, 134-136]. However, we did not obtain greater power by using the 2DF JMA test as compared to SNP main effects alone. Part of the reason might be due to the above-mentioned caveats of dietary data which showed different characteristics from other environmental risk factors, such as smoking, found in the literature. Moreover, incorporating dietary factors that yield small and/or heterogeneous effects on blood lipids may not increase our power to discover novel loci to the extent that we expected. We expect that using well-characterized environmental/dietary factors in large relatively homogeneous populations may yield more fruitful results.

For our miRNA fGWIS for interaction term, no miRSNPs passed our pre-determined Bonferroni-corrected threshold. We therefore explored our miRNA fGWIS results with a lower threshold (**Supplemental Table 2.1.7**). None of these suggestive loci reported significant in GLGC 2013 results [6] suggesting that G×E signals (interaction terms,

genetic variants whose effects are modified by environmental factors) do not depend on SNP main/marginal effects.

The current study provides miRNA-related mechanisms and hypotheses for earlier known lipid-associated genetic variants, and several examples follow below. In agreement with the expected effect on *APOA5* (*apolipoprotein A5*), rs2266788 was significantly associated with HDL-C levels in miRNA fGWAS (**Table 2.1.2**) and ln-TG and HDL-C levels in 2DF fGWIS (date not shown). MiRNAs hsa-miR-190a, hsa-miR-190b, hsa-miR-376b-5p, hsa-miR-376c-5p, hsa-miR-491-3p, hsa-miR-3201, hsa-miR-4791 were predicted to bind the protective allele, while other miRNAs hsa-miR-105-3p, hsa-miR-143-5p, hsa-miR-432-3p, hsa-miR-455-5p, hsa-miR-576-3p, hsa-miR-3944-5p, hsa-miR-4764-5p were predicted to bind its risk allele (**Table 2.1.5**). The risk allele may be further regulated by a liver expressed hsa-miR-455-5p. *NECTIN2* encodes a component of adherens junctions, and its expression levels in the atherosclerotic arterial wall were found to be positively associated with plasma cholesterol levels in human, suggesting its role in atherosclerosis development. [137] The miRSNP rs6859 A (minor) allele was associated with higher LDL-C. A life style factor (if found in future study) may benefit A carriers by elevating hsa-miR-26b-3p, hsa-miR-218-5p or hsa-miR-512-3p in relevant tissues to promote the interaction between the miRNA and its host gene *NECTIN2*. The C allele of miRSNP rs1433099 in *LDLR* was associated with higher LDL-C (**Table 2.1.2**), but it may be regulated by liver expressed hsa-miR-1307-5p (**Table 2.1.5**).

We replicated our previous findings of an association between miRSNP rs13702 in *LPL* and LnTG and HDL-C (**Table 2.1.2**) [61, 65]. However, we did not find any significant interactions with any tested macronutrients for triglycerides and HDL-C in the current meta-analyses as we had observed previously. Different characteristics of populations and their dietary fat composition may have influenced these results.

In conclusion, we demonstrated a hypothesis-driven approach in association and interaction study for blood lipid levels based on a class of functional genetic variants, miRNA-related SNPs. This approach based on SNP predicted function might also be applied to other molecular mechanisms for lipids or for other traits of interest. Our findings generate interesting hypotheses for miRNA-mediated regulation and its relationship to diet to improve blood lipids, but functional tests are needed to determine their clinical relevance.

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DISCLOSURE DECLARATION
None of the authors had a potential conflict of interest.

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Table 2.1.1. Summary characteristics of the participating CHARGE cohort studies

Study	ARIC (Atherosclerosis Risk in Communities Study)	GOLDN (Genetics of Lipid Lowering Drugs and Diet Network)	GOYA Study (Genetics of extremely overweight young adults study; ADIGEN study)	InCHIANTI (Invecchiare in Chianti, aging in the Chianti area)	Inter99 Study (Inter99 Study)	RS-I (Rotterdam Study Baseline)	RS-II (Rotterdam Study Extension of Baseline)	RS-III (Rotterdam Study Extension of Baseline)	YFS (Cardiovascular Risk in Young Finns Study)
N	6546	781	466	1125	6105	3265	2117	2045	1508
City/Country of origin	Forsyth County, NC; Jackson, MS; Minneapolis, MN; Washington County, MD; USA	Minneapolis, MN,; Salt Lake City, UT, USA	Copenhagen and surrounding regions (Frederiksborg, Roskilde, Storstroem, and West Zealand), Denmark	Tuscany, Italy	Copenhagen, Denmark	Rotterdam, Netherlands; Ommoord district	Rotterdam, Netherlands; Ommoord district	Rotterdam, Netherlands; Ommoord district	Tampere, Turku, Kuopio, Oulu, Helsinki, Finland
Age, y	53.8 (5.6)	47.7 (15.9)	45.6 (7.9)	68.3 (15.7)	46.2 (7.9)	72.4 (7.1)	64.8 (8.0)	56.0 (5.8)	37.7 (5.0)
Female, %	52.4	51.3	0	55.7	51.0	57.8	54.4	56.0	58.2
ln-TG, ln-mmol/L; mmol/L; mg/dL	0.23 (0.49); 1.26 (1.63); 111	0.26 (0.58); 1.30 (1.79); 115	0.34 (0.52): 1.40 (1.68); 124	0.19 (0.45) 1.21 (1.57); 107	0.12 (0.53); 1.13 (1.70); 100	0.32 (0.43); 1.38 (1.54); 122	0.35 (0.45); 1.42 (1.57); 126	0.28 (0.32); 1.32 (1.38); 117	0.07, (0.40); 1.07 (1.49); 95
LDL-C, mmol/L; mg/dL	3.53 (0.96); 136	3.16 (0.82); 122	4.21 (1.02); 163	3.40 (0.85); 131	3.50 (0.97); 135	3.75 (0.90); 145	3.72 (0.90); 144	3.46 (0.96); 134	3.04 (0.71); 117
HDL-C, mmol/L; mg/dL	1.34 (0.44); 52	1.21 (0.33); 47	1.29 (0.41); 50	1.43 (0.35) 55	1.43 (0.40); 55	1.39 (0.42); 54	1.37 (0.37); 53	1.45 (0.45); 56	1.35 (0.71); 52
LDL-C estimated using Friedewald (F) or measured (M)	F	M	F	F	F	F	F	F	F
Carbohydrate intake, % energy	48.2 (9.2)	48.8 (8.4)	43.5 (6.9)	51.6 (6.7)	49.1 (8.1)	43.2 (6.9)	50.2 (9.9)	49.7 (9.0)	46.1 (5.7)
Protein intake, % energy	17.7 (4.0)	15.8 (2.7)	15.7 (2.4)	15.8 (2.1)	13.8 (2.6)	16.8 (3.1)	14.9 (3.9)	15.1 (2.7)	17.5 (2.4)
Total fat intake, % energy	33.5 (6.7)	35.5 (6.8)	32.5 (5.0)	31.0 (5.1)	32.4 (7.2)	36.4 (6.2)	30.4 (9.4)	31.7 (8.1)	32.8 (4.8)
SFA intake, % energy	12.4 (3.0)	11.8 (2.6)	13.6 (2.5)	10.5 (2.3)	12.5 (3.6)	14.4 (3.2)	11.4 (3.3)	11.3 (3.1)	11.8 (2.4)
MUFA intake, % energy	12.8 (2.9)	13.3 (2.8)	9.8 (1.8)	15.5 (0.7)	10.7 (2.8)	12.3 (2.7)	10.3 (3.1)	10.7 (3.0)	11.0 (2.0)
PUFA intake, % energy	5.1 (1.5)	7.7 (2.2)	4.1 (0.7)	3.4 (0.7)	4.9 (1.5)	6.9 (2.8)	6.5 (2.5)	6.8 (2.4)	5.3 (1.1)
Energy intake, kcal	1652 (609)	2057 (893)	2418 (628)	1989 (598)	2395 (874)	1926 (503)	2357 (808)	2683 (856)	2383 (773)
BMI (kg/m^2)	26.5 (4.5)	28.3 (5.4)	30.3 (6.8)	27.2 (4.1)	26.2 (4.6)	26.8 (4.0)	27.2 (3.4)	27.8 (4.6)	25.4 (4.4)
Diabetes (%)	4.8	8.6	0.2	9.0	0.05	10.8	10.8	8.6	0.7

Values are means (SD) or percentages (%).Abbreviations: CHO, carbohydrate; SFA, saturated fat; MUFA, mono-unsaturated fat; PUFA, poly-unsaturated fat

Figure 2.1.1. Analysis flow chart

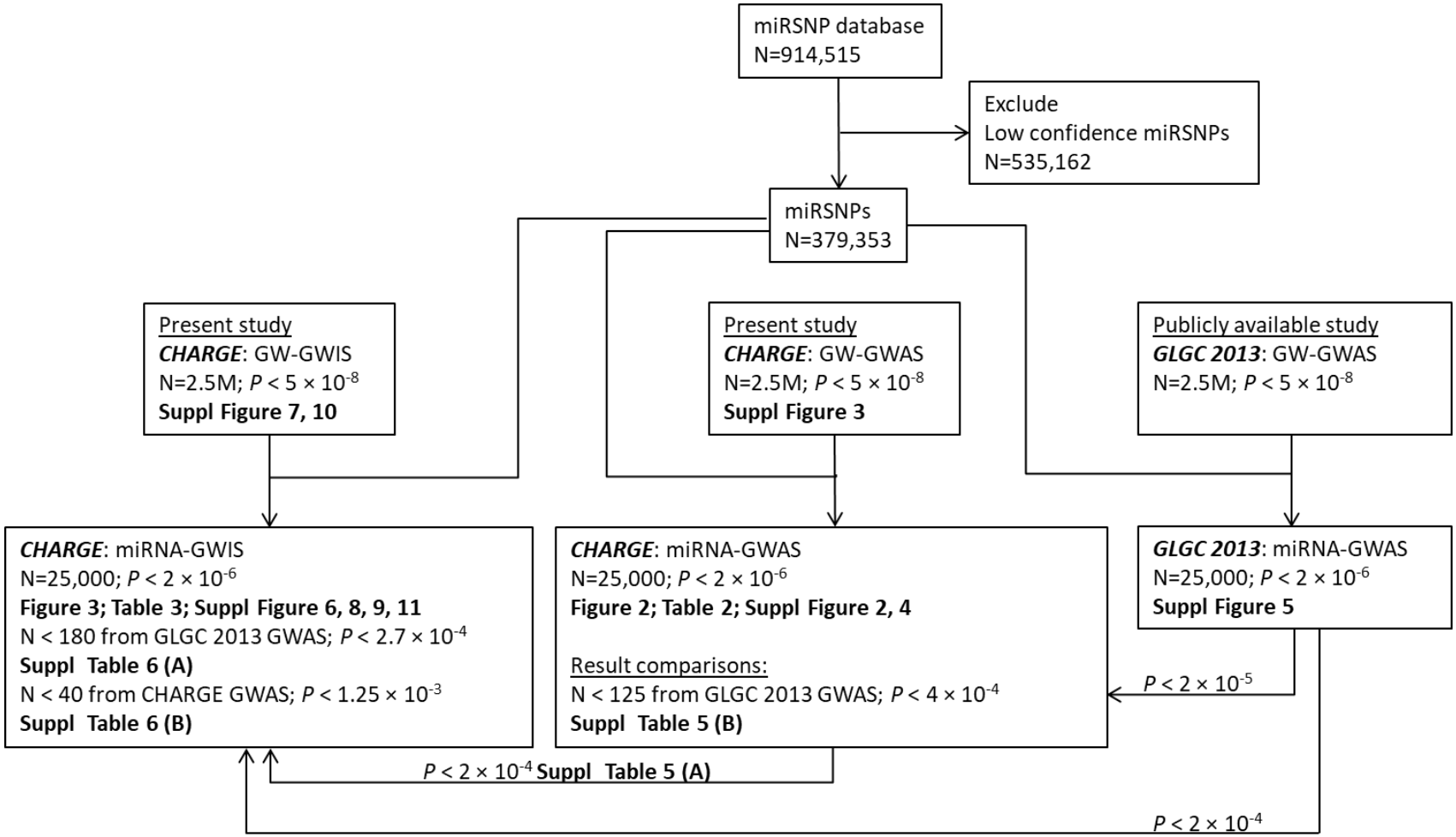
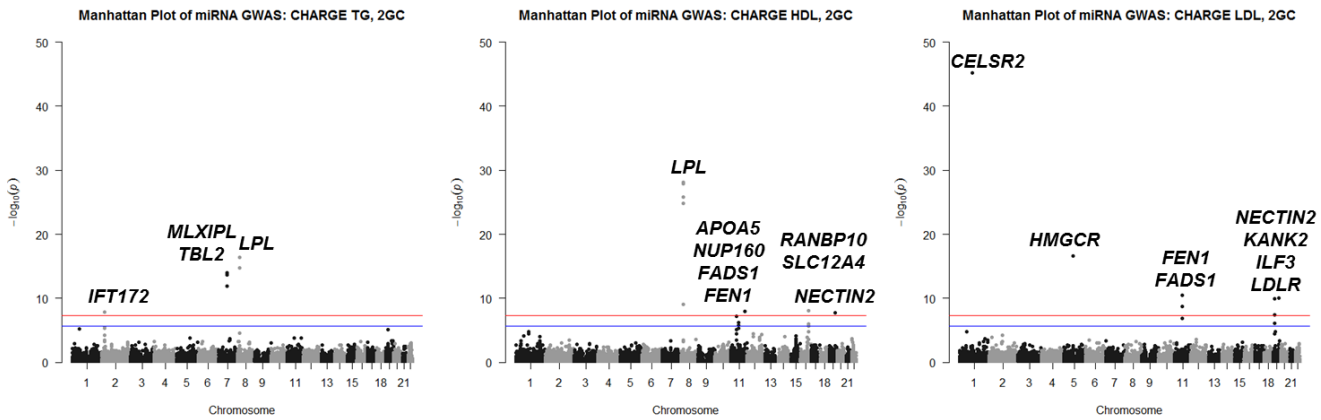


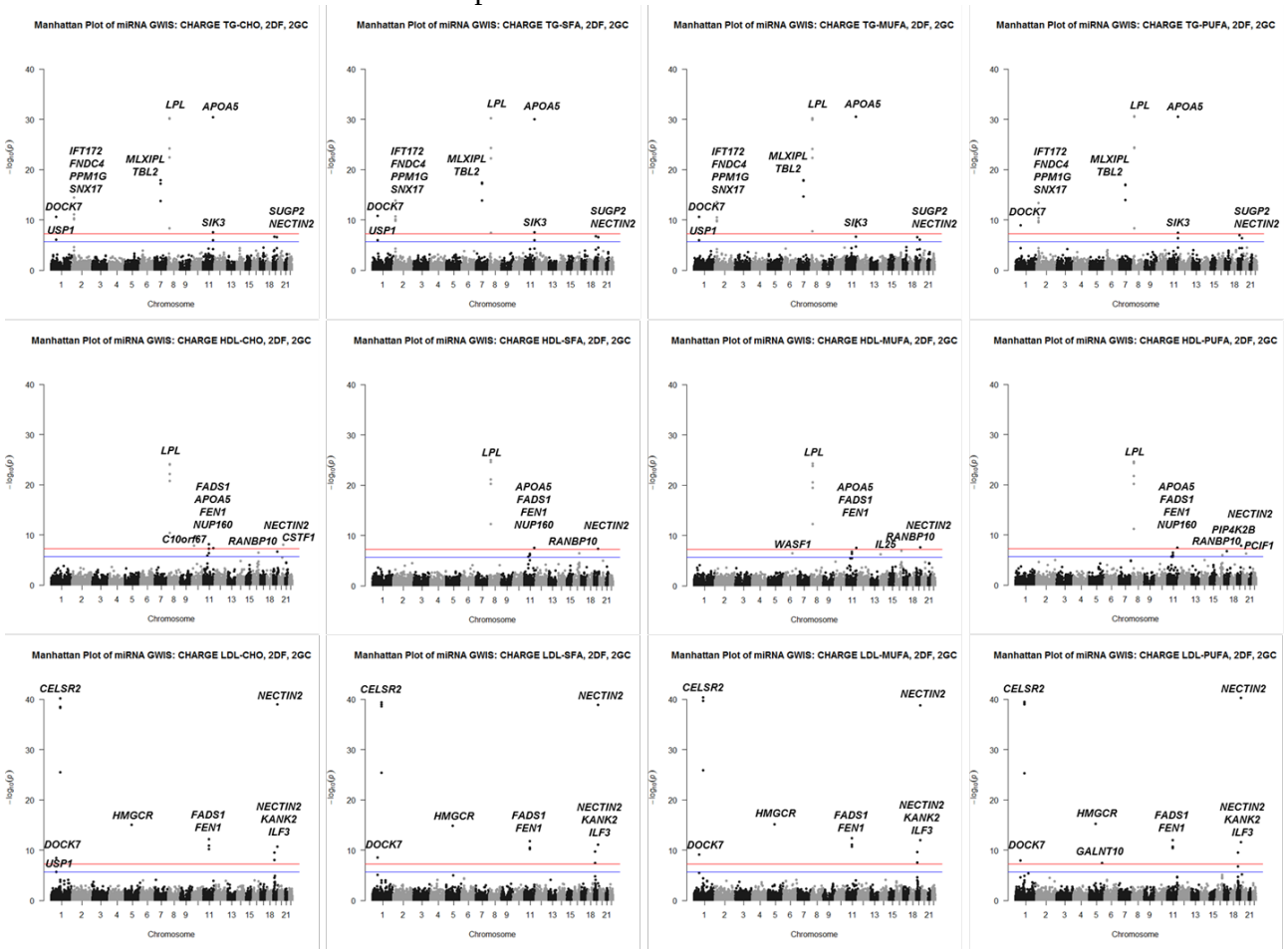
Figure 2.1.2. Manhattan plots for miRNA genome-wide association meta-analysis on blood lipid levels in the CHARGE consortium

(A) Ln-TG (B) HDL-C (C) LDL-C



Manhattan plots show the –log10(*P*-values) of ~25,000 SNPs from the miRNA GWAS meta-analysis for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex and study-specific covariates, after applying double genomic control (2GC)) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.

Figure 2.1.3. Manhattan plots for miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels in the CHARGE consortium



Manhattan plots show the –log10(*P*-values) of ~25,000 SNPs from the miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.

Table 2.1.2. MiRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-6}$

Phen	SNP	Chr	Position hg19	Gene	Alleles (minor/ major, effect)	MAF[1] (SE)	CHARGE GWAS Model 1 GC1 β (SE)	Model 1 GC1 P value	Model 1 GC2 P value	Model 2 P value	Model 3 β (SE)	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N	miR score	eQTL[2]	Gene Exp Lipid Meta P value	Global Lipids GWAS P value
ln-TG	rs15285	8	19824667	*LPL*	T/C,T	0.17(0.059)	-0.041(0.005)	1.51E-17	4.47E-17	6.41E-32	-0.067(0.006)	1.58E-32	---------	0	0.75	24065	12	++	>0.05	2.40E-173
ln-TG	rs13702	8	19824492	*LPL*	C/T,T	0.29(0.016)	0.031(0.004)	3.13E-16	1.66E-15	2.13E-35	0.057(0.005)	1.40E-35	+++++++++	0	0.86	24065	12	++	>0.05	6.60E-187
ln-TG	rs1051921	7	73007943	*MLXIPL*	A/G,A	0.20(0.013)	-0.034(0.004)	6.08E-15	9.28E-15	1.36E-24	-0.054(0.005)	8.68E-25	---------	0	0.81	24065	6	+++	NA	7.37E-96
ln-TG	rs13232120	7	72983310	*TBL2*	T/A,A	0.12(0.008)	0.040(0.005)	1.19E-14	2.17E-14	6.69E-22	0.061(0.006)	4.43E-22	+++++++++	0	0.91	24065	11	+	>0.05	4.85E-88
ln-TG	rs14415	7	72984780	*TBL2*	C/T,T	0.29(0.022)	0.027(0.004)	2.68E-13	1.18E-12	1.26E-22	0.045(0.005)	9.41E-23	+++++++++	0	0.97	24065	8		>0.05	4.92E-75
ln-TG	rs4803	2	27667297	*IFT172, KRTCAP3*	G/A,A	0.41(0.024)	0.020(0.004)	6.68E-09	1.50E-08	1.32E-17	0.037(0.004)	1.88E-18	++-++++++	0	0.58	24065	5	++	>0.05	NA (not new)
HDL-C	rs3735964	8	19824045	*LPL*	A/C,A	0.12(0.018)	0.064(0.006)	2.58E-30	8.26E-29	3.15E-38	0.066(0.005)	7.60E-38	+++++++++	38.8	0.11	25112	9	+++	>0.05	5.90E-145
HDL-C	rs1059611	8	19824563	*LPL*	C/T,T	0.12(0.018)	-0.064(0.006)	3.43E-30	1.22E-28	4.47E-38	-0.065(0.005)	1.11E-37	---------	37.4	0.12	25112	13	+++	>0.05	1.10E-144
HDL-C	rs13702	8	19824492	*LPL*	C/T,T	0.31(0.034)	-0.041(0.004)	4.10E-27	1.45E-26	6.94E-33	-0.042(0.004)	8.57E-33	---------	30.4	0.17	25112	12	++	>0.05	1.30E-160
HDL-C	rs15285	8	19824667	*LPL*	T/C,T	0.22(0.105)	0.050(0.005)	1.21E-26	1.68E-25	1.37E-34	0.053(0.004)	1.54E-34	+++++++++	17	0.29	25112	12	++	>0.05	4.20E-150
HDL-C	rs3289	8	19823192	*LPL*	C/T,T	0.03(0.007)	0.070(0.011)	4.36E-10	8.89E-10	7.42E-13	0.073(0.010)	6.02E-13	+++++++-+	34.5	0.14	25112	11		>0.05	6.44E-46
HDL-C	rs4474673	16	67758778	*RANBP10*	T/C,T	0.11(0.022)	0.032(0.006)	4.36E-09	8.93E-09	4.98E-10	0.031(0.005)	4.16E-10	+++++++++	0	0.67	25112	9	++	2.56E-09	9.34E-52
HDL-C	rs2266788	11	116660686	*APOA5*	G/A,A	0.08(0.011)	0.040(0.007)	5.96E-09	1.09E-08	2.17E-09	0.038(0.006)	8.54E-10	+++++++++	0	0.68	25112	10		>0.05	1.19E-35
HDL-C	rs6857	19	45392254	*NECTIN2*	T/C,T	0.18(0.043)	-0.030(0.005)	9.67E-09	2.01E-08	4.01E-13	-0.035(0.005)	8.97E-14	---------	50.5	0.04	25112	6	++	>0.05	2.63E-17
HDL-C	rs9909	11	47799775	*NUP160*	G/C,C	0.36(0.036)	0.020(0.004)	2.32E-08	6.73E-08	1.64E-08	0.019(0.003)	1.10E-08	+++++++++	23.1	0.24	25112	7	+++	0.0017	3.75E-20
HDL-C	rs174546	11	61569830	*FADS1*	T/C,T	0.32(0.047)	-0.019(0.004)	2.71E-07	6.53E-07	4.25E-09	-0.020(0.003)	2.32E-09	--+------	18.7	0.28	25112	8	+++	>0.05	8.30E-28
HDL-C	rs1109166	16	67977382	*SLC12A4, LCAT*	C/T,T	0.19(0.030)	-0.023(0.005)	6.62E-07	9.81E-07	1.30E-07	-0.023(0.004)	1.03E-07	--+------	0	0.60	25112	6	++++	NA	1.15E-42
HDL-C	rs4246215	11	61564299	*FEN1*	T/G,T	0.33(0.045)	-0.018(0.004)	8.48E-07	1.91E-06	1.37E-08	-0.019(0.003)	6.43E-09	--+------	0	0.47	25112	5		NA	5.40E-21
HDL-C	rs12449157	16	67708897	*GFOD2*	G/A,A	0.14(0.019)	-0.023(0.005)	1.31E-06	2.22E-06	3.43E-07	-0.023(0.004)	2.46E-07	---+-----	0	0.67	25112	8	++	NA	7.85E-37
LDL-C	rs629301	1	109818306	*CELSR2*	G/T,T	0.23(0.013)	0.145(0.010)	8.46E-48	6.87E-46	7.80E-47	0.140(0.010)	7.27E-47	+++++++++	28	0.20	23958	8	+++	>0.05	5.40E-241
LDL-C	rs12916	5	74656539	*HMGCR*	C/T,T	0.40(0.021)	-0.067(0.008)	1.01E-17	2.55E-17	1.16E-17	-0.071(0.008)	3.08E-17	--+------	58	0.01	23958	12		NA	7.79E-78
LDL-C	rs4246215	11	61564299	*FEN1*	T/G,T	0.36(0.027)	-0.059(0.009)	2.11E-11	3.39E-11	1.16E-12	-0.062(0.009)	4.40E-13	---------	0	0.54	23958	5		NA	4.47E-31
LDL-C	rs6859	19	45382034	*NECTIN2*	A/G,A	0.43(0.026)	0.055(0.008)	6.14E-11	1.00E-10	1.11E-15	0.069(0.009)	5.79E-15	+-+++++++	28.1	0.19	23958	5	++++	0.042	4.65E-88
LDL-C	rs7188	19	11275139	*KANK2*	C/A,A	0.32(0.017)	-0.064(0.01)	6.46E-11	1.22E-10	6.41E-14	-0.072(0.010)	8.28E-14	---------	0	0.51	23958	8	+++	NA	9.39E-31
LDL-C	rs174546	11	61569830	*FADS1*	T/C,T	0.34(0.028)	-0.048(0.008)	1.15E-09	2.08E-09	4.61E-14	-0.066(0.009)	1.40E-14	---------	0	0.76	23958	8	+++	>0.05	1.63E-39
LDL-C	rs13465	19	10802792	*ILF3*	A/G,A	0.06(0.008)	-0.107(0.019)	2.14E-08	3.81E-08	5.04E-09	-0.107(0.019)	1.07E-08	----+----	38.1	0.11	23957	7		NA	3.97E-30
LDL-C	rs174545	11	61569306	*FADS1*	G/C,C	0.35(0.031)	0.047(0.009)	8.71E-08	1.23E-07	2.72E-12	0.070(0.010)	8.48E-13	++++++++?	0	0.77	17853	13	+++	>0.05	7.17E-21
LDL-C	rs1433099	19	11242658	*LDLR*	T/C,T	0.27(0.008)	-0.046(0.009)	5.95E-07	7.73E-07	2.01E-06	-0.047(0.010)	1.80E-06	---------	0	0.64	23958	6	+	0.0002	2.51E-16

Abbreviations: Phen, phenotype; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; GC1, single genomic control correction; GC2, double genomic control correction; β, beta coefficient; SE, standard error; I^2, heterogeneity index; Het, heterogeneity test statistic; miR, miRNA; eQTL, expression quantitative trait loci; Exp, expression.

Additive allele mode. Basic association analyses (Model 1) adjusted for age, sex and study-specific covariates (e.g., family relationship, study site, population stratification by principal components, when applicable). Model 2 adjusted for Model 1 covariates and body mass index; and Model 3 adjusted for Model 2 covariates and diabetes mellitus status [as dichotomous variable]. Association beta coefficients are shown as β (SE). β represents the change in ln-TG, HDL-C or LDL-C (mmol/L) per each additional copy of the effect allele. Study order in direction: ARIC, GOLDN, GOYA, InCHIANTI, RSI/II/III, YFS and Inter99.

[1]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.

[2]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicate the number of the data source.

Table 2.1.3. Selected miRNA-related SNPs from 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels at $P < 2 \times 10^{-6}$

Phen	Macro-nutrient	SNP	Chr	Position_ hg19	Gene	Alleles (minor/ Major, effect)	MAF[1] (SE)	Model 1 GC1 SNP β (SE)	Model 1 GC1 Int β (SE)	Model 1 GC1 P value	Model 1 GC2 P value	Model 2 P value	Model 3 SNP β (SE)	Model 3 Int β (SE)	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	Model 3 N	miR score	eQTL[2]	Gene Exp Lipid Meta P value	Global Lipids GWAS P value
HDL-C	CHO	rs174546	11	61569830	*FADS1*	T/C,T	0.32(0.041)	0.035(0.022)	-0.0011(0.0004)	3.11E-09	7.11E-09	1.43E-09	0.024(0.021)	-0.0009(0.0004)	7.49E-10	-+--+++++	--++-----	0.22	21975	8	+++	>0.05	8.3E-28
HDL-C	CHO	rs4246215	11	61564299	*FEN1*	T/G,T	0.33(0.040)	0.030(0.022)	-0.001(0.0004)	2.23E-08	5.65E-08	5.27E-09	0.021(0.021)	-0.0009(0.0004)	2.46E-09	-+--+++++	--++-----	0.25	21975	5		NA	5.4E-21
LDL-C	MUFA	rs13465	19	10802792	*ILF3*	A/G,A	0.05(0.008)	-0.233(0.076)	0.0103(0.0062)	1.34E-08	2.73E-08	4.84E-09	-0.250(0.076)	0.0118(0.0062)	9.37E-09	----++---	++++--+++	0.27	21826	7		NA	4.0E-30

											CHARGE 2DF JMA GWIS												
Phen	Macro-nutrient	SNP	Chr	Position_ hg19	Gene	miR score	eQTL	Gene Exp Lipid Meta P value	Global Lipids GWAS P value	Alleles (minor/ Major, effect)	MAF[1] (SE)	Model 1 GC1 SNP β (SE)	Model 1 GC1 Int β (SE)	Model 1 GC1 P value	Model 1 GC2 P value	Model 2 P value	Model 3 SNP β (SE)	Model 3 Int β (SE)	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int		Model 3 Het P value	Model 3 N
HDL-C	CHO	rs174546	11	61569830	*FADS1*	8	+++	>0.050	8.3E-28	T/C,T	0.32(0.041)	0.035(0.022)	-0.0011(0.0004)	3.11E-09	7.11E-09	1.43E-09	0.024(0.021)	-0.0009(0.0004)	7.49E-10	-+--+++++	--++-----		0.22	21975
HDL-C	CHO	rs4246215	11	61564299	*FEN1*	5		NA	5.4E-21	T/G,T	0.33(0.040)	0.030(0.022)	-0.0010(0.0004)	2.23E-08	5.65E-08	5.27E-09	0.021(0.021)	-0.0009(0.0004)	2.46E-09	-+--+++++	--++-----		0.25	21975
LDL-C	MUFA	rs13465	19	10802792	*ILF3*	7		NA	4.0E-30	A/G,A	0.05(0.008)	-0.233(0.076)	0.0103(0.0062)	1.34E-08	2.73E-08	4.84E-09	-0.250(0.076)	0.0118(0.0062)	9.37E-09	----++---	++++--+++		0.27	21826

			CHARGE 1DF GWIS						
Phen	Macro-nutrient	SNP	Model 3 Int β (SE)	Model 3 P value	Model 3 Direction Int	I^2 (%)	Model 3 Het P value	Model 3 N
HDL-C	CHO	rs174546	-0.001(0.0004)	0.0192	--++-----	38.2	0.11	21975
HDL-C	CHO	rs4246215	-0.001(0.0004)	0.0272	--++-----	40.2	0.10	21975
LDL-C	MUFA	rs13465	0.012(0.0069)	0.0795	++++--+++	12.7	0.33	21826

			CHARGE GWAS					
Phen	Macro-nutrient	SNP	Model 3 SNP β (SE)	Model 3 P value	Model 3 Direction SNP	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
HDL-C	CHO	rs174546	-0.020(0.003)	2.32E-09	--+-----	18.7	0.28	25112
HDL-C	CHO	rs4246215	-0.019(0.003)	6.43E-09	--+-----	0	0.47	25112
LDL-C	MUFA	rs13465	-0.107(0.019)	1.07E-08	----+----	38.1	0.11	23957

Abbreviations: Phen, phenotype; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; 2DF, 2 degrees of freedom; JMA, joint meta-analysis; GC1, single genomic control correction; GC2, double genomic control correction; Int, interaction term; β, beta coefficient; SE, standard error; I^2, heterogeneity index; Het, heterogeneity test statistic; miR, miRNA; eQTL, expression quantitative trait loci; Exp, expression.

Additive allele mode. Basic interaction analyses (Model 1) adjusted for age, sex, total energy intake and study-specific covariates (e.g., family relationship, study site, population stratification by principal components, when applicable). Model 2 adjusted for Model 1 covariates and body mass index; and Model 3 adjusted for Model 2 covariates and diabetes mellitus status [as dichotomous variable]. Beta coefficients for SNP effect and interaction between SNP and macronutrient are shown as SNP β (SE) and Int β (SE), respectively. Int β represents the change in ln-TG, HDL-C or LDL-C (mmol/L) with each additional percentage energy of CHO, SFA, MUFA or PUFA intake, per each additional copy of the effect allele. Study order in direction: ARIC, GOLDN, GOYA, InCHIANTI, RSI/II/III, YFS and Inter99.

[1]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.

[2]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicates the number of the data sources.

Table 2.1.4. Selected potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis)

Phen	Macro-nutrient	SNP	Chr	Position_ hg19	Gene	Alleles (minor/ Major, effect)	MAF[1] (SE)	Model 1 GC1 Int B (SE)	Model 1 GC1 P value	Model 1 GC2 P value	Model 2 P value	Model 3 Int B (SE)	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N	miR score	eQTL[2]	Gene Exp Lipid Meta P value	Global Lipids GWAS P value
ln-TG	**CHO**	rs10151030	14	53506409	*DDHD1*	T/C,T	0.16(0.023)	0.004(0.001)	3.41E-06	7.85E-06	1.54E-05	0.004(0.001)	1.82E-05	++++-++-?	51.6	0.04	15939	4	++	NA	0.29
ln-TG	**CHO**	rs944450	14	53503668	*DDHD1*	T/C,T	0.14(0.020)	0.004(0.001)	5.54E-06	7.85E-06	3.81E-05	0.004(0.001)	4.27E-05	++++-++-?	59.3	0.02	15939	6	++	NA	0.54
ln-TG	**CHO**	rs10009	22	22051709	*PPIL2*	G/A,A	0.41(0.032)	-0.003(0.001)	1.22E-05	4.81E-05	4.34E-06	-0.003(0.001)	3.35E-06	-------?	0	0.85	15939	9	+++	NA	0.93
ln-TG	**CHO**	rs1860	22	22055394	*YPEL1*	A/G,A	0.39(0.031)	0.003(0.001)	8.96E-05	2.68E-04	3.45E-05	0.003(0.001)	3.49E-05	++++++++?	0	0.84	15938	6	+	>0.05	0.99
ln-TG	**PUFA**	rs17831587	18	55147888	*ONECUT2*	C/A,A	0.02(0.018)	-0.052(0.013)	5.17E-05	7.11E-05	3.55E-05	-0.050(0.012)	2.89E-05	--??-?--?	48.4	0.10	13320	8		>0.05	0.71
ln-TG	**PUFA**	rs10503013	18	55148861	*ONECUT2*	T/A,A	0.02(0.018)	-0.052(0.013)	5.25E-05	7.11E-05	3.62E-05	-0.050(0.012)	2.96E-05	--??-?--?	48	0.10	13320	10		>0.05	0.59
ln-TG	**PUFA**	rs11934922	4	41957431	*TMEM33*	G/A,A	0.02(0.002)	0.037(0.009)	5.45E-05	6.65E-05	7.13E-05	0.038(0.009)	3.93E-05	+++++++-?	22.9	0.25	15939	4		1.42E-06	0.83
ln-TG	**PUFA**	rs6566883	18	55146343	*ONECUT2*	G/A,A	0.02(0.019)	-0.052(0.013)	7.57E-05	1.03E-04	5.09E-05	-0.049(0.012)	4.37E-05	--??-?--?	54.8	0.07	13320	8		>0.05	NA
HDL-C	**SFA**	rs6436677	2	228176872	*COL4A3, LOC654841 (ncRNA)*	T/C,T	0.01(0.005)	-0.026(0.006)	6.55E-05	8.57E-05	0.00025	-0.025(0.007)	0.00034	-+?-----?	0	0.59	15657	8		>0.05	0.98
LDL-C	**CHO**	rs3732975	3	9540323	*LHFPL4*	T/C,T	0.18(0.016)	0.007(0.002)	1.67E-05	3.05E-05	1.21E-05	0.007(0.002)	1.32E-05	+++-++++?	27.4	0.21	15844	5		>0.05	0.52
LDL-C	**CHO**	rs10488193	7	12274220	*TMEM106B*	G/A,A	0.10(0.005)	0.008(0.002)	4.16E-05	5.76E-05	6.61E-06	0.009(0.002)	8.99E-06	++++++++?	15.1	0.31	15844	7	+	>0.05	0.47
LDL-C	**CHO**	rs13111	20	30922399	*KIF3B*	A/G,A	0.15(0.009)	-0.007(0.002)	8.07E-05	8.70E-05	6.07E-05	-0.007(0.002)	5.62E-05	-------?	2.2	0.41	15844	6		>0.05	0.54
LDL-C	**CHO**	rs1056776	20	30782543	*PLAGL2*	G/C,C	0.15(0.008)	0.007(0.002)	9.23E-05	1.10E-04	9.73E-05	0.007(0.002)	9.29E-05	+-+-++++?	8.7	0.36	15844	7		>0.05	0.91
LDL-C	**SFA**	rs13861	16	81079681	*ATMIN*	A/G,A	0.03(0.021)	0.053(0.012)	1.73E-05	1.96E-05	1.55E-05	0.053(0.013)	3.46E-05	++?-++++?	0	0.66	15513	9		>0.05	0.25
LDL-C	**SFA**	rs16967028	17	30190348	*UTP6*	G/A,A	0.03(0.014)	-0.040(0.010)	3.69E-05	4.18E-05	3.74E-05	-0.040(0.009)	1.89E-05	---+----?	0	0.51	15844	9		>0.05	0.52
LDL-C	**SFA**	rs11051966	12	32530580	*BICD1*	A/G,A	0.11(0.011)	0.023(0.006)	8.35E-05	8.16E-05	1.13E-05	0.025(0.006)	5.83E-06	++++++++?	0	0.92	15844	3		>0.05	0.95
LDL-C	**SFA**	rs3739283	8	124693444	*ANXA13*	C/T,T	0.29(0.026)	0.016(0.004)	8.47E-05	1.16E-04	2.19E-05	0.017(0.004)	4.09E-05	++++++++?	22.2	0.25	15844	6	+	0.0079	0.96
LDL-C	**SFA**	rs7812	8	124027562	*DERL1*	T/C,T	0.11(0.008)	-0.022(0.006)	9.32E-05	9.48E-05	3.08E-05	-0.023(0.006)	4.13E-05	-+---+--?	27.7	0.21	15844	5	++	>0.05	0.94
LDL-C	**PUFA**	rs1567487	2	220330804	*SPEG*	T/C,T	0.48(0.016)	-0.023(0.005)	9.99E-06	1.37E-05	9.51E-06	-0.023(0.005)	9.46E-06	-------?	31.3	0.18	15844	10		NA	NA
LDL-C	**PUFA**	rs9213	2	218386	*SH3YL1*	A/G,A	0.36(0.013)	-0.022(0.005)	3.12E-05	3.37E-05	8.25E-05	-0.021(0.005)	8.78E-05	-------?	28.1	0.20	15844	7	++	NA	0.40
LDL-C	**PUFA**	rs7031344	9	74299442	*TMEM2*	C/A,A	0.02(0.003)	0.055(0.014)	5.53E-05	6.51E-05	1.55E-05	0.062(0.015)	2.46E-05	+++-+-++?	0	0.56	15844	5		0.042	0.88

Table 2.1.4. Selected potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis)

Phen	Macro-nutrient	SNP	Chr	Position_ hg19	Gene	miR score	eQTL	Gene Exp Lipid Meta P value	Global Lipids GWAS P value	Alleles (minor/ Major, effect)	MAF[a] (SE)	CHARGE 1DF GWIS Model 1 GC1 Int β (SE)	Model 1 GC1 P value	Model 1 GC2 P value	Model 2 P value	Model 3 Int β (SE)	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
In-TG	CHO	rs10151030	14	53506409	*DDHD1*	4	++	NA	0.2885	T/C,T	0.16(0.023)	0.004(0.001)	3.41E-06	7.85E-06	1.54E-05	0.004(0.001)	1.82E-05	++++-++-?	51.6	0.04	15939
In-TG	CHO	rs944450	14	53503668	*DDHD1*	6	++	NA	0.5394	T/C,T	0.14(0.020)	0.004(0.001)	5.54E-06	7.85E-06	3.81E-05	0.004(0.001)	4.27E-05	++++-++-?	59.3	0.02	15939
In-TG	CHO	rs10009	22	22051709	*PPIL2*	9	+++	NA	0.9307	G/A,A	0.41(0.032)	-0.003(0.001)	1.22E-05	4.81E-05	4.34E-06	-0.003(0.001)	3.35E-06	--------?	0	0.85	15939
In-TG	CHO	rs1860	22	22055394	*YPEL1*	6	+	>0.050	0.9969	A/G,A	0.39(0.031)	0.003(0.001)	8.96E-05	2.68E-04	3.45E-05	0.003(0.001)	3.49E-05	++++++++?	0	0.84	15938
In-TG	PUFA	rs17831587	18	55147888	*ONECUT2*	8		>0.050	0.7063	C/A,A	0.02(0.018)	-0.052(0.013)	5.17E-05	7.11E-05	3.55E-05	-0.050(0.012)	2.89E-05	--??-?--?	48.4	0.10	13320
In-TG	PUFA	rs10503013	18	55148861	*ONECUT2*	10		>0.050	0.5855	T/A,A	0.02(0.018)	-0.052(0.013)	5.25E-05	7.11E-05	3.62E-05	-0.050(0.012)	2.96E-05	--??-?--?	48	0.10	13320
In-TG	PUFA	rs11934922	4	41957431	*TMEM33*	4		1.42E-06	0.8339	G/A,A	0.02(0.002)	0.037(0.009)	5.45E-05	6.65E-05	7.13E-05	0.038(0.009)	3.93E-05	+++++++-?	22.9	0.25	15939
In-TG	PUFA	rs6566883	18	55146343	*ONECUT2*	8		>0.050	NA	G/A,A	0.02(0.019)	-0.052(0.013)	7.57E-05	1.03E-04	5.09E-05	-0.049(0.012)	4.37E-05	--??-?--?	54.8	0.07	13320
HDL-C	SFA	rs6436677	2	228176872	*COL4A3, LOC654841 (ncRNA)*	8		>0.050	0.9835	T/C,T	0.01(0.005)	-0.026(0.006)	6.55E-05	8.57E-05	0.000251	-0.025(0.007)	0.000347	-+?-----?	0	0.59	15657
LDL-C	CHO	rs3732975	3	9540323	*LHFPL4*	5		>0.050	0.5243	T/C,T	0.18(0.016)	0.007(0.002)	1.67E-05	3.05E-05	1.21E-05	0.007(0.002)	1.32E-05	+++-++++?	27.4	0.21	15844
LDL-C	CHO	rs10488193	7	12274220	*TMEM106B*	7	+	>0.050	0.4686	G/A,A	0.10(0.005)	0.008(0.002)	4.16E-05	5.76E-05	6.61E-06	0.009(0.002)	8.99E-06	++++++++?	15.1	0.31	15844
LDL-C	CHO	rs13111	20	30922399	*KIF3B*	6		>0.050	0.5376	A/G,A	0.15(0.009)	-0.007(0.002)	8.07E-05	8.70E-05	6.07E-05	-0.007(0.002)	5.62E-05	--------?	2.2	0.41	15844
LDL-C	CHO	rs1056776	20	30782543	*PLAGL2*	7		>0.050	0.9091	G/C,C	0.15(0.008)	0.007(0.002)	9.23E-05	1.10E-04	9.73E-05	0.007(0.002)	9.29E-05	+-+-++++?	8.7	0.36	15844
LDL-C	SFA	rs13861	16	81079681	*ATMIN*	9		>0.050	0.2467	A/G,A	0.03(0.021)	0.053(0.012)	1.73E-05	1.96E-05	1.55E-05	0.053(0.013)	3.46E-05	++?-++++?	0	0.66	15513
LDL-C	SFA	rs16967028	17	30190348	*UTP6*	9		>0.050	0.5205	G/A,A	0.03(0.014)	-0.040(0.010)	3.69E-05	4.18E-05	3.74E-05	-0.040(0.009)	1.89E-05	---+----?	0	0.51	15844
LDL-C	SFA	rs11051966	12	32530580	*BICD1*	3		>0.050	0.9456	A/G,A	0.11(0.011)	0.023(0.006)	8.35E-05	8.16E-05	1.13E-05	0.025(0.006)	5.83E-06	++++++++?	0	0.92	15844
LDL-C	SFA	rs3739283	8	124693444	*ANXA13*	6	+	0.0079	0.9606	C/T,T	0.29(0.026)	0.016(0.004)	8.47E-05	1.16E-04	2.19E-05	0.017(0.004)	4.09E-05	++++++++?	22.2	0.25	15844
LDL-C	SFA	rs7812	8	124027562	*DERL1*	5	++	>0.050	0.9424	T/C,T	0.11(0.008)	-0.022(0.006)	9.32E-05	9.48E-05	3.08E-05	-0.023(0.006)	4.13E-05	-+---+--?	27.7	0.21	15844
LDL-C	PUFA	rs1567487	2	220330804	*SPEG*	10		NA	NA	T/C,T	0.48(0.016)	-0.023(0.005)	9.99E-06	1.37E-05	9.51E-06	-0.023(0.005)	9.46E-06	--------?	31.3	0.18	15844
LDL-C	PUFA	rs9213	2	218386	*SH3YL1*	7	++	NA	0.3952	A/G,A	0.36(0.013)	-0.022(0.005)	3.12E-05	3.37E-05	8.25E-05	-0.021(0.005)	8.78E-05	--------?	28.1	0.20	15844
LDL-C	PUFA	rs7031344	9	74299442	*TMEM2*	5		0.0415	0.8848	C/A,A	0.02(0.003)	0.055(0.014)	5.53E-05	6.51E-05	1.55E-05	0.062(0.015)	2.46E-05	+++-+-++?	0	0.56	15844

Phen	Macro-nutrient	SNP	CHARGE 2DF JMA GWIS Model 3 SNP β (SE)	Model 3 Int β (SE)	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	Model 3 N
In-TG	CHO	rs10151030	-0.161(0.038)	0.0033(0.0008)	9.06E-05	----+--+?	++++-++-?	0.00092	15939
In-TG	CHO	rs944450	-0.152(0.039)	0.0031(0.0008)	0.000542	----+--+?	++++-++-?	0.00016	15939
In-TG	CHO	rs10009	0.116(0.029)	-0.0025(0.0006)	0.000131	++++++++?	--------?	0.33	15939
In-TG	CHO	rs1860	-0.104(0.029)	0.0022(0.0006)	0.001007	--------?	++++++++?	0.40	15938
In-TG	PUFA	rs17831587	0.237(0.061)	-0.0451(0.0106)	0.000115	++??+?++?	--??-?--?	0.11	13320
In-TG	PUFA	rs10503013	0.236(0.061)	-0.045(0.0106)	0.000121	++??+?++?	--??-?--?	0.11	13320
In-TG	PUFA	rs11934922	-0.204(0.05)	0.0351(0.008)	6.98E-05	-------+?	+++++++-?	0.58	15939
In-TG	PUFA	rs6566883	0.233(0.061)	-0.0448(0.0108)	0.000153	++??+?++?	--??-?--?	0.08	13320
HDL-C	SFA	rs6436677	0.336(0.077)	-0.0266(0.0061)	6.65E-05	+-?+++++?	-+?-----?	0.61	15657
LDL-C	CHO	rs3732975	-0.306(0.073)	0.0063(0.0015)	0.000151	---+----?	+++-++++?	0.34	15844
LDL-C	CHO	rs10488193	-0.386(0.093)	0.0086(0.0019)	2.25E-05	---+----?	++++++++?	0.75	15844
LDL-C	CHO	rs13111	0.308(0.083)	-0.0062(0.0017)	0.000917	++++++++?	--------?	0.10	15844
LDL-C	CHO	rs1056776	-0.286(0.077)	0.0057(0.0016)	0.000927	-+------?	+-+-++++?	0.21	15844
LDL-C	SFA	rs13861	-0.49(0.147)	0.0418(0.0121)	0.002418	--?+----?	++?-++++?	0.21	15513
LDL-C	SFA	rs16967028	0.441(0.110)	-0.0367(0.0088)	0.000174	+++-++++?	---+----?	0.43	15844
LDL-C	SFA	rs11051966	-0.251(0.064)	0.0215(0.0052)	0.000128	--------?	++++++++?	0.92	15844
LDL-C	SFA	rs3739283	-0.135(0.048)	0.0112(0.0037)	0.01113	-+------?	++++++++?	0.042	15844
LDL-C	SFA	rs7812	0.251(0.066)	-0.0181(0.0051)	0.000489	+-+++-++?	-+---+--?	0.091	15844
LDL-C	PUFA	rs1567487	0.116(0.028)	-0.0188(0.0046)	0.000177	++++++++?	--------?	0.22	15844
LDL-C	PUFA	rs9213	0.098(0.028)	-0.0154(0.0046)	0.002465	++++++++?	--------?	0.27	15844
LDL-C	PUFA	rs7031344	-0.217(0.082)	0.0438(0.0125)	0.001027	---+-+--?	+++-+-++?	0.50	15844

Phen	Macro-nutrient	SNP	CHARGE GWAS Model 3 SNP B (SE)	Model 3 P value	Model 3 Direction SNP	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
In-TG	CHO	rs10151030	-0.005(0.006)	0.47	-+----++?	60.6	0.013	17953
In-TG	CHO	rs944450	-0.004(0.007)	0.54	-++---++?	60.8	0.013	17953
In-TG	CHO	rs10009	-0.002(0.005)	0.72	+++---++?	20	0.27	17953
In-TG	CHO	rs1860	0.001(0.005)	0.90	-+-++--?	22.3	0.25	17952
In-TG	PUFA	rs17831587	-0.011(0.02)	0.58	-+?---++?	0	0.75	17485
In-TG	PUFA	rs10503013	-0.011(0.02)	0.58	-+?---++?	0	0.75	17485
In-TG	PUFA	rs11934922	-0.003(0.018)	0.89	+---+++-?	0	0.67	17953
In-TG	PUFA	rs6566883	-0.013(0.02)	0.53	-+?---++?	0	0.71	17485
HDL-C	SFA	rs6436677	0.008(0.017)	0.61	+--+-+--+?	26.6	0.22	19004
LDL-C	CHO	rs3732975	-0.0001(0.013)	0.99	-+---+++?	0	0.47	17853
LDL-C	CHO	rs10488193	0.021(0.016)	0.19	++-+++-+?	0	0.98	17853
LDL-C	CHO	rs13111	0.017(0.014)	0.23	+--+++++?	5	0.39	17853
LDL-C	CHO	rs1056776	-0.022(0.013)	0.09	--+----?	0	0.52	17853
LDL-C	SFA	rs13861	-0.013(0.032)	0.69	-+++--+?	66	0.0045	17853
LDL-C	SFA	rs16967028	-0.012(0.027)	0.67	-++---++?	0	0.55	17853
LDL-C	SFA	rs11051966	0.001(0.015)	0.93	++++----?	0	0.92	17853
LDL-C	SFA	rs3739283	0.006(0.011)	0.61	-+-+--++?	3.4	0.40	17853
LDL-C	SFA	rs7812	0.025(0.015)	0.10	++++++--?	29.9	0.19	17853
LDL-C	PUFA	rs1567487	0.001(0.010)	0.96	++++---++?	28	0.20	17853
LDL-C	PUFA	rs9213	0.009(0.010)	0.35	+++-+-++?	0	0.98	17853
LDL-C	PUFA	rs7031344	0.066(0.035)	0.06	++++++++?	0	0.97	17853

Table 2.1.4. Selected potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis (continued)

Abbreviations: Phen, phenotype; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; 1DF, 1 degree of freedom; GC1, single genomic control correction; GC2, double genomic control correction; Int, interaction term; β, beta coefficient; SE, standard error; I^2, heterogeneity index; Het, heterogeneity test statistic; miR, miRNA; eQTL, expression quantitative trait loci; Exp, expression.

Additive allele mode. Basic interaction analyses (Model 1) adjusted for age, sex, total energy intake and study-specific covariates (e.g., family relationship, study site, population stratification by principal components, when applicable). Model 2 adjusted for Model 1 covariates and body mass index; and Model 3 adjusted for Model 2 covariates and diabetes mellitus status [as dichotomous variable]. Beta coefficients for interaction between SNP and macronutrient are shown as Int β (SE). Int β represents the change in ln-TG, HDL-C or LDL-C (mmol/L) with each additional percentage energy of CHO, SFA, MUFA or PUFA intake, per each additional copy of the effect allele. Study order in direction: ARIC, GOLDN, GOYA, InCHIANTI, RSI/II/III, YFS and Inter99.
[1]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.
[2]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicate the number of the data sources.

Table 2.1.5. MiRNA annotation for selected miRNA-related SNPs from miRNA GWAS and GWIS

SNP	Gene	Chr	Position	Alleles (minor/ major, effect)	EAF[1]	DNA Allele 1 (minor)[2]	DNA Allele 2 (major)[2]	Gene Exp (L,A,I)[3]	miR score	Potential regulatory miRNA for A1	Potential regulatory miRNA for A2	miRNA Exp[4]	eQTL[5]
rs629301	*CELSR2*	1	109818306	G/T,T	0.77	G	T	LLL	8	hsa-miR-138-2-3p|hsa-miR-454-5p|hsa-miR-652-5p	hsa-miR-1279|hsa-miR-3145-3p	hsa-miR-454-5p (L)	+++ (L)
rs9213	*SH3YL1*	2	218386	A/G,A	0.35	A (T)	G (C)	LLM	7	hsa-miR-155-3p|hsa-miR-187-5p|hsa-miR-549a|hsa-miR-618	hsa-miR-4431		++ (A*,I,B)
rs4803	*IFT172, KRTCAP3*	2	27667297	G/A,A	0.59	G	A	LLL	5	NA	hsa-miR-606		++ (A*,B)
rs1567487	*SPEG*	2	220330804	T/C,T	0.48	T	C	LLL	10	hsa-miR-552	hsa-miR-339-3p|hsa-miR-657|hsa-miR-3665|hsa-miR-6090	hsa-miR-339-3p (L)	
rs6436677	*COL4A3, LOC654841 (ncRNA)*	2	228176872	T/C,T	0.01	T	C	LLL	8	hsa-miR-197-3p|hsa-miR-6511b-3p	hsa-miR-142-3p|hsa-miR-6073	hsa-miR-142-3p (L)	
rs3732975	*LHFPL4*	3	9540323	T/C,T	0.18	T (A)	C (G)	LLL	5	hsa-miR-299-3p|hsa-miR-4265|hsa-miR-4296|hsa-miR-4322	hsa-miR-132-5p		
rs11934922	*TMEM33*	4	41957431	G/A,A	0.98	G	A	LLL	4	NA	hsa-miR-4699-5p		
rs12916	*HMGCR*	5	74656539	C/T,T	0.60	C	T	LLL	12	hsa-miR-342-5p|hsa-miR-608|hsa-miR-1207-5p|hsa-miR-1909-3p|hsa-miR-4710|hsa-miR-4763-3p|hsa-miR-6722-3p|hsa-miR-6782-5p	hsa-miR-122-5p|hsa-miR-665|hsa-miR-921|hsa-miR-4433-3p|hsa-miR-4433b-3p|hsa-miR-4722-5p	hsa-miR-122-5p (L)	
rs10488193	*TMEM106B*	7	12274220	G/A,A	0.90	G	A	LLL	7	hsa-miR-188-3p|hsa-miR-191-5p|hsa-miR-662|hsa-miR-1260a|hsa-miR-1260b|hsa-miR-3156-3p	hsa-miR-490-5p|hsa-miR-875-3p|hsa-miR-3148|hsa-miR-3688-3p|hsa-miR-6124	hsa-miR-191-5p (L)	+ (B)
rs13232120	*TBL2*	7	72983310	T/A,A	0.88	T (A)	A (T)	LLL	11	hsa-miR-142-3p|hsa-miR-145-3p|hsa-miR-384|hsa-miR-648|hsa-miR-5571-3p|hsa-miR-7975	hsa-miR-595|hsa-miR-3691-3p|hsa-miR-6513-3p	hsa-miR-142-3p (L), hsa-miR-145-3p (L)	+ (B)
rs14415	*TBL2*	7	72984780	C/T,T	0.71	C (G)	T (A)	LLL	8	hsa-miR-122-3p|hsa-miR-339-3p|hsa-miR-503-5p|hsa-miR-646	hsa-miR-33b-3p|hsa-miR-34a-5p|hsa-miR-34c-5p|hsa-miR-148a-3p|hsa-miR-148b-3p|hsa-miR-152|hsa-miR-371a-3p|hsa-miR-371b-3p|hsa-miR-449a|hsa-miR-449b-5p|hsa-miR-515-3p|hsa-miR-519e-3p|hsa-miR-4519|hsa-miR-4659a-5p|hsa-miR-4659b-5p	hsa-miR-122-3p (L), hsa-miR-339-3p (L), hsa-miR-34a-5p (AL), hsa-miR-148a-3p (L), hsa-miR-148b-3p (L), hsa-miR-152 (L)	
rs1051921	*MLXIPL*	7	73007943	A/G,A	0.20	A (T)	G (C)	HMM	6	hsa-miR-214-3p|hsa-miR-455-3p|hsa-miR-761|hsa-miR-1910|hsa-miR-4274	hsa-miR-4321|hsa-miR-4746-5p	hsa-miR-214-3p (L)	+++ (A*,B)
rs3289	*LPL*	8	19823192	C/T,T	0.97	C	T	LHL	11	hsa-miR-145-5p|hsa-miR-935|hsa-miR-5195-3p	NA	hsa-miR-145-5p (L)	
rs3735964	*LPL*	8	19824045	A/C,A	0.11	A	C	LHL	9	hsa-miR-568	hsa-miR-1277-3p|hsa-miR-5197-3p		+++ (A,B)
rs13702	*LPL*	8	19824492	C/T,T	0.71	C	T	LHL	12	hsa-miR-518a-5p|hsa-miR-527|hsa-miR-545-3p|hsa-miR-548p	hsa-miR-7-1-3p|hsa-miR-7-2-3p|hsa-miR-410 (V)|hsa-miR-495-3p|hsa-miR-520d-5p|hsa-miR-524-5p	hsa-miR-410 (AL)	++ (B)
rs1059611	*LPL*	8	19824563	C/T,T	0.89	C	T	LHL	13	hsa-miR-299-5p|hsa-miR-1468-5p	hsa-miR-136-5p (V)	hsa-miR-136-5p (AL)	+++ (A,B)
rs15285	*LPL*	8	19824667	T/C,T	0.18	T	C	LHL	12	hsa-miR-382-5p|hsa-miR-495-5p	hsa-miR-219-1-3p|hsa-miR-219a-1-3p|hsa-miR-571|hsa-miR-759|hsa-miR-921|hsa-miR-3174|hsa-miR-5586-3p		++ (B)
rs7812	*DERL1*	8	124027562	T/C,T	0.11	T	C	LMM	5	hsa-miR-431-5p|hsa-miR-511-5p|hsa-miR-643	hsa-miR-6818-3p	hsa-miR-511-5p (AL)	++ (B)
rs3739283	*ANXA13*	8	124693444	C/T,T	0.71	C	T	LLH	6	hsa-miR-4484|hsa-miR-6070	hsa-miR-218-1-3p|hsa-miR-876-3p		+
rs7031344	*TMEM2*	9	74299442	C/A,A	0.98	C	A	LLL	5	hsa-miR-3189-5p|hsa-miR-4758-3p|hsa-miR-5699-5p	NA		
rs9909	*NUP160*	11	47799775	G/C,C	0.66	G (C)	C (G)	LLL	7	hsa-miR-3976|hsa-miR-5186	hsa-let-7f-2-3p|hsa-miR-10b-3p|hsa-miR-1185-1-3p|hsa-miR-1185-2-3p|hsa-miR-5683	hsa-let-7f-2-3p (AL), hsa-miR-10b (L)	+++ (A,B)
rs4246215	*FEN1*	11	61564299	T/G,T	0.36	T	G	LLL	5	hsa-miR-643|hsa-miR-3149|hsa-miR-3713	hsa-miR-6818-3p		
rs174545	*FADS1*	11	61569306	G/C,C	0.66	G (C)	C (G)	MML	13	hsa-miR-106b-3p|hsa-miR-124-3p|hsa-miR-506-3p|hsa-miR-605-3p|hsa-miR-1253|hsa-miR-3154|hsa-miR-3622a-5p|hsa-miR-3910|hsa-miR-4423-3p|hsa-miR-5582-5p|hsa-miR-6126|hsa-miR-6770-5p	hsa-miR-181a-2-3p (V)|hsa-miR-449b-3p|hsa-miR-4252|hsa-miR-4691-3p|hsa-miR-4786-3p|hsa-miR-6509-3p	hsa-miR-106b-3p (L), hsa-miR-124-3p (L), hsa-miR-181a-2-3p (AL)	+++ (A*,B)
rs174546	*FADS1*	11	61569830	T/C,T	0.34	T (A)	C (G)	MML	8	hsa-miR-9-5p|hsa-miR-1251-3p|hsa-miR-6071|hsa-miR-6728-3p	hsa-miR-212-5p|hsa-miR-3189-3p|hsa-miR-4312|hsa-miR-5001-3p	hsa-miR-212-5p (AL)	+++ (A*,B)
rs2266788	*APOA5*	11	116660686	G/A,A	0.93	G (C)	A (T)	HLL	10	hsa-miR-105-3p|hsa-miR-143-5p|hsa-miR-432-3p|hsa-miR-455-5p|hsa-miR-576-3p|hsa-miR-3944-5p|hsa-miR-4764-5p	hsa-miR-190a|hsa-miR-190b|hsa-miR-376b-5p|hsa-miR-376c-5p|hsa-miR-491-3p|hsa-miR-3201|hsa-miR-4791	hsa-miR-455-5p (L)	
rs11051966	*BICD1*	12	32530580	A/G,A	0.11	A	G	LLL	3	hsa-miR-2355-3p|hsa-miR-3912-5p|hsa-miR-4646-3p|hsa-miR-8068	NA		
rs944450	*DDHD1*	14	53503668	T/C,T	0.14	T	C	LLL	6	hsa-miR-554|hsa-miR-26b-3p|hsa-miR-182-3p	hsa-miR-145-5p|hsa-miR-5195-3p|hsa-miR-622|hsa-miR-3925-3p|hsa-miR-3180-5p	hsa-miR-26b-3p (L), hsa-miR-145-5p (L), hsa-miR-622 (L)	++
rs10151030	*DDHD1*	14	53506409	T/C,T	0.16	T	C	LLL	4	hsa-miR-1277-5p	hsa-miR-582-5p		++
rs12449157	*GFOD2*	16	67708897	G/A,A	0.84	G (C)	A (T)	MLL	8	hsa-miR-125a-3p|hsa-miR-214-3p|hsa-miR-552|hsa-miR-657|hsa-miR-761|hsa-miR-764|hsa-miR-3665|hsa-miR-4792	hsa-miR-556-5p|hsa-miR-922|hsa-miR-1245b-3p|hsa-miR-4468	hsa-miR-214-3p (L), hsa-miR-4792 (L)	++ (B)

SNP	Gene	Chr	Position	Alleles (minor/ major, effect)	EAF[1]	DNA Allele 1 (minor)[2]	DNA Allele 2 (major)[2]	Gene Exp (L,A,I)[3]	miR score	Potential regulatory miRNA for A1	Potential regulatory miRNA for A2	miRNA Exp[4]	eQTL[5]
rs4474673	*RANBP10*	16	67758778	T/C,T	0.12	T (A)	C (G)	LLL	9	hsa-miR-297|hsa-miR-643|hsa-miR-675-3p|hsa-miR-3149|hsa-miR-6844	hsa-miR-450b-5p|hsa-miR-507|hsa-miR-557|hsa-miR-3680-3p|hsa-miR-4666b|hsa-miR-5011-3p		++ (B)
rs1109166	*SLC12A4, LCAT*	16	67977382	C/T,T	0.83	C (G)	T (A)	MHM, HMM	6	hsa-miR-221-5p|hsa-miR-596|hsa-miR-661|hsa-miR-6849-3p	hsa-miR-622	hsa-miR-221-5p (AL), hsa-miR-622 (L)	++++ (A*,B)
rs13861	*ATMIN*	16	81079681	A/G,A	0.03	A	G	LLL	9	NA	hsa-miR-3622a-5p|hsa-miR-4423-3p|hsa-miR-5582-5p		
rs16967028	*UTP6*	17	30190348	G/A,A	0.97	G	A	LLL	9	hsa-miR-200b-3p|hsa-miR-200c-3p|hsa-miR-429|hsa-miR-452-5p|hsa-miR-892c-3p|hsa-miR-4676-3p	hsa-miR-138-2-3p|hsa-miR-205-3p|hsa-miR-8084	hsa-miR-200b-3p (L), hsa-miR-200c-3p (L), hsa-miR-429 (L), hsa-miR-205-3p (L)	
rs6566883	*ONECUT2*	18	55146343	G/A,A	0.97	G	A	MLL	8	hsa-miR-642a-5p|hsa-miR-1470|hsa-miR-4446-5p|hsa-miR-4667-3p|hsa-miR-4755-5p|hsa-miR-5006-3p	hsa-miR-3124-3p|hsa-miR-3667-3p|hsa-miR-6734-3p|hsa-miR-6826-3p|hsa-miR-6868-3p		
rs17831587	*ONECUT2*	18	55147888	C/A,A	0.97	C	A	MLL	8	hsa-miR-26b-3p|hsa-miR-1208|hsa-miR-2117|hsa-miR-4273|hsa-miR-7156-5p	hsa-miR-627-3p|hsa-miR-4768-5p|hsa-miR-5003-3p|hsa-miR-6809-3p|hsa-miR-6833-3p	hsa-miR-26b-3p (L), hsa-miR-627-3p (L)	
rs10503013	*ONECUT2*	18	55148861	T/A,A	0.97	T (A)	A (T)	MLL	10	hsa-miR-5571-5p	hsa-miR-200b-3p|hsa-miR-200c-3p|hsa-miR-369-3p|hsa-miR-374a-5p|hsa-miR-374b-5p|hsa-miR-429|hsa-miR-5692b|hsa-miR-5692c|hsa-miR-8084	hsa-miR-200b-3p (L), hsa-miR-200c-3p (L), hsa-miR-374a-5p (L), hsa-miR-374b-5p (L), hsa-miR-429 (L)	
rs13465	*ILF3*	19	10802792	A/G,A	0.06	A	G	LLL	7	hsa-miR-642b-5p|hsa-miR-670|hsa-miR-670-5p|hsa-miR-1202|hsa-miR-4446-5p|hsa-miR-4722-3p|hsa-miR-4755-5p|hsa-miR-4755-3p|hsa-miR-5006-5p|hsa-miR-5006-3p|hsa-miR-6727-3p|hsa-miR-6752-3p	hsa-miR-3679-3p|hsa-miR-4258|hsa-miR-6763-3p		
rs1433099	*LDLR*	19	11242658	T/C,T	0.27	T	C	LLL	6	hsa-miR-199a-5p|hsa-miR-199b-5p|hsa-miR-5190	hsa-miR-1307-5p	hsa-miR-199a-5p (L), hsa-miR-1307-5p (L)	+ (B)
rs7188	*KANK2*	19	11275139	C/A,A	0.69	C (G)	A (T)	LMM	8	NA	hsa-miR-573|hsa-miR-595|hsa-miR-1252-5p|hsa-miR-4280		+++ (A*,B)
rs6859	*NECTIN2*	19	45382034	A/G,A	0.43	A	G	MMM	5	hsa-miR-26b-3p|hsa-miR-218-5p|hsa-miR-512-3p	hsa-miR-371a-3p|hsa-miR-455-5p|hsa-miR-550b-2-5p	hsa-miR-26b-3p (L), hsa-miR-218-5p (AL), hsa-miR-455-5p (L)	++++ (A,B)
rs6857	*NECTIN2*	19	45392254	T/C,T	0.17	T	C	MMM	6	hsa-miR-18b-3p|hsa-miR-320a|hsa-miR-320b|hsa-miR-320c|hsa-miR-320d|hsa-miR-320e (V)	hsa-miR-645|hsa-miR-3929|hsa-miR-4419b|hsa-miR-4478|hsa-miR-4505|hsa-miR-5787	hsa-miR-18b-3p (L); hsa-miR-320a (L); hsa-miR-320e (AL)	++ (B)
rs1056776	*PLAGL2*	20	30782543	G/C,C	0.85	G	C	LLL	7	hsa-miR-1243|hsa-miR-3654	hsa-miR-3681-5p|hsa-miR-6849-5p		
rs13111	*KIF3B*	20	30922399	A/G,A	0.15	A	G	LLM	6	hsa-miR-153-5p|hsa-miR-2355-3p|hsa-miR-3912-5p|hsa-miR-4646-3p	hsa-miR-1250-3p	hsa-miR-153-5p (AL)	
rs10009	*PPIL2*	22	22051709	G/A,A	0.60	G	A	LLL	9	hsa-miR-1234-3p|hsa-miR-7107-5p	hsa-miR-2392|hsa-miR-6735-3p		+++ (A*,B)
rs1860	*YPEL1*	22	22055394	A/G,A	0.38	A (T)	G (C)	LLL	6	hsa-miR-607	hsa-miR-1252|hsa-miR-1298		+ (L)

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome; EAF, effect allele frequency; Exp, expression; L,A,I, gene expression in liver, adipose, small intestine tissues; miR, miRNA; eQTL, expression quantitative trait loci.

[1]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.

[2]DNA alleles A1 and A2 refer to the alleles on the strand which transcribes the mRNA.

[3]Gene expression levels in liver, adipose, small intestine tissues. L, M, H refer to low, medium and high respectively.

[4]miRNA present in adipose (A) and/or liver (L).

[5]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicate the number of the data source. L, A, I, B refer to liver, adipose, small intestine and blood respectively. Asterisk marks strong evidence for the specific tissue.

Supplemental Information

Supplemental Tables

Supplemental Table 2.1.1. Participating CHARGE cohort study descriptions and acknowledgments
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Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids
(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium
(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:
MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$)
Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis
(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$)
(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$)
Supplemental Table 2.1.7. Full list of potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis)
Supplemental Table 2.1.8. CHARGE authors and affiliations

Abbreviations for Supplemental Tables:

Cohort study name (study acronym): Atherosclerosis Risk in Communities Study (ARIC), Genetics of Lipid Lowering Drugs and Diet Network (GOLDN), Genetics of extremely overweight young adults (GOYA) study, Invecchiare in Chianti, aging in the Chianti area (InCHIANTI), Inter99, Rotterdam Study (RS) and the Young Finns Study (YFS).

CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; GLGC, Global Lipid Genetics Consortium; SNP, Single Nucleotide Polymorphism; GWAS, genome-wide association study; GWIS, GWAS, genome-wide interaction study**;** TG, triglycerides; HDL-C or HDL, high-density lipoprotein cholesterol; LDL-C or LDL, low-density lipoprotein cholesterol, HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; NA, not available; PCA, principal component analysis; FFQ, food frequency questionnaire.

Supplementary Figures

Supplemental Figure 2.1.1. Proportion of different miRNA confidence levels of dbmiRSNP
Supplemental Figure 2.1.2. QQ plots for miRNA genome-wide association meta-analysis on blood lipid levels in the CHARGE consortium
Supplemental Figure 2.1.3. Manhattan and QQ plots for genome-wide association meta-analysis on blood lipid levels in the CHARGE consortium
Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium
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Supplemental Figure 2.1.6. QQ plots for miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels in the CHARGE consortium
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Supplemental Figure 2.1.8. Forest plots for the selected SNPs from miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels (model 3) in the CHARGE consortium
Supplemental Figure 2.1.9. Manhattan and QQ plots for miRNA genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium
Supplemental Figure 2.1.10. Manhattan and QQ plots for genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium
Supplemental Figure 2.1.11. Forest plots for the selected SNPs from miRNA genome-wide interaction meta-analysis (1 degree of freedom) with macronutrients on blood lipid levels (model 3) in the CHARGE consortium

Abbreviations for Supplemental Figures:
miRNA, microRNA; SNP, Single Nucleotide Polymorphism; dbmiRSNP, miRSNP database; QQ plot, quantile-quantile plot; GWAS, genome-wide association study; GWIS, GWAS, genome-wide interaction study; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CHO, carbohydrates, SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Supplemental Table 2.1.1. Participating CHARGE cohort study descriptions and acknowledgements

Cohort	Country	Study Descriptions and Acknowledgements	Web Link and Key Study-Related Reference (PMID)
Atherosclerosis Risk In Communities (ARIC)	USA	The ARIC study is a population-based cohort study designed to study established and suspected risk factors for atherosclerosis and community trends in coronary heart disease. In 1987-89, baseline data was collected from 15,792 adults, aged 45–64 years, living in 4 U.S. communities (Forsyth County, NC; Jackson, MI; northwest Minneapolis suburbs, MN; Washington County, MD). The baseline exam information was collected from Americans of European descent (whites), African Americans, and a small number of other ethnicities. Information consent was obtained from all individuals before enrollment, and 15,792 adults were enrolled (8,710 women and 7,082 men). A total of 6,546 Caucasian adults with available valid outcome (plasma lipids), genotype data, dietary information and consent to share genetic data were eligible for the current analysis. The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C and HHSN268201100012C), N01-HC-55015, N01-HC-55016, N01-C-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute Contract U01HG004402; and National Institutes of Health Contract HHSN268200625226C. Infrastructure was partly supported by Grant No. UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. The authors thank the staff and participants of the ARIC Study for their important contributions.	http://www.cscc.unc.edu/aric/ PMID: 2646917 [1]
Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	USA	The GOLDN study is a population-based study with a primary aim of characterizing the genetic components of triglyceride response following a high fat meal and hypolipidemic drug, fenofibrate. GOLDN is part of the Program for Genetic Interactions (PROGENI) Network, a group of NIH-funded intervention studies of gene-environmental interactions. Study participants were re-recruited from the ongoing National Heart and Lung and Blood Institutes (NHLBI) Family Heart Study (FHS) from 2 field centers in Minneapolis, MN and Salt Lake City, UT from 2002-2009. The overall population consists of 1,120 white men and women of Northern European origin. The protocol was approved by the Institutional Review Boards at the University of Minnesota, University of Utah, Tufts University/New England Medical Center and the University of Alabama at Birmingham. Written informed consent was obtained from all participants. For the current study, a total of 781 individuals had valid outcome (baseline plasma lipids), genotype and covariates data available for association analyses, and 758 individuals had additional valid dietary data for interaction analyses.	https://dsgweb.wustl.edu/goldn/ PMID: 8651220 [2]; 17446329 [3]

Cohort	Country	Study Descriptions and Acknowledgements	Web Link and Key Study-Related Reference (PMID)
		The authors are grateful to the study participants, the staff of the GOLDN study for the assistance in data collection and management. This study was supported by the NHLBI [grants U01HL072524 (Genetic and Environmental Determinants of Triglycerides), NHLBI R01 HL091357 (Genomewide Association Study of Lipid Response to Fenofibrate and Dietary Fat), HL54776, and HL078885 and by contracts 53-K06-5-10 and 58-1950-9-001 from the USDA, Agriculture Research Service. CES is supported by K08HL112845.	
Genetics of extremely overweight young adults (GOYA) study; Adiposity and Genetic Study (ADIGEN)	Denmark	The ADIGEN study is the followed-up subset of the GOYA study. GOYA is a longitudinal case-cohort (obese, non-obese) dataset comprising 673 extremely overweight and 792 controls selected after examination of 362,200 Caucasian men at the mean age of 20 years at the draft boards in Copenhagen and its surrounding areas during 1943–77. Obesity was defined as 35% overweight relative to a local standard in use at the time (mid 1970's), corresponding to a BMI $\geq$ 31.0 kg/m^2, which proved to be above the 99th percentile. With a sampling fraction of 0.5% (50% of 1%), these controls represent about 158,000 men among whom the case group was the most obese. All extremely overweight men and a random sample of half the men, who were still living in the region, were invited to a follow-up survey in 1992–94 at the mean age of 46 years. The ADIGEN participants comprised 466 males, of the age range between 39-48 years and available genotype and phenotype data, and 311 males had additional valid dietary data. This study was conducted as part of the activities of the Gene-diet Interactions in Obesity project (GENDINOB, www.gendinob.dk) and the MRC center for Causal Analyses in Translational Epidemiology (MRC CAiTE). The authors thank the staff of the Copenhagen City Heart Study for their skillful examination of the study subjects in collection of baseline and follow-up data.	PMID: 21935397 [4]; 26558825 [5]
Invecchiare in Chianti, aging in the Chianti area (InCHIANTI)	Italy	InCHIANTI is a population-based study designed to evaluate the factors that influence mobility in older people in the Chianti region of Tuscany, Italy. A total of 1,616 residents were selected from the population registry of Greve (a rural area: 11,709 residents with 19.3% of the population greater than 65 years of age), and Bagno a Ripoli (Antella village near Florence; 4,704 inhabitants, with 20.3% greater than 65 years of age). The participation rate was 90% (n=1,453), and the participants ranged between 21-102 years of age. For the present study, 1,125 adults with available valid plasma lipids and genotype data and who provided complete dietary information were eligible for the current study. The InCHIANTI study investigators thank the Intramural Research Program of the NIH, National Institute on Aging who are responsible for the InCHIANTI samples. Investigators also thank the InCHIANTI participants. The InCHIANTI study baseline (1998-2000) was supported as a "targeted project" (ICS110.1/RF97.71) by the Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts: 263 MD 9164 and 263 MD 821336).	http://www.inchiantistudy.net/bindex.html PMID: 11129752 [6]
Inter99 Study	Denmark	The Inter99 Study (N=6,089, aged 30-60 years) is a Danish population-based, non-pharmacological intervention study for the prevention of ischemic heart disease conducted at the Research Centre for	www.inter99.dk

Cohort	Country	Study Descriptions and Acknowledgements	Web Link and Key Study-Related Reference (PMID)
		Prevention and Health (RCPH) in Glostrup, Denmark (ClinicalTrials.gov ID-no: NCT00289237, www.inter99.dk). The study was approved by the Scientific Ethics Committee of the Capital Region of Denmark (KA-98155) and all participants provided written informed consent. A total of 6,105 adults with available valid plasma lipids and genotype data and consent to share genetic data were eligible for the current analysis, and 5,983 individuals had additional valid dietary data. The Inter99 Study was supported by research grants from the Danish Research Council, the Danish Centre for Health Technology Assessment, Novo Nordisk Inc., Research Foundation of Copenhagen County, Ministry of Internal Affairs and Health, the Danish Heart Foundation, the Danish Pharmaceutical Association, the Augustinus Foundation, the Ib Henriksen Foundation, the Becket Foundation, and the Danish Diabetes Association. Genetic studies were supported by The Lundbeck Foundation Centre for Applied Medical Genomics in Personalised Disease Prediction, Prevention and Care (LuCamp, www.lucamp.org). The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center at the University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk).	PMID: 14663300 [7]; 25599387 [8]
Rotterdam Study (RS: RS-I, RS-II, RS-III)	Netherlands	The RS is a prospective population-based cohort in Ommoord, a suburb of Rotterdam, the Netherlands. The RS currently comprises three sub-cohorts. The first cohort (RS-I) was recruited between 1990 and 1993 and comprises of 7,983 participants (78% of 10,215 invitees) aged 55 years and over. In 2000-2001, the study was extended with a second sub-cohort (RS-II) of new individuals (n=3,011) who had become 55 years of age or moved into the study area after 1990. In 2006-2008, a third sub-cohort (RS-III) was recruited with new individuals aged 45 years and older (n=3,932). For all cohorts, trained research assistants collected data on current health status, use of medication, medical history, lifestyle and risk indicators for chronic diseases during an extensive home interview. Subsequently, the participants visited the study center for detailed clinical examinations. Follow up visits were held every 3-5 years. For the current analyses, 3,265, 2,117, and 2,045 adults with available valid plasma lipids and genotype data and consent to share genetic data were eligible for the current analysis for RS-I, RS-II, and RS-III, respectively. 2,844, 1,163, and 1,568 individuals had additional valid dietary information for interaction analysis in RS-I, RS-II, and RS-III, respectively. The RS is funded by Erasmus Medical Center and Erasmus University, Rotterdam, the Netherlands Organization for Scientific Research (NWO), the Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Netherlands Genomics Initiative (NGI), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII) and the Municipality of Rotterdam. The generation and management of GWAS genotype data for the RS was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC,	http://www.epib.nl/research/ergo.htm PMID: 29064009 [9]

Cohort	Country	Study Descriptions and Acknowledgements	Web Link and Key Study-Related Reference (PMID)
		Rotterdam, Netherlands. The GWAS was supported by the Netherlands Organisation of Scientific Research NWO Investments (No. 175.010.2005.011, 911-03-012), the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO) Netherlands Consortium for Healthy Aging (NCHA), project No. 050-060-810. The RS investigators thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Sander Bervoets, Lizbeth Herrera and Carolina Medina-Gomez for their help in creating the GWAS database. The authors are very grateful to the participants and staff from the RS, the participating general practitioners and the pharmacists. We would like to thank Dr. Tobias A. Knoch, Luc V. de Zeeuw, Anis Abuseiris, and Rob de Graaf as well as their institutions the Erasmus Computing Grid, Rotterdam, the Netherlands, and especially the national German MediGRID and Services@MediGRID part of the German D-Grid, for access to their grid resources.	
Cardiovascular Risk in Young Finns Study (YFS)	Finland	The YFS is a population-based 27 year follow-up study. The first cross-sectional survey was conducted in 1980, when 3,596 White individuals aged 3-18 years participated. The 27-year follow-up examination was conducted in 2007 with individuals aged 30-45 years (n=1,684 participants). The study cohort for the present analysis comprised 1,508 subjects who participated in the study in 2007 and had validated dietary data, available genotype and other risk factor data. The study was approved by the local Ethical Committees and was performed according to Helsinki declaration. The YFS has been financially supported by the Academy of Finland: grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; and Diabetes Research Foundation of Finnish Diabetes Association. The investigators gratefully acknowledge the expert technical assistance in data management and statistical analyses by Irina Lisinen, Ville Aalto and Mika Helminen.	http://med.utu.fi/cardio/youngfinnsstudy/. PMID: 18263651 [10]
Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium		We acknowledge the CHARGE Consortium for encouraging CHARGE studies to participate in this effort and for the contributions of CHARGE members to the analyses conducted for this research. The CHARGE Consortium is supported by R01HL105756.	

Supplemental Table 2.1.2. Methods for measuring blood lipid traits used in participating CHARGE cohort studies

Cohort	Blood Source	Methods for measuring circulating blood lipids
ARIC	Serum	TG was measured by enzymatic procedures with reagents from Boehriner Mannheim Biochemical (analysis adapted for use in Cobas-Bio Analyzer, Roche). HDL-C was measured by enzymatic procedures with reagents from Boehriner Mannheim Biochemical (analysis adapted for use in Cobas-Bio Analyzer, Roche). LDL-C was calculated with the Friedewald equation.
GOLDN	Plasma	TG was measured using a glycerol-blanked enzymatic method. HDL-C was measured using the same method as TG following precipitation of non-HDL-C with magnesium/dextran. LDL-C was measured by a homogeneous direct method (LDL Direct Liquid Select™ Cholesterol Reagent; Equal Diagnostics, Exton, PA, USA). All lipids were measured using the Roche/Hitachi 911 Automatic Analyzer (Roche Diagnostics Corporation, Basel, Switzerland). Circulating blood lipids were measured at baseline. Samples were collected and processed using a standardized protocol, aliquoted, and stored at -70 degrees C until the end of the study. All samples for each individual were analyzed in the same batch to minimize variability.
GOYA	Serum	TG was analyzed on a COBAS MIRA Plus (Roche Diagnostic Systems GmbH, Mannheim, Germany) using an enzymatic colorimetric test with MPR2 Triglycerides (Boehringer and Mannheim GmbH Diagnostica, Germany) and the GPO-PAP method. Intra-assay variation coefficient was 0.6% and inter-assay variation coefficient was 2.8%. HDL-C was analyzed on a COBAS MIRA Plus (Roche Diagnostic Systems GmbH, Mannheim, Germany) using a homogenous enzymatic colorimetric test with a HDL-C plus kit (Boehringer and Mannheim GmbH Diagnostica, Germany). Intra-assay variation coefficient was 1.6% and inter-assay variation coefficient was 4.4%. LDL-C was calculated from Friedwald equation.
InCHIANTI	Serum	Commercial enzymatic test (Roche Diagnostics, Basel, Switzerland) was used for determining serum TG concentrations from fresh samples drawn after 12 hours overnight fasting. Commercial enzymatic test (Roche Diagnostics, Basel, Switzerland) was used for determining serum HDL-C concentrations from fresh samples drawn after 12 hours overnight fasting. LDL-C was calculated with Friedewald formula.
Inter99	Serum	TG was determined with enzymatic techniques (Boehringer Mannheim, Germany). HDL-C was determined with enzymatic techniques (Boehringer Mannheim, Germany). LDL-C was calculated by Friedewald equation.
RS (I, II and III)	Serum	In 1990, nonfasting serum total cholesterol and HDL-C levels were measured, using enzymatic colorimetric methods (Kone Specific Analyzer, Kone Instruments). From 1997 onward, fasting total cholesterol and HDL-C as well as fasting TG levels were determined using comparable enzymatic procedures (Hitachi Analyzer, Roche Diagnostics). The Friedewald equation was used to estimate LDL-C.
YFS	Serum	TG was assayed by using the enzymatic glycerol kinase (Triglyceride reagent, Olympus). Fasting HDL-C was measured with a fully enzymatic cholesterol oxidase p-aminophenazone method, quantified by precipitating with dextran. LDL-C was calculated by using the Friedewald formula.

Supplemental Table 2.1.3. Dietary assessment methods used in participating CHARGE cohort studies

Cohort	Dietary Assessment
ARIC	Diet was assessed using an interviewer-administered, 66-item semi-quantitative FFQ that was modified from the validated Willett 61-item FFQ[11] (modifications described elsewhere[12]). Participants were asked to indicate how often, on average, they consumed various foods and beverages over the past year according to 9 frequency categories, ranging from never or < 1 time/mo to ≥ 6 times/d. Standard portion sizes given as a reference for intake estimation. Supplementary questions included regarding frequency of fried food consumption and brand name of the breakfast cereal most commonly consumed (open-ended response). Dietary information was judged as unreliable and excluded from further analysis if total energy intake was estimated to be < 500 or > 3600 kcal for women and < 600 or > 4,200 kcal for men or if 10 or more items of the FFQ were unanswered.
GOLDN	Habitual dietary intake was estimated using the validated dietary history questionnaire (DHQ) developed by the National Cancer Institute and administered by the interviewer[13-15]. The DHQ contains 124 food items and includes questions related to portion size and dietary supplements. Participants with energy intakes outside of the range of 550-5,000 kcal/day for women and 600-6,000 kcal/day for men were excluded from analysis.
GOYA	Dietary intake was assessed with an estimated 7-d dietary record method. Participants were carefully instructed to fill in the dietary records for 7 consecutive days. The preprinted questionnaires were chronologically divided into sections for food consumed for every meal and in-between snacks. The preprinted options of food items, dishes, and beverages commonly consumed were complemented by an open answer option. Portion sizes were given in common household measures, but specific types of foods (rice, pasta, vegetables) or meals (mixed dish, mixed salad, raw food) were quantified using a photo-sequence of 4 portion sizes. Also, the amount of fat spread on a slice of rye or wheat bread was quantified using photos. Furthermore, participants completed an additional questionnaire with details on use of household fats (frequency, type, and amount) and use of milk, cream, and sugar in coffee and tea. Finally, participants were asked to state whether in the week of recording their dietary intake they had been eating as usual, a little differently from usual, or a lot differently from usual. Dietary data were computerized twice and any discrepancy was adjusted. Nutrient calculation of dietary intake was assessed using SAS 9.1 (SAS Institute) by combining reported food intake with standard portion sizes, subtraction of loss of water and fat during cooking, and nutrient composition based on the Danish Food Composition tables from 1996. All extreme numbers of portions were compared with the number in the original dietary record to check for data entry error. In total, 10 errors were corrected. In addition, the original dietary records for 10 randomly selected participants (registrations for all 7 d) were compared with the electronic files. Only 1 discrepancy between the registration and the file for the 70 records was detected. Thus, a good agreement between the reported and computerized dietary intake for all participants was assumed[16].
InCHIANTI	The diet was assessed using an interviewer administered 236-item FFQ that investigates how frequently (weekly, monthly, yearly) each specific food was usually consumed[17, 18]. The participant was asked to specify the size of the portion usually consumed, in comparison to a range of portion presented in colored photographs. Nutrient data for specific foods were obtained from the Food Composition Database for Epidemiological Studies in Italy[19]. Dietary information was judged as unreliable and excluded from further analysis if reported energy intakes less than 600 kcal/d or greater than 4,000 kcal/d and 4,200 kcal/d in women and men, respectively.
Inter99	The habitual dietary intake of nutrients was assessed using a self-administered FFQ including 198 food items and beverages with additional questions regarding portion sizes of some selected food items[20]. The participants were asked to report their dietary intake during the past month. When no portion size was specified, a standard portion size for women and men, respectively, was used (A. Biltoft-Jensen, Danish Veterinary and Food Administration, personal communication[21]).
RS (I, II and III)	Dietary intake was assessed using a 170-item semi-quantitative FFQ in RS-I (baseline) and using an updated 389-item FFQ in RS-II (third visit) and RS-III (baseline)[22]. For RS-I, an FFQ was applied in a two-stage approach. In the first stage, participants indicated which foods they consumed at least twice a month in the preceding year using a self-administered checklist of 170 food items. In a second stage, a trained dietician used this list to identify how often and in which amounts the foods were consumed. For RS-II and RS-III, a self-administered semi-quantitative 389-item FFQ was used to assess dietary intake. From both FFQs, information on portion size, type of food item, and preparation method were collected. Nutrient data were calculated from the Dutch Food Composition Table. We excluded participants who had an unreliable dietary intake according to the trained nutritionist who performed the interview or because their estimated daily energy intake was < 500 or > 5000 kcal/d. Both FFQs have been evaluated in several validation studies which showed that the FFQs were able to adequately rank participants according to their dietary intake.

YFS	The dietary intake of nutrients was assessed using a modified 131-item FFQ developed by the Finnish National Institute for Health and Welfare[23].

Supplemental Table 2.1.4. Genotyping, imputation and statistical methods used in participating CHARGE cohort studies

Cohort	**Genotyping platform**	**Imputation software**	**Quality control (QC) and procedures**	**Cohort specific covariates (population structure, center and familial relationship)**	**Statistical analysis software and methods used for GWAS and GWIS**
ARIC	Affymetrix 6.0	MACH	ARIC Study samples were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 (Santa Clara, California); for the current analysis white and African American participants were analyzed. Sample exclusion criteria included discordant with previous genotype data, genotypic and phenotypic sex mismatch, suspected first-degree relative of an included individual based on genotype data, genotic outlier as assessed by Identity by State (IBS) using PLINK and > 8 SD along any of the first 10 principal components in EIGENSTRAT with 5 iterations. Autosomal SNPs were used for imputation after exclusion of SNPs with HWE deviation $P < 5 \times 10^{-5}$, call rate < 95%, or MAF < 1%.	Principal components and study center	ProbABEL
GOLDN	Affymetrix Genome-Wide Human SNP Array 6.0	MACH 1.0, build 36	A total of 906,600 SNPs were genotyped using the Affymetrix Genome-Wide Human 6.0 array (Affymetrix Inc., Santa Clara, California, USA) and the Birdseed calling algorithm (Broad Institute, Cambridge, Massachusetts, USA). Monomorphic SNPs (55,530) or those with a call rate <96% (82,462) were removed from the analysis. Additionally, SNPs were excluded from the analysis based on the number of families with Mendelian error as follows: MAF ≥ 20%, removed if errors are present in >3 families (1,486 SNPs); for 20% > MAF ≥ 10%, removed if errors are present in >2 families (1,338 SNPs); for 10% > MAF ≥ 5%, removed if errors are present in > 1 family (1,767 SNPs); for MAF < 5%, removed if any errors are present (9,592 SNPs). In families with remaining errors, SNPs that exhibited Mendelian error were set to missing (31,595 SNPs). Furthermore, 16 participants with call rates less than 96% were also removed from any subsequent analyses. Subsequently, 748 SNPs failing the HWE test at *P*-value $< 10^{-6}$ were excluded from analyses. Following exclusion for MAF < 1%, HWE (*P* <	The first 10 principal components, study center and family relationship	R GWAF (version 2.0) GWAS: Fitting linear mixed effects (LME) model to test associations between a continuous blood lipid phenotype and miRNASNPs in family data under additive genetic model. The SNP genotype is treated as a fixed effect, and a random effect correlated according to degree of relatedness within a family is also fitted. GWIS: Fitting Generalized Estimation Equation (GEE) model to test gene-by-environment interactions for a continuous blood lipid phenotype in family data under additive genetic model. Each pedigree is treated as a cluster, with independence working correlation matrix used in the robust variance estimator.

Cohort	Genotyping platform	Imputation software	Quality control (QC) and procedures	Cohort specific covariates (population structure, center and familial relationship)	Statistical analysis software and methods used for GWAS and GWIS
			10^{-6}), missing strand information, or discrepancies with the mlinfo file, MACH software (Version 1.0.16) was used to impute untyped SNPs using the phased haplotypes for CEU from HapMap (release 22, build 36) as the reference. The final hybrid dataset included 2,543,887 SNPs (584,029 genotyped and 1,959,858 imputed).		
GOYA	Illumina 610k Quad chip	MACH 1.0, Markov Chain Haplotyping	Genome-wide genotyping on the Illumina 610 k quad chip was carried out at the Centre National de Génotypage (CNG), Evry, France. We excluded SNPs with MAF < 1%, > 5% missing genotypes or which failed an exact test of HWE in the controls ($P < 10^{-7}$). We also excluded any individual who did not cluster with the CEU individuals (Utah residents with ancestry from northern and western Europe) in a multidimensional scaling analysis seeded with individuals from the International HapMap release 22 (22 individuals), who had >5% missing data (5 individuals), outlying heterozygosity of > 35% or < 30.2% (35 individuals), both samples in the case of genetic duplicates (4 individuals), one of each pair of genetically related individuals (50 individuals), 4 individuals with sex discrepancies and one individual whose genotyping was discordant with a previous project. After data cleaning, 5,373 individuals (2,633 extremely overweight and 2,740 random controls) and 545,349 SNPs remained. We carried out imputation to HapMap release 22 (CEU individuals) using Mach 1.0, Markov Chain Haplotyping.	NA	Quicktest
InCHIANTI	Illumina 550K	MACH	Genotyping in InCHIANTI was conducted using Illumina 550K. Samples QC: call rate filter was set at > 98.5%; sex misspecification. SNPs QC: MAF > 1%; HWE > 10^{-4}; call rate > 99%. Imputation was made using MACH software: Ratio of variance of dosage to expected variance under binomial model > 0.3, MAF > 1%.	Genomic control and study site	merlinoffline
Inter99	Metabochip	NA	Individuals with a first- or second-degree familial relationship, an extreme inbreeding coefficient, a low call rate, mislabeled sex, and high discordance to previous genotyping were excluded. Genotyping	NA	Quicktest

Cohort	Genotyping platform	Imputation software	Quality control (QC) and procedures	Cohort specific covariates (population structure, center and familial relationship)	Statistical analysis software and methods used for GWAS and GWIS
			quality for each SNP was assessed by the call rate (> 98%) and the presence of HWE.		
RS (I, II and III)	Illumina Human 550K and 610k Quad	MACH	Genotyping was conducted using the Illumina 550K and 610K arrays among participants of self-reported European descent. SNPs were excluded for MAF < 1%, HWE *P*-value < 10^{-6}, or SNP call rate < 90% resulting in data on 530,683 SNPs. We excluded participants for excess autosomal heterozygosity, mismatch between called and phenotypic gender or being outliers identified by the IBS clustering analysis.	NA	ProbABEL
YFS	Illumina Human 670K BeadChip	MACH 1.0 (HapMap II CEU, NCBI 36)	DNA was extracted from blood samples drawn on all participants in 2001 and 2007. In 2009 genotyping was performed at the Sanger institute (UK) using the custom-built Illumina BeadChip Human670K from 2,442 YF participants (1,123 males, 1,319 females) including 546,677 SNPs. Genotypes were called using Illumina's clustering algorithm[24]. In the start of QC protocol we had 2,556 samples in YF intensity file, after initial clustering we removed 2 subjects (CR < 0.90), thus the main clustering include 2,554 subjects, from these 54 samples failed QC. Thus genotyping pipeline contained 2,500 subject s from these 54 were removed due to Sanger genotyping pipeline QC criteria (i.e., duplicated samples, heterozygosity, low call rate, or Sequenom fingerprint discrepancy). After genotyping pipeline QC the following filters were applied to the remaining data: MAF 0.01, GENO 0.05, MIND 0.05, and HWE 10^{-6}. 3 of 2,500 individuals were removed for low genotyping (MIND > 0.05), 11,766 markers were excluded based on HWE test ($p \leq 10^{-6}$), 7,746 SNPs failed missingness test (GENO > 0.05), 34,596 SNPs failed frequency test (MAF < 0.01) and one individual failed gender check. None were removed by subsequent heterozygosity check. New binary files were created after removing the individual which failed the gender-check and identity-by-descent (IBD) matrix was subsequently calculated in PLINK[25]. There	Principal components and study center	ProbABEL, PLINK

Cohort	Genotyping platform	Imputation software	Quality control (QC) and procedures	Cohort specific covariates (population structure, center and familial relationship)	Statistical analysis software and methods used for GWAS and GWIS
			were 546,770 SNPs and 2,496 individuals at this point which were utilized to generate the genome file. There were 51 pairs of individuals with pi-hat greater than 0.2 thus these individuals removed due to possible relatedness. One of the pair was removed using greater missingness as criteria. After final frequency and genotyping running, there was 546,677 SNPs available from sample of 2,442 YF subjects. From these a total of 546,677 genotyped autosomal SNPs, those SNPs that were present on HapMap and that passed QC measures were used for imputation with MACH version 1.0 (http://www.sph.umich.edu/csg/abecasis/MACH/).		

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium (ln-TG)

Phen	SNP	Gene	Chr	Position_ hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/ major, effect)	MAF[2]	FreqSE	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction
ln-TG	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.17	0.059	-0.041	0.005	1.51E-17	4.47E-17	---------
ln-TG	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.016	0.031	0.004	3.13E-16	1.66E-15	+++++++++
ln-TG	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.20	0.013	-0.034	0.004	6.08E-15	9.28E-15	---------
ln-TG	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.008	0.040	0.005	1.19E-14	2.17E-14	+++++++++
ln-TG	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.022	0.027	0.004	2.68E-13	1.18E-12	+++++++++
ln-TG	rs4803	*KRTCAP3, IFT172*	2	27667297	5	+	NA	G/A,A	0.41	0.024	0.020	0.004	6.68E-09	1.50E-08	++-++++++
ln-TG	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.40	0.024	-0.017	0.004	2.90E-06	3.55E-06	--+-----?
ln-TG	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.41	0.024	0.017	0.004	3.29E-06	4.04E-06	++-+++++?
ln-TG	rs13472	*SNX17*	2	27600239	9	+	7.51E-35	A/G,A	0.40	0.024	-0.017	0.004	4.07E-06	5.22E-06	--+-----?
ln-TG	rs3810444	*SFRS14*	19	19103986	7		1.57E-16	A/T,A	0.07	0.006	-0.036	0.008	4.99E-06	7.28E-06	---------
ln-TG	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.35	0.022	0.018	0.004	5.47E-06	5.63E-06	++++++++?
ln-TG	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006	-0.047	0.011	2.04E-05	2.66E-05	------+--
ln-TG	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.11	0.024	-0.025	0.006	2.38E-05	2.95E-05	--------?
ln-TG	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.004	0.017	0.004	3.92E-05	5.41E-05	+++++++++
ln-TG	rs7730801	*TSSK1B*	5	112768340	5	+	0.1937	A/T,A	0.19	0.006	0.018	0.005	0.0001258	0.0001598	+++-++++?
ln-TG	rs512555	*MS4A2*	11	59863253	5	+	0.07883	T/C,T	0.02	0.006	0.052	0.014	0.0001299	0.0001638	++++++-+?
ln-TG	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.007	-0.016	0.004	0.0001374	0.0001453	-------+-
ln-TG	rs17773605	PPP1R9A	7	94924538	5		0.1728	T/G,T	0.06	0.009	0.030	0.008	0.000173	0.0002211	++-+++++?

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium (ln-TG, continued)

Phen	SNP	Gene	Model 2 SNP β	Model 2 SE	Model 2 P value	Model 2 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
ln-TG	rs15285	*LPL*	-0.066	0.006	6.41E-32	---------	-0.067	0.006	1.58E-32	---------	0	0.75	24065
ln-TG	rs13702	*LPL*	0.057	0.005	2.13E-35	+++++++++	0.057	0.005	1.40E-35	+++++++++	0	0.86	24065
ln-TG	rs1051921	*MLXIPL*	-0.054	0.005	1.36E-24	---------	-0.054	0.005	8.68E-25	---------	0	0.81	24065
ln-TG	rs13232120	*TBL2*	0.061	0.006	6.69E-22	+++++++++	0.061	0.006	4.43E-22	+++++++++	0	0.91	24065
ln-TG	rs14415	*TBL2*	0.045	0.005	1.26E-22	+++++++++	0.045	0.005	9.41E-23	+++++++++	0	0.97	24065
ln-TG	rs4803	*KRTCAP3, IFT172*	0.036	0.004	1.32E-17	++-++++++	0.037	0.004	1.88E-18	++-++++++	0	0.58	24065
ln-TG	rs8395	*FNDC4*	-0.036	0.005	1.74E-14	--+-----?	-0.037	0.005	4.94E-15	--+-----?	0	0.48	17953
ln-TG	rs4582	*PPM1G*	0.035	0.005	1.63E-13	++-+++++?	0.036	0.005	3.87E-14	++-+++++?	0	0.53	17953
ln-TG	rs13472	*SNX17*	-0.035	0.005	1.65E-13	--+-----?	-0.036	0.005	4.40E-14	--+-----?	0	0.56	17953
ln-TG	rs3810444	*SFRS14*	-0.049	0.009	6.75E-08	------+--	-0.051	0.009	2.26E-08	------+--	36.5	0.13	24065
ln-TG	rs583609	*USP1*	0.030	0.005	1.02E-09	++++++++?	0.031	0.005	4.40E-10	++++++++?	0	0.81	17953
ln-TG	rs3289	*LPL*	-0.094	0.013	1.77E-12	-------+-	-0.094	0.013	1.51E-12	---------	13.7	0.32	24065
ln-TG	rs1035237	*SIK3*	-0.044	0.007	1.68E-09	--------?	-0.044	0.007	1.68E-09	--------?	0	0.69	17953
ln-TG	rs1881396	*ZNF512*	0.027	0.005	8.82E-08	+++++++++	0.028	0.005	2.00E-08	+++++++++	0	0.67	24065
ln-TG	rs7730801	*TSSK1B*	0.015	0.006	0.01219	+++-++++?	0.015	0.006	0.01243	+++-++++?	0	0.45	17953
ln-TG	rs512555	*MS4A2*	0.057	0.017	0.0006595	++++++++?	0.055	0.017	0.001014	++++++++?	8.9	0.36	17937
ln-TG	rs619054	*APOA5*	-0.029	0.005	8.92E-09	--+----+-	-0.029	0.005	9.60E-09	--+----+-	47.6	0.05	24065
ln-TG	rs17773605	*PPP1R9A*	0.018	0.010	0.07412	+--++++-?	0.016	0.010	0.1169	+--++++-?	0	0.45	17953

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium (HDL-C)

Phen	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/ major, effect)	MAF[2]	FreqSE	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction
HDL-C	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.12	0.018	0.064	0.006	2.58E-30	8.26E-29	+++++++++
HDL-C	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.12	0.018	-0.064	0.006	3.43E-30	1.22E-28	---------
HDL-C	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.31	0.034	-0.041	0.004	4.10E-27	1.45E-26	---------
HDL-C	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.22	0.105	0.050	0.005	1.21E-26	1.68E-25	+++++++++
HDL-C	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.007	0.070	0.011	4.36E-10	8.89E-10	+++++++-+
HDL-C	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.022	0.032	0.006	4.36E-09	8.93E-09	++-++++++
HDL-C	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.08	0.011	0.040	0.007	5.96E-09	1.09E-08	++++-++++
HDL-C	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.18	0.043	-0.030	0.005	9.67E-09	2.01E-08	---------
HDL-C	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.36	0.036	0.020	0.004	2.32E-08	6.73E-08	+++++++++
HDL-C	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.32	0.047	-0.019	0.004	2.71E-07	6.53E-07	--++-----
HDL-C	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.19	0.030	-0.023	0.005	6.62E-07	9.81E-07	--+------
HDL-C	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.33	0.045	-0.018	0.004	8.48E-07	1.91E-06	--++-----
HDL-C	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.14	0.019	-0.023	0.005	1.31E-06	2.22E-06	--++-----
HDL-C	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.039	0.020	0.004	3.22E-06	4.90E-06	++--++++?
HDL-C	rs7679	*ZNF335*	20	44576502	3		6.73E-38	C/T,T	0.19	0.026	0.021	0.005	4.70E-06	8.65E-06	+++++++-+
HDL-C	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.34	0.038	0.017	0.004	6.03E-06	8.29E-06	+++++++++
HDL-C	rs11043	*RBM35B*	16	68262958	14	+	1.22E-39	A/G,A	0.14	0.021	0.023	0.005	1.02E-05	1.62E-05	++-++++++
HDL-C	rs660240	*CELSR2*	1	109817838	4	+	1.57E-14	T/C,T	0.23	0.039	0.018	0.004	1.35E-05	1.79E-05	+++++++++
HDL-C	rs12740374	*CELSR2*	1	109817590	7	+	1.69E-15	T/G,T	0.21	0.023	0.018	0.004	1.46E-05	2.45E-05	+++++++++
HDL-C	rs629301	*CELSR2*	1	109818306	8	+	7.61E-13	G/T,T	0.25	0.038	-0.018	0.004	1.57E-05	2.72E-05	---------
HDL-C	rs2293577	*SLC39A13*	11	47437202	12		NA	C/T,T	0.33	0.025	0.018	0.004	2.24E-05	3.77E-05	++++++++?
HDL-C	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.32	0.020	-0.018	0.004	2.31E-05	3.77E-05	--------?
HDL-C	rs7528419	*CELSR2*	1	109817192	7	+	9.55E-11	G/A,A	0.22	0.016	-0.021	0.005	2.59E-05	3.24E-05	--------?
HDL-C	rs10773003	*SBNO1*	12	123775127	3	+	1.46E-13	A/G,A	0.10	0.010	0.026	0.006	2.60E-05	4.26E-05	+++++++++
HDL-C	rs3741414	*INHBC*	12	57844049	7		6.10E-14	T/C,T	0.27	0.051	0.017	0.004	2.79E-05	4.00E-05	+++++++-+
HDL-C	rs3088303	*SBNO1*	12	123779489	4	+	3.04E-06	A/G,A	0.10	0.011	0.028	0.007	3.72E-05	4.90E-05	++++++++?
HDL-C	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.34	0.037	0.015	0.004	5.05E-05	7.21E-05	+-++++++++
HDL-C	rs7883	*LEPROT, LEPR*	1	65897869	8		0.00735	A/G,A	0.05	0.012	-0.037	0.009	5.10E-05	7.20E-05	--------?
HDL-C	rs473465	*INHBE*	12	57851182	7	+	9.72E-08	A/G,A	0.23	0.054	-0.017	0.004	5.88E-05	9.88E-05	--+--+---
HDL-C	rs1983072	*PTPRJ*	11	48190134	3		NA	A/G,A	0.44	0.028	0.016	0.004	6.02E-05	9.92E-05	++++++++?
HDL-C	rs788793	*LGR6*	1	202287813	3	+	NA	T/C,T	0.38	0.022	-0.017	0.004	7.18E-05	9.90E-05	-++-----?
HDL-C	rs788792	*LGR6*	1	202288462	6	+	0.3668	C/A,A	0.38	0.022	0.017	0.004	7.35E-05	9.90E-05	+--+++++?
HDL-C	rs1060681	*SYNJ2BP, SYNJ2BP-COX16*	14	70836753	4	+	0.0008337	A/C,A	0.38	0.038	-0.016	0.004	8.98E-05	0.0001094	--------?
HDL-C	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.44	0.046	0.014	0.004	9.01E-05	0.0001132	+++++-+++
HDL-C	rs877710	*MMAB*	12	109993976	10	+	1.86E-17	C/G,C	0.50	0.036	-0.014	0.004	9.20E-05	0.0001421	---------
HDL-C	rs11067231	*MMAB*	12	109993603	8	+	2.16E-19	C/A,A	0.45	0.054	0.013	0.004	0.0001312	0.0001988	+++++++++
HDL-C	rs6738	*TPM1*	15	63363901	4		6.83E-05	C/T,T	0.34	0.026	0.016	0.004	0.0001403	0.0001916	++++++++?
HDL-C	rs2305001	*BID*	22	18218210	7		0.2667	C/T,T	0.02	0.007	0.051	0.014	0.0001774	0.0002343	+-++++-+?
HDL-C	rs6499137	*CTCF*	16	67671804	10	+	5.90E-28	G/T,T	0.10	0.029	-0.023	0.006	0.0001981	0.0002811	--++-+---

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium (HDL-C, continued)

Phen	SNP	Gene	Model 2 SNP β	Model 2 SE	Model 2 P value	Model 2 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
HDL-C	rs3735964	*LPL*	0.066	0.005	3.15E-38	+++++++++	0.066	0.005	7.60E-38	+++++++++	38.8	0.11	25112
HDL-C	rs1059611	*LPL*	-0.066	0.005	4.47E-38	---------	-0.065	0.005	1.11E-37	---------	37.4	0.12	25112
HDL-C	rs13702	*LPL*	-0.042	0.004	6.94E-33	---------	-0.042	0.004	8.57E-33	---------	30.4	0.17	25112
HDL-C	rs15285	*LPL*	0.053	0.004	1.37E-34	+++++++++	0.053	0.004	1.54E-34	+++++++++	17	0.29	25112
HDL-C	rs3289	*LPL*	0.073	0.010	7.42E-13	+++++++-+	0.073	0.010	6.02E-13	+++++++-+	34.5	0.14	25112
HDL-C	rs4474673	*RANBP10*	0.031	0.005	4.98E-10	+++++++++	0.031	0.005	4.16E-10	+++++++++	0	0.67	25112
HDL-C	rs2266788	*APOA5*	0.037	0.006	2.17E-09	+++++++++	0.038	0.006	8.54E-10	+++++++++	0	0.68	25112
HDL-C	rs6857	*NECTIN2*	-0.034	0.005	4.01E-13	---------	-0.035	0.005	8.97E-14	---------	50.5	0.04	25112
HDL-C	rs9909	*NUP160*	0.019	0.003	1.64E-08	+++++++++	0.019	0.003	1.10E-08	+++++++++	23.1	0.24	25112
HDL-C	rs174546	*FADS1*	-0.020	0.003	4.25E-09	--+------	-0.020	0.003	2.32E-09	--+------	18.7	0.28	25112
HDL-C	rs1109166	*SLC12A4, LCAT*	-0.022	0.004	1.30E-07	--+------	-0.023	0.004	1.03E-07	--+------	0	0.60	25112
HDL-C	rs4246215	*FEN1*	-0.019	0.003	1.37E-08	--+------	-0.019	0.003	6.43E-09	--+------	0	0.47	25112
HDL-C	rs12449157	*GFOD2*	-0.022	0.004	3.43E-07	---+-----	-0.023	0.004	2.46E-07	---+-----	0	0.67	25112
HDL-C	rs174545	*FADS1*	0.020	0.004	9.10E-08	++-+++++?	0.020	0.004	5.79E-08	++-+++++?	28.5	0.20	19004
HDL-C	rs7679	*ZNF335*	0.022	0.004	1.09E-07	+++++++-+	0.022	0.004	1.14E-07	+++++++-+	0	0.62	25111
HDL-C	rs1057233	*SPI1*	0.017	0.004	2.42E-06	+++++++++	0.017	0.004	1.62E-06	+++++++++	11.1	0.34	25112
HDL-C	rs11043	*RBM35B*	0.024	0.005	7.85E-07	+++++++++	0.023	0.005	8.38E-07	+++++++++	0	0.83	25112
HDL-C	rs660240	*CELSR2*	0.019	0.004	1.47E-06	+++++++++	0.019	0.004	1.37E-06	+++++++++	0.3	0.43	25112
HDL-C	rs12740374	*CELSR2*	0.018	0.004	1.36E-06	+++++++++	0.018	0.004	1.14E-06	+++++++++	7.4	0.37	25112
HDL-C	rs629301	*CELSR2*	-0.018	0.004	1.38E-06	---------	-0.018	0.004	1.12E-06	---------	6.2	0.38	25112
HDL-C	rs2293577	*SLC39A13*	0.016	0.004	2.80E-05	++++++++?	0.017	0.004	1.63E-05	++++++++?	25.9	0.22	19004
HDL-C	rs2293578	*SLC39A13*	-0.016	0.004	2.87E-05	-------?	-0.017	0.004	1.68E-05	-------?	25.8	0.22	19004
HDL-C	rs7528419	*CELSR2*	-0.019	0.004	1.27E-05	-------?	-0.019	0.004	1.05E-05	-------?	18.7	0.28	19004
HDL-C	rs10773003	*SBNO1*	0.030	0.006	6.56E-08	+++++++++	0.029	0.006	1.97E-07	+++++++++	0	0.99	25099
HDL-C	rs3741414	*INHBC*	0.018	0.004	9.55E-07	++++++--+	0.018	0.004	8.55E-07	++++++--+	45.1	0.07	25112
HDL-C	rs3088303	*SBNO1*	0.032	0.006	2.85E-07	++++++++?	0.030	0.006	7.07E-07	++++++++?	0	0.98	19004
HDL-C	rs8468	*LACTB*	0.020	0.003	9.56E-09	+-+++++++	0.019	0.003	1.02E-08	+-+++++++	0	0.67	25103
HDL-C	rs7883	*LEPROT, LEPR*	-0.031	0.009	0.0002877	-------?	-0.029	0.009	0.0006319	-------?	0	0.96	18977
HDL-C	rs473465	*INHBE*	-0.014	0.004	0.0003156	--+---+--	-0.014	0.004	0.000277	--+---+--	15.3	0.31	25112
HDL-C	rs1983072	*PTPRJ*	0.014	0.004	0.0001245	++++++++?	0.014	0.004	0.000132	++++++++?	0.7	0.42	19004
HDL-C	rs788793	*LGR6*	-0.013	0.004	0.0008741	-+------?	-0.012	0.004	0.001661	-+---+--?	0	0.48	19004
HDL-C	rs788792	*LGR6*	0.012	0.004	0.0008992	+-++++++?	0.012	0.004	0.001711	+-+++-++?	0	0.49	19004
HDL-C	rs1060681	*SYNJ2BP, SYNJ2BP-COX16*	-0.014	0.004	0.0001078	-+------?	-0.015	0.004	6.42E-05	-+------?	0	0.81	19004
HDL-C	rs37029	*SLC12A3*	0.013	0.003	8.13E-05	+++++++++	0.012	0.003	0.0001061	+++++++++	0	0.55	25112
HDL-C	rs877710	*MMAB*	-0.012	0.003	0.0001555	---------	-0.012	0.003	0.000202	---------	0	0.65	25112
HDL-C	rs11067231	*MMAB*	0.012	0.003	0.0002162	+++++++++	0.012	0.003	0.0002843	+++++++++	0	0.66	25112
HDL-C	rs6738	*TPM1*	0.020	0.004	2.63E-07	+++-++++?	0.019	0.004	4.93E-07	+++-++++?	0	0.70	19004
HDL-C	rs2305001	*BID*	0.031	0.012	0.01245	+++-++-+?	0.031	0.012	0.01227	+++-++-+?	33.8	0.16	19004
HDL-C	rs6499137	*CTCF*	-0.022	0.006	9.15E-05	---+-----	-0.022	0.006	8.76E-05	---+-----	0	0.76	25112

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium (LDL-C)

Phen	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/ major, effect)	MAF[2]	FreqSE	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction
LDL-C	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013	0.145	0.010	8.46E-48	6.87E-46	+++++++++
LDL-C	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.40	0.021	-0.067	0.008	1.01E-17	2.55E-17	--+------
LDL-C	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.36	0.027	-0.059	0.009	2.11E-11	3.39E-11	---------
LDL-C	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.43	0.026	0.055	0.008	6.14E-11	1.00E-10	+-+++++++
LDL-C	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.017	-0.064	0.010	6.46E-11	1.22E-10	?-------
LDL-C	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.028	-0.048	0.008	1.15E-09	2.08E-09	---------
LDL-C	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.06	0.008	-0.107	0.019	2.14E-08	3.81E-08	---------
LDL-C	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.35	0.031	0.047	0.009	8.71E-08	1.23E-07	++++++++?
LDL-C	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.008	-0.046	0.009	5.95E-07	7.73E-07	---------
LDL-C	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.35	0.027	0.039	0.009	1.23E-05	1.73E-05	+-+-++++?
LDL-C	rs3810444	*SFRS14*	19	19103986	7		2.60E-12	A/T,A	0.07	0.008	-0.080	0.018	1.32E-05	1.78E-05	------++-
LDL-C	rs4804572	*KANK2*	19	11277074	9	+	NA	T/C,T	0.37	0.021	0.050	0.012	2.44E-05	3.53E-05	?+++++++?
LDL-C	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007	-0.046	0.011	3.31E-05	4.74E-05	------+--
LDL-C	rs11674517	*BCL2L11*	2	111903832	4	+	0.6536	T/C,T	0.49	0.026	-0.035	0.009	4.13E-05	5.60E-05	--++----?
LDL-C	rs2254487	*LGALS8, HEATR1*	1	236714335	3	+	NA	C/T,T	0.34	0.030	-0.036	0.009	7.08E-05	9.06E-05	--------?
LDL-C	rs10942729	*LOC100131794*	5	74364300	3	+	1.02E-17	A/G,A	0.36	0.018	0.039	0.010	8.42E-05	0.0001059	++-+++++?
LDL-C	rs1172294	*DNAJC27*	2	25169200	8	+	0.09507	G/A,A	0.47	0.019	-0.029	0.008	0.000117	0.0001407	--++-+---
LDL-C	rs12747251	*NSL1*	1	212903089	6	+	0.104	G/A,A	0.48	0.028	-0.032	0.009	0.0001629	0.0002115	--------?

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(A) Full list of miRNA-related SNPs associated with blood lipids at $P < 2 \times 10^{-4}$ in the CHARGE consortium (LDL-C, continued)

Phen	SNP	Gene	Model 2 SNP β	Model 2 SE	Model 2 P value	Model 2 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
LDL-C	rs629301	*CELSR2*	0.140	0.010	7.80E-47	+++++++++	0.140	0.010	7.27E-47	+++++++++	28	0.20	23958
LDL-C	rs12916	*HMGCR*	-0.072	0.008	1.16E-17	--+------	-0.071	0.008	3.08E-17	--+------	58	0.01	23958
LDL-C	rs4246215	*FEN1*	-0.061	0.009	1.16E-12	---------	-0.062	0.009	4.40E-13	---------	0	0.54	23958
LDL-C	rs6859	*NECTIN2*	0.071	0.009	1.11E-15	+-++++++++	0.069	0.009	5.79E-15	+-++++++++	28.1	0.19	23958
LDL-C	rs7188	*KANK2*	-0.072	0.010	6.41E-14	---------	-0.072	0.010	8.28E-14	---------	0	0.51	23958
LDL-C	rs174546	*FADS1*	-0.065	0.009	4.61E-14	---------	-0.066	0.009	1.40E-14	---------	0	0.76	23958
LDL-C	rs13465	*ILF3*	-0.110	0.019	5.04E-09	----+----	-0.107	0.019	1.07E-08	----+----	38.1	0.11	23957
LDL-C	rs174545	*FADS1*	0.069	0.010	2.72E-12	++++++++?	0.070	0.010	8.48E-13	++++++++?	0	0.77	17853
LDL-C	rs1433099	*LDLR*	-0.047	0.010	2.01E-06	---------	-0.047	0.010	1.80E-06	---------	0	0.64	23958
LDL-C	rs583609	*USP1*	0.053	0.010	9.05E-08	+++-++++?	0.053	0.010	1.07E-07	+++-++++?	0	0.47	17853
LDL-C	rs3810444	*SFRS14*	-0.079	0.018	1.03E-05	------+--	-0.079	0.018	1.07E-05	------+--	12.9	0.33	23958
LDL-C	rs4804572	*KANK2*	0.060	0.012	2.17E-07	++++++++?	0.059	0.012	2.49E-07	++++++++?	0	0.85	17853
LDL-C	rs17034539	*KIAA1324*	-0.047	0.011	1.73E-05	---------	-0.047	0.011	2.17E-05	------+--	0	0.59	23958
LDL-C	rs11674517	*BCL2L11*	-0.033	0.009	0.000453	--++----?	-0.032	0.009	0.0005842	--++--+-?	52.5	0.04	17853
LDL-C	rs2254487	*LGALS8, HEATR1*	-0.036	0.010	0.000333	-------?	-0.035	0.010	0.0003505	-------?	0	0.87	17853
LDL-C	rs10942729	*LOC100131794*	0.040	0.010	4.33E-05	++-+++++?	0.039	0.010	5.80E-05	++-+++++?	0	0.78	17853
LDL-C	rs1172294	*DNAJC27*	-0.024	0.008	0.003932	--++-+---	-0.023	0.008	0.004828	--++-+---	29.7	0.18	23958
LDL-C	rs12747251	*NSL1*	-0.038	0.009	5.53E-05	------+-?	-0.037	0.009	8.37E-05	------+-?	0	0.78	17853

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:

MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$) (Ln-TG)

Phen	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/ major, effect)	MAF[2]	FreqSE	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction
ln-TG	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.17	0.059	-0.041	0.005	1.51E-17	4.47E-17	---------
ln-TG	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.016	0.031	0.004	3.13E-16	1.66E-15	+++++++++
ln-TG	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.20	0.013	-0.034	0.004	6.08E-15	9.28E-15	---------
ln-TG	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.008	0.040	0.005	1.19E-14	2.17E-14	+++++++++
ln-TG	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.022	0.027	0.004	2.68E-13	1.18E-12	+++++++++
ln-TG	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.40	0.024	-0.017	0.004	2.90E-06	3.55E-06	--+-----?
ln-TG	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.41	0.024	0.017	0.004	3.29E-06	4.04E-06	++-+++++?
ln-TG	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.40	0.024	-0.017	0.004	4.07E-06	5.22E-06	--+-----?
ln-TG	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.006	-0.036	0.008	4.99E-06	7.28E-06	---------
ln-TG	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.35	0.022	0.018	0.004	5.47E-06	5.63E-06	++++++++?
ln-TG	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006	-0.047	0.011	2.04E-05	2.66E-05	------+--
ln-TG	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.11	0.024	-0.025	0.006	2.38E-05	2.95E-05	--------?
ln-TG	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.004	0.017	0.004	3.92E-05	5.41E-05	+++++++++
ln-TG	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.007	-0.016	0.004	0.000137	0.000145	-------+-
ln-TG	rs8731	*GPN1*	2	27873326	11	+	1.04E-35	G/C,C	0.22	0.008	0.015	0.004	0.000304	0.00031	+++-+-+++
ln-TG	rs6857	*NECTIN2*	19	45392254	6		4.55E-19	T/C,T	0.16	0.017	0.018	0.005	0.000343	0.000449	+++--++++

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:

MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$) (Ln-TG, continued)

Phen	SNP	Gene	Model 2 SNP β	Model 2 SE	Model 2 P value	Model 2 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
ln-TG	rs15285	*LPL*	-0.066	0.006	6.41E-32	---------	-0.067	0.006	1.58E-32	---------	0	0.75	24065
ln-TG	rs13702	*LPL*	0.057	0.005	2.13E-35	+++++++++	0.057	0.005	1.40E-35	+++++++++	0	0.86	24065
ln-TG	rs1051921	*MLXIPL*	-0.054	0.005	1.36E-24	---------	-0.054	0.005	8.68E-25	---------	0	0.81	24065
ln-TG	rs13232120	*TBL2*	0.061	0.006	6.69E-22	+++++++++	0.061	0.006	4.43E-22	+++++++++	0	0.91	24065
ln-TG	rs14415	*TBL2*	0.045	0.005	1.26E-22	+++++++++	0.045	0.005	9.41E-23	+++++++++	0	0.97	24065
ln-TG	rs8395	*FNDC4*	-0.036	0.005	1.74E-14	--+-----?	-0.037	0.005	4.94E-15	--+-----?	0	0.48	17953
ln-TG	rs4582	*PPM1G*	0.035	0.005	1.63E-13	++-+++++?	0.036	0.005	3.87E-14	++-+++++?	0	0.53	17953
ln-TG	rs13472	*SNX17, ZNF513*	-0.035	0.005	1.65E-13	--+-----?	-0.036	0.005	4.40E-14	--+-----?	0	0.56	17953
ln-TG	rs3810444	*SUGP2*	-0.049	0.009	6.75E-08	------+--	-0.051	0.009	2.26E-08	------+--	36.5	0.13	24065
ln-TG	rs583609	*USP1*	0.030	0.005	1.02E-09	++++++++?	0.031	0.005	4.40E-10	++++++++?	0	0.81	17953
ln-TG	rs3289	*LPL*	-0.094	0.013	1.77E-12	-------+-	-0.094	0.013	1.51E-12	---------	13.7	0.32	24065
ln-TG	rs1035237	*SIK3*	-0.044	0.007	1.68E-09	--------?	-0.044	0.007	1.68E-09	--------?	0	0.69	17953
ln-TG	rs1881396	*ZNF512*	0.027	0.005	8.82E-08	+++++++++	0.028	0.005	2.00E-08	+++++++++	0	0.67	24065
ln-TG	rs619054	*APOA5*	-0.029	0.005	8.92E-09	--+----+-	-0.029	0.005	9.60E-09	--+----+-	47.6	0.05	24065
ln-TG	rs8731	*GPN1*	0.025	0.005	8.65E-07	+++-+++++	0.026	0.005	2.02E-07	+++++++++	0	0.61	24065
ln-TG	rs6857	*NECTIN2*	0.041	0.006	2.91E-11	+++-+++++	0.042	0.006	7.39E-12	+++-+++++	56.4	0.02	24065

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:

MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$) (HDL-C)

Phen	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/ major, effect)	MAF[2]	FreqSE	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction
HDL-C	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.12	0.018	0.064	0.006	2.58E-30	8.26E-29	+++++++++
HDL-C	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.12	0.018	-0.064	0.006	3.43E-30	1.22E-28	---------
HDL-C	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.31	0.034	-0.041	0.004	4.10E-27	1.45E-26	---------
HDL-C	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.22	0.105	0.050	0.005	1.21E-26	1.68E-25	+++++++++
HDL-C	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.007	0.070	0.011	4.36E-10	8.89E-10	+++++++-+
HDL-C	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.022	0.032	0.006	4.36E-09	8.93E-09	++-++++++
HDL-C	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.08	0.011	0.040	0.007	5.96E-09	1.09E-08	++++-++++
HDL-C	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.18	0.043	-0.030	0.005	9.67E-09	2.01E-08	---------
HDL-C	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.36	0.036	0.020	0.004	2.32E-08	6.73E-08	+++++++++
HDL-C	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.32	0.047	-0.019	0.004	2.71E-07	6.53E-07	--++-----
HDL-C	rs1109166	*LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.19	0.030	-0.023	0.005	6.62E-07	9.81E-07	--+------
HDL-C	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.33	0.045	-0.018	0.004	8.48E-07	1.91E-06	--++-----
HDL-C	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.14	0.019	-0.023	0.005	1.31E-06	2.22E-06	--++-----
HDL-C	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.039	0.020	0.004	3.22E-06	4.90E-06	++--++++?
HDL-C	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.19	0.026	0.021	0.005	4.70E-06	8.65E-06	+++++++-+
HDL-C	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.34	0.038	0.017	0.004	6.03E-06	8.29E-06	+++++++++
HDL-C	rs11043	*ESRP2, NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.14	0.021	0.023	0.005	1.02E-05	1.62E-05	++-++++++
HDL-C	rs660240	*CELSR2*	1	109817838	4	+	1.57E-14	T/C,T	0.23	0.039	0.018	0.004	1.35E-05	1.79E-05	+++++++++
HDL-C	rs12740374	*CELSR2*	1	109817590	7	+	1.69E-15	T/G,T	0.21	0.023	0.018	0.004	1.46E-05	2.45E-05	+++++++++
HDL-C	rs629301	*CELSR2*	1	109818306	8	+	7.61E-13	G/T,T	0.25	0.038	-0.018	0.004	1.57E-05	2.72E-05	---------
HDL-C	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.32	0.020	-0.018	0.004	2.31E-05	3.77E-05	--------?
HDL-C	rs7528419	*CELSR2*	1	109817192	7	+	9.55E-11	G/A,A	0.22	0.016	-0.021	0.005	2.59E-05	3.24E-05	--------?
HDL-C	rs10773003	*SBNO1*	12	123775127	3	+	1.46E-13	A/G,A	0.10	0.010	0.026	0.006	2.60E-05	4.26E-05	+++++++++
HDL-C	rs3741414	*INHBC*	12	57844049	7		6.10E-14	T/C,T	0.27	0.051	0.017	0.004	2.79E-05	4.00E-05	+++++++-+
HDL-C	rs3088303	*SBNO1*	12	123779489	4	+	3.04E-06	A/G,A	0.10	0.011	0.028	0.007	3.72E-05	4.90E-05	++++++++?
HDL-C	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.34	0.037	0.015	0.004	5.05E-05	7.21E-05	+-+++++++
HDL-C	rs473465	*INHBE*	12	57851182	7	+	9.72E-08	A/G,A	0.23	0.054	-0.017	0.004	5.88E-05	9.88E-05	--+--+---
HDL-C	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.44	0.046	0.014	0.004	9.01E-05	0.000113	+++++-+++
HDL-C	rs877710	*MMAB*	12	109993976	10	+	1.86E-17	C/G,C	0.50	0.036	-0.014	0.004	9.20E-05	0.000142	---------
HDL-C	rs11067231	*MMAB*	12	109993603	8	+	2.16E-19	C/A,A	0.45	0.054	0.013	0.004	0.000131	0.000199	+++++++++
HDL-C	rs6499137	*CTCF*	16	67671804	10	+	5.90E-28	G/T,T	0.10	0.029	-0.023	0.006	0.000198	0.000281	--++-+---
HDL-C	rs11570892	*LPL*	8	19823617	10	+	4.81E-24	G/A,A	0.15	0.021	-0.017	0.005	0.000275	0.000386	-+-----+-
HDL-C	rs1044269	*CELF1*	11	47487740	6	+	2.66E-25	G/A,A	0.15	0.041	-0.017	0.005	0.000276	0.000386	---+-----
HDL-C	rs2058807	*UBE3B*	12	109973273	7	+	1.12E-13	T/C,T	0.47	0.038	-0.015	0.004	0.000293	0.000386	--------?
HDL-C	rs10900522	*NUCKS1*	1	205684067	12		1.22E-06	C/T,T	0.22	0.033	0.015	0.004	0.000305	0.000409	+++++++-+
HDL-C	rs4922115	*LPL*	8	19822830	6	+	3.55E-25	A/G,A	0.17	0.018	0.017	0.005	0.000322	0.000451	+-++++++-+
HDL-C	rs1051921	*MLXIPL*	7	73007943	6		1.14E-11	A/G,A	0.18	0.033	0.016	0.005	0.000334	0.00046	+++++++++

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:

MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$) (HDL-C, continued)

Phen	SNP	Gene	Model 2 SNP β	Model 2 SE	Model 2 P value	Model 2 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
HDL-C	rs3735964	*LPL*	0.066	0.005	3.15E-38	+++++++++	0.066	0.005	7.60E-38	+++++++++	38.8	0.11	25112
HDL-C	rs1059611	*LPL*	-0.066	0.005	4.47E-38	---------	-0.065	0.005	1.11E-37	---------	37.4	0.12	25112
HDL-C	rs13702	*LPL*	-0.042	0.004	6.94E-33	---------	-0.042	0.004	8.57E-33	---------	30.4	0.17	25112
HDL-C	rs15285	*LPL*	0.053	0.004	1.37E-34	+++++++++	0.053	0.004	1.54E-34	+++++++++	17	0.29	25112
HDL-C	rs3289	*LPL*	0.073	0.010	7.42E-13	+++++++-+	0.073	0.010	6.02E-13	+++++++-+	34.5	0.14	25112
HDL-C	rs4474673	*RANBP10*	0.031	0.005	4.98E-10	+++++++++	0.031	0.005	4.16E-10	+++++++++	0	0.67	25112
HDL-C	rs2266788	*APOA5*	0.037	0.006	2.17E-09	+++++++++	0.038	0.006	8.54E-10	+++++++++	0	0.68	25112
HDL-C	rs6857	*NECTIN2*	-0.034	0.005	4.01E-13	---------	-0.035	0.005	8.97E-14	---------	50.5	0.04	25112
HDL-C	rs9909	*NUP160*	0.019	0.003	1.64E-08	+++++++++	0.019	0.003	1.10E-08	+++++++++	23.1	0.24	25112
HDL-C	rs174546	*FADS1*	-0.020	0.003	4.25E-09	--+------	-0.020	0.003	2.32E-09	--+------	18.7	0.28	25112
HDL-C	rs1109166	*LCAT*	-0.022	0.004	1.30E-07	--+------	-0.023	0.004	1.03E-07	--+------	0	0.60	25112
HDL-C	rs4246215	*FEN1*	-0.019	0.003	1.37E-08	--+------	-0.019	0.003	6.43E-09	--+------	0	0.47	25112
HDL-C	rs12449157	*GFOD2*	-0.022	0.004	3.43E-07	---+-----	-0.023	0.004	2.46E-07	---+-----	0	0.67	25112
HDL-C	rs174545	*FADS1*	0.020	0.004	9.10E-08	++-+++++?	0.020	0.004	5.79E-08	++-+++++?	28.5	0.20	19004
HDL-C	rs7679	*PCIF1*	0.022	0.004	1.09E-07	+++++++-+	0.022	0.004	1.14E-07	+++++++-+	0	0.62	25111
HDL-C	rs1057233	*SPI1*	0.017	0.004	2.42E-06	+++++++++	0.017	0.004	1.62E-06	+++++++++	11.1	0.34	25112
HDL-C	rs11043	*ESRP2, NFATC3*	0.024	0.005	7.85E-07	+++++++++	0.023	0.005	8.38E-07	+++++++++	0	0.83	25112
HDL-C	rs660240	*CELSR2*	0.019	0.004	1.47E-06	+++++++++	0.019	0.004	1.37E-06	+++++++++	0.3	0.43	25112
HDL-C	rs12740374	*CELSR2*	0.018	0.004	1.36E-06	+++++++++	0.018	0.004	1.14E-06	+++++++++	7.4	0.37	25112
HDL-C	rs629301	*CELSR2*	-0.018	0.004	1.38E-06	---------	-0.018	0.004	1.12E-06	---------	6.2	0.38	25112
HDL-C	rs2293578	*SLC39A13*	-0.016	0.004	2.87E-05	--------?	-0.017	0.004	1.68E-05	--------?	25.8	0.22	19004
HDL-C	rs7528419	*CELSR2*	-0.019	0.004	1.27E-05	--------?	-0.019	0.004	1.05E-05	--------?	18.7	0.28	19004
HDL-C	rs10773003	*SBNO1*	0.030	0.006	6.56E-08	+++++++++	0.029	0.006	1.97E-07	+++++++++	0	0.99	25099
HDL-C	rs3741414	*INHBC*	0.018	0.004	9.55E-07	++++++--+	0.018	0.004	8.55E-07	++++++--+	45.1	0.07	25112
HDL-C	rs3088303	*SBNO1*	0.032	0.006	2.85E-07	++++++++?	0.030	0.006	7.07E-07	++++++++?	0	0.98	19004
HDL-C	rs8468	*LACTB*	0.020	0.003	9.56E-09	+-+++++++	0.019	0.003	1.02E-08	+-+++++++	0	0.67	25103
HDL-C	rs473465	*INHBE*	-0.014	0.004	0.000316	--+---+--	-0.014	0.004	0.000277	--+---+--	15.3	0.31	25112
HDL-C	rs37029	*SLC12A3*	0.013	0.003	8.13E-05	+++++++++	0.012	0.003	0.000106	+++++++++	0	0.55	25112
HDL-C	rs877710	*MMAB*	-0.012	0.003	0.000156	---------	-0.012	0.003	0.000202	---------	0	0.65	25112
HDL-C	rs11067231	*MMAB*	0.012	0.003	0.000216	+++++++++	0.012	0.003	0.000284	+++++++++	0	0.66	25112
HDL-C	rs6499137	*CTCF*	-0.022	0.006	9.15E-05	---+-----	-0.022	0.006	8.76E-05	---+-----	0	0.76	25112
HDL-C	rs11570892	*LPL*	-0.016	0.004	0.000164	-+-----+-	-0.016	0.004	0.000155	-+-------	0	0.66	25112
HDL-C	rs1044269	*CELF1*	-0.020	0.004	4.59E-06	---------	-0.020	0.004	3.84E-06	---------	0	0.97	25112
HDL-C	rs2058807	*UBE3B*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HDL-C	rs10900522	*NUCKS1*	0.014	0.004	0.00032	++++++--+	NA	NA	NA	NA	NA	NA	NA
HDL-C	rs4922115	*LPL*	0.017	0.004	0.000114	+-++++++-+	0.017	0.004	0.000105	+-++++++-+	0	0.61	25112
HDL-C	rs1051921	*MLXIPL*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:

MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$) (LDL-C)

Phen	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/ major, effect)	MAF[2]	FreqSE	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction
LDL-C	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013	0.145	0.010	8.46E-48	6.87E-46	+++++++++
LDL-C	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.40	0.021	-0.067	0.008	1.01E-17	2.55E-17	--+------
LDL-C	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.36	0.027	-0.059	0.009	2.11E-11	3.39E-11	---------
LDL-C	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.43	0.026	0.055	0.008	6.14E-11	1.00E-10	+-+++++++
LDL-C	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.017	-0.064	0.010	6.46E-11	1.22E-10	?--------
LDL-C	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.028	-0.048	0.008	1.15E-09	2.08E-09	---------
LDL-C	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.06	0.008	-0.107	0.019	2.14E-08	3.81E-08	---------
LDL-C	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.35	0.031	0.047	0.009	8.71E-08	1.23E-07	++++++++?
LDL-C	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.008	-0.046	0.009	5.95E-07	7.73E-07	---------
LDL-C	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.35	0.027	0.039	0.009	1.23E-05	1.73E-05	+-+-++++?
LDL-C	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.008	-0.080	0.018	1.32E-05	1.78E-05	------++-
LDL-C	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007	-0.046	0.011	3.31E-05	4.74E-05	------+--
LDL-C	rs10942729	*ANKRD31*	5	74364300	3	+	1.02E-17	A/G,A	0.36	0.018	0.039	0.010	8.42E-05	0.000106	++-+++++?

Supplemental Table 2.1.5. Potential miRNA-related SNPs associated with blood lipids

(B) Replication of the GLGC 2013 top miRNA-related SNPs in the CHARGE consortium:

MiRNA-related SNPs associated with blood lipids at $P < 4 \times 10^{-4}$ in the CHARGE consortium (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-5}$) (LDL-C, continued)

Phen	SNP	Gene	Model 2 SNP β	Model 2 SE	Model 2 P value	Model 2 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het P value	Model 3 N
LDL-C	rs629301	*CELSR2*	0.140	0.010	7.80E-47	+++++++++	0.140	0.010	7.27E-47	+++++++++	28	0.20	23958
LDL-C	rs12916	*HMGCR*	-0.072	0.008	1.16E-17	--+------	-0.071	0.008	3.08E-17	--+------	58	0.01	23958
LDL-C	rs4246215	*FEN1*	-0.061	0.009	1.16E-12	---------	-0.062	0.009	4.40E-13	---------	0	0.54	23958
LDL-C	rs6859	*NECTIN2*	0.071	0.009	1.11E-15	+-+++++++	0.069	0.009	5.79E-15	+-+++++++	28.1	0.19	23958
LDL-C	rs7188	*KANK2*	-0.072	0.010	6.41E-14	---------	-0.072	0.010	8.28E-14	---------	0	0.51	23958
LDL-C	rs174546	*FADS1*	-0.065	0.009	4.61E-14	---------	-0.066	0.009	1.40E-14	---------	0	0.76	23958
LDL-C	rs13465	*ILF3*	-0.110	0.019	5.04E-09	----+----	-0.107	0.019	1.07E-08	----+----	38.1	0.11	23957
LDL-C	rs174545	*FADS1*	0.069	0.010	2.72E-12	++++++++?	0.070	0.010	8.48E-13	++++++++?	0	0.77	17853
LDL-C	rs1433099	*LDLR*	-0.047	0.010	2.01E-06	---------	-0.047	0.010	1.80E-06	---------	0	0.64	23958
LDL-C	rs583609	*USP1*	0.053	0.010	9.05E-08	+++-++++?	0.053	0.010	1.07E-07	+++-++++?	0	0.47	17853
LDL-C	rs3810444	*SUGP2*	-0.079	0.018	1.03E-05	------+--	-0.079	0.018	1.07E-05	------+--	12.9	0.33	23958
LDL-C	rs17034539	*KIAA1324*	-0.047	0.011	1.73E-05	---------	-0.047	0.011	2.17E-05	------+--	0	0.59	23958
LDL-C	rs10942729	*ANKRD31*	0.040	0.010	4.33E-05	++-+++++?	0.039	0.010	5.80E-05	++-+++++?	0	0.78	17853

Abbreviations: Phen, phenotype; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; FreqSE, standard error of MAF; GC1, single genomic control correction; GC2, double genomic control correction; β, beta coefficient; SE, standard error; I^2, heterogeneity index; Het, heterogeneity test statistic; miR, miRNA; eQTL, expression quantitative trait loci; Exp, expression.

Additive allele mode. Basic association analyses (Model 1) adjusted for age, sex and study-specific covariates (e.g., family relationship, study site, population stratification by principal components, when applicable). Model 2 adjusted for Model 1 covariates and body mass index; and Model 3 adjusted for Model 2 covariates and diabetes mellitus status [as dichotomous variable]. Association beta coefficients are shown as β (SE). β represents the change in ln-TG, HDL-C or LDL-C (mmol/L) per each additional copy of the effect allele. Study order in direction: ARIC, GOLDN, GOYA, InCHIANTI, RSI/II/III, YFS and Inter99.

[1]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicate the number of the data source.

[2]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
TGCHO	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.34	0.025
TGCHO	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGCHO	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.4	0.034
TGCHO	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGCHO	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGCHO	rs8731	*GPN1*	2	27873326	11	+	1.04E-35	G/C,C	0.22	0.01
TGCHO	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.01
TGCHO	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGCHO	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.2	0.016
TGCHO	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGCHO	rs3735964	*LPL*	8	19824045	9		3.92E-187	A/C,A	0.11	0.011
TGCHO	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGCHO	rs1059611	*LPL*	8	19824563	13	+	1.13E-190	C/T,T	0.11	0.011
TGCHO	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGCHO	rs1129555	*GPAM*	10	113910721	4		6.72E-09	A/G,A	0.29	0.015
TGCHO	rs174545	*FADS1*	11	61569306	13	+	1.03E-26	G/C,C	0.34	0.029
TGCHO	rs2266788	*APOA5*	11	116660686	10		4.08E-232	G/A,A	0.07	0.006
TGCHO	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGCHO	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGCHO	rs10892082	*PAFAH1B2*	11	117039325	3	+	9.27E-40	T/G,T	0.11	0.012
TGCHO	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009
TGCHO	rs2285628	*MAU2*	19	19467996	11	+	1.91E-24	A/T,A	0.18	0.022
TGCHO	rs6857	*NECTIN2*	19	45392254	6		4.55E-19	T/C,T	0.16	0.023
TGCHO	rs10119	*TOMM40*	19	45406673	8		3.85E-12	A/G,A	0.29	0.026
TGCHO	rs7679	*PCIF1*	20	44576502	3		8.44E-31	C/T,T	0.18	0.014
TGSFA	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.34	0.025
TGSFA	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGSFA	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.4	0.034
TGSFA	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGSFA	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGSFA	rs8731	*GPN1*	2	27873326	11	+	1.04E-35	G/C,C	0.22	0.01
TGSFA	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.01
TGSFA	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGSFA	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.2	0.016
TGSFA	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGSFA	rs3735964	*LPL*	8	19824045	9		3.92E-187	A/C,A	0.11	0.011
TGSFA	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGSFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-190	C/T,T	0.11	0.011
TGSFA	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGSFA	rs1129555	*GPAM*	10	113910721	4		6.72E-09	A/G,A	0.29	0.015
TGSFA	rs174545	*FADS1*	11	61569306	13	+	1.03E-26	G/C,C	0.34	0.029
TGSFA	rs2266788	*APOA5*	11	116660686	10		4.08E-232	G/A,A	0.07	0.006
TGSFA	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGSFA	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGSFA	rs10892082	*PAFAH1B2*	11	117039325	3	+	9.27E-40	T/G,T	0.11	0.012
TGSFA	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009
TGSFA	rs2285628	*MAU2*	19	19467996	11	+	1.91E-24	A/T,A	0.18	0.022
TGSFA	rs6857	*NECTIN2*	19	45392254	6		4.55E-19	T/C,T	0.16	0.023
TGSFA	rs10119	*TOMM40*	19	45406673	8		3.85E-12	A/G,A	0.29	0.026
TGSFA	rs7679	*PCIF1*	20	44576502	3		8.44E-31	C/T,T	0.18	0.014

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
TGCHO	rs583609	*USP1*	0.0541	0.0313	-0.0005	0.0006	4.65E-07	7.58E-07	+--+-+++?	-++-+---?
TGCHO	rs13472	*SNX17, ZNF513*	0.0079	0.0306	-0.0009	0.0006	3.20E-11	8.24E-11	+---+-++?	-+++----?
TGCHO	rs4582	*PPM1G*	-0.0029	0.0306	0.0008	0.0006	2.39E-11	5.39E-11	-+++-+--?	+---++++?
TGCHO	rs8395	*FNDC4*	0.0064	0.0306	-0.0009	0.0006	4.35E-12	8.33E-12	+---+-++?	-+++-+--?
TGCHO	rs1881396	*ZNF512*	0.0646	0.0319	-0.0008	0.0007	1.80E-05	2.38E-05	++--+++++	--++-----
TGCHO	rs8731	*GPN1*	0.0604	0.0316	-0.0008	0.0006	9.01E-05	0.000137	++--+++++	--+++----
TGCHO	rs13232120	*TBL2*	0.0088	0.04	0.0011	0.0008	6.43E-19	6.40E-18	++-+-----	--+++++++
TGCHO	rs14415	*TBL2*	0.0322	0.0295	0.0002	0.0006	1.96E-15	1.85E-14	+--+--++-	-++-++--+
TGCHO	rs1051921	*MLXIPL*	-0.0189	0.0338	-0.0007	0.0007	3.62E-19	1.38E-18	--+-+++++	++-+-----
TGCHO	rs3289	*LPL*	-0.2634	0.0852	0.0036	0.0017	1.25E-09	4.15E-09	-----+---	+++-+-+++
TGCHO	rs3735964	*LPL*	-0.0762	0.0412	-0.0002	0.0008	2.53E-32	6.52E-31	------+--	++-++--++
TGCHO	rs13702	*LPL*	0.044	0.0287	0.0002	0.0006	6.25E-26	6.55E-25	++--+++++	+-++-+--+
TGCHO	rs1059611	*LPL*	0.0744	0.0412	0.0003	0.0008	2.68E-32	7.46E-31	++++++-++	--+--++-+
TGCHO	rs15285	*LPL*	-0.0565	0.0355	-0.0002	0.0007	1.98E-24	3.31E-23	-----+---	-++-+--+-
TGCHO	rs1129555	*GPAM*	0.0135	0.029	-0.0007	0.0006	0.000187	0.000282	++-+-+-++	--+---+--
TGCHO	rs174545	*FADS1*	0.0147	0.0311	-0.0008	0.0006	2.45E-05	4.66E-05	+---+++-?	-+++---+?
TGCHO	rs2266788	*APOA5*	-0.117	0.0555	0	0.0011	2.27E-33	4.14E-31	-++-+----	+--+-+-++
TGCHO	rs619054	*APOA5*	-0.0518	0.0307	0.0004	0.0006	1.41E-08	3.11E-08	--+-+----	-+-+-+++-
TGCHO	rs1035237	*SIK3*	-0.0641	0.0478	0.0004	0.001	5.67E-07	9.77E-07	----++--?	++++---+?
TGCHO	rs10892082	*PAFAH1B2*	0.0752	0.0477	-0.0008	0.001	3.92E-05	6.30E-05	++++--++?	----++--?
TGCHO	rs3810444	*SUGP2*	-0.0994	0.0539	0.0009	0.0011	1.05E-07	2.29E-07	-++-+-++-	+--+-+--+
TGCHO	rs2285628	*MAU2*	-0.0235	0.0341	-0.0001	0.0007	6.62E-05	0.000102	++----+--	--+++--++
TGCHO	rs6857	*NECTIN2*	0.022	0.0393	0.0003	0.0008	1.32E-07	2.45E-07	-+++++++-	+---+-+-+
TGCHO	rs10119	*TOMM40*	0.046	0.035	-0.0004	0.0007	2.83E-05	4.13E-05	+++--++++	---++-+--
TGCHO	rs7679	*PCIF1*	-0.0447	0.0345	0.0004	0.0007	0.000115	0.000157	-+-+---+-	--+-+++-+
TGSFA	rs583609	*USP1*	0.0253	0.0223	0.0004	0.0017	5.36E-07	1.09E-06	+++++++-?	+----+-+?
TGSFA	rs13472	*SNX17, ZNF513*	-0.0497	0.0215	0.0011	0.0017	4.69E-11	1.44E-10	--++-+--?	+-----+-?
TGSFA	rs4582	*PPM1G*	0.0481	0.0214	-0.0009	0.0017	3.20E-11	7.24E-11	++-++-++?	-++++++-+?
TGSFA	rs8395	*FNDC4*	-0.0515	0.0215	0.0011	0.0017	6.30E-12	1.99E-11	-+++-+--?	+-----+-?
TGSFA	rs1881396	*ZNF512*	0.0116	0.0216	0.0011	0.0017	4.16E-05	5.64E-05	++-+++-++	+++--++++
TGSFA	rs8731	*GPN1*	0.0055	0.0213	0.0014	0.0017	0.000158	0.000219	++++++--+	+++--++++
TGSFA	rs13232120	*TBL2*	0.0956	0.0273	-0.0027	0.0021	9.94E-19	5.92E-18	--+++++++	++-------
TGSFA	rs14415	*TBL2*	0.0444	0.0198	-0.0003	0.0016	3.91E-15	1.25E-14	-++++-++	+--+--+--
TGSFA	rs1051921	*MLXIPL*	-0.0825	0.023	0.0024	0.0018	5.38E-19	3.89E-18	++-------	--+++++++
TGSFA	rs3289	*LPL*	-0.0134	0.0601	-0.006	0.0047	1.50E-08	3.22E-08	+----+-+-	-++++-+--
TGSFA	rs3735964	*LPL*	-0.0771	0.0282	-0.0008	0.0022	4.14E-32	6.53E-31	-+-------	--++--+++
TGSFA	rs13702	*LPL*	0.0514	0.0196	0.0002	0.0015	1.10E-25	5.31E-25	+--+-++++	+++-++---
TGSFA	rs1059611	*LPL*	0.0797	0.0282	0.0006	0.0022	4.46E-32	5.89E-31	+-+++++++	++--++---
TGSFA	rs15285	*LPL*	-0.0563	0.0235	-0.0006	0.0019	4.98E-24	5.96E-23	-+-------	--++-+-++
TGSFA	rs1129555	*GPAM*	-0.043	0.0199	0.0019	0.0016	0.000247	0.000377	------+--	++-+++-++
TGSFA	rs174545	*FADS1*	-0.0523	0.0224	0.0023	0.0018	3.69E-05	5.87E-05	--+-----?	++-+++++?
TGSFA	rs2266788	*APOA5*	-0.0716	0.0364	-0.0034	0.0029	3.23E-32	1.01E-30	--------	--++-+++-
TGSFA	rs619054	*APOA5*	-0.014	0.0208	-0.0015	0.0016	1.30E-08	2.59E-08	-+---++--	--+++--++
TGSFA	rs1035237	*SIK3*	0.0014	0.034	-0.0037	0.0027	5.38E-07	1.02E-06	+++++---?	-----+-+?
TGSFA	rs10892082	*PAFAH1B2*	-0.0045	0.0341	0.0034	0.0027	3.26E-05	4.77E-05	+----++-?	+++++-++?
TGSFA	rs3810444	*SUGP2*	-0.0272	0.037	-0.0022	0.0029	1.11E-07	1.73E-07	---+--+-+	-+--+--+-
TGSFA	rs2285628	*MAU2*	-0.0068	0.0227	-0.0016	0.0018	5.19E-05	7.79E-05	---+-++-+	++-----+-
TGSFA	rs6857	*NECTIN2*	0.0145	0.0264	0.0019	0.0021	1.68E-07	2.94E-07	+---+-+-+	++++-+-++
TGSFA	rs10119	*TOMM40*	0.006	0.0234	0.0018	0.0018	2.09E-05	2.91E-05	+-+-+++--	++-+-+-++
TGSFA	rs7679	*PCIF1*	0.0047	0.0237	-0.0024	0.0019	9.75E-05	0.000145	--+--++--	-+-+---+-

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
TGCHO	rs583609	*USP1*	3.81E-08	0.0459	0.0292	-0.0003	0.0006	1.55E-08	+--+-+++?	-++-+-+-?	0.27	16110
TGCHO	rs13472	*SNX17, ZNF513*	1.11E-11	0.0032	0.0288	-0.0008	0.0006	6.77E-12	+---+--+?	-+++-+--?	0.79	16110
TGCHO	rs4582	*PPM1G*	1.07E-11	0.0006	0.0287	0.0007	0.0006	5.43E-12	++++-++-?	+---+-++?	0.77	16110
TGCHO	rs8395	*FNDC4*	1.07E-12	0.0023	0.0288	-0.0008	0.0006	6.76E-13	+-+-+--+?	-+++-+--?	0.71	16110
TGCHO	rs1881396	*ZNF512*	5.64E-07	0.0713	0.0297	-0.0009	0.0006	1.94E-07	++--+++++	--++-----	0.85	22103
TGCHO	rs8731	*GPN1*	2.96E-06	0.0666	0.0295	-0.0009	0.0006	1.31E-06	++-++++++	--+------	0.76	22103
TGCHO	rs13232120	*TBL2*	3.21E-21	0.0207	0.0381	0.0009	0.0008	1.61E-21	++-------	--+++++++	0.68	22103
TGCHO	rs14415	*TBL2*	2.44E-19	0.0444	0.0276	0	0.0006	2.16E-19	++-+--++-	--+++-++	0.73	22103
TGCHO	rs1051921	*MLXIPL*	6.02E-22	-0.0321	0.0319	-0.0005	0.0007	2.67E-22	--+-+++++	++-+-----	0.39	22103
TGCHO	rs3289	*LPL*	6.17E-12	-0.1902	0.0765	0.002	0.0016	1.50E-11	---+-+---	+---+-+++	0.51	22103
TGCHO	rs3735964	*LPL*	6.84E-37	-0.076	0.0395	-0.0003	0.0008	6.34E-37	--+------	-+--+---+	0.56	22103
TGCHO	rs13702	*LPL*	2.52E-29	0.0553	0.0273	0	0.0006	1.39E-29	++--+-+++	--++-+---	0.94	22103
TGCHO	rs1059611	*LPL*	7.69E-37	0.0741	0.0395	0.0003	0.0008	7.66E-37	++-++++++	+-++-+++-	0.59	22103
TGCHO	rs15285	*LPL*	1.80E-27	-0.0645	0.0338	0	0.0007	2.71E-28	--++-+---	-+--+-+++	0.83	22103
TGCHO	rs1129555	*GPAM*	0.000321	0.0121	0.0275	-0.0006	0.0006	0.000417	++-+++-+-	------+--	0.59	22103
TGCHO	rs174545	*FADS1*	6.67E-06	0.0085	0.0289	-0.0007	0.0006	2.07E-06	+----++-?	-+++---+?	0.65	16110
TGCHO	rs2266788	*APOA5*	2.70E-36	-0.1266	0.0513	0.0003	0.001	3.06E-37	-++-+----	+--+-++++	0.39	22103
TGCHO	rs619054	*APOA5*	3.05E-09	-0.0459	0.0291	0.0003	0.0006	3.92E-09	--+-+----	-+-+-+++-	0.03	22103
TGCHO	rs1035237	*SIK3*	2.71E-08	-0.0828	0.0453	0.0008	0.0009	4.37E-08	----++--?	++++---+?	0.2	16110
TGCHO	rs10892082	*PAFAH1B2*	4.42E-06	0.082	0.0452	-0.0009	0.0009	8.78E-06	++++--++?	----++--?	0.04	16109
TGCHO	rs3810444	*SUGP2*	1.33E-07	-0.0892	0.0524	0.0007	0.0011	6.31E-08	-++-+-++-	+--+-+--+	0.1	22103
TGCHO	rs2285628	*MAU2*	1.64E-05	-0.0228	0.0322	-0.0001	0.0007	7.62E-06	+++---+--	---+++-++	0.11	22103
TGCHO	rs6857	*NECTIN2*	7.61E-11	-0.0184	0.0373	0.0013	0.0008	1.84E-11	+++-++++-	+-+++++-+	0.02	22103
TGCHO	rs10119	*TOMM40*	1.27E-06	0.014	0.0332	0.0003	0.0007	5.60E-07	+++--+--+	+--++-++-	0.17	22103
TGCHO	rs7679	*PCIF1*	2.69E-05	-0.0451	0.0322	0.0004	0.0007	1.50E-05	-+-+---+-	--+-+++-+	0.18	22102
TGSFA	rs583609	*USP1*	4.10E-08	0.0294	0.0211	0.0001	0.0017	1.96E-08	+++++++-?	+---++-+?	0.21	16110
TGSFA	rs13472	*SNX17, ZNF513*	9.00E-12	-0.0621	0.0209	0.0021	0.0016	5.49E-12	--+--+--?	+--++-++?	0.8	16110
TGSFA	rs4582	*PPM1G*	7.44E-12	0.0624	0.0208	-0.0022	0.0016	3.97E-12	++-++-++?	-++--+--?	0.8	16110
TGSFA	rs8395	*FNDC4*	7.74E-13	-0.0649	0.0208	0.0022	0.0016	5.01E-13	--+--+--?	+--++-++?	0.66	16110
TGSFA	rs1881396	*ZNF512*	1.97E-06	0.0135	0.0204	0.0011	0.0016	6.13E-07	++++-+--+	+-+-++++-	0.72	22103
TGSFA	rs8731	*GPN1*	8.41E-06	0.0088	0.0202	0.0014	0.0016	3.20E-06	++++-+--+	+---++++-	0.55	22103
TGSFA	rs13232120	*TBL2*	6.69E-21	0.0797	0.0258	-0.0013	0.002	4.44E-21	--+++++++	++-----++	0.31	22103
TGSFA	rs14415	*TBL2*	7.82E-19	0.0339	0.0187	0.0008	0.0015	4.48E-19	-++-++-++	++-+--++-	0.78	22103
TGSFA	rs1051921	*MLXIPL*	2.56E-21	-0.0706	0.0218	0.0014	0.0017	1.14E-21	++-------	--+-+++-+	0.3	22103
TGSFA	rs3289	*LPL*	1.80E-10	-0.0553	0.0544	-0.0029	0.0043	1.75E-10	+----+-+-	-++++-+--	0.22	22103
TGSFA	rs3735964	*LPL*	6.27E-37	-0.0892	0.0273	0	0.0022	5.71E-37	-+-------	--++--+++	0.29	22103
TGSFA	rs13702	*LPL*	4.51E-29	0.0504	0.0188	0.0004	0.0015	1.77E-29	+-++-++++	+++-+--++	0.88	22103
TGSFA	rs1059611	*LPL*	6.61E-37	0.0922	0.0273	-0.0003	0.0022	6.46E-37	+-+++++++	++--++---	0.32	22103
TGSFA	rs15285	*LPL*	8.34E-28	-0.0576	0.0226	-0.0007	0.0018	2.06E-28	-+-------	--++-+-+-	0.51	22103
TGSFA	rs1129555	*GPAM*	0.000356	-0.0373	0.019	0.0015	0.0015	0.000425	------+--	+++++++-++	0.42	22103
TGSFA	rs174545	*FADS1*	6.10E-06	-0.0511	0.0208	0.0021	0.0016	2.43E-06	--+----+?	++-++++-?	0.79	16110
TGSFA	rs2266788	*APOA5*	4.05E-35	-0.0824	0.0341	-0.0024	0.0027	4.51E-36	---------	--++---+-	0.77	22103
TGSFA	rs619054	*APOA5*	4.36E-09	-0.0195	0.02	-0.001	0.0016	5.95E-09	-++--++--	---++--++	0.1	22103
TGSFA	rs1035237	*SIK3*	1.11E-08	-0.0018	0.0323	-0.0036	0.0026	1.71E-08	+++++---?	-----+-+?	0.18	16110
TGSFA	rs10892082	*PAFAH1B2*	2.16E-06	0.0029	0.0326	0.0029	0.0026	4.02E-06	+----++-?	+++++-++?	0.23	16109
TGSFA	rs3810444	*SUGP2*	8.24E-08	-0.0306	0.0357	-0.0019	0.0028	3.25E-08	---+--+-+	+++-++---	0.29	22103
TGSFA	rs2285628	*MAU2*	1.14E-05	-0.0111	0.0218	-0.0013	0.0017	4.14E-06	---++-+-+	+++------	0.07	22103
TGSFA	rs6857	*NECTIN2*	5.39E-10	0.0335	0.0249	0.0008	0.002	1.73E-10	+-+-+++-+	++-+-+-++	0.002	22103
TGSFA	rs10119	*TOMM40*	1.76E-06	0.0168	0.0221	0.0011	0.0017	7.33E-07	+-+-+++-+	-+-+-+-++	0.23	22103
TGSFA	rs7679	*PCIF1*	2.27E-05	-0.0052	0.0222	-0.0017	0.0017	1.34E-05	--+--++--	-+-+---+-	0.59	22102

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
TGCHO	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGCHO	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGCHO	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGCHO	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.037	0.0047	4.94E-15	--+-----?	0	0.48
TGCHO	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.005	2.00E-08	+++++++++	0	0.67
TGCHO	rs8731	*GPN1*	0.015	0.0041	3.04E-04	3.10E-04	+++-+-+++	0.0259	0.005	2.02E-07	+++++++++	0	0.61
TGCHO	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGCHO	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGCHO	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGCHO	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGCHO	rs3735964	*LPL*	NA	NA	NA	NA	NA	-0.0873	0.0066	3.78E-40	---------	0.9	0.43
TGCHO	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGCHO	rs1059611	*LPL*	NA	NA	NA	NA	NA	0.0871	0.0066	4.96E-40	+++++++++	0	0.53
TGCHO	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGCHO	rs1129555	*GPAM*	-0.0095	0.0039	1.42E-02	1.63E-02	-+-+--+--	-0.0183	0.0046	7.55E-05	-+-+-----	0	0.53
TGCHO	rs174545	*FADS1*	-0.0103	0.0038	7.24E-03	7.54E-03	--+-----?	-0.0252	0.0049	2.38E-07	--+-----?	0	0.68
TGCHO	rs2266788	*APOA5*	NA	NA	NA	NA	NA	-0.1136	0.0081	8.86E-45	---------	35.9	0.13
TGCHO	rs619054	*APOA5*	-0.0158	0.0041	1.37E-04	1.45E-04	-------+-	-0.0285	0.005	9.60E-09	--+----+-	47.6	0.05
TGCHO	rs1035237	*SIK3*	-0.025	0.0059	2.38E-05	2.95E-05	--------?	-0.0442	0.0073	1.68E-09	--------?	0	0.69
TGCHO	rs10892082	*PAFAH1B2*	0.0174	0.0059	3.53E-03	3.65E-03	++++++++?	0.0367	0.0075	9.44E-07	++++++++?	0	0.65
TGCHO	rs3810444	*SUGP2*	-0.0364	0.008	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13
TGCHO	rs2285628	*MAU2*	-0.0147	0.0045	1.18E-03	1.28E-03	-----+---	-0.0266	0.0054	8.35E-07	---------	48.7	0.05
TGCHO	rs6857	*NECTIN2*	0.0178	0.005	3.43E-04	4.49E-04	+++--++++	0.0418	0.0061	7.39E-12	+++-+++++	56.4	0.02
TGCHO	rs10119	*TOMM40*	0.0115	0.0044	8.48E-03	9.98E-03	+++--++++	0.0278	0.0054	2.44E-07	+++-+++++	39.5	0.1
TGCHO	rs7679	*PCIF1*	-0.0082	0.0044	6.04E-02	6.62E-02	---+++---	-0.0278	0.0053	1.83E-07	--++-----	0	0.54
TGSFA	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGSFA	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGSFA	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGSFA	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.037	0.0047	4.94E-15	--+-----?	0	0.48
TGSFA	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.005	2.00E-08	+++++++++	0	0.67
TGSFA	rs8731	*GPN1*	0.015	0.0041	3.04E-04	3.10E-04	+++-+-+++	0.0259	0.005	2.02E-07	+++++++++	0	0.61
TGSFA	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGSFA	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGSFA	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGSFA	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGSFA	rs3735964	*LPL*	NA	NA	NA	NA	NA	-0.0873	0.0066	3.78E-40	---------	0.9	0.43
TGSFA	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGSFA	rs1059611	*LPL*	NA	NA	NA	NA	NA	0.0871	0.0066	4.96E-40	+++++++++	0	0.53
TGSFA	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGSFA	rs1129555	*GPAM*	-0.0095	0.0039	1.42E-02	1.63E-02	-+-+--+--	-0.0183	0.0046	7.55E-05	-+-+-----	0	0.53
TGSFA	rs174545	*FADS1*	-0.0103	0.0038	7.24E-03	7.54E-03	--+-----?	-0.0252	0.0049	2.38E-07	--+-----?	0	0.68
TGSFA	rs2266788	*APOA5*	NA	NA	NA	NA	NA	-0.1136	0.0081	8.86E-45	---------	35.9	0.13
TGSFA	rs619054	*APOA5*	-0.0158	0.0041	1.37E-04	1.45E-04	-------+-	-0.0285	0.005	9.60E-09	--+----+-	47.6	0.05
TGSFA	rs1035237	*SIK3*	-0.025	0.0059	2.38E-05	2.95E-05	--------?	-0.0442	0.0073	1.68E-09	--------?	0	0.69
TGSFA	rs10892082	*PAFAH1B2*	0.0174	0.0059	3.53E-03	3.65E-03	++++++++?	0.0367	0.0075	9.44E-07	++++++++?	0	0.65
TGSFA	rs3810444	*SUGP2*	-0.0364	0.008	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13
TGSFA	rs2285628	*MAU2*	-0.0147	0.0045	1.18E-03	1.28E-03	-----+---	-0.0266	0.0054	8.35E-07	---------	48.7	0.05
TGSFA	rs6857	*NECTIN2*	0.0178	0.005	3.43E-04	4.49E-04	+++--++++	0.0418	0.0061	7.39E-12	+++-+++++	56.4	0.02
TGSFA	rs10119	*TOMM40*	0.0115	0.0044	8.48E-03	9.98E-03	+++--++++	0.0278	0.0054	2.44E-07	+++-+++++	39.5	0.1
TGSFA	rs7679	*PCIF1*	-0.0082	0.0044	6.04E-02	6.62E-02	---+++---	-0.0278	0.0053	1.83E-07	--++-----	0	0.54

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis (A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
TGMUFA	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.34	0.025
TGMUFA	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGMUFA	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.4	0.034
TGMUFA	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGMUFA	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGMUFA	rs8731	*GPN1*	2	27873326	11	+	1.04E-35	G/C,C	0.22	0.01
TGMUFA	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.01
TGMUFA	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGMUFA	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.2	0.016
TGMUFA	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGMUFA	rs3735964	*LPL*	8	19824045	9		3.92E-187	A/C,A	0.11	0.011
TGMUFA	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGMUFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-190	C/T,T	0.11	0.011
TGMUFA	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGMUFA	rs1129555	*GPAM*	10	113910721	4		6.72E-09	A/G,A	0.29	0.015
TGMUFA	rs174545	*FADS1*	11	61569306	13	+	1.03E-26	G/C,C	0.34	0.029
TGMUFA	rs2266788	*APOA5*	11	116660686	10		4.08E-232	G/A,A	0.07	0.006
TGMUFA	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGMUFA	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGMUFA	rs10892082	*PAFAH1B2*	11	117039325	3	+	9.27E-40	T/G,T	0.11	0.012
TGMUFA	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009
TGMUFA	rs2285628	*MAU2*	19	19467996	11	+	1.91E-24	A/T,A	0.18	0.022
TGMUFA	rs6857	*NECTIN2*	19	45392254	6		4.55E-19	T/C,T	0.16	0.023
TGMUFA	rs10119	*TOMM40*	19	45406673	8		3.85E-12	A/G,A	0.29	0.026
TGMUFA	rs7679	*PCIF1*	20	44576502	3		8.44E-31	C/T,T	0.18	0.014
TGPUFA	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.35	0.019
TGPUFA	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGPUFA	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.4	0.034
TGPUFA	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGPUFA	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGPUFA	rs8731	*GPN1*	2	27873326	11	+	1.04E-35	G/C,C	0.22	0.01
TGPUFA	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.01
TGPUFA	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGPUFA	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.2	0.016
TGPUFA	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGPUFA	rs3735964	*LPL*	8	19824045	9		3.92E-187	A/C,A	0.11	0.011
TGPUFA	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGPUFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-190	C/T,T	0.11	0.011
TGPUFA	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGPUFA	rs174545	*FADS1*	11	61569306	13	+	1.03E-26	G/C,C	0.34	0.029
TGPUFA	rs2266788	*APOA5*	11	116660686	10		4.08E-232	G/A,A	0.07	0.006
TGPUFA	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGPUFA	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGPUFA	rs10892082	*PAFAH1B2*	11	117039325	3	+	9.27E-40	T/G,T	0.11	0.012
TGPUFA	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009
TGPUFA	rs2285628	*MAU2*	19	19467996	11	+	1.91E-24	A/T,A	0.18	0.022
TGPUFA	rs6857	*NECTIN2*	19	45392254	6		4.55E-19	T/C,T	0.16	0.023
TGPUFA	rs10119	*TOMM40*	19	45406673	8		3.85E-12	A/G,A	0.29	0.026
TGPUFA	rs7679	*PCIF1*	20	44576502	3		8.44E-31	C/T,T	0.18	0.014

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis (A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
TGMUFA	rs583609	*USP1*	0.0395	0.0225	-0.0008	0.0018	4.71E-07	1.02E-06	-++-+-+-?	+--+-+++?
TGMUFA	rs13472	*SNX17, ZNF513*	-0.0334	0.0214	-0.0002	0.0017	6.52E-11	1.85E-10	-+-+----?	+-+-----?
TGMUFA	rs4582	*PPM1G*	0.0335	0.0214	0.0002	0.0017	4.32E-11	1.12E-10	+-+-++++?	-+-+++++?
TGMUFA	rs8395	*FNDC4*	-0.0361	0.0214	-0.0001	0.0017	8.81E-12	2.95E-11	-+-+-+--?	+-+-----?
TGMUFA	rs1881396	*ZNF512*	0.0308	0.0219	-0.0005	0.0018	3.66E-05	5.91E-05	+--++--+	+++---++-
TGMUFA	rs8731	*GPN1*	0.0317	0.0216	-0.0007	0.0018	0.000172	0.000254	++++++--+	+++---++-
TGMUFA	rs13232120	*TBL2*	0.1122	0.0281	-0.0042	0.0023	2.02E-19	1.41E-18	+-++++++++	++-------
TGMUFA	rs14415	*TBL2*	0.0669	0.0196	-0.0021	0.0016	3.59E-16	2.03E-15	+++++++++	+-----++-
TGMUFA	rs1051921	*MLXIPL*	-0.0808	0.0227	0.0023	0.0019	1.74E-19	1.35E-18	++-------	--++++++-+
TGMUFA	rs3289	*LPL*	0.0343	0.0563	-0.01	0.0046	7.17E-09	1.72E-08	+-+--++++	-+-++----
TGMUFA	rs3735964	*LPL*	-0.0841	0.0264	-0.0003	0.0021	2.90E-32	5.60E-31	-+-----+-	--+--++-+
TGMUFA	rs13702	*LPL*	0.0487	0.0193	0.0004	0.0016	5.69E-26	7.87E-25	+--++++++	+++++-++-
TGMUFA	rs1059611	*LPL*	0.0841	0.0264	0.0002	0.0021	3.11E-32	1.04E-30	+-++++++-+	++-++--+-
TGMUFA	rs15285	*LPL*	-0.0494	0.0228	-0.0012	0.0019	2.98E-24	4.16E-23	-+-+---+-	--+--+--+
TGMUFA	rs1129555	*GPAM*	-0.0696	0.0201	0.0042	0.0016	2.14E-05	3.44E-05	--+---+--	++-+++-++
TGMUFA	rs174545	*FADS1*	-0.0613	0.0216	0.0031	0.0017	2.37E-05	4.21E-05	--+----+?	++-++++-?
TGMUFA	rs2266788	*APOA5*	-0.0492	0.0355	-0.0055	0.0029	8.80E-33	2.97E-31	+--+-----	-++-+--+-
TGMUFA	rs619054	*APOA5*	0.0178	0.0209	-0.0042	0.0017	6.75E-10	1.89E-09	-++--++--	-------+-
TGMUFA	rs1035237	*SIK3*	0.0075	0.0333	-0.0044	0.0027	9.36E-08	2.02E-07	+++++---?	-----+-+?
TGMUFA	rs10892082	*PAFAH1B2*	-0.0081	0.0335	0.0038	0.0027	1.27E-05	2.10E-05	----++++?	+++++-+-?
TGMUFA	rs3810444	*SUGP2*	-0.0168	0.0372	-0.0031	0.0031	1.58E-07	2.80E-07	+-------+	-+-++-+--
TGMUFA	rs2285628	*MAU2*	-0.0086	0.0229	-0.0015	0.0019	5.54E-05	8.69E-05	----+-+-+	++-+-+-+-
TGMUFA	rs6857	*NECTIN2*	0.038	0.0265	-0.0001	0.0022	4.36E-07	9.15E-07	+-++++-+	-+---++++
TGMUFA	rs10119	*TOMM40*	0.0276	0.0229	0	0.0019	3.83E-05	6.16E-05	+++-+++--	-+---++++
TGMUFA	rs7679	*PCIF1*	0.0083	0.0232	-0.0028	0.0019	8.76E-05	0.000132	--+++++-+	++-----+-
TGPUFA	rs583609	*USP1*	0.0273	0.016	0	0.0025	2.73E-05	4.48E-05	+++++-+??	-+-+-++??
TGPUFA	rs13472	*SNX17, ZNF513*	-0.0474	0.0147	0.0021	0.0024	8.41E-11	2.69E-10	-+++----?	+---+-++?
TGPUFA	rs4582	*PPM1G*	0.0481	0.0146	-0.0021	0.0024	5.12E-11	1.40E-10	+---+-++?	-+++-+--?
TGPUFA	rs8395	*FNDC4*	-0.0496	0.0146	0.0022	0.0024	1.26E-11	3.71E-11	-+++----?	+---+-++?
TGPUFA	rs1881396	*ZNF512*	0.0346	0.0156	-0.0016	0.0026	2.28E-05	3.80E-05	++++++--+	------++-
TGPUFA	rs8731	*GPN1*	0.0354	0.0154	-0.0022	0.0026	0.000116	0.000167	++++++--+	------++-
TGPUFA	rs13232120	*TBL2*	0.0914	0.0202	-0.0054	0.0034	2.01E-18	1.27E-17	+-++++++-+	-+-+---+-
TGPUFA	rs14415	*TBL2*	0.0572	0.0145	-0.0029	0.0024	2.89E-15	1.21E-14	-++-+++-+	+--+---+-
TGPUFA	rs1051921	*MLXIPL*	-0.0771	0.0168	0.0045	0.0028	1.15E-18	8.58E-18	-+-----+-	--+-+++-+
TGPUFA	rs3289	*LPL*	0.0303	0.0405	-0.021	0.007	1.72E-09	4.41E-09	+-++-++++	-+-------
TGPUFA	rs3735964	*LPL*	-0.0719	0.0203	-0.0028	0.0034	8.30E-33	3.01E-31	-+-++--+-	--+--+--+
TGPUFA	rs13702	*LPL*	0.0438	0.0138	0.0018	0.0023	4.05E-26	5.36E-25	+----++-+	+++++--++
TGPUFA	rs1059611	*LPL*	0.0709	0.0203	0.003	0.0034	8.92E-33	2.49E-31	+-+--++-+	++-++-++-
TGPUFA	rs15285	*LPL*	-0.0203	0.0174	-0.0081	0.003	3.08E-26	4.00E-25	++-++--+-	--+--+---
TGPUFA	rs174545	*FADS1*	-0.0231	0.0153	-0.0002	0.0025	9.06E-05	0.000143	-+++---+?	-----++-?
TGPUFA	rs2266788	*APOA5*	-0.1019	0.0271	-0.0024	0.0047	8.71E-33	3.31E-31	---------	-+++---++
TGPUFA	rs619054	*APOA5*	-0.0216	0.0153	-0.002	0.0026	1.58E-08	3.56E-08	-+++-++--	+------++
TGPUFA	rs1035237	*SIK3*	-0.0268	0.0237	-0.0034	0.004	2.34E-07	4.54E-07	-+-+----?	--+--+-+?
TGPUFA	rs10892082	*PAFAH1B2*	0.0275	0.0236	0.0021	0.0039	2.07E-05	3.52E-05	+-+-+++-+?	-+-++-+-?
TGPUFA	rs3810444	*SUGP2*	-0.0228	0.0274	-0.0059	0.0047	5.43E-08	1.15E-07	+-------	-+++--++-
TGPUFA	rs2285628	*MAU2*	-0.0473	0.0172	0.0038	0.003	2.77E-05	4.35E-05	-++--+---	+--++-+++
TGPUFA	rs6857	*NECTIN2*	0.0523	0.0196	-0.0027	0.0033	2.30E-07	4.69E-07	+++++++-+	+-+--+-+-
TGPUFA	rs10119	*TOMM40*	0.0191	0.0167	0.0016	0.0028	2.34E-05	3.79E-05	+++++++++	+----+---
TGPUFA	rs7679	*PCIF1*	0.0115	0.0171	-0.0065	0.0029	1.74E-05	2.96E-05	--++++++-	++-------

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis (A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
TGMUFA	rs583609	*USP1*	3.74E-08	0.0422	0.0211	-0.0009	0.0017	2.09E-08	-++-+-+-?	+--+-+-+?	0.28	16110
TGMUFA	rs13472	*SNX17, ZNF513*	2.39E-11	-0.038	0.0205	0.0002	0.0016	1.23E-11	-+-+----?	+-+-+--+?	0.72	16110
TGMUFA	rs4582	*PPM1G*	2.25E-11	0.039	0.0205	-0.0003	0.0016	9.87E-12	+-+-++++?	-+-+-++-?	0.74	16110
TGMUFA	rs8395	*FNDC4*	2.12E-12	-0.0413	0.0205	0.0003	0.0016	1.16E-12	-+-+----?	+-+-+--+?	0.65	16110
TGMUFA	rs1881396	*ZNF512*	2.14E-06	0.0319	0.0203	-0.0003	0.0017	5.55E-07	++++++--+	+-+--+++-	0.44	22102
TGMUFA	rs8731	*GPN1*	1.12E-05	0.0346	0.0201	-0.0007	0.0016	3.05E-06	++++++--+	+-+--+++-	0.29	22102
TGMUFA	rs13232120	*TBL2*	1.42E-21	0.1036	0.027	-0.0034	0.0022	6.90E-22	+-+++++++	++-------	0.15	22102
TGMUFA	rs14415	*TBL2*	2.26E-19	0.0593	0.0188	-0.0013	0.0015	1.61E-19	--+++++++	++-----+-	0.56	22102
TGMUFA	rs1051921	*MLXIPL*	1.03E-21	-0.0726	0.0219	0.0016	0.0018	4.46E-22	++-------	--+++++-+	0.06	22102
TGMUFA	rs3289	*LPL*	6.04E-11	-0.0227	0.0527	-0.0058	0.0042	6.24E-11	+-+--+++-	-+-++----	0.29	22102
TGMUFA	rs3735964	*LPL*	6.18E-37	-0.1004	0.0264	0.001	0.0021	6.09E-37	-+--+----	--+--++-+	0.36	22102
TGMUFA	rs13702	*LPL*	2.62E-29	0.0522	0.0186	0.0002	0.0015	8.77E-30	+--++++++	+++-+-+--	0.98	22102
TGMUFA	rs1059611	*LPL*	7.17E-37	0.1004	0.0264	-0.001	0.0021	7.55E-37	+-++-++++	++-++--+-	0.39	22102
TGMUFA	rs15285	*LPL*	1.09E-27	-0.0567	0.0222	-0.0008	0.0018	3.01E-28	-+-------	--+--+--+	0.82	22102
TGMUFA	rs1129555	*GPAM*	1.79E-05	-0.0668	0.0192	0.0041	0.0016	2.47E-05	--+---+--	++-+++-++	0.77	22102
TGMUFA	rs174545	*FADS1*	1.15E-05	-0.0486	0.0205	0.002	0.0016	5.23E-06	--+----+?	++-++++-?	0.15	16110
TGMUFA	rs2266788	*APOA5*	1.32E-35	-0.0578	0.0337	-0.0045	0.0027	1.40E-36	+--+-----	-+--+----	0.49	22102
TGMUFA	rs619054	*APOA5*	4.55E-10	0.0097	0.02	-0.0035	0.0016	4.52E-10	--+--++--	----+--++	0.17	22102
TGMUFA	rs1035237	*SIK3*	4.26E-09	0.0091	0.032	-0.0045	0.0026	7.21E-09	++++----?	-----+-+?	0.23	16110
TGMUFA	rs10892082	*PAFAH1B2*	1.66E-06	-0.0013	0.0323	0.0033	0.0026	3.01E-06	----++-+?	+++++-+-?	0.15	16109
TGMUFA	rs3810444	*SUGP2*	9.90E-08	-0.0279	0.0358	-0.0022	0.003	4.58E-08	--------+	-++++++--	0.25	22102
TGMUFA	rs2285628	*MAU2*	1.24E-05	-0.0162	0.0218	-0.001	0.0018	4.94E-06	----+---+	++++--++-	0.16	22102
TGMUFA	rs6857	*NECTIN2*	5.83E-10	0.0554	0.0249	-0.0011	0.0021	1.73E-10	+-+++++-+	-+---+-+-	0.01	22102
TGMUFA	rs10119	*TOMM40*	1.61E-06	0.0436	0.0217	-0.0012	0.0018	6.36E-07	+++++++--	-------++	0.17	22102
TGMUFA	rs7679	*PCIF1*	1.76E-05	-0.0016	0.022	-0.0021	0.0018	1.07E-05	--++-++-+	-+-----+-	0.56	22101
TGPUFA	rs583609	*USP1*	9.13E-08	0.0289	0.0145	0.0003	0.0023	4.41E-08	+++-+-+-?	-+-+-+-+?	0.9	14573
TGPUFA	rs13472	*SNX17, ZNF513*	3.01E-11	-0.0438	0.014	0.0015	0.0023	1.64E-11	-+++----?	+-+-+-++?	0.24	16110
TGPUFA	rs4582	*PPM1G*	2.49E-11	0.0442	0.0139	-0.0015	0.0023	1.15E-11	+---++++?	-+++-+--?	0.26	16110
TGPUFA	rs8395	*FNDC4*	3.11E-12	-0.0453	0.0139	0.0015	0.0023	1.80E-12	-+++----?	+-+-+-++?	0.17	16110
TGPUFA	rs1881396	*ZNF512*	1.32E-06	0.0391	0.0146	-0.0019	0.0024	2.93E-07	++++++--+	-----+++-	0.63	22103
TGPUFA	rs8731	*GPN1*	7.64E-06	0.0403	0.0144	-0.0026	0.0024	1.83E-06	++++++--+	-----+++-	0.57	22103
TGPUFA	rs13232120	*TBL2*	8.52E-21	0.0833	0.019	-0.0037	0.0032	5.78E-21	+-+++++++	-+-+---+-	0.95	22103
TGPUFA	rs14415	*TBL2*	4.40E-19	0.0578	0.0136	-0.0025	0.0023	3.40E-19	+++-+++++	+--+---+-	0.91	22103
TGPUFA	rs1051921	*MLXIPL*	8.25E-22	-0.0734	0.0158	0.0035	0.0027	3.92E-22	-+-+---+-	--+-+++-+	0.67	22103
TGPUFA	rs3289	*LPL*	3.69E-12	0.0093	0.0365	-0.0184	0.0062	3.60E-12	+-++-+++-	-+-------	0.5	22103
TGPUFA	rs3735964	*LPL*	1.17E-37	-0.0749	0.0193	-0.0026	0.0033	1.03E-37	-+--+--+-	--+--+--+	0.02	22103
TGPUFA	rs13702	*LPL*	1.36E-29	0.0485	0.0132	0.0012	0.0022	3.54E-30	+-++-++++	++-++---+	0.75	22103
TGPUFA	rs1059611	*LPL*	1.37E-37	0.0739	0.0193	0.0028	0.0033	1.30E-37	+-++-++-+	++-++-++-	0.03	22103
TGPUFA	rs15285	*LPL*	2.37E-30	-0.0228	0.0164	-0.008	0.0028	3.92E-31	++--+--+-	--+--+---	0.07	22103
TGPUFA	rs174545	*FADS1*	1.62E-05	-0.0224	0.0144	-0.0005	0.0024	6.88E-06	++++---+?	-----++-?	0.32	16110
TGPUFA	rs2266788	*APOA5*	5.37E-35	-0.1125	0.0251	0.0003	0.0043	5.44E-36	---------	-+++---++	0.36	22103
TGPUFA	rs619054	*APOA5*	2.87E-09	-0.0286	0.0143	-0.0006	0.0024	3.76E-09	-+++-++--	+---+--++	0.04	22103
TGPUFA	rs1035237	*SIK3*	1.36E-08	-0.0199	0.0225	-0.0047	0.0038	1.42E-08	-+-+----?	--+--+-+?	0.62	16110
TGPUFA	rs10892082	*PAFAH1B2*	2.02E-06	0.0174	0.0224	0.0039	0.0037	2.61E-06	+-+-++-+?	-+-++-+-?	0.59	16109
TGPUFA	rs3810444	*SUGP2*	8.93E-08	-0.0335	0.0265	-0.0037	0.0046	4.32E-08	+-------	-+++--+++	0.09	22103
TGPUFA	rs2285628	*MAU2*	6.88E-06	-0.0447	0.0163	0.0031	0.0028	2.96E-06	-+---+---	+--+--+++	0.46	22103
TGPUFA	rs6857	*NECTIN2*	2.29E-10	0.0537	0.0186	-0.0018	0.0031	6.50E-11	++-++++-+	+-+-++-+-	0.01	22103
TGPUFA	rs10119	*TOMM40*	9.19E-07	0.0255	0.0161	0.001	0.0027	3.78E-07	+++-+++++	+--+-+---	0.4	22103
TGPUFA	rs7679	*PCIF1*	7.70E-06	-0.001	0.016	-0.0045	0.0027	4.44E-06	--+-+++--	++-+----+	0.57	22102

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
TGMUFA	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGMUFA	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGMUFA	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGMUFA	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.037	0.0047	4.94E-15	--+-----?	0	0.48
TGMUFA	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.005	2.00E-08	+++++++++	0	0.67
TGMUFA	rs8731	*GPN1*	0.015	0.0041	3.04E-04	3.10E-04	+++-+-+++	0.0259	0.005	2.02E-07	+++++++++	0	0.61
TGMUFA	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGMUFA	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGMUFA	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGMUFA	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGMUFA	rs3735964	*LPL*	NA	NA	NA	NA	NA	-0.0873	0.0066	3.78E-40	---------	0.9	0.43
TGMUFA	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGMUFA	rs1059611	*LPL*	NA	NA	NA	NA	NA	0.0871	0.0066	4.96E-40	+++++++++	0	0.53
TGMUFA	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGMUFA	rs1129555	*GPAM*	-0.0095	0.0039	1.42E-02	1.63E-02	-+-+--+--	-0.0183	0.0046	7.55E-05	-+-+-----	0	0.53
TGMUFA	rs174545	*FADS1*	-0.0103	0.0038	7.24E-03	7.54E-03	--+-----?	-0.0252	0.0049	2.38E-07	--+-----?	0	0.68
TGMUFA	rs2266788	*APOA5*	NA	NA	NA	NA	NA	-0.1136	0.0081	8.86E-45	---------	35.9	0.13
TGMUFA	rs619054	*APOA5*	-0.0158	0.0041	1.37E-04	1.45E-04	-------+-	-0.0285	0.005	9.60E-09	--+----+-	47.6	0.05
TGMUFA	rs1035237	*SIK3*	-0.025	0.0059	2.38E-05	2.95E-05	-------?	-0.0442	0.0073	1.68E-09	-------?	0	0.69
TGMUFA	rs10892082	*PAFAH1B2*	0.0174	0.0059	3.53E-03	3.65E-03	++++++++?	0.0367	0.0075	9.44E-07	++++++++?	0	0.65
TGMUFA	rs3810444	*SUGP2*	-0.0364	0.008	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13
TGMUFA	rs2285628	*MAU2*	-0.0147	0.0045	1.18E-03	1.28E-03	-----+---	-0.0266	0.0054	8.35E-07	---------	48.7	0.05
TGMUFA	rs6857	*NECTIN2*	0.0178	0.005	3.43E-04	4.49E-04	+++--++++	0.0418	0.0061	7.39E-12	+++-+++++	56.4	0.02
TGMUFA	rs10119	*TOMM40*	0.0115	0.0044	8.48E-03	9.98E-03	+++--++++	0.0278	0.0054	2.44E-07	+++-+++++	39.5	0.1
TGMUFA	rs7679	*PCIF1*	-0.0082	0.0044	6.04E-02	6.62E-02	---+++---	-0.0278	0.0053	1.83E-07	--++-----	0	0.54
TGPUFA	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGPUFA	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGPUFA	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGPUFA	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.037	0.0047	4.94E-15	--+-----?	0	0.48
TGPUFA	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.005	2.00E-08	+++++++++	0	0.67
TGPUFA	rs8731	*GPN1*	0.015	0.0041	3.04E-04	3.10E-04	+++-+-+++	0.0259	0.005	2.02E-07	+++++++++	0	0.61
TGPUFA	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGPUFA	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGPUFA	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGPUFA	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGPUFA	rs3735964	*LPL*	NA	NA	NA	NA	NA	-0.0873	0.0066	3.78E-40	---------	0.9	0.43
TGPUFA	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGPUFA	rs1059611	*LPL*	NA	NA	NA	NA	NA	0.0871	0.0066	4.96E-40	+++++++++	0	0.53
TGPUFA	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGPUFA	rs174545	*FADS1*	-0.0103	0.0038	7.24E-03	7.54E-03	--+-----?	-0.0252	0.0049	2.38E-07	--+-----?	0	0.68
TGPUFA	rs2266788	*APOA5*	NA	NA	NA	NA	NA	-0.1136	0.0081	8.86E-45	---------	35.9	0.13
TGPUFA	rs619054	*APOA5*	-0.0158	0.0041	1.37E-04	1.45E-04	-------+-	-0.0285	0.005	9.60E-09	--+----+-	47.6	0.05
TGPUFA	rs1035237	*SIK3*	-0.025	0.0059	2.38E-05	2.95E-05	-------?	-0.0442	0.0073	1.68E-09	-------?	0	0.69
TGPUFA	rs10892082	*PAFAH1B2*	0.0174	0.0059	3.53E-03	3.65E-03	++++++++?	0.0367	0.0075	9.44E-07	++++++++?	0	0.65
TGPUFA	rs3810444	*SUGP2*	-0.0364	0.008	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13
TGPUFA	rs2285628	*MAU2*	-0.0147	0.0045	1.18E-03	1.28E-03	-----+---	-0.0266	0.0054	8.35E-07	---------	48.7	0.05
TGPUFA	rs6857	*NECTIN2*	0.0178	0.005	3.43E-04	4.49E-04	+++--++++	0.0418	0.0061	7.39E-12	+++-+++++	56.4	0.02
TGPUFA	rs10119	*TOMM40*	0.0115	0.0044	8.48E-03	9.98E-03	+++--++++	0.0278	0.0054	2.44E-07	+++-+++++	39.5	0.1
TGPUFA	rs7679	*PCIF1*	-0.0082	0.0044	6.04E-02	6.62E-02	---+++---	-0.0278	0.0053	1.83E-07	--++-----	0	0.54

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
HDLCHO	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLCHO	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.12	0.016
HDLCHO	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.31	0.031
HDLCHO	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.12	0.016
HDLCHO	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.2	0.096
HDLCHO	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.34	0.033
HDLCHO	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.33	0.01
HDLCHO	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.36	0.032
HDLCHO	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.33	0.04
HDLCHO	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLCHO	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.32	0.041
HDLCHO	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.08	0.009
HDLCHO	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.34	0.036
HDLCHO	rs5805	*SLC12A3*	16	56947522	4	+	4.38E-08	A/G,A	0.45	0.028
HDLCHO	rs3812964	*SLC12A3*	16	56948841	7	+	1.95E-08	C/T,T	0.45	0.028
HDLCHO	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.43	0.035
HDLCHO	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.15	0.018
HDLCHO	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.018
HDLCHO	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.19	0.028
HDLCHO	rs11043	*ESRP2 (RBM35B), NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.14	0.02
HDLCHO	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.18	0.041
HDLCHO	rs3810291	*ZC3H4*	19	47569003	10		1.97E-05	G/A,A	0.32	0.041
HDLCHO	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.19	0.024
HDLSFA	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLSFA	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.11	0.011
HDLSFA	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.29	0.019
HDLSFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.11	0.011
HDLSFA	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.18	0.066
HDLSFA	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.32	0.013
HDLSFA	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.33	0.01
HDLSFA	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.34	0.01
HDLSFA	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.35	0.022
HDLSFA	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLSFA	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.34	0.025
HDLSFA	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.07	0.006
HDLSFA	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.32	0.015
HDLSFA	rs5805	*SLC12A3*	16	56947522	4	+	4.38E-08	A/G,A	0.45	0.028
HDLSFA	rs3812964	*SLC12A3*	16	56948841	7	+	1.95E-08	C/T,T	0.45	0.028
HDLSFA	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.45	0.026
HDLSFA	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.16	0.009
HDLSFA	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.01
HDLSFA	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.17	0.008
HDLSFA	rs11043	*ESRP2 (RBM35B), NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.13	0.007
HDLSFA	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.16	0.023
HDLSFA	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.18	0.014

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
HDLCHO	rs3289	*LPL*	0.1101	0.0609	-0.0008	0.0012	1.69E-11	3.76E-11	+++++++++	---+-+---
HDLCHO	rs3735964	*LPL*	0.0051	0.0348	0.0012	0.0007	3.62E-26	8.48E-25	+-+++--+-	++---++-+
HDLCHO	rs13702	*LPL*	0.0032	0.0239	-0.0009	0.0005	2.70E-22	1.54E-21	-++--++-+	---++--+-
HDLCHO	rs1059611	*LPL*	-0.0033	0.0348	-0.0012	0.0007	4.84E-26	1.05E-24	-+---++-+	--+++--+-
HDLCHO	rs15285	*LPL*	0.0207	0.0291	0.0006	0.0006	2.81E-23	7.33E-23	--+++--+-	++---++-+
HDLCHO	rs1057233	*SPI1*	0.0471	0.0232	-0.0006	0.0005	3.10E-05	5.44E-05	+-++--+++	-+--++---
HDLCHO	rs2293578	*SLC39A13*	-0.0331	0.0257	0.0003	0.0005	0.000218	0.000361	-+--++--?	+-+---++?
HDLCHO	rs9909	*NUP160*	0.0516	0.0222	-0.0007	0.0005	6.28E-07	1.20E-06	+-++--+++	-++-++-+-
HDLCHO	rs4246215	*FEN1*	0.0304	0.0217	-0.001	0.0004	2.23E-08	5.65E-08	-+--+++++	--++-----
HDLCHO	rs174545	*FADS1*	-0.0247	0.0248	0.001	0.0005	3.28E-07	4.07E-07	+-++----?	++--++++?
HDLCHO	rs174546	*FADS1*	0.0346	0.0217	-0.0011	0.0004	3.11E-09	7.11E-09	-+--+++++	--++-----
HDLCHO	rs2266788	*APOA5*	0.0382	0.0409	0	0.0008	1.95E-08	4.03E-08	+-+++---+	-+---+++-
HDLCHO	rs8468	*LACTB*	0.0444	0.0219	-0.0006	0.0004	5.04E-05	9.19E-05	++-++++++	--+----+-
HDLCHO	rs5805	*SLC12A3*	0.0245	0.0247	-0.0002	0.0005	0.00016	0.000221	+-+++++-?	-+-++--+?
HDLCHO	rs3812964	*SLC12A3*	-0.024	0.0246	0.0001	0.0005	0.000167	0.000257	-+-+-+-+?	+-+--++-?
HDLCHO	rs37029	*SLC12A3*	0.0115	0.0214	0.0001	0.0004	3.18E-05	5.19E-05	+-+-+-+--	-+-++--++
HDLCHO	rs12449157	*GFOD2*	-0.0591	0.0294	0.0008	0.0006	4.84E-05	8.63E-05	--++++---	+++---+++
HDLCHO	rs4474673	*RANBP10*	0.058	0.0338	-0.0006	0.0007	1.77E-07	3.14E-07	+++---+++	-+-+++---
HDLCHO	rs1109166	*SLC12A4, LCAT*	-0.0464	0.0284	0.0005	0.0006	1.02E-05	1.92E-05	---+++---	+++---+++
HDLCHO	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0039	0.0316	0.0004	0.0006	5.07E-05	7.77E-05	+-+---+++	++-+++---
HDLCHO	rs6857	*NECTIN2*	-0.0536	0.0315	0.0005	0.0006	1.09E-07	2.00E-07	---+-+---	+++-+-+++
HDLCHO	rs3810291	*ZC3H4*	0.0388	0.0241	-0.0011	0.0005	0.000218	0.000362	++++++-++	------+--
HDLCHO	rs7679	*PCIF1*	-0.0092	0.0276	0.0007	0.0006	1.33E-06	3.12E-06	-+--++++-	+-++----+
HDLSFA	rs3289	*LPL*	0.0021	0.0426	0.0058	0.0033	1.17E-13	4.98E-13	-+-+----+	+-+-+++++
HDLSFA	rs3735964	*LPL*	0.1234	0.0238	-0.0049	0.0019	4.77E-27	9.20E-26	+-++++++++	-+--+----
HDLSFA	rs13702	*LPL*	-0.0625	0.0162	0.0019	0.0013	4.39E-22	4.79E-21	--+-+----	++-+-++++
HDLSFA	rs1059611	*LPL*	-0.125	0.0237	0.0051	0.0018	6.02E-27	2.58E-25	---------	+-++-++++
HDLSFA	rs15285	*LPL*	0.0824	0.0194	-0.0027	0.0015	5.01E-23	7.24E-22	+-++++++++	-+-------
HDLSFA	rs1057233	*SPI1*	-0.0009	0.0158	0.0015	0.0012	2.72E-05	5.59E-05	-+-+++---	+-+-+-+++
HDLSFA	rs2293578	*SLC39A13*	0.0008	0.0187	-0.0015	0.0015	0.000212	0.000313	+-+---++?	-+-+-+--?
HDLSFA	rs9909	*NUP160*	0.0055	0.0152	0.0011	0.0012	8.55E-07	1.71E-06	+--++++-+	+++-+--++
HDLSFA	rs4246215	*FEN1*	-0.0455	0.015	0.0022	0.0012	3.30E-07	8.52E-07	-++------	+--++++++
HDLSFA	rs174545	*FADS1*	0.0461	0.0183	-0.0021	0.0015	3.39E-06	8.50E-06	+--+++++?	-++-----?
HDLSFA	rs174546	*FADS1*	-0.0437	0.0149	0.002	0.0012	1.86E-07	4.55E-07	-++------	+--++++++
HDLSFA	rs2266788	*APOA5*	0.0361	0.0267	0.0003	0.0021	1.26E-08	3.10E-08	++++-+++-	---++---+
HDLSFA	rs8468	*LACTB*	0.0017	0.0151	0.0012	0.0012	6.15E-05	0.000111	--+++-+++	++--++++-
HDLSFA	rs5805	*SLC12A3*	0.024	0.0177	-0.0005	0.0014	0.000126	0.000249	+++-+-++?	+-++-+--?
HDLSFA	rs3812964	*SLC12A3*	-0.0245	0.0177	0.0006	0.0014	0.000129	0.000228	---+-+--?	-+--+-++?
HDLSFA	rs37029	*SLC12A3*	0.0264	0.0144	-0.0008	0.0011	2.64E-05	5.28E-05	+++-+-+++	+-++-+-+-
HDLSFA	rs12449157	*GFOD2*	-0.0036	0.0197	-0.0014	0.0015	6.27E-05	0.000102	-+-----++	--++++---
HDLSFA	rs4474673	*RANBP10*	0.0113	0.0229	0.0016	0.0018	1.45E-07	3.59E-07	+++++++-+	+---+--++
HDLSFA	rs1109166	*SLC12A4, LCAT*	-0.0195	0.0191	-0.0002	0.0015	1.61E-05	2.80E-05	-+-----+-	+-+++++--
HDLSFA	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0262	0.0215	-0.0003	0.0017	0.000106	0.000185	++-++++-+	----+--++
HDLSFA	rs6857	*NECTIN2*	-0.0157	0.0208	-0.0012	0.0016	1.44E-08	4.44E-08	-++-+-++-	-----+--+
HDLSFA	rs7679	*PCIF1*	0.0029	0.0185	0.0015	0.0014	5.52E-06	1.07E-05	++-+-----	-++-+++++

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
HDLCHO	rs3289	*LPL*	4.38E-13	0.0675	0.0561	0.0002	0.0012	3.61E-13	++--+++++	-+++--+-+	0.7	22142
HDLCHO	rs3735964	*LPL*	2.24E-32	0.0045	0.0315	0.0013	0.0006	1.83E-32	--+++--+-	++++-++-+	0.05	22142
HDLCHO	rs13702	*LPL*	5.41E-27	-0.0047	0.022	-0.0007	0.0004	6.97E-27	-++--++--	----+--+-	0.11	22142
HDLCHO	rs1059611	*LPL*	2.97E-32	-0.0023	0.0315	-0.0013	0.0006	2.55E-32	++---++-+	----+--+-	0.04	22142
HDLCHO	rs15285	*LPL*	7.00E-28	0.0213	0.0267	0.0006	0.0005	8.42E-28	---++--++	++++-++-+	0.3	22142
HDLCHO	rs1057233	*SPI1*	1.29E-05	0.0547	0.0215	-0.0008	0.0004	1.18E-05	+-++--+++	-+--++---	0.32	22142
HDLCHO	rs2293578	*SLC39A13*	0.000694	-0.0374	0.0237	0.0005	0.0005	0.000369	-+--++--?	+-++--++?	0.39	16153
HDLCHO	rs9909	*NUP160*	5.47E-07	0.0489	0.0206	-0.0006	0.0004	4.53E-07	+--+--+++	-+++++---	0.29	22142
HDLCHO	rs4246215	*FEN1*	5.27E-09	0.0207	0.0205	-0.0009	0.0004	2.46E-09	-+--+++++	--+-----	0.25	22142
HDLCHO	rs174545	*FADS1*	1.63E-07	-0.0126	0.0233	0.0007	0.0005	1.02E-07	+-++----?	++--++++?	0.18	16153
HDLCHO	rs174546	*FADS1*	1.43E-09	0.0242	0.0205	-0.0009	0.0004	7.49E-10	-+--+++++	--++-----	0.22	22142
HDLCHO	rs2266788	*APOA5*	1.35E-07	0.0389	0.0377	0	0.0008	5.09E-08	+-+++---+	-+---+++-	0.44	22142
HDLCHO	rs8468	*LACTB*	5.08E-07	0.0372	0.0204	-0.0004	0.0004	3.94E-07	++-++++++	--+------	0.93	22133
HDLCHO	rs5805	*SLC12A3*	6.08E-06	0.0331	0.0224	-0.0003	0.0005	1.55E-05	+---+++-?	-++++--+?	0.58	16153
HDLCHO	rs3812964	*SLC12A3*	6.27E-06	-0.0327	0.0224	0.0003	0.0005	1.61E-05	-+++---+?	+----++-?	0.58	16153
HDLCHO	rs37029	*SLC12A3*	1.43E-05	0.0321	0.0198	-0.0004	0.0004	3.41E-05	+---+++-+	-++++--+-	0.55	22142
HDLCHO	rs12449157	*GFOD2*	1.21E-06	-0.056	0.0268	0.0007	0.0006	7.94E-07	--++++---	++----+++	0.46	22142
HDLCHO	rs4474673	*RANBP10*	7.43E-10	0.0478	0.0307	-0.0003	0.0006	4.36E-10	+-----+++	-+++++--+	0.6	22142
HDLCHO	rs1109166	*SLC12A4, LCAT*	1.54E-07	-0.044	0.0258	0.0004	0.0005	1.47E-07	--++++---	++----+++	0.38	22142
HDLCHO	rs11043	*ESRP2 (RBM35B), NFATC3*	4.18E-07	-0.0065	0.0288	0.0007	0.0006	2.28E-07	+-----+++	-+++++--+	0.66	22142
HDLCHO	rs6857	*NECTIN2*	2.24E-10	-0.0261	0.0302	-0.0002	0.0006	5.24E-11	---+-+-++	+++-+-+--	0.13	22142
HDLCHO	rs3810291	*ZC3H4*	0.03568	0.0191	0.0225	-0.0006	0.0005	0.03557	-++++--++	-----++--	0.44	22142
HDLCHO	rs7679	*PCIF1*	1.40E-06	0.0037	0.0256	0.0004	0.0005	1.56E-06	-+--+++++	+-++--+-+	0.66	22141
HDLSFA	rs3289	*LPL*	4.93E-13	0.0381	0.0399	0.0028	0.003	4.43E-13	-+++----+	+---++++-	0.09	22142
HDLSFA	rs3735964	*LPL*	7.11E-33	0.135	0.0221	-0.0057	0.0017	4.39E-33	+++++++++	----+----	0.47	22142
HDLSFA	rs13702	*LPL*	4.15E-26	-0.0633	0.0152	0.0019	0.0012	2.51E-26	----+----	++++-++++	0.39	22142
HDLSFA	rs1059611	*LPL*	7.72E-33	-0.137	0.0221	0.0059	0.0017	4.82E-33	---------	++++-++++	0.47	22142
HDLSFA	rs15285	*LPL*	1.79E-27	0.0865	0.0183	-0.0029	0.0014	1.18E-27	+-+++++++	-+-------	0.88	22142
HDLSFA	rs1057233	*SPI1*	3.28E-05	-0.0067	0.015	0.0018	0.0012	2.20E-05	-+-+++---	+-+-+-+++	0.43	22142
HDLSFA	rs2293578	*SLC39A13*	0.000746	0.0076	0.0175	-0.0019	0.0014	0.000433	+-+---++?	-+-+-+--?	0.43	16153
HDLSFA	rs9909	*NUP160*	1.04E-06	0.0025	0.0143	0.0013	0.0011	7.48E-07	++-+-++-+	-++-+-+++	0.31	22142
HDLSFA	rs4246215	*FEN1*	4.41E-08	-0.0454	0.0141	0.0021	0.0011	2.70E-08	-+++-----	+---+++++	0.32	22142
HDLSFA	rs174545	*FADS1*	8.48E-07	0.0407	0.0172	-0.0016	0.0014	7.03E-07	+--+++++?	-+++----?	0.2	16153
HDLSFA	rs174546	*FADS1*	1.90E-08	-0.0438	0.0142	0.0019	0.0011	1.29E-08	-++------	+---+++++	0.31	22142
HDLSFA	rs2266788	*APOA5*	3.99E-08	0.0528	0.0256	-0.0012	0.002	1.49E-08	++++-++++	----+-+-+	0.85	22142
HDLSFA	rs8468	*LACTB*	4.75E-07	0.01	0.0143	0.0007	0.0011	6.16E-07	--+-+++++	++-+-+-+-	0.85	22133
HDLSFA	rs5805	*SLC12A3*	8.04E-06	0.021	0.0163	-0.0002	0.0013	1.85E-05	-++-+-+-?	+--+-+-+?	0.31	16153
HDLSFA	rs3812964	*SLC12A3*	8.28E-06	-0.0214	0.0163	0.0003	0.0013	1.91E-05	+--+-+-+?	-++-+-+-?	0.3	16153
HDLSFA	rs37029	*SLC12A3*	2.50E-05	0.0213	0.0137	-0.0005	0.0011	5.59E-05	-++-+-+-+	+--+-+-+-	0.27	22142
HDLSFA	rs12449157	*GFOD2*	2.19E-06	-0.0094	0.0185	-0.0011	0.0015	1.91E-06	-------++	--++++---	0.22	22142
HDLSFA	rs4474673	*RANBP10*	2.90E-09	0.0225	0.0213	0.0009	0.0017	2.62E-09	++++-++-+	+---+--++	0.55	22142
HDLSFA	rs1109166	*SLC12A4, LCAT*	4.77E-07	-0.0237	0.0179	0	0.0014	4.25E-07	-------+-	+-+++++--	0.17	22142
HDLSFA	rs11043	*ESRP2 (RBM35B), NFATC3*	2.75E-06	0.0411	0.0198	-0.0013	0.0016	2.55E-06	+++-+++-+	---++-++-	0.73	22142
HDLSFA	rs6857	*NECTIN2*	2.82E-11	-0.0327	0.0203	-0.0003	0.0016	6.76E-12	-++++--+-	+----+--+	0.11	22142
HDLSFA	rs7679	*PCIF1*	1.32E-06	0.0029	0.0175	0.0015	0.0014	1.23E-06	++-++----	-++-+++++	0.59	22141

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
HDLCHO	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	+++++++-+	0.073	0.0101	6.02E-13	+++++++-+	34.5	0.14
HDLCHO	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.60E-38	+++++++++	38.8	0.11
HDLCHO	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	---------	-0.0418	0.0035	8.57E-33	---------	30.4	0.17
HDLCHO	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	---------	-0.0653	0.0051	1.11E-37	---------	37.4	0.12
HDLCHO	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.54E-34	+++++++++	17	0.29
HDLCHO	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	1.62E-06	+++++++++	11.1	0.34
HDLCHO	rs2293578	*SLC39A13*	-0.0181	0.0043	2.31E-05	3.77E-05	--------?	-0.0165	0.0038	1.68E-05	--------?	25.8	0.22
HDLCHO	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.019	0.0033	1.10E-08	+++++++++	23.1	0.24
HDLCHO	rs4246215	*FEN1*	-0.018	0.0037	8.48E-07	1.91E-06	--++-----	-0.0193	0.0033	6.43E-09	--+------	0	0.47
HDLCHO	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.2
HDLCHO	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	--++-----	-0.0198	0.0033	2.32E-09	--+------	18.7	0.28
HDLCHO	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.54E-10	+++++++++	0	0.68
HDLCHO	rs8468	*LACTB*	0.015	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.02E-08	+-+++++++	0	0.67
HDLCHO	rs5805	*SLC12A3*	0.014	0.0041	6.21E-04	8.28E-04	+++++-++?	0.0138	0.0036	0.000132	++++++++?	0	0.53
HDLCHO	rs3812964	*SLC12A3*	-0.0141	0.0041	5.67E-04	7.60E-04	-----+--?	-0.0139	0.0036	0.000127	--------?	0	0.53
HDLCHO	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	1.13E-04	+++++-+++	0.0124	0.0032	0.000106	+++++++++	0	0.55
HDLCHO	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	--++-----	-0.0226	0.0044	2.46E-07	---+-----	0	0.67
HDLCHO	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.005	4.16E-10	+++++++++	0	0.67
HDLCHO	rs1109166	*SLC12A4, LCAT*	-0.023	0.0046	6.62E-07	9.81E-07	--+------	-0.0225	0.0042	1.03E-07	--+------	0	0.6
HDLCHO	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.38E-07	+++++++++	0	0.83
HDLCHO	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	---------	-0.0349	0.0047	8.97E-14	---------	50.5	0.04
HDLCHO	rs3810291	*ZC3H4*	-0.0117	0.004	3.77E-03	4.19E-03	---+---+-	-0.0084	0.0037	0.02175	-------+-	0	0.88
HDLCHO	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	+++++++-+	0.0218	0.0041	1.14E-07	+++++++-+	0	0.62
HDLSFA	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	+++++++-+	0.073	0.0101	6.02E-13	+++++++-+	34.5	0.14
HDLSFA	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.60E-38	+++++++++	38.8	0.11
HDLSFA	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	---------	-0.0418	0.0035	8.57E-33	---------	30.4	0.17
HDLSFA	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	---------	-0.0653	0.0051	1.11E-37	---------	37.4	0.12
HDLSFA	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.54E-34	+++++++++	17	0.29
HDLSFA	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	1.62E-06	+++++++++	11.1	0.34
HDLSFA	rs2293578	*SLC39A13*	-0.0181	0.0043	2.31E-05	3.77E-05	--------?	-0.0165	0.0038	1.68E-05	--------?	25.8	0.22
HDLSFA	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.019	0.0033	1.10E-08	+++++++++	23.1	0.24
HDLSFA	rs4246215	*FEN1*	-0.018	0.0037	8.48E-07	1.91E-06	--++-----	-0.0193	0.0033	6.43E-09	--+------	0	0.47
HDLSFA	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.2
HDLSFA	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	--++-----	-0.0198	0.0033	2.32E-09	--+------	18.7	0.28
HDLSFA	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.54E-10	+++++++++	0	0.68
HDLSFA	rs8468	*LACTB*	0.015	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.02E-08	+-+++++++	0	0.67
HDLSFA	rs5805	*SLC12A3*	0.014	0.0041	6.21E-04	8.28E-04	+++++-++?	0.0138	0.0036	0.000132	++++++++?	0	0.53
HDLSFA	rs3812964	*SLC12A3*	-0.0141	0.0041	5.67E-04	7.60E-04	-----+--?	-0.0139	0.0036	0.000127	--------?	0	0.53
HDLSFA	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	1.13E-04	+++++-+++	0.0124	0.0032	0.000106	+++++++++	0	0.55
HDLSFA	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	--++-----	-0.0226	0.0044	2.46E-07	---+-----	0	0.67
HDLSFA	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.005	4.16E-10	+++++++++	0	0.67
HDLSFA	rs1109166	*SLC12A4, LCAT*	-0.023	0.0046	6.62E-07	9.81E-07	--+------	-0.0225	0.0042	1.03E-07	--+------	0	0.6
HDLSFA	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.38E-07	+++++++++	0	0.83
HDLSFA	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	---------	-0.0349	0.0047	8.97E-14	---------	50.5	0.04
HDLSFA	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	+++++++-+	0.0218	0.0041	1.14E-07	+++++++-+	0	0.62

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
HDLMUFA	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLMUFA	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.11	0.011
HDLMUFA	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.29	0.019
HDLMUFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.11	0.011
HDLMUFA	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.18	0.066
HDLMUFA	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.32	0.013
HDLMUFA	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.34	0.01
HDLMUFA	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.35	0.022
HDLMUFA	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLMUFA	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.34	0.025
HDLMUFA	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.07	0.006
HDLMUFA	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.32	0.015
HDLMUFA	rs5805	*SLC12A3*	16	56947522	4	+	4.38E-08	A/G,A	0.45	0.028
HDLMUFA	rs3812964	*SLC12A3*	16	56948841	7	+	1.95E-08	C/T,T	0.45	0.028
HDLMUFA	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.45	0.026
HDLMUFA	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.16	0.009
HDLMUFA	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.01
HDLMUFA	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.17	0.008
HDLMUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.13	0.007
HDLMUFA	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.16	0.023
HDLMUFA	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.18	0.014
HDLPUFA	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLPUFA	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.11	0.011
HDLPUFA	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.29	0.019
HDLPUFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.11	0.011
HDLPUFA	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.18	0.066
HDLPUFA	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.32	0.013
HDLPUFA	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.34	0.01
HDLPUFA	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.35	0.022
HDLPUFA	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLPUFA	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.34	0.025
HDLPUFA	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.07	0.006
HDLPUFA	rs6738	*TPM1*	15	63363901	4		6.83E-05	C/T,T	0.34	0.018
HDLPUFA	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.32	0.015
HDLPUFA	rs5805	*SLC12A3*	16	56947522	4	+	4.38E-08	A/G,A	0.45	0.028
HDLPUFA	rs3812964	*SLC12A3*	16	56948841	7	+	1.95E-08	C/T,T	0.45	0.028
HDLPUFA	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.45	0.026
HDLPUFA	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.16	0.009
HDLPUFA	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.01
HDLPUFA	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.17	0.008
HDLPUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.13	0.007
HDLPUFA	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.16	0.023
HDLPUFA	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.18	0.012

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
HDLMUFA	rs3289	*LPL*	-0.0206	0.039	0.0077	0.0031	9.65E-14	4.79E-13	-+-+++--+	+-+--++++
HDLMUFA	rs3735964	*LPL*	0.0827	0.0225	-0.0016	0.0018	3.43E-26	4.44E-25	+++++++-+	----++-+-
HDLMUFA	rs13702	*LPL*	-0.0466	0.0159	0.0007	0.0013	3.67E-21	3.14E-20	----+----	+++--++--
HDLMUFA	rs1059611	*LPL*	-0.0828	0.0225	0.0017	0.0018	5.00E-26	1.59E-24	-------+-	++++--+-+
HDLMUFA	rs15285	*LPL*	0.0508	0.0188	-0.0002	0.0015	1.73E-22	2.97E-21	+-+++++-+	-+-----++
HDLMUFA	rs1057233	*SPI1*	0.0254	0.0155	-0.0008	0.0013	9.49E-05	0.000158	++-+++-++	--+--++-+
HDLMUFA	rs9909	*NUP160*	0.0294	0.0147	-0.0009	0.0012	1.95E-06	3.57E-06	++-+++-++	--+-+++-+
HDLMUFA	rs4246215	*FEN1*	-0.0508	0.0144	0.0027	0.0012	1.62E-07	4.27E-07	-+++-----	+---+++++
HDLMUFA	rs174545	*FADS1*	0.0507	0.0174	-0.0025	0.0014	1.93E-06	3.55E-06	+---++++?	-+++----?
HDLMUFA	rs174546	*FADS1*	-0.0479	0.0144	0.0024	0.0012	9.77E-08	1.91E-07	-+++-----	+---+++++
HDLMUFA	rs2266788	*APOA5*	0.0188	0.0264	0.0018	0.0022	1.12E-08	2.94E-08	++-+-+++-	--+++---+
HDLMUFA	rs8468	*LACTB*	0.0066	0.0149	0.0008	0.0012	0.000115	0.000191	+++---+++	+--++++-+
HDLMUFA	rs5805	*SLC12A3*	0.019	0.0172	-0.0001	0.0014	0.000161	0.000261	+++++---?	+----+++?
HDLMUFA	rs3812964	*SLC12A3*	-0.0191	0.0172	0.0001	0.0014	0.000167	0.000239	-----+++?	-++++---?
HDLMUFA	rs37029	*SLC12A3*	0.0243	0.0142	-0.0007	0.0012	3.51E-05	6.45E-05	+++++---+	+----+++-
HDLMUFA	rs12449157	*GFOD2*	-0.0047	0.0194	-0.0014	0.0016	4.99E-05	7.97E-05	++-----+-	--++++--+
HDLMUFA	rs4474673	*RANBP10*	0.0066	0.0227	0.0022	0.0019	4.87E-08	1.05E-07	-+-++++-+	+-+-+-++-
HDLMUFA	rs1109166	*SLC12A4, LCAT*	-0.0199	0.0187	-0.0002	0.0015	1.20E-05	1.89E-05	+++----+-	---++++-+
HDLMUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0416	0.0211	-0.0015	0.0017	5.06E-05	8.72E-05	++-++++-+	--+----+-
HDLMUFA	rs6857	*NECTIN2*	-0.01	0.021	-0.0018	0.0018	8.93E-09	2.27E-08	--+----++	-+-+-+---
HDLMUFA	rs7679	*PCIF1*	0.0067	0.0185	0.0012	0.0015	9.25E-06	1.97E-05	+--+--+--	-++++++++
HDLPUFA	rs3289	*LPL*	0.053	0.0287	0.004	0.005	1.68E-12	7.02E-12	-+++++--+	+----++++
HDLPUFA	rs3735964	*LPL*	0.048	0.0172	0.0028	0.0029	1.47E-26	2.40E-25	++---++-+	+-++++-+-
HDLPUFA	rs13702	*LPL*	-0.048	0.0112	0.0016	0.0019	5.32E-22	6.72E-21	-------+-	+-+--++--
HDLPUFA	rs1059611	*LPL*	-0.0475	0.0172	-0.0028	0.0029	2.17E-26	4.68E-25	--+++--+-	-+----+-+
HDLPUFA	rs15285	*LPL*	0.0248	0.0143	0.0045	0.0025	1.24E-23	1.60E-22	++---++-+	++++++-++
HDLPUFA	rs1057233	*SPI1*	0.0227	0.0113	-0.0011	0.0019	5.96E-05	8.95E-05	+++-+-+++	---+-+--+
HDLPUFA	rs9909	*NUP160*	0.0253	0.0108	-0.0011	0.0019	1.19E-06	2.23E-06	+++-+--++	--++-++--
HDLPUFA	rs4246215	*FEN1*	-0.0323	0.0105	0.0024	0.0018	5.24E-07	1.02E-06	--++---+-	+---+++--
HDLPUFA	rs174545	*FADS1*	0.0421	0.0117	-0.0038	0.0019	1.19E-06	2.20E-06	++--+++-?	--++---+?
HDLPUFA	rs174546	*FADS1*	-0.0338	0.0103	0.0026	0.0018	1.67E-07	3.64E-07	--++---++	++--+++--
HDLPUFA	rs2266788	*APOA5*	0.0502	0.0198	-0.0019	0.0035	1.63E-08	3.84E-08	++-+--+++	+-+-++---
HDLPUFA	rs6738	*TPM1*	0.0036	0.0124	0.0024	0.0021	0.000177	0.000261	+---++++?	-++++--+?
HDLPUFA	rs8468	*LACTB*	0.0059	0.0109	0.0018	0.0018	6.81E-05	0.000108	+---++-+-	++++--+-+
HDLPUFA	rs5805	*SLC12A3*	0.0212	0.0119	-0.0006	0.0019	0.000121	0.000185	+++++-+-?	+---+-++?
HDLPUFA	rs3812964	*SLC12A3*	-0.0211	0.0119	0.0006	0.0019	0.000126	0.000193	-----+-+?	-+++-+--?
HDLPUFA	rs37029	*SLC12A3*	0.0227	0.0104	-0.0012	0.0018	3.48E-05	6.57E-05	+++++-+-+	+---+-++-
HDLPUFA	rs12449157	*GFOD2*	-0.0229	0.0141	0.0005	0.0024	0.00023	0.00033	-++----+-	---+++--+
HDLPUFA	rs4474673	*RANBP10*	0.0432	0.0163	-0.0024	0.0028	4.66E-07	1.02E-06	++-+++--+	+++---++-
HDLPUFA	rs1109166	*SLC12A4, LCAT*	-0.0344	0.0135	0.0024	0.0023	2.04E-05	3.65E-05	-++-----	+--++++-+
HDLPUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0471	0.0151	-0.0045	0.0026	2.55E-05	4.07E-05	++-++++-+	-++----+-
HDLPUFA	rs6857	*NECTIN2*	-0.0517	0.0157	0.0032	0.0026	5.69E-09	1.37E-08	-------?-	-++++++?+
HDLPUFA	rs7679	*PCIF1*	-0.002	0.0135	0.0047	0.0023	2.30E-07	5.14E-07	+--+---?-	-++-+++?+

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(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
HDLMUFA	rs3289	*LPL*	9.92E-14	0.056	0.0164	0.0013	0.0008	1.24E-13	-++-+---+	+-++++++-	0.58	22141
HDLMUFA	rs3735964	*LPL*	1.06E-31	0.0576	0.0091	0.0005	0.0005	9.18E-32	+++++++-+	---+++-+-	0.27	22141
HDLMUFA	rs13702	*LPL*	8.22E-26	-0.032	0.0063	-0.0006	0.0004	5.52E-26	----+----	+++--+++-	0.18	22141
HDLMUFA	rs1059611	*LPL*	1.63E-31	-0.0572	0.0091	-0.0005	0.0005	1.43E-31	-------+-	+++---+-+	0.25	22141
HDLMUFA	rs15285	*LPL*	2.03E-26	0.0458	0.0078	0.0003	0.0004	1.30E-26	++++++++	-+-++--++	0.86	22141
HDLMUFA	rs1057233	*SPI1*	0.000105	0.015	0.0065	0.0001	0.0004	7.53E-05	++-++--+-	--+-+++-+	0.36	22141
HDLMUFA	rs9909	*NUP160*	1.52E-06	0.016	0.0062	0.0002	0.0004	1.27E-06	++-+++-++	--+++++-+	0.51	22141
HDLMUFA	rs4246215	*FEN1*	7.70E-08	-0.0274	0.0061	0.0006	0.0004	4.64E-08	-++------	+--++++-+	0.02	22141
HDLMUFA	rs174545	*FADS1*	9.68E-07	0.0276	0.0068	-0.0005	0.0004	8.60E-07	+--+++++?	-++----+?	0.01	16153
HDLMUFA	rs174546	*FADS1*	3.97E-08	-0.0265	0.006	0.0005	0.0004	3.09E-08	-++------	+--++++-+	0.02	22141
HDLMUFA	rs2266788	*APOA5*	1.01E-07	0.0312	0.0107	0.0005	0.0006	3.20E-08	++-+-++++	--+-+-+-+	0.75	22141
HDLMUFA	rs8468	*LACTB*	7.54E-07	0.0218	0.006	-0.0002	0.0003	8.24E-07	++-+-++++	+---+--++	0.92	22132
HDLMUFA	rs5805	*SLC12A3*	7.07E-06	0.0112	0.0066	0.0004	0.0004	1.59E-05	-++-+-+-?	+--+-+++?	0.44	16153
HDLMUFA	rs3812964	*SLC12A3*	7.06E-06	-0.0111	0.0066	-0.0004	0.0004	1.58E-05	+--+-+-+?	-++-+---?	0.44	16153
HDLMUFA	rs37029	*SLC12A3*	1.50E-05	0.0075	0.0058	0.0005	0.0003	3.10E-05	-++-+-+-+	+--+-+++-	0.44	22141
HDLMUFA	rs12449157	*GFOD2*	1.88E-06	-0.0282	0.008	0.0003	0.0005	1.43E-06	++-+---+-	--+-++--+	0.21	22141
HDLMUFA	rs4474673	*RANBP10*	8.56E-10	0.0282	0.0096	0.0004	0.0006	7.53E-10	-++-+++-+	+-++--++-	0.37	22141
HDLMUFA	rs1109166	*SLC12A4, LCAT*	2.32E-07	-0.0272	0.0077	0.0002	0.0005	2.04E-07	++-+---+-	--+-+++-+	0.3	22141
HDLMUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	9.78E-07	0.0289	0.0087	-0.0002	0.0005	9.84E-07	+++-+++-+	+--+---+-	0.58	22141
HDLMUFA	rs6857	*NECTIN2*	3.12E-11	-0.0303	0.0092	-0.0004	0.0006	8.95E-12	--+++--+-	-+---+---	0.15	22141
HDLMUFA	rs7679	*PCIF1*	1.25E-06	0.0188	0.0076	0.0003	0.0005	1.31E-06	+-----+--	-++++++++	0.51	22140
HDLPUFA	rs3289	*LPL*	8.68E-13	0.0701	0.0288	0.001	0.0051	1.03E-12	+++++---+	+----+++-	0.36	22142
HDLPUFA	rs3735964	*LPL*	3.87E-31	0.0532	0.0158	0.0021	0.0027	3.36E-31	++++-++-+	+-++++-+-	0.33	22142
HDLPUFA	rs13702	*LPL*	4.20E-26	-0.0553	0.0106	0.0027	0.0018	1.72E-26	-------+-	+-++-++-+	0.56	22142
HDLPUFA	rs1059611	*LPL*	6.38E-31	-0.0531	0.0158	-0.0021	0.0027	5.70E-31	----+--+-	-+----+-+	0.31	22142
HDLPUFA	rs15285	*LPL*	2.68E-27	0.0307	0.0133	0.0037	0.0023	1.14E-27	+++--++-+	++++++-+-	0.49	22142
HDLPUFA	rs1057233	*SPI1*	6.31E-05	0.0194	0.0108	-0.0006	0.0018	4.97E-05	+++-+--++	---+-++-+	0.19	22142
HDLPUFA	rs9909	*NUP160*	9.93E-07	0.0231	0.0103	-0.0008	0.0018	8.27E-07	+++-+--++	---+-++-+	0.23	22142
HDLPUFA	rs4246215	*FEN1*	9.71E-08	-0.0273	0.0102	0.0013	0.0017	5.55E-08	--++---+-	----+++--	0.2	22142
HDLPUFA	rs174545	*FADS1*	3.84E-07	0.0388	0.0112	-0.0032	0.0019	3.16E-07	++-++++-?	+-++---+?	0.17	16153
HDLPUFA	rs174546	*FADS1*	3.43E-08	-0.0299	0.01	0.0018	0.0017	2.38E-08	--+----++	-+--+++--	0.12	22142
HDLPUFA	rs2266788	*APOA5*	1.14E-07	0.0577	0.0191	-0.0037	0.0033	3.94E-08	++-+--+++	--+-++---	0.39	22142
HDLPUFA	rs6738	*TPM1*	4.74E-05	0.0032	0.0116	0.0024	0.0019	7.41E-05	+---+++-?	+++++--+?	0.23	16153
HDLPUFA	rs8468	*LACTB*	6.66E-07	0.0114	0.0103	0.0013	0.0018	8.17E-07	+---++-++	+--+--+++	0.85	22133
HDLPUFA	rs5805	*SLC12A3*	9.78E-06	0.0184	0.0111	-0.0001	0.0018	2.16E-05	+++++++-?	+-+-+--+?	0.68	16153
HDLPUFA	rs3812964	*SLC12A3*	1.02E-05	-0.0184	0.0111	0	0.0018	2.25E-05	-------+?	-+-+-++-?	0.69	16153
HDLPUFA	rs37029	*SLC12A3*	3.03E-05	0.0168	0.0099	-0.0004	0.0017	6.62E-05	+++++++-+	+-+-+--+-	0.53	22142
HDLPUFA	rs12449157	*GFOD2*	5.03E-06	-0.0207	0.0137	-0.0004	0.0024	3.56E-06	-++----+-	---+++--+	0.56	22142
HDLPUFA	rs4474673	*RANBP10*	2.28E-09	0.0403	0.0158	-0.0013	0.0027	1.98E-09	++-+++--+	+-+---++-	0.33	22142
HDLPUFA	rs1109166	*SLC12A4, LCAT*	4.16E-07	-0.0328	0.013	0.0016	0.0022	3.22E-07	-++----+-	---++++-+	0.51	22142
HDLPUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	3.24E-07	0.0462	0.0143	-0.0037	0.0025	3.42E-07	++-++++-+	-++----+-	0.47	22142
HDLPUFA	rs6857	*NECTIN2*	5.54E-11	-0.0439	0.0148	0.0016	0.0025	1.66E-11	-------+-	-+++--+-+	0.002	20605
HDLPUFA	rs7679	*PCIF1*	1.59E-06	0.0049	0.0128	0.0031	0.0022	1.39E-06	+--+---++	-++-+++-+	0.55	20604

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
HDLMUFA	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	+++++++-+	0.073	0.0101	6.02E-13	+++++++-+	34.5	0.14
HDLMUFA	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.60E-38	+++++++++	38.8	0.11
HDLMUFA	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	---------	-0.0418	0.0035	8.57E-33	---------	30.4	0.17
HDLMUFA	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	---------	-0.0653	0.0051	1.11E-37	---------	37.4	0.12
HDLMUFA	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.54E-34	+++++++++	17	0.29
HDLMUFA	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	1.62E-06	+++++++++	11.1	0.34
HDLMUFA	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.019	0.0033	1.10E-08	+++++++++	23.1	0.24
HDLMUFA	rs4246215	*FEN1*	-0.018	0.0037	8.48E-07	1.91E-06	--++-----	-0.0193	0.0033	6.43E-09	--+------	0	0.47
HDLMUFA	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.2
HDLMUFA	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	--++-----	-0.0198	0.0033	2.32E-09	--+------	18.7	0.28
HDLMUFA	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.54E-10	+++++++++	0	0.68
HDLMUFA	rs8468	*LACTB*	0.015	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.02E-08	+-+++++++	0	0.67
HDLMUFA	rs5805	*SLC12A3*	0.014	0.0041	6.21E-04	8.28E-04	+++++-++?	0.0138	0.0036	0.000132	++++++++?	0	0.53
HDLMUFA	rs3812964	*SLC12A3*	-0.0141	0.0041	5.67E-04	7.60E-04	-----+--?	-0.0139	0.0036	0.000127	--------?	0	0.53
HDLMUFA	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	1.13E-04	+++++-+++	0.0124	0.0032	0.000106	+++++++++	0	0.55
HDLMUFA	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	--++-----	-0.0226	0.0044	2.46E-07	---+-----	0	0.67
HDLMUFA	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.005	4.16E-10	+++++++++	0	0.67
HDLMUFA	rs1109166	*SLC12A4, LCAT*	-0.023	0.0046	6.62E-07	9.81E-07	--+------	-0.0225	0.0042	1.03E-07	--+------	0	0.6
HDLMUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.38E-07	+++++++++	0	0.83
HDLMUFA	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	---------	-0.0349	0.0047	8.97E-14	---------	50.5	0.04
HDLMUFA	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	+++++++-+	0.0218	0.0041	1.14E-07	+++++++-+	0	0.62
HDLPUFA	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	+++++++-+	0.073	0.0101	6.02E-13	+++++++-+	34.5	0.14
HDLPUFA	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.60E-38	+++++++++	38.8	0.11
HDLPUFA	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	---------	-0.0418	0.0035	8.57E-33	---------	30.4	0.17
HDLPUFA	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	---------	-0.0653	0.0051	1.11E-37	---------	37.4	0.12
HDLPUFA	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.54E-34	+++++++++	17	0.29
HDLPUFA	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	1.62E-06	+++++++++	11.1	0.34
HDLPUFA	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.019	0.0033	1.10E-08	+++++++++	23.1	0.24
HDLPUFA	rs4246215	*FEN1*	-0.018	0.0037	8.48E-07	1.91E-06	--++-----	-0.0193	0.0033	6.43E-09	--+------	0	0.47
HDLPUFA	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.2
HDLPUFA	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	--++-----	-0.0198	0.0033	2.32E-09	--+------	18.7	0.28
HDLPUFA	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.54E-10	+++++++++	0	0.68
HDLPUFA	rs6738	*TPM1*	0.016	0.0042	1.40E-04	1.92E-04	++++++++?	0.019	0.0038	4.93E-07	+++-++++?	0	0.7
HDLPUFA	rs8468	*LACTB*	0.015	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.02E-08	+-+++++++	0	0.67
HDLPUFA	rs5805	*SLC12A3*	0.014	0.0041	6.21E-04	8.28E-04	+++++-++?	0.0138	0.0036	0.000132	++++++++?	0	0.53
HDLPUFA	rs3812964	*SLC12A3*	-0.0141	0.0041	5.67E-04	7.60E-04	-----+--?	-0.0139	0.0036	0.000127	--------?	0	0.53
HDLPUFA	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	1.13E-04	+++++-+++	0.0124	0.0032	0.000106	+++++++++	0	0.55
HDLPUFA	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	--++-----	-0.0226	0.0044	2.46E-07	---+-----	0	0.67
HDLPUFA	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.005	4.16E-10	+++++++++	0	0.67
HDLPUFA	rs1109166	*SLC12A4, LCAT*	-0.023	0.0046	6.62E-07	9.81E-07	--+------	-0.0225	0.0042	1.03E-07	--+------	0	0.6
HDLPUFA	rs11043	*ESRP2 (RBM35B), NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.38E-07	+++++++++	0	0.83
HDLPUFA	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	---------	-0.0349	0.0047	8.97E-14	---------	50.5	0.04
HDLPUFA	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	+++++++-+	0.0218	0.0041	1.14E-07	+++++++-+	0	0.62

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
LDLCHO	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLCHO	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLCHO	rs7528419	*CELSR2*	1	109817192	7	+	1.55E-165	G/A,A	0.23	0.014
LDLCHO	rs12740374	*CELSR2*	1	109817590	7	+	2.41E-272	T/G,T	0.23	0.013
LDLCHO	rs660240	*CELSR2*	1	109817838	4	+	9.00E-265	T/C,T	0.22	0.016
LDLCHO	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLCHO	rs464218	*SORT1*	1	109856306	7		1.41E-11	G/A,A	0.46	0.017
LDLCHO	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.4	0.02
LDLCHO	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLCHO	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLCHO	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLCHO	rs2266788	*APOA5*	11	116660686	10		3.77E-23	G/A,A	0.07	0.006
LDLCHO	rs2288000	*DHODH*	16	72058881	8	+	1.51E-12	A/G,A	0.43	0.013
LDLCHO	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLCHO	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLCHO	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLCHO	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLCHO	rs2285627	*MAU2*	19	19467937	11	+	1.78E-11	T/C,T	0.34	0.029
LDLCHO	rs1063966	*GATAD2A*	19	19616742	10	+	1.52E-10	A/G,A	0.35	0.031
LDLCHO	rs1054284	*GATAD2A*	19	19616953	9	+	9.15E-10	G/T,T	0.35	0.03
LDLCHO	rs6909	*GATAD2A*	19	19619542	7	+	1.58E-10	G/A,A	0.35	0.031
LDLCHO	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023
LDLCHO	rs6857	*NECTIN2*	19	45392254	6		5.12E-110	T/C,T	0.16	0.023
LDLSFA	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLSFA	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLSFA	rs7528419	*CELSR2*	1	109817192	7	+	1.55E-165	G/A,A	0.23	0.014
LDLSFA	rs12740374	*CELSR2*	1	109817590	7	+	2.41E-272	T/G,T	0.23	0.013
LDLSFA	rs660240	*CELSR2*	1	109817838	4	+	9.00E-265	T/C,T	0.22	0.016
LDLSFA	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLSFA	rs464218	*SORT1*	1	109856306	7		1.41E-11	G/A,A	0.46	0.017
LDLSFA	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.4	0.02
LDLSFA	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLSFA	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLSFA	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLSFA	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLSFA	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLSFA	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLSFA	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLSFA	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023
LDLSFA	rs6857	*NECTIN2*	19	45392254	6		5.12E-110	T/C,T	0.16	0.023

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(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
LDLCHO	rs583609	*USP1*	-0.0809	0.0601	0.0028	0.0012	1.19E-06	1.91E-06	--+--+-+?	++-+++++?
LDLCHO	rs17034539	*KIAA1324*	0.0276	0.067	-0.0016	0.0014	0.000133	0.000181	-+++++++-	--------+
LDLCHO	rs7528419	*CELSR2*	0.156	0.0691	-0.0005	0.0014	3.89E-27	3.36E-26	++++++++?	+----+--?
LDLCHO	rs12740374	*CELSR2*	-0.1456	0.0594	0.0001	0.0012	1.02E-41	3.02E-39	---------	-++++-++-
LDLCHO	rs660240	*CELSR2*	-0.1575	0.0599	0.0003	0.0012	2.25E-41	5.07E-39	---------	-++++-++-
LDLCHO	rs629301	*CELSR2*	0.1429	0.0594	0	0.0012	4.71E-42	6.31E-41	+++++++++	+----+--+
LDLCHO	rs464218	*SORT1*	0.0798	0.0507	-0.0009	0.001	6.45E-05	8.86E-05	+-+++-+++	-++-++--+
LDLCHO	rs12916	*HMGCR*	-0.096	0.0518	0.0004	0.0011	3.75E-16	9.03E-16	-+++-----	+---+++++
LDLCHO	rs4246215	*FEN1*	-0.1108	0.0539	0.001	0.0011	6.77E-12	1.33E-11	--+----+-	-+-+-++-+
LDLCHO	rs174545	*FADS1*	0.1137	0.0617	-0.0009	0.0013	1.60E-11	6.15E-11	++-++++-?	+-+-+--+?
LDLCHO	rs174546	*FADS1*	-0.1119	0.0541	0.0009	0.0011	2.88E-13	5.83E-13	--+----+-	-+-+-++-+
LDLCHO	rs2266788	*APOA5*	0.1428	0.0975	-0.0042	0.002	8.85E-05	0.000138	+++-+--+-	---+-++--
LDLCHO	rs2288000	*DHODH*	0.0094	0.051	-0.0009	0.001	0.000147	0.000173	+--+++--+	-++---++-
LDLCHO	rs13465	*ILF3*	0.059	0.1157	-0.0036	0.0024	3.72E-09	9.41E-09	-+-+---++	--+-++---
LDLCHO	rs1433099	*LDLR*	-0.0473	0.0611	0	0.0013	2.34E-05	2.91E-05	-+-++-+--	--+--+-++
LDLCHO	rs7188	*KANK2*	-0.0847	0.0673	0.0002	0.0014	1.29E-10	2.86E-10	?-+++--+-	?+---++-+
LDLCHO	rs3810444	*SUGP2*	-0.303	0.1031	0.0046	0.0021	7.74E-06	1.36E-05	-++--++--	+--++--++
LDLCHO	rs2285627	*MAU2*	-0.1364	0.0526	0.0021	0.0011	0.000129	0.000206	---------	+++++++++
LDLCHO	rs1063966	*GATAD2A*	-0.1343	0.0517	0.0021	0.0011	0.000204	0.000265	---------	+++++++++
LDLCHO	rs1054284	*GATAD2A*	0.135	0.0517	-0.0021	0.0011	0.000251	0.000383	+++++++++	---------
LDLCHO	rs6909	*GATAD2A*	0.1355	0.0517	-0.0021	0.0011	0.000188	0.000311	+++++++++	---------
LDLCHO	rs6859	*NECTIN2*	0.0878	0.054	-0.0004	0.0011	4.21E-12	2.19E-11	--+-+++++	++++-----
LDLCHO	rs6857	*NECTIN2*	0.195	0.0766	-0.0004	0.0016	1.49E-41	1.06E-39	+++++--++	+--+-++--
LDLSFA	rs583609	*USP1*	0.1052	0.044	-0.0044	0.0035	6.08E-06	8.09E-06	+++-+-++?	--++-+--?
LDLSFA	rs17034539	*KIAA1324*	-0.0262	0.046	-0.0017	0.0036	0.000214	0.000306	------+-+	-+++++-+-
LDLSFA	rs7528419	*CELSR2*	0.1476	0.0506	-0.0011	0.004	6.90E-27	3.59E-26	+--+++++?	+++---+-?
LDLSFA	rs12740374	*CELSR2*	-0.1449	0.0409	0.0004	0.0032	3.16E-41	3.61E-40	-++------	+--+++-+-
LDLSFA	rs660240	*CELSR2*	-0.147	0.0414	0.0005	0.0032	5.87E-41	2.56E-39	-++------	---+++-+-
LDLSFA	rs629301	*CELSR2*	0.1461	0.0409	-0.0005	0.0032	1.57E-41	1.10E-39	+--++++++	-++---+-+
LDLSFA	rs464218	*SORT1*	0.0481	0.0352	-0.0008	0.0028	7.88E-05	0.000109	++-++++-+	+-+----+-
LDLSFA	rs12916	*HMGCR*	-0.0567	0.0362	-0.0015	0.0029	3.06E-16	1.47E-15	+-+++++--	-++-----+
LDLSFA	rs4246215	*FEN1*	-0.0621	0.037	-0.0002	0.0029	1.23E-11	2.98E-11	--++-++--	-+--+--++
LDLSFA	rs174545	*FADS1*	0.0544	0.0443	0.0015	0.0035	2.06E-11	5.59E-11	++--+--+?	+-++-++-?
LDLSFA	rs174546	*FADS1*	-0.055	0.037	-0.0011	0.0029	4.40E-13	1.45E-12	--++-++--	-+--+--+-
LDLSFA	rs13465	*ILF3*	-0.1839	0.0767	0.0056	0.006	1.64E-08	3.20E-08	-++++--+-	+----++-+
LDLSFA	rs1433099	*LDLR*	-0.0768	0.042	0.0022	0.0033	1.03E-05	1.49E-05	--++---+-	++--+++--
LDLSFA	rs7188	*KANK2*	-0.0427	0.0423	-0.0025	0.0033	8.61E-11	1.93E-10	?-++-++--	?---+--+-
LDLSFA	rs3810444	*SUGP2*	-0.0436	0.0734	-0.0032	0.0057	5.22E-05	7.56E-05	-------++	+++-+++--
LDLSFA	rs6859	*NECTIN2*	0.051	0.0364	0.0014	0.0028	3.05E-12	7.82E-12	+++++--++	----+++-+
LDLSFA	rs6857	*NECTIN2*	0.1633	0.0498	0.0008	0.0039	6.66E-41	1.30E-39	+++-+++++	---+----+

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
LDLCHO	rs583609	*USP1*	1.31E-06	-0.0734	0.0594	0.0026	0.0012	2.37E-06	--++-+-+?	++--++++?	0.34	16009
LDLCHO	rs17034539	*KIAA1324*	3.95E-05	0.0293	0.0659	-0.0016	0.0014	4.31E-05	-+++++++-	--------+	0.19	21995
LDLCHO	rs7528419	*CELSR2*	1.72E-26	0.1458	0.0676	-0.0003	0.0014	7.89E-27	++++++++?	+----++-?	0.64	16009
LDLCHO	rs12740374	*CELSR2*	5.48E-42	-0.1428	0.0585	0.0001	0.0012	1.56E-42	---------	-++++--+-	0.6	21995
LDLCHO	rs660240	*CELSR2*	1.05E-41	-0.1559	0.059	0.0003	0.0012	3.94E-42	---------	-++++--+-	0.45	21995
LDLCHO	rs629301	*CELSR2*	2.63E-42	0.1404	0.0585	0	0.0012	7.36E-43	+++++++++	+----++-+	0.59	21995
LDLCHO	rs464218	*SORT1*	2.35E-05	0.0885	0.0497	-0.001	0.001	1.87E-05	+--++-+++	-++-++--+	0.61	21995
LDLCHO	rs12916	*HMGCR*	2.36E-17	-0.1131	0.0505	0.0008	0.001	5.22E-17	-+++-----	+---+++++	0.01	21995
LDLCHO	rs4246215	*FEN1*	1.82E-12	-0.1026	0.0516	0.0008	0.0011	7.67E-13	--+----+-	-+-+-++-+	0.78	21995
LDLCHO	rs174545	*FADS1*	3.29E-12	0.1024	0.0582	-0.0006	0.0012	1.14E-12	++-++++-?	+-+-+--+?	0.93	16009
LDLCHO	rs174546	*FADS1*	6.12E-14	-0.1041	0.0518	0.0007	0.0011	2.07E-14	--+----+-	-+-+-++-+	0.94	21995
LDLCHO	rs2266788	*APOA5*	0.000182	0.1527	0.0955	-0.0043	0.002	0.000183	+++-+--++	---+-++--	0.13	21995
LDLCHO	rs2288000	*DHODH*	0.000757	0.0031	0.0498	-0.0007	0.001	0.000536	+--+++--+	-++---++-	0.002	21995
LDLCHO	rs13465	*ILF3*	2.03E-09	0.0974	0.1129	-0.0044	0.0023	2.73E-09	-+-+---++	--+-++---	0.61	21994
LDLCHO	rs1433099	*LDLR*	1.98E-05	-0.0376	0.0598	-0.0002	0.0012	2.12E-05	-+-++-+--	--+--+-++	0.78	21995
LDLCHO	rs7188	*KANK2*	1.67E-12	-0.091	0.0607	0.0004	0.0012	2.15E-12	--+++--+-	+----++-+	0.59	15418
LDLCHO	rs3810444	*SUGP2*	4.41E-06	-0.3202	0.1019	0.005	0.0021	4.11E-06	-++--++--	+--++--++	0.51	21995
LDLCHO	rs2285627	*MAU2*	7.36E-05	-0.1344	0.0515	0.0021	0.0011	9.84E-05	---------	+++-+++++	0.24	21995
LDLCHO	rs1063966	*GATAD2A*	0.000129	-0.1316	0.0508	0.0021	0.001	0.000178	---------	++++++++	0.09	21995
LDLCHO	rs1054284	*GATAD2A*	0.000163	0.1322	0.0508	-0.0021	0.001	0.000222	++++++++	---------	0.09	21995
LDLCHO	rs6909	*GATAD2A*	0.000118	0.133	0.0508	-0.0021	0.001	0.000162	++++++++	---------	0.09	21995
LDLCHO	rs6859	*NECTIN2*	2.37E-13	0.0675	0.0532	0	0.0011	6.37E-13	--+-+++-+	++++---+-	0.19	21995
LDLCHO	rs6857	*NECTIN2*	2.06E-45	0.1598	0.0763	0.0004	0.0016	5.20E-45	+++-+--++	+--+-++--	0.11	21995
LDLSFA	rs583609	*USP1*	4.89E-06	0.1088	0.043	-0.0049	0.0034	7.07E-06	+++-+-++?	--++-+--?	0.46	16009
LDLSFA	rs17034539	*KIAA1324*	8.81E-05	-0.0294	0.0447	-0.0015	0.0035	9.44E-05	------+-+	-+++++-+-	0.54	21995
LDLSFA	rs7528419	*CELSR2*	1.65E-26	0.148	0.0492	-0.0013	0.0039	6.64E-27	+--+++++?	+++---+-?	0.53	16009
LDLSFA	rs12740374	*CELSR2*	8.80E-42	-0.1466	0.0402	0.0005	0.0031	2.24E-42	-++------	+--+++-+-	0.5	21995
LDLSFA	rs660240	*CELSR2*	1.40E-41	-0.1479	0.0406	0.0006	0.0032	4.80E-42	-++------	---+++-+-	0.37	21995
LDLSFA	rs629301	*CELSR2*	4.37E-42	0.1476	0.0401	-0.0006	0.0031	1.11E-42	+--++++++	-++---+-+	0.49	21995
LDLSFA	rs464218	*SORT1*	2.78E-05	0.0377	0.034	0.0002	0.0027	2.34E-05	++-++++-+	+-+----+-	0.29	21995
LDLSFA	rs12916	*HMGCR*	3.09E-17	-0.0478	0.0348	-0.0022	0.0027	7.58E-17	-++-++++-	--+-----+	0.07	21995
LDLSFA	rs4246215	*FEN1*	2.83E-12	-0.0583	0.0354	-0.0006	0.0028	1.22E-12	--++-+---	-+--+--+-	0.21	21995
LDLSFA	rs174545	*FADS1*	3.90E-12	0.0552	0.0416	0.0016	0.0033	1.38E-12	++--+--+?	+-++-++-?	0.35	16009
LDLSFA	rs174546	*FADS1*	8.72E-14	-0.0527	0.0354	-0.0014	0.0028	3.04E-14	--++-+--	-+--+--+-	0.42	21995
LDLSFA	rs13465	*ILF3*	1.12E-08	-0.1909	0.0754	0.0065	0.0059	2.61E-08	-++++----	+----++-+	0.29	21994
LDLSFA	rs1433099	*LDLR*	8.56E-06	-0.0763	0.0407	0.0023	0.0032	1.03E-05	--++---+-	++--+++--	0.6	21995
LDLSFA	rs7188	*KANK2*	1.24E-12	-0.0519	0.0394	-0.0018	0.0031	1.47E-12	--++-++--	+---+--+-	0.48	15418
LDLSFA	rs3810444	*SUGP2*	5.21E-05	-0.0398	0.0708	-0.0034	0.0055	4.88E-05	-------++	+++-+++--	0.62	21995
LDLSFA	rs6859	*NECTIN2*	1.67E-13	0.0563	0.0356	0.0011	0.0028	3.94E-13	+++++--++	----+++-+	0.46	21995
LDLSFA	rs6857	*NECTIN2*	1.26E-44	0.1821	0.0493	-0.0004	0.0039	3.53E-44	+++-+++++	---+----+	0.07	21995

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2	Model 3 Het P value
LDLCHO	rs583609	*USP1*	0.0393	0.009	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.07E-07	+++-++++?	0	0.47
LDLCHO	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.011	2.17E-05	------+--	0	0.59
LDLCHO	rs7528419	*CELSR2*	NA	NA	NA	NA	NA	0.1318	0.0114	4.44E-31	++++++++?	14.8	0.31
LDLCHO	rs12740374	*CELSR2*	NA	NA	NA	NA	NA	-0.1394	0.0097	1.15E-46	--------	27.4	0.2
LDLCHO	rs660240	*CELSR2*	NA	NA	NA	NA	NA	-0.1402	0.0098	3.38E-46	--------	34.8	0.14
LDLCHO	rs629301	*CELSR2*	0.1445	0.01	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.27E-47	+++++++++	28	0.2
LDLCHO	rs464218	*SORT1*	0.0236	0.0077	2.20E-03	2.56E-03	+-++++++	0.0378	0.0083	5.70E-06	+-++++-++	12.1	0.33
LDLCHO	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.08E-17	--+------	58	0.01
LDLCHO	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	--------	-0.0623	0.0086	4.40E-13	--------	0	0.54
LDLCHO	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLCHO	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	--------	-0.066	0.0086	1.40E-14	--------	0	0.76
LDLCHO	rs2266788	*APOA5*	-0.0463	0.0149	1.94E-03	2.23E-03	-+-------	-0.0596	0.0161	0.00021	--------	0	0.67
LDLCHO	rs2288000	*DHODH*	-0.0229	0.0077	3.00E-03	3.43E-03	-+-------	-0.031	0.0083	0.000181	-------+-	38.8	0.11
LDLCHO	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	--------	-0.1073	0.0188	1.07E-08	----+----	38.1	0.11
LDLCHO	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	--------	-0.0468	0.0098	1.80E-06	--------	0	0.64
LDLCHO	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?-------	-0.0719	0.0096	8.28E-14	--------	0	0.51
LDLCHO	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	1.07E-05	------+--	12.9	0.33
LDLCHO	rs2285627	*MAU2*	-0.0246	0.008	2.22E-03	2.48E-03	-+----+--	-0.0336	0.0087	0.000113	-----++--	46.5	0.06
LDLCHO	rs1063966	*GATAD2A*	-0.0202	0.0079	1.12E-02	1.19E-02	-+---++--	-0.0321	0.0086	0.000183	-----++--	48.5	0.05
LDLCHO	rs1054284	*GATAD2A*	0.0197	0.0079	1.34E-02	1.41E-02	+-+++--++	0.0315	0.0086	0.00024	+++++--++	49	0.05
LDLCHO	rs6909	*GATAD2A*	0.0202	0.0079	1.11E-02	1.19E-02	+-+++--++	0.0322	0.0086	0.000175	+++++--++	48.4	0.05
LDLCHO	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-+++++++	0.0691	0.0088	5.79E-15	+-+++++++	28.1	0.19
LDLCHO	rs6857	*NECTIN2*	NA	NA	NA	NA	NA	0.173	0.0121	1.02E-46	+++++++++	59.1	0.01
LDLSFA	rs583609	*USP1*	0.0393	0.009	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.07E-07	+++-++++?	0	0.47
LDLSFA	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.011	2.17E-05	------+--	0	0.59
LDLSFA	rs7528419	*CELSR2*	NA	NA	NA	NA	NA	0.1318	0.0114	4.44E-31	++++++++?	14.8	0.31
LDLSFA	rs12740374	*CELSR2*	NA	NA	NA	NA	NA	-0.1394	0.0097	1.15E-46	--------	27.4	0.2
LDLSFA	rs660240	*CELSR2*	NA	NA	NA	NA	NA	-0.1402	0.0098	3.38E-46	--------	34.8	0.14
LDLSFA	rs629301	*CELSR2*	0.1445	0.01	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.27E-47	+++++++++	28	0.2
LDLSFA	rs464218	*SORT1*	0.0236	0.0077	2.20E-03	2.56E-03	+-++++++	0.0378	0.0083	5.70E-06	+-++++-++	12.1	0.33
LDLSFA	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.08E-17	--+------	58	0.01
LDLSFA	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	--------	-0.0623	0.0086	4.40E-13	--------	0	0.54
LDLSFA	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLSFA	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	--------	-0.066	0.0086	1.40E-14	--------	0	0.76
LDLSFA	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	--------	-0.1073	0.0188	1.07E-08	----+----	38.1	0.11
LDLSFA	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	--------	-0.0468	0.0098	1.80E-06	--------	0	0.64
LDLSFA	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?-------	-0.0719	0.0096	8.28E-14	--------	0	0.51
LDLSFA	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	1.07E-05	------+--	12.9	0.33
LDLSFA	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-+++++++	0.0691	0.0088	5.79E-15	+-+++++++	28.1	0.19
LDLSFA	rs6857	*NECTIN2*	NA	NA	NA	NA	NA	0.173	0.0121	1.02E-46	+++++++++	59.1	0.01

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Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
LDLMUFA	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLMUFA	rs7528419	*CELSR2*	1	109817192	7	+	1.55E-165	G/A,A	0.23	0.014
LDLMUFA	rs12740374	*CELSR2*	1	109817590	7	+	2.41E-272	T/G,T	0.23	0.013
LDLMUFA	rs660240	*CELSR2*	1	109817838	4	+	9.00E-265	T/C,T	0.22	0.016
LDLMUFA	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLMUFA	rs464218	*SORT1*	1	109856306	7		1.41E-11	G/A,A	0.46	0.017
LDLMUFA	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.4	0.02
LDLMUFA	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLMUFA	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLMUFA	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLMUFA	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLMUFA	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLMUFA	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLMUFA	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLMUFA	rs2285627	*MAU2*	19	19467937	11	+	1.78E-11	T/C,T	0.34	0.029
LDLMUFA	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023
LDLMUFA	rs6857	*NECTIN2*	19	45392254	6		5.12E-110	T/C,T	0.16	0.023
LDLPUFA	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLPUFA	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLPUFA	rs3197232	*KIAA1324*	1	109748940	6		6.81E-05	A/G,A	0.26	0.012
LDLPUFA	rs7528419	*CELSR2*	1	109817192	7	+	1.55E-165	G/A,A	0.23	0.014
LDLPUFA	rs12740374	*CELSR2*	1	109817590	7	+	2.41E-272	T/G,T	0.23	0.013
LDLPUFA	rs660240	*CELSR2*	1	109817838	4	+	9.00E-265	T/C,T	0.22	0.016
LDLPUFA	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLPUFA	rs464218	*SORT1*	1	109856306	7		1.41E-11	G/A,A	0.46	0.017
LDLPUFA	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.4	0.02
LDLPUFA	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLPUFA	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLPUFA	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLPUFA	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLPUFA	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLPUFA	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLPUFA	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLPUFA	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023
LDLPUFA	rs6857	*NECTIN2*	19	45392254	6		5.12E-110	T/C,T	0.16	0.023

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
LDLMUFA	rs583609	*USP1*	0.14	0.0447	-0.0074	0.0036	1.84E-06	3.50E-06	++--+++-?	--++-+-+?
LDLMUFA	rs7528419	*CELSR2*	0.1362	0.051	-0.0001	0.0041	1.65E-27	1.39E-26	+--+++++?	-++----+?
LDLMUFA	rs12740374	*CELSR2*	-0.1734	0.0406	0.0027	0.0034	2.09E-42	2.12E-40	-++------	+--++++-+
LDLMUFA	rs660240	*CELSR2*	-0.1655	0.0409	0.002	0.0034	6.20E-42	2.01E-40	-++------	+--++++-+
LDLMUFA	rs629301	*CELSR2*	0.1746	0.0406	-0.0028	0.0034	9.58E-43	3.94E-41	+--++++++	-++----+-
LDLMUFA	rs464218	*SORT1*	-0.0068	0.0346	0.0039	0.0028	2.73E-05	4.09E-05	-+--+++-+	+-++---+-
LDLMUFA	rs12916	*HMGCR*	-0.0362	0.0352	-0.0033	0.0029	1.59E-16	7.52E-16	----++++-	++++----+
LDLMUFA	rs4246215	*FEN1*	-0.0034	0.0361	-0.0052	0.003	2.16E-12	8.48E-12	--++-++-+	-----+--+-
LDLMUFA	rs174545	*FADS1*	0.0248	0.0433	0.004	0.0034	9.49E-12	2.09E-11	++--+--+?	++++-++-?
LDLMUFA	rs174546	*FADS1*	-0.0115	0.0363	-0.0048	0.003	1.15E-13	4.14E-13	--++-++-+	----+--+-
LDLMUFA	rs13465	*ILF3*	-0.233	0.0764	0.0103	0.0062	1.34E-08	2.73E-08	----++---	++++--+++
LDLMUFA	rs1433099	*LDLR*	-0.0588	0.0406	0.0008	0.0034	1.48E-05	2.36E-05	-------++	++-++++--
LDLMUFA	rs7188	*KANK2*	-0.1071	0.0424	0.0029	0.0036	9.27E-11	2.18E-10	?-+--++--	?-+++----
LDLMUFA	rs3810444	*SUGP2*	-0.0331	0.0741	-0.004	0.0061	0.000112	0.000155	-------++	+++++++--
LDLMUFA	rs2285627	*MAU2*	0.0223	0.0351	-0.0048	0.0029	0.000202	0.000273	--+-+++++	++-+-----
LDLMUFA	rs6859	*NECTIN2*	0.1507	0.0363	-0.0071	0.003	3.53E-13	1.04E-12	+++++++++	--+--+---
LDLMUFA	rs6857	*NECTIN2*	0.1378	0.0506	0.0031	0.0043	3.77E-41	1.49E-39	+++-+++--	---+---++
LDLPUFA	rs583609	*USP1*	0.0667	0.0284	-0.003	0.0046	1.74E-05	2.54E-05	+-+-+++-?	++-+---+?
LDLPUFA	rs17034539	*KIAA1324*	-0.1187	0.0314	0.0128	0.0053	8.77E-06	1.34E-05	-+++-----	+---+++++
LDLPUFA	rs3197232	*KIAA1324*	-0.1002	0.0272	0.0125	0.0046	0.000182	0.000251	-+++-----	+---+++++
LDLPUFA	rs7528419	*CELSR2*	0.1395	0.0329	-0.0011	0.0054	6.52E-27	5.25E-26	+-++++++?	-++-+--+?
LDLPUFA	rs12740374	*CELSR2*	-0.1535	0.0286	0.0024	0.0049	1.99E-41	6.23E-40	-+-------	+--+-++-+
LDLPUFA	rs660240	*CELSR2*	-0.1538	0.0289	0.0023	0.0049	5.60E-41	1.05E-39	-+-------	+--+-++-+
LDLPUFA	rs629301	*CELSR2*	0.1546	0.0285	-0.0025	0.0049	9.69E-42	3.31E-40	+-++++++	-++-+--+-
LDLPUFA	rs464218	*SORT1*	0.0373	0.0249	0.0002	0.0042	6.88E-05	9.55E-05	++--+++-+	+-+++--++
LDLPUFA	rs12916	*HMGCR*	-0.1071	0.0247	0.0057	0.0042	1.51E-16	5.66E-16	---+-+++-	+-+-+---+
LDLPUFA	rs4246215	*FEN1*	-0.0404	0.0254	-0.0043	0.0043	8.24E-12	2.06E-11	--++-++--	++-----++
LDLPUFA	rs174545	*FADS1*	0.0511	0.0286	0.0038	0.0046	1.62E-11	3.95E-11	++--+--+?	--+++++-?
LDLPUFA	rs174546	*FADS1*	-0.0464	0.0253	-0.004	0.0043	3.14E-13	1.02E-12	--++-++--	++-----+-
LDLPUFA	rs13465	*ILF3*	-0.0919	0.0538	-0.0031	0.0092	1.01E-07	1.88E-07	+--------	--+++-++-
LDLPUFA	rs1433099	*LDLR*	-0.054	0.0293	0.0009	0.005	1.52E-05	2.22E-05	-+-+---++	--+-+++--
LDLPUFA	rs7188	*KANK2*	-0.0862	0.0304	0.0023	0.005	1.34E-10	3.01E-10	?++----+-	?-++++--+
LDLPUFA	rs3810444	*SUGP2*	-0.0952	0.0531	0.003	0.0092	0.000171	0.000231	+---+--+-	-+++-++--
LDLPUFA	rs6859	*NECTIN2*	0.1159	0.026	-0.0088	0.0044	8.26E-13	2.77E-12	+++++++++	--+------
LDLPUFA	rs6857	*NECTIN2*	0.2296	0.0362	-0.0097	0.0061	1.75E-42	4.74E-41	+++-+++-+	---+---+-

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
LDLMUFA	rs583609	*USP1*	1.62E-06	0.1423	0.0441	-0.0077	0.0035	1.84E-06	++--+++-?	--++-+-+?	0.65	16009
LDLMUFA	rs7528419	*CELSR2*	4.93E-27	0.1446	0.0508	-0.001	0.0041	2.47E-27	+--+++++?	-++-----?	0.08	16009
LDLMUFA	rs12740374	*CELSR2*	8.09E-43	-0.1761	0.0406	0.003	0.0034	2.52E-43	-++------	+--++++++	0.1	21994
LDLMUFA	rs660240	*CELSR2*	2.32E-42	-0.1684	0.041	0.0023	0.0034	9.98E-43	-++------	+--++++++	0.1	21994
LDLMUFA	rs629301	*CELSR2*	3.82E-43	0.1774	0.0406	-0.003	0.0034	1.20E-43	+--++++++	-++------	0.11	21994
LDLMUFA	rs464218	*SORT1*	7.87E-06	-0.0082	0.0343	0.0041	0.0028	6.84E-06	-+--+++-+	+-++---+-	0.38	21994
LDLMUFA	rs12916	*HMGCR*	2.70E-17	-0.0422	0.0346	-0.0028	0.0028	6.78E-17	----+++-	++++----+	0.05	21994
LDLMUFA	rs4246215	*FEN1*	9.35E-13	-0.0112	0.0352	-0.0046	0.0029	3.34E-13	-+++-++--	----+--+-	0.28	21994
LDLMUFA	rs174545	*FADS1*	2.78E-12	0.0352	0.0419	0.0033	0.0033	9.12E-13	+---+--+?	++++-++-?	0.32	16009
LDLMUFA	rs174546	*FADS1*	4.49E-14	-0.0202	0.0354	-0.0042	0.0029	1.35E-14	-+++-++-+	----+--+-	0.41	21994
LDLMUFA	rs13465	*ILF3*	4.84E-09	-0.2496	0.0764	0.0118	0.0062	9.37E-09	----++---	++++--+++	0.27	21993
LDLMUFA	rs1433099	*LDLR*	1.09E-05	-0.0629	0.0399	0.0012	0.0033	1.22E-05	-------++	++-++++--	0.72	21994
LDLMUFA	rs7188	*KANK2*	8.94E-13	-0.1053	0.0395	0.0027	0.0033	1.20E-12	-----++--	--+++----	0.62	15417
LDLMUFA	rs3810444	*SUGP2*	8.34E-05	-0.0258	0.0728	-0.0046	0.006	7.78E-05	---+---++	+++-+++--	0.56	21994
LDLMUFA	rs2285627	*MAU2*	0.000111	0.0209	0.0349	-0.0047	0.0028	0.000176	-++--++++	+--+-----	0.26	21994
LDLMUFA	rs6859	*NECTIN2*	8.15E-15	0.1593	0.0356	-0.0077	0.0029	2.15E-14	++-++++++	--+-+----	0.38	21994
LDLMUFA	rs6857	*NECTIN2*	4.73E-45	0.1492	0.0499	0.0025	0.0043	1.36E-44	+++++++--	---+---++	0.04	21994
LDLPUFA	rs583609	*USP1*	1.32E-05	0.0611	0.0285	-0.0021	0.0046	1.80E-05	+-+-+++-?	++-+---+?	0.69	16009
LDLPUFA	rs17034539	*KIAA1324*	3.54E-06	-0.1209	0.032	0.0131	0.0054	4.68E-06	-+++-----	+---+++++	0.83	21995
LDLPUFA	rs3197232	*KIAA1324*	8.18E-05	-0.1027	0.0276	0.0126	0.0047	8.91E-05	-+++-----	+---+++++	0.88	21995
LDLPUFA	rs7528419	*CELSR2*	1.74E-26	0.1405	0.0328	-0.0016	0.0053	9.37E-27	+-++++++?	-++-+---?	0.66	16009
LDLPUFA	rs12740374	*CELSR2*	5.64E-42	-0.1593	0.0285	0.0035	0.0048	1.99E-42	-+-------	+--+-++++	0.63	21995
LDLPUFA	rs660240	*CELSR2*	1.34E-41	-0.1579	0.0288	0.0031	0.0049	6.67E-42	-+-------	+--+-++++	0.43	21995
LDLPUFA	rs629301	*CELSR2*	2.96E-42	0.16	0.0285	-0.0035	0.0048	1.03E-42	+++++++++	-++-+----	0.63	21995
LDLPUFA	rs464218	*SORT1*	2.67E-05	0.0453	0.025	-0.0009	0.0042	2.05E-05	++--+++-+	+-+++--+-	0.71	21995
LDLPUFA	rs12916	*HMGCR*	2.98E-17	-0.1024	0.0246	0.0049	0.0042	6.53E-17	-+-+-+++-	+-+-+---+	0.02	21995
LDLPUFA	rs4246215	*FEN1*	2.70E-12	-0.0502	0.0253	-0.0028	0.0043	1.01E-12	--++-++--	++-----++	0.17	21995
LDLPUFA	rs174545	*FADS1*	3.59E-12	0.0633	0.0283	0.0021	0.0046	1.11E-12	++--+--+?	--+++++-?	0.22	16009
LDLPUFA	rs174546	*FADS1*	8.78E-14	-0.0576	0.0252	-0.0023	0.0043	2.68E-14	--++-++--	++-----++	0.28	21995
LDLPUFA	rs13465	*ILF3*	9.98E-08	-0.0843	0.0532	-0.004	0.0091	1.51E-07	+-------	--+++-++-	0.21	21994
LDLPUFA	rs1433099	*LDLR*	9.87E-06	-0.0527	0.029	0.0007	0.005	1.07E-05	-+-+---++	--+-+++--	0.5	21995
LDLPUFA	rs7188	*KANK2*	1.01E-12	-0.0769	0.0287	0.0005	0.0049	1.44E-12	-++------	--++++--+	0.49	15418
LDLPUFA	rs3810444	*SUGP2*	0.000152	-0.09	0.0522	0.0022	0.009	0.000135	+---+--+-	-+++-++-+	0.39	21995
LDLPUFA	rs6859	*NECTIN2*	3.04E-14	0.1194	0.0257	-0.0091	0.0044	7.95E-14	++-++++++	--+------	0.66	21995
LDLPUFA	rs6857	*NECTIN2*	2.03E-46	0.239	0.0361	-0.0107	0.0061	5.08E-46	+++-+++-+	---+---+-	0.15	21995

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(A) Dietary interaction analysis of GLGC 2013 top miRNA-related SNPs in the CHARGE consortium: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 2.7 \times 10^{-4}$ (selected from the GLGC 2013 GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3 I^2	Model 3 Het P value
LDLMUFA	rs583609	*USP1*	0.0393	0.009	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.07E-07	+++-++++?	0	0.47
LDLMUFA	rs7528419	*CELSR2*	NA	NA	NA	NA	NA	0.1318	0.0114	4.44E-31	++++++++?	14.8	0.31
LDLMUFA	rs12740374	*CELSR2*	NA	NA	NA	NA	NA	-0.1394	0.0097	1.15E-46	---------	27.4	0.2
LDLMUFA	rs660240	*CELSR2*	NA	NA	NA	NA	NA	-0.1402	0.0098	3.38E-46	---------	34.8	0.14
LDLMUFA	rs629301	*CELSR2*	0.1445	0.01	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.27E-47	+++++++++	28	0.2
LDLMUFA	rs464218	*SORT1*	0.0236	0.0077	2.20E-03	2.56E-03	+-+++++-+	0.0378	0.0083	5.70E-06	+-++++-++	12.1	0.33
LDLMUFA	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.08E-17	--+------	58	0.01
LDLMUFA	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	---------	-0.0623	0.0086	4.40E-13	---------	0	0.54
LDLMUFA	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLMUFA	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	---------	-0.066	0.0086	1.40E-14	---------	0	0.76
LDLMUFA	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	---------	-0.1073	0.0188	1.07E-08	----+----	38.1	0.11
LDLMUFA	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	---------	-0.0468	0.0098	1.80E-06	---------	0	0.64
LDLMUFA	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?-------	-0.0719	0.0096	8.28E-14	---------	0	0.51
LDLMUFA	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	1.07E-05	------+--	12.9	0.33
LDLMUFA	rs2285627	*MAU2*	-0.0246	0.008	2.22E-03	2.48E-03	-+----+--	-0.0336	0.0087	0.000113	-----++--	46.5	0.06
LDLMUFA	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-+++++++	0.0691	0.0088	5.79E-15	+-+++++++	28.1	0.19
LDLMUFA	rs6857	*NECTIN2*	NA	NA	NA	NA	NA	0.173	0.0121	1.02E-46	+++++++++	59.1	0.01
LDLPUFA	rs583609	*USP1*	0.0393	0.009	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.07E-07	+++-++++?	0	0.47
LDLPUFA	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.011	2.17E-05	------+--	0	0.59
LDLPUFA	rs3197232	*KIAA1324*	-0.0266	0.0089	2.67E-03	3.27E-03	---+--+--	-0.0311	0.0095	0.001083	---------	0	0.64
LDLPUFA	rs7528419	*CELSR2*	NA	NA	NA	NA	NA	0.1318	0.0114	4.44E-31	++++++++?	14.8	0.31
LDLPUFA	rs12740374	*CELSR2*	NA	NA	NA	NA	NA	-0.1394	0.0097	1.15E-46	---------	27.4	0.2
LDLPUFA	rs660240	*CELSR2*	NA	NA	NA	NA	NA	-0.1402	0.0098	3.38E-46	---------	34.8	0.14
LDLPUFA	rs629301	*CELSR2*	0.1445	0.01	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.27E-47	+++++++++	28	0.2
LDLPUFA	rs464218	*SORT1*	0.0236	0.0077	2.20E-03	2.56E-03	+-+++++-+	0.0378	0.0083	5.70E-06	+-++++-++	12.1	0.33
LDLPUFA	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.08E-17	--+------	58	0.01
LDLPUFA	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	---------	-0.0623	0.0086	4.40E-13	---------	0	0.54
LDLPUFA	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLPUFA	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	---------	-0.066	0.0086	1.40E-14	---------	0	0.76
LDLPUFA	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	---------	-0.1073	0.0188	1.07E-08	----+----	38.1	0.11
LDLPUFA	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	---------	-0.0468	0.0098	1.80E-06	---------	0	0.64
LDLPUFA	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?-------	-0.0719	0.0096	8.28E-14	---------	0	0.51
LDLPUFA	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	1.07E-05	------+--	12.9	0.33
LDLPUFA	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-+++++++	0.0691	0.0088	5.79E-15	+-+++++++	28.1	0.19
LDLPUFA	rs6857	*NECTIN2*	NA	NA	NA	NA	NA	0.173	0.0121	1.02E-46	+++++++++	59.1	0.01

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
TGCHO	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.34	0.025
TGCHO	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGCHO	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.40	0.034
TGCHO	rs4803	*KRTCAP3, IFT172*	2	27667297	5	+	NA	G/A,A	0.40	0.031
TGCHO	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGCHO	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGCHO	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.010
TGCHO	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGCHO	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.20	0.016
TGCHO	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGCHO	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGCHO	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGCHO	rs512555	*MS4A2*	11	59863253	5	+	0.07883	T/C,T	0.02	0.006
TGCHO	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGCHO	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGCHO	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009
TGSFA	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.34	0.025
TGSFA	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGSFA	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.40	0.034
TGSFA	rs4803	*KRTCAP3, IFT172*	2	27667297	5	+	NA	G/A,A	0.40	0.031
TGSFA	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGSFA	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGSFA	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.010
TGSFA	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGSFA	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.20	0.016
TGSFA	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGSFA	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGSFA	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGSFA	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGSFA	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGSFA	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
TGCHO	rs583609	*USP1*	0.0541	0.0313	-0.0005	0.0006	4.65E-07	7.58E-07	+--+-+++?	-++-+---?
TGCHO	rs13472	*SNX17, ZNF513*	0.0079	0.0306	-0.0009	0.0006	3.20E-11	8.24E-11	+---+-++?	-+++----?
TGCHO	rs4582	*PPM1G*	-0.0029	0.0306	0.0008	0.0006	2.39E-11	5.39E-11	-+++-+--?	+---++++?
TGCHO	rs4803	*KRTCAP3, IFT172*	0.0049	0.0272	0.0007	0.0006	2.32E-15	3.55E-15	-+++-+--+	+---+-+++
TGCHO	rs8395	*FNDC4*	0.0064	0.0306	-0.0009	0.0006	4.35E-12	8.33E-12	+---+-++?	-+++-+--?
TGCHO	rs1881396	*ZNF512*	0.0646	0.0319	-0.0008	0.0007	1.80E-05	2.38E-05	++--+++++	--++-----
TGCHO	rs13232120	*TBL2*	0.0088	0.0400	0.0011	0.0008	6.43E-19	6.40E-18	++-+-----	--+++++++
TGCHO	rs14415	*TBL2*	0.0322	0.0295	0.0002	0.0006	1.96E-15	1.85E-14	+--+--++-	-++-++--+
TGCHO	rs1051921	*MLXIPL*	-0.0189	0.0338	-0.0007	0.0007	3.62E-19	1.38E-18	--+-+++++	++-+-----
TGCHO	rs3289	*LPL*	-0.2634	0.0852	0.0036	0.0017	1.25E-09	4.15E-09	-----+---	+++-+-+++
TGCHO	rs13702	*LPL*	0.0440	0.0287	0.0002	0.0006	6.25E-26	6.55E-25	++--+++++	+-++-+--+
TGCHO	rs15285	*LPL*	-0.0565	0.0355	-0.0002	0.0007	1.98E-24	3.31E-23	-----+---	-++-+--+-
TGCHO	rs512555	*MS4A2*	-0.1295	0.0977	0.0039	0.0020	0.000852	0.001193	--?---+-?	++?+++-+?
TGCHO	rs619054	*APOA5*	-0.0518	0.0307	0.0004	0.0006	1.41E-08	3.11E-08	--+-+----	-+-+-+++-
TGCHO	rs1035237	*SIK3*	-0.0641	0.0478	0.0004	0.0010	5.67E-07	9.77E-07	----++--?	++++---+?
TGCHO	rs3810444	*SUGP2*	-0.0994	0.0539	0.0009	0.0011	1.05E-07	2.29E-07	-++-+-++-	+--+-+--+
TGSFA	rs583609	*USP1*	0.0253	0.0223	0.0004	0.0017	5.36E-07	1.09E-06	+++++++-?	+----+-+?
TGSFA	rs13472	*SNX17, ZNF513*	-0.0497	0.0215	0.0011	0.0017	4.69E-11	1.44E-10	--++-+--?	+-----+-?
TGSFA	rs4582	*PPM1G*	0.0481	0.0214	-0.0009	0.0017	3.20E-11	7.24E-11	++-++-++?	-+++++-+?
TGSFA	rs4803	*KRTCAP3, IFT172*	0.0499	0.0181	-0.0010	0.0014	2.37E-15	1.33E-14	+--++-+++	-+++++-+-
TGSFA	rs8395	*FNDC4*	-0.0515	0.0215	0.0011	0.0017	6.30E-12	1.99E-11	-+++-+--?	+-----+-?
TGSFA	rs1881396	*ZNF512*	0.0116	0.0216	0.0011	0.0017	4.16E-05	5.64E-05	++-+++-++	+++--++++
TGSFA	rs13232120	*TBL2*	0.0956	0.0273	-0.0027	0.0021	9.94E-19	5.92E-18	--+++++++	++-------
TGSFA	rs14415	*TBL2*	0.0444	0.0198	-0.0003	0.0016	3.91E-15	1.25E-14	-+++++-++	+--+--+--
TGSFA	rs1051921	*MLXIPL*	-0.0825	0.0230	0.0024	0.0018	5.38E-19	3.89E-18	++-------	--+++++++
TGSFA	rs3289	*LPL*	-0.0134	0.0601	-0.0060	0.0047	1.50E-08	3.22E-08	+----+-+-	-++++-+--
TGSFA	rs13702	*LPL*	0.0514	0.0196	0.0002	0.0015	1.10E-25	5.31E-25	+--+-++++	+++-++---
TGSFA	rs15285	*LPL*	-0.0563	0.0235	-0.0006	0.0019	4.98E-24	5.96E-23	-+-------	--++-+-++
TGSFA	rs619054	*APOA5*	-0.0140	0.0208	-0.0015	0.0016	1.30E-08	2.59E-08	-+---++--	--+++--++
TGSFA	rs1035237	*SIK3*	0.0014	0.0340	-0.0037	0.0027	5.38E-07	1.02E-06	+++++---?	-----+-+?
TGSFA	rs3810444	*SUGP2*	-0.0272	0.0370	-0.0022	0.0029	1.11E-07	1.73E-07	---+--+-+	-+--+--+-

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
TGCHO	rs583609	*USP1*	3.81E-08	0.0459	0.0292	-0.0003	0.0006	1.55E-08	+--+-+++?	-++-+-+-?	0.27	16110
TGCHO	rs13472	*SNX17, ZNF513*	1.11E-11	0.0032	0.0288	-0.0008	0.0006	6.77E-12	+---+--+?	-+++-+--?	0.79	16110
TGCHO	rs4582	*PPM1G*	1.07E-11	0.0006	0.0287	0.0007	0.0006	5.43E-12	++++-++-?	+---+-++?	0.77	16110
TGCHO	rs4803	*KRTCAP3, IFT172*	4.38E-15	0.0073	0.0258	0.0006	0.0005	7.29E-16	++++-++-+	+---+-+++	0.80	22103
TGCHO	rs8395	*FNDC4*	1.07E-12	0.0023	0.0288	-0.0008	0.0006	6.76E-13	+-+-+--+?	-+++-+--?	0.71	16110
TGCHO	rs1881396	*ZNF512*	5.64E-07	0.0713	0.0297	-0.0009	0.0006	1.94E-07	++--+++++	--++-----	0.85	22103
TGCHO	rs13232120	*TBL2*	3.21E-21	0.0207	0.0381	0.0009	0.0008	1.61E-21	++-------	--++++++	0.68	22103
TGCHO	rs14415	*TBL2*	2.44E-19	0.0444	0.0276	0.0000	0.0006	2.16E-19	++-+--++-	--+-++-++	0.73	22103
TGCHO	rs1051921	*MLXIPL*	6.02E-22	-0.0321	0.0319	-0.0005	0.0007	2.67E-22	--+-+++++	++-+-----	0.39	22103
TGCHO	rs3289	*LPL*	6.17E-12	-0.1902	0.0765	0.0020	0.0016	1.50E-11	---+-+---	+---+-+++	0.51	22103
TGCHO	rs13702	*LPL*	2.52E-29	0.0553	0.0273	0.0000	0.0006	1.39E-29	++--+-+++	--++-+---	0.94	22103
TGCHO	rs15285	*LPL*	1.80E-27	-0.0645	0.0338	0.0000	0.0007	2.71E-28	--++-+---	-+--+-+++	0.83	22103
TGCHO	rs512555	*MS4A2*	0.001582	-0.0924	0.0956	0.0031	0.0020	0.001994	---+--++?	+++++-++?	0.46	15764
TGCHO	rs619054	*APOA5*	3.05E-09	-0.0459	0.0291	0.0003	0.0006	3.92E-09	--+-+----	-+-+-+++-	0.03	22103
TGCHO	rs1035237	*SIK3*	2.71E-08	-0.0828	0.0453	0.0008	0.0009	4.37E-08	----++--?	++++---+?	0.20	16110
TGCHO	rs3810444	*SUGP2*	1.33E-07	-0.0892	0.0524	0.0007	0.0011	6.31E-08	-++-+-++-	+--+-+--+	0.10	22103
TGSFA	rs583609	*USP1*	4.10E-08	0.0294	0.0211	0.0001	0.0017	1.96E-08	+++++++-?	+---++-+?	0.21	16110
TGSFA	rs13472	*SNX17, ZNF513*	9.00E-12	-0.0621	0.0209	0.0021	0.0016	5.49E-12	--+--+--?	+--++-++?	0.80	16110
TGSFA	rs4582	*PPM1G*	7.44E-12	0.0624	0.0208	-0.0022	0.0016	3.97E-12	++-++-++?	-++--+--?	0.80	16110
TGSFA	rs4803	*KRTCAP3, IFT172*	1.58E-15	0.0589	0.0176	-0.0018	0.0014	4.94E-16	++-++-+++	-++--+---	0.80	22103
TGSFA	rs8395	*FNDC4*	7.74E-13	-0.0649	0.0208	0.0022	0.0016	5.01E-13	--+--+--?	+--++-++?	0.66	16110
TGSFA	rs1881396	*ZNF512*	1.97E-06	0.0135	0.0204	0.0011	0.0016	6.13E-07	++++-+--+	+-+-++++-	0.72	22103
TGSFA	rs13232120	*TBL2*	6.69E-21	0.0797	0.0258	-0.0013	0.0020	4.44E-21	--++++++	++-----++	0.31	22103
TGSFA	rs14415	*TBL2*	7.82E-19	0.0339	0.0187	0.0008	0.0015	4.48E-19	-++-++-++	++-+--++-	0.78	22103
TGSFA	rs1051921	*MLXIPL*	2.56E-21	-0.0706	0.0218	0.0014	0.0017	1.14E-21	++-------	--+-+++-+	0.30	22103
TGSFA	rs3289	*LPL*	1.80E-10	-0.0553	0.0544	-0.0029	0.0043	1.75E-10	+----+-+-	-++++-+--	0.22	22103
TGSFA	rs13702	*LPL*	4.51E-29	0.0504	0.0188	0.0004	0.0015	1.77E-29	+-++-++++	+++-+--++	0.88	22103
TGSFA	rs15285	*LPL*	8.34E-28	-0.0576	0.0226	-0.0007	0.0018	2.06E-28	-+-------	--++-+-+-	0.51	22103
TGSFA	rs619054	*APOA5*	4.36E-09	-0.0195	0.0200	-0.0010	0.0016	5.95E-09	-++--++--	---++--++	0.10	22103
TGSFA	rs1035237	*SIK3*	1.11E-08	-0.0018	0.0323	-0.0036	0.0026	1.71E-08	+++++---?	-----+-+?	0.18	16110
TGSFA	rs3810444	*SUGP2*	8.24E-08	-0.0306	0.0357	-0.0019	0.0028	3.25E-08	---+--+-+	+++-++---	0.29	22103

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGCHO, TGSFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
TGCHO	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGCHO	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGCHO	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGCHO	rs4803	*KRTCAP3, IFT172*	0.0201	0.0035	6.68E-09	1.50E-08	++-++++++	0.0366	0.0042	1.88E-18	++-++++++	0	0.58
TGCHO	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.0370	0.0047	4.94E-15	--+-----?	0	0.48
TGCHO	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.0050	2.00E-08	+++++++++	0	0.67
TGCHO	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGCHO	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGCHO	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGCHO	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGCHO	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGCHO	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGCHO	rs512555	*MS4A2*	0.0520	0.0136	0.00013	0.000164	++++++-+?	0.0552	0.0168	1.01E-03	++++++++?	8.9	0.36
TGCHO	rs619054	*APOA5*	-0.0158	0.0041	0.000137	0.000145	-------+-	-0.0285	0.0050	9.60E-09	--+----+-	47.6	0.05
TGCHO	rs1035237	*SIK3*	-0.0250	0.0059	2.38E-05	2.95E-05	--------?	-0.0442	0.0073	1.68E-09	--------?	0	0.69
TGCHO	rs3810444	*SUGP2*	-0.0364	0.0080	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13
TGSFA	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGSFA	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGSFA	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGSFA	rs4803	*KRTCAP3, IFT172*	0.0201	0.0035	6.68E-09	1.50E-08	++-++++++	0.0366	0.0042	1.88E-18	++-++++++	0	0.58
TGSFA	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.0370	0.0047	4.94E-15	--+-----?	0	0.48
TGSFA	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.0050	2.00E-08	+++++++++	0	0.67
TGSFA	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGSFA	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGSFA	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGSFA	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGSFA	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGSFA	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGSFA	rs619054	*APOA5*	-0.0158	0.0041	0.000137	0.000145	-------+-	-0.0285	0.0050	9.60E-09	--+----+-	47.6	0.05
TGSFA	rs1035237	*SIK3*	-0.0250	0.0059	2.38E-05	2.95E-05	--------?	-0.0442	0.0073	1.68E-09	--------?	0	0.69
TGSFA	rs3810444	*SUGP2*	-0.0364	0.0080	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
TGMUFA	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.34	0.025
TGMUFA	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGMUFA	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.40	0.034
TGMUFA	rs4803	*KRTCAP3, IFT172*	2	27667297	5	+	NA	G/A,A	0.40	0.031
TGMUFA	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGMUFA	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGMUFA	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.010
TGMUFA	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGMUFA	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.20	0.016
TGMUFA	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGMUFA	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGMUFA	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGMUFA	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGMUFA	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGMUFA	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009
TGPUFA	rs583609	*USP1*	1	62916796	12	+	4.37E-32	C/T,T	0.35	0.019
TGPUFA	rs13472	*SNX17, ZNF513*	2	27600239	9	+	7.51E-35	A/G,A	0.39	0.034
TGPUFA	rs4582	*PPM1G*	2	27604279	9	+	2.56E-35	G/A,A	0.40	0.034
TGPUFA	rs4803	*KRTCAP3, IFT172*	2	27667297	5	+	NA	G/A,A	0.40	0.031
TGPUFA	rs8395	*FNDC4*	2	27715207	8	+	3.27E-29	A/T,A	0.39	0.034
TGPUFA	rs1881396	*ZNF512*	2	27844601	11	+	4.25E-41	G/T,T	0.21	0.005
TGPUFA	rs13232120	*TBL2*	7	72983310	11		4.85E-88	T/A,A	0.12	0.010
TGPUFA	rs14415	*TBL2*	7	72984780	8		4.92E-75	C/T,T	0.29	0.026
TGPUFA	rs1051921	*MLXIPL*	7	73007943	6		7.37E-96	A/G,A	0.20	0.016
TGPUFA	rs3289	*LPL*	8	19823192	11		3.67E-33	C/T,T	0.03	0.006
TGPUFA	rs13702	*LPL*	8	19824492	12	+	6.56E-187	C/T,T	0.29	0.019
TGPUFA	rs15285	*LPL*	8	19824667	12		2.42E-173	T/C,T	0.18	0.066
TGPUFA	rs619054	*APOA5*	11	116660813	11	+	4.83E-33	A/G,A	0.23	0.009
TGPUFA	rs1035237	*SIK3*	11	116727850	3	+	1.53E-50	G/C,C	0.12	0.022
TGPUFA	rs3810444	*SUGP2*	19	19103986	7		1.57E-16	A/T,A	0.07	0.009

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
TGMUFA	rs583609	*USP1*	0.0395	0.0225	-0.0008	0.0018	4.71E-07	1.02E-06	-++-+-+-?	+--+-+++?
TGMUFA	rs13472	*SNX17, ZNF513*	-0.0334	0.0214	-0.0002	0.0017	6.52E-11	1.85E-10	-+-+----?	+-+-----?
TGMUFA	rs4582	*PPM1G*	0.0335	0.0214	0.0002	0.0017	4.32E-11	1.12E-10	+-+-++++?	-+-+++++?
TGMUFA	rs4803	*KRTCAP3, IFT172*	0.0358	0.0182	0.0001	0.0015	3.96E-15	2.43E-14	+-+-+-+++	-+-++++++
TGMUFA	rs8395	*FNDC4*	-0.0361	0.0214	-0.0001	0.0017	8.81E-12	2.95E-11	-+-+-+--?	+-+-----?
TGMUFA	rs1881396	*ZNF512*	0.0308	0.0219	-0.0005	0.0018	3.66E-05	5.91E-05	+--+++--+	+++---++-
TGMUFA	rs13232120	*TBL2*	0.1122	0.0281	-0.0042	0.0023	2.02E-19	1.41E-18	+-+++++++	++-------
TGMUFA	rs14415	*TBL2*	0.0669	0.0196	-0.0021	0.0016	3.59E-16	2.03E-15	+++++++++	+-----++-
TGMUFA	rs1051921	*MLXIPL*	-0.0808	0.0227	0.0023	0.0019	1.74E-19	1.35E-18	++-------	--+++++-+
TGMUFA	rs3289	*LPL*	0.0343	0.0563	-0.0100	0.0046	7.17E-09	1.72E-08	+-+--++++	-+-++----
TGMUFA	rs13702	*LPL*	0.0487	0.0193	0.0004	0.0016	5.69E-26	7.87E-25	+--++++++	+++++-++-
TGMUFA	rs15285	*LPL*	-0.0494	0.0228	-0.0012	0.0019	2.98E-24	4.16E-23	-+-+---+-	--+--+--+
TGMUFA	rs619054	*APOA5*	0.0178	0.0209	-0.0042	0.0017	6.75E-10	1.89E-09	-++--++--	-------+-
TGMUFA	rs1035237	*SIK3*	0.0075	0.0333	-0.0044	0.0027	9.36E-08	2.02E-07	+++++---?	-----+-+?
TGMUFA	rs3810444	*SUGP2*	-0.0168	0.0372	-0.0031	0.0031	1.58E-07	2.80E-07	+-------+	-+-++-+--
TGPUFA	rs583609	*USP1*	0.0273	0.0160	0.0000	0.0025	2.73E-05	4.48E-05	+++++-+??	-+-+-++??
TGPUFA	rs13472	*SNX17, ZNF513*	-0.0474	0.0147	0.0021	0.0024	8.41E-11	2.69E-10	-+++----?	+---+-++?
TGPUFA	rs4582	*PPM1G*	0.0481	0.0146	-0.0021	0.0024	5.12E-11	1.40E-10	+---+-++?	-+++-+--?
TGPUFA	rs4803	*KRTCAP3, IFT172*	0.0396	0.0130	-0.0005	0.0022	9.88E-15	4.16E-14	+---+-++-	-+++-+--+
TGPUFA	rs8395	*FNDC4*	-0.0496	0.0146	0.0022	0.0024	1.26E-11	3.71E-11	-+++----?	+---+-++?
TGPUFA	rs1881396	*ZNF512*	0.0346	0.0156	-0.0016	0.0026	2.28E-05	3.80E-05	++++++--+	------++-
TGPUFA	rs13232120	*TBL2*	0.0914	0.0202	-0.0054	0.0034	2.01E-18	1.27E-17	+-+++++-+	-+-+---+-
TGPUFA	rs14415	*TBL2*	0.0572	0.0145	-0.0029	0.0024	2.89E-15	1.21E-14	-++-+++-+	+--+---+-
TGPUFA	rs1051921	*MLXIPL*	-0.0771	0.0168	0.0045	0.0028	1.15E-18	8.58E-18	-+-----+-	--+-+++-+
TGPUFA	rs3289	*LPL*	0.0303	0.0405	-0.0210	0.0070	1.72E-09	4.41E-09	+-++-++++	-+-------
TGPUFA	rs13702	*LPL*	0.0438	0.0138	0.0018	0.0023	4.05E-26	5.36E-25	+----++-+	+++++--++
TGPUFA	rs15285	*LPL*	-0.0203	0.0174	-0.0081	0.0030	3.08E-26	4.00E-25	++-++--+-	--+--+---
TGPUFA	rs619054	*APOA5*	-0.0216	0.0153	-0.0020	0.0026	1.58E-08	3.56E-08	-+++-++--	+------++
TGPUFA	rs1035237	*SIK3*	-0.0268	0.0237	-0.0034	0.0040	2.34E-07	4.54E-07	-+-+----?	--+--+-+?
TGPUFA	rs3810444	*SUGP2*	-0.0228	0.0274	-0.0059	0.0047	5.43E-08	1.15E-07	+--------	-+++--++-

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
TGMUFA	rs583609	*USP1*	3.74E-08	0.0422	0.0211	-0.0009	0.0017	2.09E-08	-++-+-+-?	+--+-+-+?	0.28	16110
TGMUFA	rs13472	*SNX17, ZNF513*	2.39E-11	-0.0380	0.0205	0.0002	0.0016	1.23E-11	-+-+----?	+-+-+--+?	0.72	16110
TGMUFA	rs4582	*PPM1G*	2.25E-11	0.0390	0.0205	-0.0003	0.0016	9.87E-12	+-+-++++?	-+-+-++-?	0.74	16110
TGMUFA	rs4803	*KRTCAP3, IFT172*	4.38E-15	0.0389	0.0174	-0.0002	0.0014	1.18E-15	+-+-+++++	-+-+-++--	0.79	22102
TGMUFA	rs8395	*FNDC4*	2.12E-12	-0.0413	0.0205	0.0003	0.0016	1.16E-12	-+-+----?	+-+-+--+?	0.65	16110
TGMUFA	rs1881396	*ZNF512*	2.14E-06	0.0319	0.0203	-0.0003	0.0017	5.55E-07	++++++--+	+-+--+++-	0.44	22102
TGMUFA	rs13232120	*TBL2*	1.42E-21	0.1036	0.0270	-0.0034	0.0022	6.90E-22	+-+++++++	++-------	0.15	22102
TGMUFA	rs14415	*TBL2*	2.26E-19	0.0593	0.0188	-0.0013	0.0015	1.61E-19	--+++++++	++-----+-	0.56	22102
TGMUFA	rs1051921	*MLXIPL*	1.03E-21	-0.0726	0.0219	0.0016	0.0018	4.46E-22	++-------	--+++++-+	0.06	22102
TGMUFA	rs3289	*LPL*	6.04E-11	-0.0227	0.0527	-0.0058	0.0042	6.24E-11	+-+--+++-	-+-++----	0.29	22102
TGMUFA	rs13702	*LPL*	2.62E-29	0.0522	0.0186	0.0002	0.0015	8.77E-30	+--++++++	+++-+-+--	0.98	22102
TGMUFA	rs15285	*LPL*	1.09E-27	-0.0567	0.0222	-0.0008	0.0018	3.01E-28	-+-------	--+--+--+	0.82	22102
TGMUFA	rs619054	*APOA5*	4.55E-10	0.0097	0.0200	-0.0035	0.0016	4.52E-10	--+--++--	----+--++	0.17	22102
TGMUFA	rs1035237	*SIK3*	4.26E-09	0.0091	0.0320	-0.0045	0.0026	7.21E-09	++++----?	-----+-+?	0.23	16110
TGMUFA	rs3810444	*SUGP2*	9.90E-08	-0.0279	0.0358	-0.0022	0.0030	4.58E-08	--------+	-++++++--	0.25	22102
TGPUFA	rs583609	*USP1*	9.13E-08	0.0289	0.0145	0.0003	0.0023	4.41E-08	+++-+-+-?	-+-+-+-+?	0.90	14573
TGPUFA	rs13472	*SNX17, ZNF513*	3.01E-11	-0.0438	0.0140	0.0015	0.0023	1.64E-11	-+++----?	+-+-+-++?	0.24	16110
TGPUFA	rs4582	*PPM1G*	2.49E-11	0.0442	0.0139	-0.0015	0.0023	1.15E-11	+---++++?	-+++-+--?	0.26	16110
TGPUFA	rs4803	*KRTCAP3, IFT172*	7.04E-15	0.0352	0.0124	0.0002	0.0021	2.10E-15	+---++++-	-+++-+--+	0.13	22103
TGPUFA	rs8395	*FNDC4*	3.11E-12	-0.0453	0.0139	0.0015	0.0023	1.80E-12	-+++----?	+-+-+-++?	0.17	16110
TGPUFA	rs1881396	*ZNF512*	1.32E-06	0.0391	0.0146	-0.0019	0.0024	2.93E-07	++++++--+	-----+++-	0.63	22103
TGPUFA	rs13232120	*TBL2*	8.52E-21	0.0833	0.0190	-0.0037	0.0032	5.78E-21	+-+++++++	-+-+---+-	0.95	22103
TGPUFA	rs14415	*TBL2*	4.40E-19	0.0578	0.0136	-0.0025	0.0023	3.40E-19	+++-+++++	+--+---+-	0.91	22103
TGPUFA	rs1051921	*MLXIPL*	8.25E-22	-0.0734	0.0158	0.0035	0.0027	3.92E-22	-+-+---+-	--+-+++-+	0.67	22103
TGPUFA	rs3289	*LPL*	3.69E-12	0.0093	0.0365	-0.0184	0.0062	3.60E-12	+-++-+++-	-+-------	0.50	22103
TGPUFA	rs13702	*LPL*	1.36E-29	0.0485	0.0132	0.0012	0.0022	3.54E-30	+-++-++++	++-++---+	0.75	22103
TGPUFA	rs15285	*LPL*	2.37E-30	-0.0228	0.0164	-0.0080	0.0028	3.92E-31	++--+--+-	--+--+---	0.07	22103
TGPUFA	rs619054	*APOA5*	2.87E-09	-0.0286	0.0143	-0.0006	0.0024	3.76E-09	-+++-++--	+---+--++	0.04	22103
TGPUFA	rs1035237	*SIK3*	1.36E-08	-0.0199	0.0225	-0.0047	0.0038	1.42E-08	-+-+----?	--+--+-+?	0.62	16110
TGPUFA	rs3810444	*SUGP2*	8.93E-08	-0.0335	0.0265	-0.0037	0.0046	4.32E-08	+--------	-+++--+++	0.09	22103

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (TGMUFA, TGPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
TGMUFA	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGMUFA	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGMUFA	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGMUFA	rs4803	*KRTCAP3, IFT172*	0.0201	0.0035	6.68E-09	1.50E-08	++-++++++	0.0366	0.0042	1.88E-18	++-++++++	0	0.58
TGMUFA	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.0370	0.0047	4.94E-15	--+-----?	0	0.48
TGMUFA	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.0050	2.00E-08	+++++++++	0	0.67
TGMUFA	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGMUFA	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGMUFA	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGMUFA	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGMUFA	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGMUFA	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGMUFA	rs619054	*APOA5*	-0.0158	0.0041	0.000137	0.000145	-------+-	-0.0285	0.0050	9.60E-09	--+----+-	47.6	0.05
TGMUFA	rs1035237	*SIK3*	-0.0250	0.0059	2.38E-05	2.95E-05	--------?	-0.0442	0.0073	1.68E-09	--------?	0	0.69
TGMUFA	rs3810444	*SUGP2*	-0.0364	0.0080	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13
TGPUFA	rs583609	*USP1*	0.0175	0.0038	5.47E-06	5.63E-06	++++++++?	0.0307	0.0049	4.40E-10	++++++++?	0	0.81
TGPUFA	rs13472	*SNX17, ZNF513*	-0.0171	0.0037	4.07E-06	5.22E-06	--+-----?	-0.0357	0.0047	4.40E-14	--+-----?	0	0.56
TGPUFA	rs4582	*PPM1G*	0.0173	0.0037	3.29E-06	4.04E-06	++-+++++?	0.0357	0.0047	3.87E-14	++-+++++?	0	0.53
TGPUFA	rs4803	*KRTCAP3, IFT172*	0.0201	0.0035	6.68E-09	1.50E-08	++-++++++	0.0366	0.0042	1.88E-18	++-++++++	0	0.58
TGPUFA	rs8395	*FNDC4*	-0.0174	0.0037	2.90E-06	3.55E-06	--+-----?	-0.0370	0.0047	4.94E-15	--+-----?	0	0.48
TGPUFA	rs1881396	*ZNF512*	0.0172	0.0042	3.92E-05	5.41E-05	+++++++++	0.0282	0.0050	2.00E-08	+++++++++	0	0.67
TGPUFA	rs13232120	*TBL2*	0.0403	0.0052	1.19E-14	2.17E-14	+++++++++	0.0607	0.0063	4.43E-22	+++++++++	0	0.91
TGPUFA	rs14415	*TBL2*	0.0274	0.0038	2.68E-13	1.18E-12	+++++++++	0.0446	0.0045	9.41E-23	+++++++++	0	0.97
TGPUFA	rs1051921	*MLXIPL*	-0.0338	0.0043	6.08E-15	9.28E-15	---------	-0.0538	0.0052	8.68E-25	---------	0	0.81
TGPUFA	rs3289	*LPL*	-0.0473	0.0111	2.04E-05	2.66E-05	------+--	-0.0937	0.0132	1.51E-12	---------	13.7	0.32
TGPUFA	rs13702	*LPL*	0.0307	0.0038	3.13E-16	1.66E-15	+++++++++	0.0565	0.0045	1.40E-35	+++++++++	0	0.86
TGPUFA	rs15285	*LPL*	-0.0409	0.0048	1.51E-17	4.47E-17	---------	-0.0668	0.0056	1.58E-32	---------	0	0.75
TGPUFA	rs619054	*APOA5*	-0.0158	0.0041	0.000137	0.000145	-------+-	-0.0285	0.0050	9.60E-09	--+----+-	47.6	0.05
TGPUFA	rs1035237	*SIK3*	-0.0250	0.0059	2.38E-05	2.95E-05	--------?	-0.0442	0.0073	1.68E-09	--------?	0	0.69
TGPUFA	rs3810444	*SUGP2*	-0.0364	0.0080	4.99E-06	7.28E-06	---------	-0.0509	0.0091	2.26E-08	------+--	36.5	0.13

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major,effect)	MAF[2]	FreqSE
HDLCHO	rs7883	*LEPROT, LEPR*	1	65897869	8		0.00735	A/G,A	0.05	0.008
HDLCHO	rs788793	*LGR6*	1	202287813	3	+	NA	T/C,T	0.39	0.008
HDLCHO	rs788792	*LGR6*	1	202288462	6	+	0.3668	C/A,A	0.39	0.008
HDLCHO	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLCHO	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.12	0.016
HDLCHO	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.31	0.031
HDLCHO	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.12	0.016
HDLCHO	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.20	0.096
HDLCHO	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.34	0.033
HDLCHO	rs2293577	*SLC39A13*	11	47437202	12		NA	C/T,T	0.33	0.010
HDLCHO	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.33	0.010
HDLCHO	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.36	0.032
HDLCHO	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.33	0.040
HDLCHO	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLCHO	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.32	0.041
HDLCHO	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.08	0.009
HDLCHO	rs10773003	*SBNO1*	12	123775127	3	+	1.46E-13	A/G,A	0.10	0.010
HDLCHO	rs3088303	*SBNO1*	12	123779489	4	+	3.04E-06	A/G,A	0.09	0.010
HDLCHO	rs6738	*TPM1*	15	63363901	4		6.83E-05	C/T,T	0.34	0.018
HDLCHO	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.34	0.036
HDLCHO	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.43	0.035
HDLCHO	rs6499137	*CTCF*	16	67671804	10	+	5.90E-28	G/T,T	0.10	0.029
HDLCHO	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.15	0.018
HDLCHO	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.018
HDLCHO	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.19	0.028
HDLCHO	rs11043	*ESRP2, NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.14	0.020
HDLCHO	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.18	0.041
HDLCHO	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.19	0.024
HDLSFA	rs7883	*LEPROT, LEPR*	1	65897869	8		0.00735	A/G,A	0.05	0.008
HDLSFA	rs629301	*CELSR2*	1	109818306	8	+	7.61E-13	G/T,T	0.23	0.013
HDLSFA	rs788793	*LGR6*	1	202287813	3	+	NA	T/C,T	0.39	0.008
HDLSFA	rs788792	*LGR6*	1	202288462	6	+	0.3668	C/A,A	0.39	0.008
HDLSFA	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLSFA	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.11	0.011
HDLSFA	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.29	0.019
HDLSFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.11	0.011
HDLSFA	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.18	0.066
HDLSFA	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.32	0.013
HDLSFA	rs2293577	*SLC39A13*	11	47437202	12		NA	C/T,T	0.33	0.010
HDLSFA	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.33	0.010
HDLSFA	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.34	0.010
HDLSFA	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.35	0.022
HDLSFA	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLSFA	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.34	0.025
HDLSFA	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.07	0.006
HDLSFA	rs3741414	*INHBC*	12	57844049	7		6.10E-14	T/C,T	0.25	0.032
HDLSFA	rs473465	*INHBE*	12	57851182	7	+	9.72E-08	A/G,A	0.23	0.030
HDLSFA	rs10773003	*SBNO1*	12	123775127	3	+	1.46E-13	A/G,A	0.09	0.010
HDLSFA	rs3088303	*SBNO1*	12	123779489	4	+	3.04E-06	A/G,A	0.09	0.010
HDLSFA	rs6738	*TPM1*	15	63363901	4		6.83E-05	C/T,T	0.34	0.018
HDLSFA	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.32	0.015
HDLSFA	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.45	0.026
HDLSFA	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.16	0.009
HDLSFA	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.010
HDLSFA	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.17	0.008
HDLSFA	rs11043	*ESRP2, NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.13	0.007
HDLSFA	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.16	0.023
HDLSFA	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.18	0.014

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
HDLCHO	rs7883	*LEPROT, LEPR*	-0.0525	0.0523	0.0004	0.0011	0.000638	0.000894	----++++?	++++----?
HDLCHO	rs788793	*LGR6*	-0.0135	0.0244	0.0000	0.0005	0.001	0.00113	-+-+++-+?	+-------?
HDLCHO	rs788792	*LGR6*	0.0133	0.0244	0.0000	0.0005	0.001033	0.001391	+-+---+-?	-+++++++?
HDLCHO	rs3289	*LPL*	0.1101	0.0609	-0.0008	0.0012	1.69E-11	3.76E-11	+++++++++	---+-+---
HDLCHO	rs3735964	*LPL*	0.0051	0.0348	0.0012	0.0007	3.62E-26	8.48E-25	+-+++--+-	++---++-+
HDLCHO	rs13702	*LPL*	0.0032	0.0239	-0.0009	0.0005	2.70E-22	1.54E-21	-++--++-+	---++--+-
HDLCHO	rs1059611	*LPL*	-0.0033	0.0348	-0.0012	0.0007	4.84E-26	1.05E-24	-+---++-+	--+++--+-
HDLCHO	rs15285	*LPL*	0.0207	0.0291	0.0006	0.0006	2.81E-23	7.33E-23	--+++--+-	++---++-+
HDLCHO	rs1057233	*SPI1*	0.0471	0.0232	-0.0006	0.0005	3.10E-05	5.44E-05	+++--+++	-+--++---
HDLCHO	rs2293577	*SLC39A13*	0.0330	0.0257	-0.0003	0.0005	0.000214	0.000261	+-++--++?	-+-+++--?
HDLCHO	rs2293578	*SLC39A13*	-0.0331	0.0257	0.0003	0.0005	0.000218	0.000361	-+--++--?	+-+---++?
HDLCHO	rs9909	*NUP160*	0.0516	0.0222	-0.0007	0.0005	6.28E-07	1.20E-06	+-++--+++	-++-++-+-
HDLCHO	rs4246215	*FEN1*	0.0304	0.0217	-0.0010	0.0004	2.23E-08	5.65E-08	-+--+++++	--++-----
HDLCHO	rs174545	*FADS1*	-0.0247	0.0248	0.0010	0.0005	3.28E-07	4.07E-07	+-++---?	++--++++?
HDLCHO	rs174546	*FADS1*	0.0346	0.0217	-0.0011	0.0004	3.11E-09	7.11E-09	-+--+++++	--++-----
HDLCHO	rs2266788	*APOA5*	0.0382	0.0409	0.0000	0.0008	1.95E-08	4.03E-08	+-+++---+	-+---+++-
HDLCHO	rs10773003	*SBNO1*	0.0454	0.0366	-0.0005	0.0008	0.000569	0.000763	+--+-++++	-++-+----
HDLCHO	rs3088303	*SBNO1*	0.0408	0.0408	-0.0003	0.0008	0.000864	0.001309	+--+-+++?	-++-+---?
HDLCHO	rs6738	*TPM1*	0.0233	0.0249	-0.0001	0.0005	0.000425	0.000646	++-++++-?	+-----++?
HDLCHO	rs8468	*LACTB*	0.0444	0.0219	-0.0006	0.0004	5.04E-05	9.19E-05	++-++++++	--+----+-
HDLCHO	rs37029	*SLC12A3*	0.0115	0.0214	0.0001	0.0004	3.18E-05	5.19E-05	+-+-+-+--	-+-++--++
HDLCHO	rs6499137	*CTCF*	0.0120	0.0377	-0.0007	0.0008	0.000711	0.000909	++-+-+--+	--+-+-++-
HDLCHO	rs12449157	*GFOD2*	-0.0591	0.0294	0.0008	0.0006	4.84E-05	8.63E-05	--++++---	+++---+++
HDLCHO	rs4474673	*RANBP10*	0.0580	0.0338	-0.0006	0.0007	1.77E-07	3.14E-07	+++---+++	-+-+++---
HDLCHO	rs1109166	*SLC12A4, LCAT*	-0.0464	0.0284	0.0005	0.0006	1.02E-05	1.92E-05	---+++---	+++---+++
HDLCHO	rs11043	*ESRP2, NFATC3*	0.0039	0.0316	0.0004	0.0006	5.07E-05	7.77E-05	+-+---+++	++-+++---
HDLCHO	rs6857	*NECTIN2*	-0.0536	0.0315	0.0005	0.0006	1.09E-07	2.00E-07	---+-+---	+++-+-+++
HDLCHO	rs7679	*PCIF1*	-0.0092	0.0276	0.0007	0.0006	1.33E-06	3.12E-06	-+--++++-	+-++---+
HDLSFA	rs7883	*LEPROT, LEPR*	-0.0541	0.0375	0.0013	0.0029	0.000162	0.000256	--+-----?	-+-+-+++?
HDLSFA	rs629301	*CELSR2*	-0.0415	0.0171	0.0022	0.0013	0.001243	0.001869	-++-+---	---+-++++
HDLSFA	rs788793	*LGR6*	-0.0086	0.0180	-0.0006	0.0014	0.000701	0.001089	++--+--?	--++-++-?
HDLSFA	rs788792	*LGR6*	0.0086	0.0180	0.0006	0.0014	0.000723	0.001131	--++-+++?	++--+--+?
HDLSFA	rs3289	*LPL*	0.0021	0.0426	0.0058	0.0033	1.17E-13	4.98E-13	-+-+---+	+-+-+++++
HDLSFA	rs3735964	*LPL*	0.1234	0.0238	-0.0049	0.0019	4.77E-27	9.20E-26	+-++++++++	-+---+----
HDLSFA	rs13702	*LPL*	-0.0625	0.0162	0.0019	0.0013	4.39E-22	4.79E-21	--+-+----	++-+-++++
HDLSFA	rs1059611	*LPL*	-0.1250	0.0237	0.0051	0.0018	6.02E-27	2.58E-25	--------	+-++-++++
HDLSFA	rs15285	*LPL*	0.0824	0.0194	-0.0027	0.0015	5.01E-23	7.24E-22	+-++++++-	-+-------
HDLSFA	rs1057233	*SPI1*	-0.0009	0.0158	0.0015	0.0012	2.72E-05	5.59E-05	-+-+++---	+-+-+-+++
HDLSFA	rs2293577	*SLC39A13*	-0.0007	0.0187	0.0015	0.0015	0.000211	0.000345	-+-+++--?	+-+-+-++?
HDLSFA	rs2293578	*SLC39A13*	0.0008	0.0187	-0.0015	0.0015	0.000212	0.000313	+-+---++?	-+-+-+--?
HDLSFA	rs9909	*NUP160*	0.0055	0.0152	0.0011	0.0012	8.55E-07	1.71E-06	+--++++-+	+++-+--++
HDLSFA	rs4246215	*FEN1*	-0.0455	0.0150	0.0022	0.0012	3.30E-07	8.52E-07	-++-----	+--++++++
HDLSFA	rs174545	*FADS1*	0.0461	0.0183	-0.0021	0.0015	3.39E-06	8.50E-06	+--+++++?	-++-----?
HDLSFA	rs174546	*FADS1*	-0.0437	0.0149	0.0020	0.0012	1.86E-07	4.55E-07	-++-----	+--++++++
HDLSFA	rs2266788	*APOA5*	0.0361	0.0267	0.0003	0.0021	1.26E-08	3.10E-08	++++-+++-	---++---+
HDLSFA	rs3741414	*INHBC*	0.0437	0.0168	-0.0024	0.0013	0.000489	0.000784	++-++-+-+	-++--+-+-
HDLSFA	rs473465	*INHBE*	-0.0363	0.0171	0.0017	0.0013	0.000642	0.000996	-++--+-+-	+--++++-+
HDLSFA	rs10773003	*SBNO1*	0.0435	0.0258	-0.0016	0.0020	0.000414	0.000679	++--+--+	--++-+++-
HDLSFA	rs3088303	*SBNO1*	0.0220	0.0299	0.0004	0.0023	0.000654	0.001008	++--+---?	--++-+++?
HDLSFA	rs6738	*TPM1*	0.0132	0.0183	0.0003	0.0014	0.000456	0.00074	+---+-++?	-++++++-?
HDLSFA	rs8468	*LACTB*	0.0017	0.0151	0.0012	0.0012	6.15E-05	0.000111	--+++-+++	++--++++-
HDLSFA	rs37029	*SLC12A3*	0.0264	0.0144	-0.0008	0.0011	2.64E-05	5.28E-05	+++-+-+++	+-+++-+-
HDLSFA	rs12449157	*GFOD2*	-0.0036	0.0197	-0.0014	0.0015	6.27E-05	0.000102	-+-----++	--++++---
HDLSFA	rs4474673	*RANBP10*	0.0113	0.0229	0.0016	0.0018	1.45E-07	3.59E-07	++++++++-+	+---+--++
HDLSFA	rs1109166	*SLC12A4, LCAT*	-0.0195	0.0191	-0.0002	0.0015	1.61E-05	2.80E-05	-+-----+-	+-+++++--
HDLSFA	rs11043	*ESRP2, NFATC3*	0.0262	0.0215	-0.0003	0.0017	0.000106	0.000185	++-++++-+	----+--++
HDLSFA	rs6857	*NECTIN2*	-0.0157	0.0208	-0.0012	0.0016	1.44E-08	4.44E-08	-++-+-++-	-----+--+
HDLSFA	rs7679	*PCIF1*	0.0029	0.0185	0.0015	0.0014	5.52E-06	1.07E-05	++-+----	-++-+++++

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
HDLCHO	rs7883	*LEPROT, LEPR*	0.005664	-0.0520	0.0484	0.0006	0.0010	0.008871	----++++?	++++-----?	0.04	16126
HDLCHO	rs788793	*LGR6*	0.001956	-0.0096	0.0223	-0.0001	0.0005	0.003664	-++-++++?	+----+--?	0.54	16153
HDLCHO	rs788792	*LGR6*	0.002012	0.0095	0.0223	0.0001	0.0005	0.003789	+-------?	-++++-++?	0.54	16153
HDLCHO	rs3289	*LPL*	4.38E-13	0.0675	0.0561	0.0002	0.0012	3.61E-13	++--+++++	-+++--+++	0.70	22142
HDLCHO	rs3735964	*LPL*	2.24E-32	0.0045	0.0315	0.0013	0.0006	1.83E-32	--+++--+-	++++-++-+	0.05	22142
HDLCHO	rs13702	*LPL*	5.41E-27	-0.0047	0.0220	-0.0007	0.0004	6.97E-27	-++--++--	----+--+-	0.11	22142
HDLCHO	rs1059611	*LPL*	2.97E-32	-0.0023	0.0315	-0.0013	0.0006	2.55E-32	++---++-+	----+--+-	0.04	22142
HDLCHO	rs15285	*LPL*	7.00E-28	0.0213	0.0267	0.0006	0.0005	8.42E-28	---++--++	++++-++-+	0.30	22142
HDLCHO	rs1057233	*SPI1*	1.29E-05	0.0547	0.0215	-0.0008	0.0004	1.18E-05	+-++--+++	-+--++---	0.32	22142
HDLCHO	rs2293577	*SLC39A13*	0.000694	0.0373	0.0237	-0.0005	0.0005	0.000369	+-++--++?	-+--++--?	0.39	16153
HDLCHO	rs2293578	*SLC39A13*	0.000694	-0.0374	0.0237	0.0005	0.0005	0.000369	-+--++--?	+-++--++?	0.39	16153
HDLCHO	rs9909	*NUP160*	5.47E-07	0.0489	0.0206	-0.0006	0.0004	4.53E-07	+--+--+++	-+++++---	0.29	22142
HDLCHO	rs4246215	*FEN1*	5.27E-09	0.0207	0.0205	-0.0009	0.0004	2.46E-09	-+--+++++	--++-----	0.25	22142
HDLCHO	rs174545	*FADS1*	1.63E-07	-0.0126	0.0233	0.0007	0.0005	1.02E-07	+-++---?	++--++++?	0.18	16153
HDLCHO	rs174546	*FADS1*	1.43E-09	0.0242	0.0205	-0.0009	0.0004	7.49E-10	-+--+++++	--++-----	0.22	22142
HDLCHO	rs2266788	*APOA5*	1.35E-07	0.0389	0.0377	0.0000	0.0008	5.09E-08	+-+++---+	-+---+++-	0.44	22142
HDLCHO	rs10773003	*SBNO1*	2.17E-05	0.0253	0.0330	0.0000	0.0007	4.37E-05	+--+-++++	-++-+---+	0.98	22129
HDLCHO	rs3088303	*SBNO1*	0.000139	0.0230	0.0363	0.0001	0.0008	0.000235	+--+-+++?	-++-+---?	0.95	16153
HDLCHO	rs6738	*TPM1*	0.000122	0.0240	0.0231	-0.0002	0.0005	0.000211	++-+++--?	--+---++?	0.37	16153
HDLCHO	rs8468	*LACTB*	5.08E-07	0.0372	0.0204	-0.0004	0.0004	3.94E-07	++-+++++++	--+-----	0.93	22133
HDLCHO	rs37029	*SLC12A3*	1.43E-05	0.0321	0.0198	-0.0004	0.0004	3.41E-05	+---+++-+	-++++--+-	0.55	22142
HDLCHO	rs6499137	*CTCF*	7.41E-05	0.0164	0.0349	-0.0009	0.0007	9.10E-05	++-+-+--+	--+-+-++-	0.46	22142
HDLCHO	rs12449157	*GFOD2*	1.21E-06	-0.0560	0.0268	0.0007	0.0006	7.94E-07	--++++---	++----+++	0.46	22142
HDLCHO	rs4474673	*RANBP10*	7.43E-10	0.0478	0.0307	-0.0003	0.0006	4.36E-10	+-----+++	-+++++--+	0.60	22142
HDLCHO	rs1109166	*SLC12A4, LCAT*	1.54E-07	-0.0440	0.0258	0.0004	0.0005	1.47E-07	--++++---	++----+++	0.38	22142
HDLCHO	rs11043	*ESRP2, NFATC3*	4.18E-07	-0.0065	0.0288	0.0007	0.0006	2.28E-07	+-----+++	-+++++--+	0.66	22142
HDLCHO	rs6857	*NECTIN2*	2.24E-10	-0.0261	0.0302	-0.0002	0.0006	5.24E-11	---+-+-++	+++-+-+--	0.13	22142
HDLCHO	rs7679	*PCIF1*	1.40E-06	0.0037	0.0256	0.0004	0.0005	1.56E-06	-+--+++++	+-++--+-+	0.66	22141
HDLSFA	rs7883	*LEPROT, LEPR*	0.003504	-0.0384	0.0354	0.0008	0.0028	0.005481	--+---+-?	-+-+++-+?	0.81	16126
HDLSFA	rs629301	*CELSR2*	0.000114	-0.0401	0.0163	0.0020	0.0013	0.000124	-++-+---	+--+-++++	0.59	22142
HDLSFA	rs788793	*LGR6*	0.001245	-0.0078	0.0167	-0.0005	0.0013	0.002096	++---+--?	--++--++?	0.70	16153
HDLSFA	rs788792	*LGR6*	0.001283	0.0079	0.0167	0.0005	0.0013	0.002162	--+++-++?	++--++--?	0.70	16153
HDLSFA	rs3289	*LPL*	4.93E-13	0.0381	0.0399	0.0028	0.0030	4.43E-13	-+++---+	+---++++-	0.09	22142
HDLSFA	rs3735964	*LPL*	7.11E-33	0.1350	0.0221	-0.0057	0.0017	4.39E-33	+++++++++	----+---	0.47	22142
HDLSFA	rs13702	*LPL*	4.15E-26	-0.0633	0.0152	0.0019	0.0012	2.51E-26	----+---	++++-++++	0.39	22142
HDLSFA	rs1059611	*LPL*	7.72E-33	-0.1370	0.0221	0.0059	0.0017	4.82E-33	---------	++++-++++	0.47	22142
HDLSFA	rs15285	*LPL*	1.79E-27	0.0865	0.0183	-0.0029	0.0014	1.18E-27	+++++++++	-+-------	0.88	22142
HDLSFA	rs1057233	*SPI1*	3.28E-05	-0.0067	0.0150	0.0018	0.0012	2.20E-05	-+-+++---	+-+-+-+++	0.43	22142
HDLSFA	rs2293577	*SLC39A13*	0.000748	-0.0076	0.0175	0.0019	0.0014	0.000433	-+-+++--?	+-+-+-++?	0.43	16153
HDLSFA	rs2293578	*SLC39A13*	0.000746	0.0076	0.0175	-0.0019	0.0014	0.000433	+-+---++?	-+-+-+--?	0.43	16153
HDLSFA	rs9909	*NUP160*	1.04E-06	0.0025	0.0143	0.0013	0.0011	7.48E-07	++-+-++-+	-+++-+++	0.31	22142
HDLSFA	rs4246215	*FEN1*	4.41E-08	-0.0454	0.0141	0.0021	0.0011	2.70E-08	-+++----	+---+++++	0.32	22142
HDLSFA	rs174545	*FADS1*	8.48E-07	0.0407	0.0172	-0.0016	0.0014	7.03E-07	+--+++++?	-+++----?	0.20	16153
HDLSFA	rs174546	*FADS1*	1.90E-08	-0.0438	0.0142	0.0019	0.0011	1.29E-08	-++-----	+---+++++	0.31	22142
HDLSFA	rs2266788	*APOA5*	3.99E-08	0.0528	0.0256	-0.0012	0.0020	1.49E-08	++++-++++	----+-+-	0.85	22142
HDLSFA	rs3741414	*INHBC*	0.000155	0.0338	0.0159	-0.0015	0.0012	0.000202	+--++-++	-++--+-+-	0.005	22142
HDLSFA	rs473465	*INHBE*	0.002909	-0.0342	0.0164	0.0017	0.0013	0.002237	-++--+-+-	+-+++++-+	0.10	22142
HDLSFA	rs10773003	*SBNO1*	6.08E-06	0.0524	0.0237	-0.0021	0.0019	1.27E-05	++--++-++	--++--++-	0.96	22129
HDLSFA	rs3088303	*SBNO1*	5.23E-05	0.0417	0.0273	-0.0011	0.0022	8.76E-05	++--++-+?	--++--++?	0.95	16153
HDLSFA	rs6738	*TPM1*	0.000131	0.0253	0.0170	-0.0007	0.0013	0.000188	+-+-+-++?	-+-+-+--?	0.05	16153
HDLSFA	rs8468	*LACTB*	4.75E-07	0.0100	0.0143	0.0007	0.0011	6.16E-07	--+++++++	++-+-+-+-	0.85	22133
HDLSFA	rs37029	*SLC12A3*	2.50E-05	0.0213	0.0137	-0.0005	0.0011	5.59E-05	-++-+-+-+	+--+-+-+-	0.27	22142
HDLSFA	rs12449157	*GFOD2*	2.19E-06	-0.0094	0.0185	-0.0011	0.0015	1.91E-06	-------++	--++++---	0.22	22142
HDLSFA	rs4474673	*RANBP10*	2.90E-09	0.0225	0.0213	0.0009	0.0017	2.62E-09	++++--++-+	+---+--++	0.55	22142
HDLSFA	rs1109166	*SLC12A4, LCAT*	4.77E-07	-0.0237	0.0179	0.0000	0.0014	4.25E-07	-------+-	+-+++++--	0.17	22142
HDLSFA	rs11043	*ESRP2, NFATC3*	2.75E-06	0.0411	0.0198	-0.0013	0.0016	2.55E-06	+++-+++-+	---++-++-	0.73	22142
HDLSFA	rs6857	*NECTIN2*	2.82E-11	-0.0327	0.0203	-0.0003	0.0016	6.76E-12	-++++--+-	+---+--+	0.11	22142
HDLSFA	rs7679	*PCIF1*	1.32E-06	0.0029	0.0175	0.0015	0.0014	1.23E-06	++-++----	-++-+++++	0.59	22141

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLCHO, HDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
HDLCHO	rs7883	*LEPROT, LEPR*	-0.0373	0.0092	5.10E-05	7.20E-05	--------?	-0.0289	0.0085	0.0006319	--------?	0	0.96
HDLCHO	rs788793	*LGR6*	-0.0167	0.0042	7.18E-05	9.90E-05	-++----?	-0.0118	0.0037	0.001661	-+--+--?	0	0.48
HDLCHO	rs788792	*LGR6*	0.0167	0.0042	7.35E-05	9.90E-05	+--+++++?	0.0117	0.0037	0.001711	+-+++-++?	0	0.49
HDLCHO	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	++++++++	0.0730	0.0101	6.019E-13	++++++++	34.5	0.14
HDLCHO	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.597E-38	+++++++++	38.8	0.11
HDLCHO	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	--------	-0.0418	0.0035	8.568E-33	---------	30.4	0.17
HDLCHO	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	--------	-0.0653	0.0051	1.106E-37	---------	37.4	0.12
HDLCHO	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.537E-34	+++++++++	17	0.29
HDLCHO	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	0.000001624	+++++++++	11.1	0.34
HDLCHO	rs2293577	*SLC39A13*	0.0181	0.0043	2.24E-05	3.77E-05	++++++++?	0.0165	0.0038	0.00001634	++++++++?	25.9	0.22
HDLCHO	rs2293578	*SLC39A13*	-0.0181	0.0043	2.31E-05	3.77E-05	--------?	-0.0165	0.0038	0.00001677	--------?	25.8	0.22
HDLCHO	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.0190	0.0033	1.099E-08	+++++++++	23.1	0.24
HDLCHO	rs4246215	*FEN1*	-0.0180	0.0037	8.48E-07	1.91E-06	--++-----	-0.0193	0.0033	6.43E-09	--+-----	0	0.47
HDLCHO	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.20
HDLCHO	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	--++-----	-0.0198	0.0033	2.322E-09	--+-----	18.7	0.28
HDLCHO	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.543E-10	+++++++++	0	0.68
HDLCHO	rs10773003	*SBNO1*	0.0255	0.0061	2.60E-05	4.26E-05	+++++++++	0.0287	0.0055	1.968E-07	+++++++++	0	0.99
HDLCHO	rs3088303	*SBNO1*	0.0282	0.0068	3.72E-05	4.90E-05	++++++++?	0.0304	0.0061	7.072E-07	++++++++?	0	0.98
HDLCHO	rs6738	*TPM1*	0.0160	0.0042	0.00014	0.000192	++++++++?	0.0190	0.0038	4.934E-07	+++-++++?	0	0.70
HDLCHO	rs8468	*LACTB*	0.0150	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.022E-08	+-+++++++	0	0.67
HDLCHO	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	0.000113	+++++-+++	0.0124	0.0032	0.0001061	+++++++++	0	0.55
HDLCHO	rs6499137	*CTCF*	-0.0230	0.0062	0.000198	0.000281	--++-+---	-0.0221	0.0056	0.00008759	---+-----	0	0.76
HDLCHO	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	--++-----	-0.0226	0.0044	2.457E-07	---+-----	0	0.67
HDLCHO	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.0050	4.162E-10	+++++++++	0	0.67
HDLCHO	rs1109166	*SLC12A4, LCAT*	-0.0230	0.0046	6.62E-07	9.81E-07	--+------	-0.0225	0.0042	1.029E-07	--+------	0	0.60
HDLCHO	rs11043	*ESRP2, NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.375E-07	+++++++++	0	0.83
HDLCHO	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	--------	-0.0349	0.0047	8.972E-14	---------	50.5	0.04
HDLCHO	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	++++++++	0.0218	0.0041	1.143E-07	++++++++	0	0.62
HDLSFA	rs7883	*LEPROT, LEPR*	-0.0373	0.0092	5.10E-05	7.20E-05	--------?	-0.0289	0.0085	0.0006319	--------?	0	0.96
HDLSFA	rs629301	*CELSR2*	-0.0180	0.0042	1.57E-05	2.72E-05	--------	-0.0184	0.0038	0.000001118	---------	6.2	0.38
HDLSFA	rs788793	*LGR6*	-0.0167	0.0042	7.18E-05	9.90E-05	-++----?	-0.0118	0.0037	0.001661	-+--+--?	0	0.48
HDLSFA	rs788792	*LGR6*	0.0167	0.0042	7.35E-05	9.90E-05	+--+++++?	0.0117	0.0037	0.001711	+-+++-++?	0	0.49
HDLSFA	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	++++++++	0.0730	0.0101	6.019E-13	++++++++	34.5	0.14
HDLSFA	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.597E-38	+++++++++	38.8	0.11
HDLSFA	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	--------	-0.0418	0.0035	8.568E-33	---------	30.4	0.17
HDLSFA	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	--------	-0.0653	0.0051	1.106E-37	---------	37.4	0.12
HDLSFA	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.537E-34	+++++++++	17	0.29
HDLSFA	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	0.000001624	+++++++++	11.1	0.34
HDLSFA	rs2293577	*SLC39A13*	0.0181	0.0043	2.24E-05	3.77E-05	++++++++?	0.0165	0.0038	0.00001634	++++++++?	25.9	0.22
HDLSFA	rs2293578	*SLC39A13*	-0.0181	0.0043	2.31E-05	3.77E-05	--------?	-0.0165	0.0038	0.00001677	--------?	25.8	0.22
HDLSFA	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.0190	0.0033	1.099E-08	+++++++++	23.1	0.24
HDLSFA	rs4246215	*FEN1*	-0.0180	0.0037	8.48E-07	1.91E-06	--+-----	-0.0193	0.0033	6.43E-09	--+-----	0	0.47
HDLSFA	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.20
HDLSFA	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	--+-----	-0.0198	0.0033	2.322E-09	--+-----	18.7	0.28
HDLSFA	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.543E-10	+++++++++	0	0.68
HDLSFA	rs3741414	*INHBC*	0.0172	0.0041	2.79E-05	4.00E-05	+++++++-+	0.0183	0.0037	8.545E-07	++++++--+	45.1	0.07
HDLSFA	rs473465	*INHBE*	-0.0171	0.0043	5.88E-05	9.88E-05	--+--+---	-0.0142	0.0039	0.000277	--+---+--	15.3	0.31
HDLSFA	rs10773003	*SBNO1*	0.0255	0.0061	2.60E-05	4.26E-05	+++++++++	0.0287	0.0055	1.968E-07	+++++++++	0	0.99
HDLSFA	rs3088303	*SBNO1*	0.0282	0.0068	3.72E-05	4.90E-05	++++++++?	0.0304	0.0061	7.072E-07	++++++++?	0	0.98
HDLSFA	rs6738	*TPM1*	0.0160	0.0042	0.00014	0.000192	++++++++?	0.0190	0.0038	4.934E-07	+++-++++?	0	0.70
HDLSFA	rs8468	*LACTB*	0.0150	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.022E-08	+-+++++++	0	0.67
HDLSFA	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	0.000113	+++++-+++	0.0124	0.0032	0.0001061	+++++++++	0	0.55
HDLSFA	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	--++-----	-0.0226	0.0044	2.457E-07	---+-----	0	0.67
HDLSFA	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.0050	4.162E-10	+++++++++	0	0.67
HDLSFA	rs1109166	*SLC12A4, LCAT*	-0.0230	0.0046	6.62E-07	9.81E-07	--+------	-0.0225	0.0042	1.029E-07	--+------	0	0.60
HDLSFA	rs11043	*ESRP2, NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.375E-07	+++++++++	0	0.83
HDLSFA	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	--------	-0.0349	0.0047	8.972E-14	---------	50.5	0.04
HDLSFA	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	++++++++	0.0218	0.0041	1.143E-07	++++++++	0	0.62

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
HDLMUFA	rs7883	*LEPROT, LEPR*	1	65897869	8		0.00735	A/G,A	0.05	0.008
HDLMUFA	rs788793	*LGR6*	1	202287813	3	+	NA	T/C,T	0.39	0.008
HDLMUFA	rs788792	*LGR6*	1	202288462	6	+	0.3668	C/A,A	0.39	0.008
HDLMUFA	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLMUFA	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.11	0.011
HDLMUFA	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.29	0.019
HDLMUFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.11	0.011
HDLMUFA	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.18	0.066
HDLMUFA	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.32	0.013
HDLMUFA	rs2293577	*SLC39A13*	11	47437202	12		NA	C/T,T	0.33	0.010
HDLMUFA	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.33	0.010
HDLMUFA	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.34	0.010
HDLMUFA	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.35	0.022
HDLMUFA	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLMUFA	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.34	0.025
HDLMUFA	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.07	0.006
HDLMUFA	rs10773003	*SBNO1*	12	123775127	3	+	1.46E-13	A/G,A	0.09	0.010
HDLMUFA	rs3088303	*SBNO1*	12	123779489	4	+	3.04E-06	A/G,A	0.09	0.010
HDLMUFA	rs6738	*TPM1*	15	63363901	4		6.83E-05	C/T,T	0.34	0.018
HDLMUFA	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.32	0.015
HDLMUFA	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.45	0.026
HDLMUFA	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.16	0.009
HDLMUFA	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.010
HDLMUFA	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.17	0.008
HDLMUFA	rs11043	*ESRP2, NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.13	0.007
HDLMUFA	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.16	0.023
HDLMUFA	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.18	0.014
HDLMUFA	rs2305001	*BID*	22	18218210	7		0.2667	C/T,T	0.02	0.007
HDLPUFA	rs7883	*LEPROT, LEPR*	1	65897869	8		0.00735	A/G,A	0.05	0.008
HDLPUFA	rs788793	*LGR6*	1	202287813	3	+	NA	T/C,T	0.39	0.008
HDLPUFA	rs788792	*LGR6*	1	202288462	6	+	0.3668	C/A,A	0.39	0.008
HDLPUFA	rs3289	*LPL*	8	19823192	11		6.44E-46	C/T,T	0.03	0.006
HDLPUFA	rs3735964	*LPL*	8	19824045	9		5.89E-145	A/C,A	0.11	0.011
HDLPUFA	rs13702	*LPL*	8	19824492	12	+	1.28E-160	C/T,T	0.29	0.019
HDLPUFA	rs1059611	*LPL*	8	19824563	13	+	1.13E-144	C/T,T	0.11	0.011
HDLPUFA	rs15285	*LPL*	8	19824667	12		4.24E-150	T/C,T	0.18	0.066
HDLPUFA	rs1057233	*SPI1*	11	47376448	12	+	4.20E-13	G/A,A	0.32	0.013
HDLPUFA	rs2293577	*SLC39A13*	11	47437202	12		NA	C/T,T	0.33	0.010
HDLPUFA	rs2293578	*SLC39A13*	11	47437403	10		5.55E-12	T/C,T	0.33	0.010
HDLPUFA	rs9909	*NUP160*	11	47799775	7	+	3.75E-20	G/C,C	0.34	0.010
HDLPUFA	rs4246215	*FEN1*	11	61564299	5		5.40E-21	T/G,T	0.35	0.022
HDLPUFA	rs174545	*FADS1*	11	61569306	13	+	1.76E-21	G/C,C	0.34	0.029
HDLPUFA	rs174546	*FADS1*	11	61569830	8	+	8.30E-28	T/C,T	0.34	0.025
HDLPUFA	rs2266788	*APOA5*	11	116660686	10		1.19E-35	G/A,A	0.07	0.006
HDLPUFA	rs473465	*INHBE*	12	57851182	7	+	9.72E-08	A/G,A	0.23	0.030
HDLPUFA	rs10773003	*SBNO1*	12	123775127	3	+	1.46E-13	A/G,A	0.09	0.010
HDLPUFA	rs3088303	*SBNO1*	12	123779489	4	+	3.04E-06	A/G,A	0.09	0.010
HDLPUFA	rs6738	*TPM1*	15	63363901	4		6.83E-05	C/T,T	0.34	0.018
HDLPUFA	rs8468	*LACTB*	15	63434110	7	+	6.12E-08	C/T,T	0.32	0.015
HDLPUFA	rs37029	*SLC12A3*	16	56949168	5	+	1.25E-12	A/G,A	0.45	0.026
HDLPUFA	rs12449157	*GFOD2*	16	67708897	8	+	7.85E-37	G/A,A	0.16	0.009
HDLPUFA	rs4474673	*RANBP10*	16	67758778	9	+	9.34E-52	T/C,T	0.11	0.010
HDLPUFA	rs1109166	*SLC12A4, LCAT*	16	67977382	6	+	1.15E-42	C/T,T	0.17	0.008
HDLPUFA	rs11043	*ESRP2, NFATC3*	16	68262958	14	+	1.22E-39	A/G,A	0.13	0.007
HDLPUFA	rs6857	*NECTIN2*	19	45392254	6		2.63E-17	T/C,T	0.16	0.023
HDLPUFA	rs7679	*PCIF1*	20	44576502	3		6.73E-38	C/T,T	0.18	0.012
HDLPUFA	rs2305001	*BID*	22	18218210	7		0.2667	C/T,T	0.02	0.004

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
HDLMUFA	rs7883	*LEPROT, LEPR*	-0.0953	0.0356	0.0048	0.0029	4.22E-05	7.10E-05	--++-----?	---+++++?
HDLMUFA	rs788793	*LGR6*	-0.0212	0.0173	0.0004	0.0014	0.000702	0.001105	-+---+--?	--++++++?
HDLMUFA	rs788792	*LGR6*	0.0213	0.0174	-0.0004	0.0014	0.000721	0.00113	+-+++-++?	++------?
HDLMUFA	rs3289	*LPL*	-0.0206	0.0390	0.0077	0.0031	9.65E-14	4.79E-13	-+-+++--+	+-+--++++
HDLMUFA	rs3735964	*LPL*	0.0827	0.0225	-0.0016	0.0018	3.43E-26	4.44E-25	++++++++-+	----++-+-
HDLMUFA	rs13702	*LPL*	-0.0466	0.0159	0.0007	0.0013	3.67E-21	3.14E-20	----+----	+++--++--
HDLMUFA	rs1059611	*LPL*	-0.0828	0.0225	0.0017	0.0018	5.00E-26	1.59E-24	-------+-	++++--+-+
HDLMUFA	rs15285	*LPL*	0.0508	0.0188	-0.0002	0.0015	1.73E-22	2.97E-21	+++++++-+	-+-----++
HDLMUFA	rs1057233	*SPI1*	0.0254	0.0155	-0.0008	0.0013	9.49E-05	0.000158	++-+++-++	--+--++-+
HDLMUFA	rs2293577	*SLC39A13*	0.0277	0.0180	-0.0009	0.0014	0.000459	0.000571	+-+-+-+-?	+-+-+-+-?
HDLMUFA	rs2293578	*SLC39A13*	-0.0278	0.0180	0.0009	0.0014	0.000463	0.000767	--+---+--?	-+-+-+-+?
HDLMUFA	rs9909	*NUP160*	0.0294	0.0147	-0.0009	0.0012	1.95E-06	3.57E-06	++-+++-++	--+-+++-+
HDLMUFA	rs4246215	*FEN1*	-0.0508	0.0144	0.0027	0.0012	1.62E-07	4.27E-07	-+++-----	+---+++++
HDLMUFA	rs174545	*FADS1*	0.0507	0.0174	-0.0025	0.0014	1.93E-06	3.55E-06	+---++++?	-+++---?
HDLMUFA	rs174546	*FADS1*	-0.0479	0.0144	0.0024	0.0012	9.77E-08	1.91E-07	-+++-----	+---+++++
HDLMUFA	rs2266788	*APOA5*	0.0188	0.0264	0.0018	0.0022	1.12E-08	2.94E-08	++-+-+++-	--+++---+
HDLMUFA	rs10773003	*SBNO1*	0.0363	0.0251	-0.0010	0.0020	0.000433	0.000671	++--+++-+	-+++--++-
HDLMUFA	rs3088303	*SBNO1*	0.0389	0.0293	-0.0010	0.0023	0.000677	0.001003	+---+++-?	-+++--++?
HDLMUFA	rs6738	*TPM1*	0.0309	0.0180	-0.0012	0.0014	0.000406	0.000619	+---++-++?	-++--++-?
HDLMUFA	rs8468	*LACTB*	0.0066	0.0149	0.0008	0.0012	0.000115	0.000191	+++---+++	+--+++++-+
HDLMUFA	rs37029	*SLC12A3*	0.0243	0.0142	-0.0007	0.0012	3.51E-05	6.45E-05	+++++---+	+----+++-
HDLMUFA	rs12449157	*GFOD2*	-0.0047	0.0194	-0.0014	0.0016	4.99E-05	7.97E-05	++-----+-	--++++--+
HDLMUFA	rs4474673	*RANBP10*	0.0066	0.0227	0.0022	0.0019	4.87E-08	1.05E-07	-+-++++-+	+-+-+-++-
HDLMUFA	rs1109166	*SLC12A4, LCAT*	-0.0199	0.0187	-0.0002	0.0015	1.20E-05	1.89E-05	+++----+-	---++++-+
HDLMUFA	rs11043	*ESRP2, NFATC3*	0.0416	0.0211	-0.0015	0.0017	5.06E-05	8.72E-05	++-++++-+	--+----+-
HDLMUFA	rs6857	*NECTIN2*	-0.0100	0.0210	-0.0018	0.0018	8.93E-09	2.27E-08	--+----++	-+-+-+---
HDLMUFA	rs7679	*PCIF1*	0.0067	0.0185	0.0012	0.0015	9.25E-06	1.97E-05	+--+--+--	-++++++++
HDLMUFA	rs2305001	*BID*	0.1640	0.0500	-0.0096	0.0038	0.000146	0.000228	++--++++?	--++----?
HDLPUFA	rs7883	*LEPROT, LEPR*	-0.0309	0.0253	-0.0014	0.0043	0.000122	0.000194	-++++---?	-----+++?
HDLPUFA	rs788793	*LGR6*	-0.0171	0.0117	0.0001	0.0019	0.000552	0.000807	-+++---?	-----+++?
HDLPUFA	rs788792	*LGR6*	0.0172	0.0118	-0.0001	0.0019	0.000572	0.000799	+---++++?	+++++---?
HDLPUFA	rs3289	*LPL*	0.0530	0.0287	0.0040	0.0050	1.68E-12	7.02E-12	-+++++--+	+----++++
HDLPUFA	rs3735964	*LPL*	0.0480	0.0172	0.0028	0.0029	1.47E-26	2.40E-25	++---++-+	+-++++-+-
HDLPUFA	rs13702	*LPL*	-0.0480	0.0112	0.0016	0.0019	5.32E-22	6.72E-21	------+-	+-+--++--
HDLPUFA	rs1059611	*LPL*	-0.0475	0.0172	-0.0028	0.0029	2.17E-26	4.68E-25	--+++--+-	-+----+-+
HDLPUFA	rs15285	*LPL*	0.0248	0.0143	0.0045	0.0025	1.24E-23	1.60E-22	++---++-+	++++++-++
HDLPUFA	rs1057233	*SPI1*	0.0227	0.0113	-0.0011	0.0019	5.96E-05	8.95E-05	+++-+-+++	---+-+--+
HDLPUFA	rs2293577	*SLC39A13*	0.0270	0.0125	-0.0017	0.0021	0.000302	0.000446	+++-+-++?	---+-++-?
HDLPUFA	rs2293578	*SLC39A13*	-0.0270	0.0125	0.0017	0.0021	0.000303	0.000447	---+-+--?	+++-+--+?
HDLPUFA	rs9909	*NUP160*	0.0253	0.0108	-0.0011	0.0019	1.19E-06	2.23E-06	+++-+--++	--++-++--
HDLPUFA	rs4246215	*FEN1*	-0.0323	0.0105	0.0024	0.0018	5.24E-07	1.02E-06	--++---+-	+---+++--
HDLPUFA	rs174545	*FADS1*	0.0421	0.0117	-0.0038	0.0019	1.19E-06	2.20E-06	++--+++-?	--++---+?
HDLPUFA	rs174546	*FADS1*	-0.0338	0.0103	0.0026	0.0018	1.67E-07	3.64E-07	--++---++	++--+++--
HDLPUFA	rs2266788	*APOA5*	0.0502	0.0198	-0.0019	0.0035	1.63E-08	3.84E-08	++-+--+++	+-+-++---
HDLPUFA	rs473465	*INHBE*	-0.0030	0.0125	-0.0023	0.0021	0.000896	0.001198	+++-++---	---+-++--
HDLPUFA	rs10773003	*SBNO1*	0.0219	0.0173	0.0004	0.0029	0.000491	0.000699	++--+++-+	--++---+-
HDLPUFA	rs3088303	*SBNO1*	0.0244	0.0193	0.0005	0.0032	0.000624	0.000912	++--+++-?	-+++---+?
HDLPUFA	rs6738	*TPM1*	0.0036	0.0124	0.0024	0.0021	0.000177	0.000261	+---++++?	-++++---+?
HDLPUFA	rs8468	*LACTB*	0.0059	0.0109	0.0018	0.0018	6.81E-05	0.000108	+---++-+-	++++--+-+
HDLPUFA	rs37029	*SLC12A3*	0.0227	0.0104	-0.0012	0.0018	3.48E-05	6.57E-05	+++++-+-+	+---+-++-
HDLPUFA	rs12449157	*GFOD2*	-0.0229	0.0141	0.0005	0.0024	0.00023	0.00033	-++----+-	---+++--+
HDLPUFA	rs4474673	*RANBP10*	0.0432	0.0163	-0.0024	0.0028	4.66E-07	1.02E-06	++-+++--+	+++---++-
HDLPUFA	rs1109166	*SLC12A4, LCAT*	-0.0344	0.0135	0.0024	0.0023	2.04E-05	3.65E-05	-++-----	+--+++++
HDLPUFA	rs11043	*ESRP2, NFATC3*	0.0471	0.0151	-0.0045	0.0026	2.55E-05	4.07E-05	++-+++++	-++----+-
HDLPUFA	rs6857	*NECTIN2*	-0.0517	0.0157	0.0032	0.0026	5.69E-09	1.37E-08	------?-	-++++++?+
HDLPUFA	rs7679	*PCIF1*	-0.0020	0.0135	0.0047	0.0023	2.30E-07	5.14E-07	+--+---?-	-++-+++?+
HDLPUFA	rs2305001	*BID*	0.1292	0.0356	-0.0165	0.0059	0.000442	0.000643	++--+++??	+-++---??

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
HDLMUFA	rs7883	*LEPROT, LEPR*	0.001429	-0.0418	0.0153	0.0009	0.0009	0.00221	-++-----?	---+++++?	0.02	16126
HDLMUFA	rs788793	*LGR6*	0.001357	-0.0112	0.0069	-0.0002	0.0004	0.002263	-+---+--?	--+-+-++?	0.71	16153
HDLMUFA	rs788792	*LGR6*	0.001398	0.0112	0.0069	0.0002	0.0004	0.00233	+-+-+-++?	++-+-+--?	0.71	16153
HDLMUFA	rs3289	*LPL*	9.92E-14	0.0560	0.0164	0.0013	0.0008	1.24E-13	-+++-+---+	+-++++++-	0.58	22141
HDLMUFA	rs3735964	*LPL*	1.06E-31	0.0576	0.0091	0.0005	0.0005	9.18E-32	+++++++-+	---+++-+-	0.27	22141
HDLMUFA	rs13702	*LPL*	8.22E-26	-0.0320	0.0063	-0.0006	0.0004	5.52E-26	----+----	+++--+++-	0.18	22141
HDLMUFA	rs1059611	*LPL*	1.63E-31	-0.0572	0.0091	-0.0005	0.0005	1.43E-31	-------+-	+++---+-+	0.25	22141
HDLMUFA	rs15285	*LPL*	2.03E-26	0.0458	0.0078	0.0003	0.0004	1.30E-26	+++++++++	-+-+--++	0.86	22141
HDLMUFA	rs1057233	*SPI1*	0.000105	0.0150	0.0065	0.0001	0.0004	7.53E-05	++-++--+-	--+-+++-+	0.36	22141
HDLMUFA	rs2293577	*SLC39A13*	0.001955	0.0141	0.0070	0.0001	0.0004	0.001294	-+-+++-+?	+-+-+-+-?	0.38	16153
HDLMUFA	rs2293578	*SLC39A13*	0.001959	-0.0141	0.0070	-0.0001	0.0004	0.001298	+-+---+-?	-+-+-+-+?	0.38	16153
HDLMUFA	rs9909	*NUP160*	1.52E-06	0.0160	0.0062	0.0002	0.0004	1.27E-06	++-+++-++	--++++-+	0.51	22141
HDLMUFA	rs4246215	*FEN1*	7.70E-08	-0.0274	0.0061	0.0006	0.0004	4.64E-08	-++-----	+--++++-+	0.02	22141
HDLMUFA	rs174545	*FADS1*	9.68E-07	0.0276	0.0068	-0.0005	0.0004	8.60E-07	+--+++++?	-++----+?	0.01	16153
HDLMUFA	rs174546	*FADS1*	3.97E-08	-0.0265	0.0060	0.0005	0.0004	3.09E-08	-++-----	+--++++-+	0.02	22141
HDLMUFA	rs2266788	*APOA5*	1.01E-07	0.0312	0.0107	0.0005	0.0006	3.20E-08	++-+-++++	--+-+-+-+	0.75	22141
HDLMUFA	rs10773003	*SBNO1*	1.08E-05	0.0271	0.0112	0.0000	0.0007	2.31E-05	++-++++-+	--+---++-	0.95	22128
HDLMUFA	rs3088303	*SBNO1*	6.74E-05	0.0278	0.0122	0.0000	0.0008	0.000116	++-++++-?	-++---++?	0.92	16153
HDLMUFA	rs6738	*TPM1*	3.16E-05	0.0264	0.0068	-0.0007	0.0004	3.85E-05	+--+++++?	-++-+---?	0.45	16153
HDLMUFA	rs8468	*LACTB*	7.54E-07	0.0218	0.0060	-0.0002	0.0003	8.24E-07	++-+-++++	+---+--++	0.92	22132
HDLMUFA	rs37029	*SLC12A3*	1.50E-05	0.0075	0.0058	0.0005	0.0003	3.10E-05	-++-+-++-	+--+-+++-	0.44	22141
HDLMUFA	rs12449157	*GFOD2*	1.88E-06	-0.0282	0.0080	0.0003	0.0005	1.43E-06	++-+---+-	--+-++--+	0.21	22141
HDLMUFA	rs4474673	*RANBP10*	8.56E-10	0.0282	0.0096	0.0004	0.0006	7.53E-10	-++-+++-+	+-++--++-	0.37	22141
HDLMUFA	rs1109166	*SLC12A4, LCAT*	2.32E-07	-0.0272	0.0077	0.0002	0.0005	2.04E-07	++-+---+-	--+-+++-+	0.30	22141
HDLMUFA	rs11043	*ESRP2, NFATC3*	9.78E-07	0.0289	0.0087	-0.0002	0.0005	9.84E-07	+++-+++-+	+--+---+-	0.58	22141
HDLMUFA	rs6857	*NECTIN2*	3.12E-11	-0.0303	0.0092	-0.0004	0.0006	8.95E-12	--+++--+-	-+---+---	0.15	22141
HDLMUFA	rs7679	*PCIF1*	1.25E-06	0.0188	0.0076	0.0003	0.0005	1.31E-06	+-----+--	-++++++++	0.51	22140
HDLMUFA	rs2305001	*BID*	0.01493	0.0579	0.0212	-0.0017	0.0010	0.01447	++-+++++?	--+----?	0.05	16153
HDLPUFA	rs7883	*LEPROT, LEPR*	0.003374	-0.0153	0.0244	-0.0023	0.0041	0.00472	--+++--?	+----+++?	0.03	16126
HDLPUFA	rs788793	*LGR6*	0.000892	-0.0182	0.0110	0.0007	0.0018	0.001509	-+-++---?	-----+++?	0.70	16153
HDLPUFA	rs788792	*LGR6*	0.000919	0.0182	0.0110	-0.0007	0.0018	0.001554	+-+-+++?	+++++---?	0.70	16153
HDLPUFA	rs3289	*LPL*	8.68E-13	0.0701	0.0288	0.0010	0.0051	1.03E-12	+++++---+	+----+++-	0.36	22142
HDLPUFA	rs3735964	*LPL*	3.87E-31	0.0532	0.0158	0.0021	0.0027	3.36E-31	++++-++-+	+-++++-+-	0.33	22142
HDLPUFA	rs13702	*LPL*	4.20E-26	-0.0553	0.0106	0.0027	0.0018	1.72E-26	-------+-	+-++-++-+	0.56	22142
HDLPUFA	rs1059611	*LPL*	6.38E-31	-0.0531	0.0158	-0.0021	0.0027	5.70E-31	----+--+-	-+----+-+	0.31	22142
HDLPUFA	rs15285	*LPL*	2.68E-27	0.0307	0.0133	0.0037	0.0023	1.14E-27	+++--++-+	++++++-+-	0.49	22142
HDLPUFA	rs1057233	*SPI1*	6.31E-05	0.0194	0.0108	-0.0006	0.0018	4.97E-05	+++-+--++	---+-++-+	0.19	22142
HDLPUFA	rs2293577	*SLC39A13*	0.001042	0.0231	0.0117	-0.0014	0.0020	0.000788	+++-+-++?	---+-++-?	0.16	16153
HDLPUFA	rs2293578	*SLC39A13*	0.001041	-0.0231	0.0117	0.0014	0.0020	0.000789	---+-+--?	+++-+--+?	0.16	16153
HDLPUFA	rs9909	*NUP160*	9.93E-07	0.0231	0.0103	-0.0008	0.0018	8.27E-07	+++-+--++	---+-++-+	0.23	22142
HDLPUFA	rs4246215	*FEN1*	9.71E-08	-0.0273	0.0102	0.0013	0.0017	5.55E-08	--+---+-	----+++--	0.20	22142
HDLPUFA	rs174545	*FADS1*	3.84E-07	0.0388	0.0112	-0.0032	0.0019	3.16E-07	++-++++-?	+-++---+?	0.17	16153
HDLPUFA	rs174546	*FADS1*	3.43E-08	-0.0299	0.0100	0.0018	0.0017	2.38E-08	--+---++	-+--+++--	0.12	22142
HDLPUFA	rs2266788	*APOA5*	1.14E-07	0.0577	0.0191	-0.0037	0.0033	3.94E-08	++-+--+++	--+-++---	0.39	22142
HDLPUFA	rs473465	*INHBE*	0.008147	-0.0032	0.0119	-0.0017	0.0020	0.006521	+++-++-+-	---+-++-+	0.17	22142
HDLPUFA	rs10773003	*SBNO1*	6.45E-06	0.0331	0.0164	-0.0010	0.0028	1.42E-05	++--+++-+	--++---+-	0.97	22129
HDLPUFA	rs3088303	*SBNO1*	4.30E-05	0.0330	0.0182	-0.0008	0.0030	7.54E-05	++--+++-?	--++---+?	0.94	16153
HDLPUFA	rs6738	*TPM1*	4.74E-05	0.0032	0.0116	0.0024	0.0019	7.41E-05	+---+++-?	+++++--+?	0.23	16153
HDLPUFA	rs8468	*LACTB*	6.66E-07	0.0114	0.0103	0.0013	0.0018	8.17E-07	+---++-++	+--+--+++	0.85	22133
HDLPUFA	rs37029	*SLC12A3*	3.03E-05	0.0168	0.0099	-0.0004	0.0017	6.62E-05	+++++++-+	+-+-+--+-	0.53	22142
HDLPUFA	rs12449157	*GFOD2*	5.03E-06	-0.0207	0.0137	-0.0004	0.0024	3.56E-06	-++----+-	---+++--+	0.56	22142
HDLPUFA	rs4474673	*RANBP10*	2.28E-09	0.0403	0.0158	-0.0013	0.0027	1.98E-09	++-+++--+	+-+---++-	0.33	22142
HDLPUFA	rs1109166	*SLC12A4, LCAT*	4.16E-07	-0.0328	0.0130	0.0016	0.0022	3.22E-07	-++----+-	---++++-+	0.51	22142
HDLPUFA	rs11043	*ESRP2, NFATC3*	3.24E-07	0.0462	0.0143	-0.0037	0.0025	3.42E-07	++-++++-+	-++----+-	0.47	22142
HDLPUFA	rs6857	*NECTIN2*	5.54E-11	-0.0439	0.0148	0.0016	0.0025	1.66E-11	-------+-	-+++--+-+	0.00	20605
HDLPUFA	rs7679	*PCIF1*	1.59E-06	0.0049	0.0128	0.0031	0.0022	1.39E-06	+--+---++	-++-+++-+	0.55	20604
HDLPUFA	rs2305001	*BID*	0.000573	0.1269	0.0341	-0.0168	0.0055	0.000581	++--++++?	--++----?	0.47	14616

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (HDLMUFA, HDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
HDLMUFA	rs7883	*LEPROT, LEPR*	-0.0373	0.0092	5.10E-05	7.20E-05	--------?	-0.0289	0.0085	0.0006319	--------?	0	0.96
HDLMUFA	rs788793	*LGR6*	-0.0167	0.0042	7.18E-05	9.90E-05	-++-----?	-0.0118	0.0037	0.001661	-+---+--?	0	0.48
HDLMUFA	rs788792	*LGR6*	0.0167	0.0042	7.35E-05	9.90E-05	+--+++++?	0.0117	0.0037	0.001711	+-+++-++?	0	0.49
HDLMUFA	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	+++++++ +	0.0730	0.0101	6.019E-13	+++++++ +	34.5	0.14
HDLMUFA	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.597E-38	+++++++++	38.8	0.11
HDLMUFA	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	--------	-0.0418	0.0035	8.568E-33	---------	30.4	0.17
HDLMUFA	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	--------	-0.0653	0.0051	1.106E-37	---------	37.4	0.12
HDLMUFA	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.537E-34	+++++++++	17	0.29
HDLMUFA	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	0.000001624	+++++++++	11.1	0.34
HDLMUFA	rs2293577	*SLC39A13*	0.0181	0.0043	2.24E-05	3.77E-05	++++++++?	0.0165	0.0038	0.00001634	++++++++?	25.9	0.22
HDLMUFA	rs2293578	*SLC39A13*	-0.0181	0.0043	2.31E-05	3.77E-05	--------?	-0.0165	0.0038	0.00001677	--------?	25.8	0.22
HDLMUFA	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.0190	0.0033	1.099E-08	+++++++++	23.1	0.24
HDLMUFA	rs4246215	*FEN1*	-0.0180	0.0037	8.48E-07	1.91E-06	---+-----	-0.0193	0.0033	6.43E-09	---+-----	0	0.47
HDLMUFA	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.20
HDLMUFA	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	---+-----	-0.0198	0.0033	2.322E-09	---+-----	18.7	0.28
HDLMUFA	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.543E-10	+++++++++	0	0.68
HDLMUFA	rs10773003	*SBNO1*	0.0255	0.0061	2.60E-05	4.26E-05	+++++++++	0.0287	0.0055	1.968E-07	+++++++++	0	0.99
HDLMUFA	rs3088303	*SBNO1*	0.0282	0.0068	3.72E-05	4.90E-05	++++++++?	0.0304	0.0061	7.072E-07	++++++++?	0	0.98
HDLMUFA	rs6738	*TPM1*	0.0160	0.0042	0.00014	0.000192	++++++++?	0.0190	0.0038	4.934E-07	+++-++++?	0	0.70
HDLMUFA	rs8468	*LACTB*	0.0150	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.022E-08	+-+++++++	0	0.67
HDLMUFA	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	0.000113	+++++-+++	0.0124	0.0032	0.0001061	+++++++++	0	0.55
HDLMUFA	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	---+-----	-0.0226	0.0044	2.457E-07	---+-----	0	0.67
HDLMUFA	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.0050	4.162E-10	+++++++++	0	0.67
HDLMUFA	rs1109166	*SLC12A4, LCAT*	-0.0230	0.0046	6.62E-07	9.81E-07	---+-----	-0.0225	0.0042	1.029E-07	---+-----	0	0.60
HDLMUFA	rs11043	*ESRP2, NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.375E-07	+++++++++	0	0.83
HDLMUFA	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	--------	-0.0349	0.0047	8.972E-14	---------	50.5	0.04
HDLMUFA	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	+++++++ +	0.0218	0.0041	1.143E-07	+++++++ +	0	0.62
HDLMUFA	rs2305001	*BID*	0.0511	0.0136	0.000177	0.000234	+-++++-+?	0.0308	0.0123	0.01227	+++-++-+?	33.8	0.16
HDLPUFA	rs7883	*LEPROT, LEPR*	-0.0373	0.0092	5.10E-05	7.20E-05	--------?	-0.0289	0.0085	0.0006319	--------?	0	0.96
HDLPUFA	rs788793	*LGR6*	-0.0167	0.0042	7.18E-05	9.90E-05	-++-----?	-0.0118	0.0037	0.001661	-+---+--?	0	0.48
HDLPUFA	rs788792	*LGR6*	0.0167	0.0042	7.35E-05	9.90E-05	+--+++++?	0.0117	0.0037	0.001711	+-+++-++?	0	0.49
HDLPUFA	rs3289	*LPL*	0.0701	0.0112	4.36E-10	8.89E-10	+++++++ +	0.0730	0.0101	6.019E-13	+++++++ +	34.5	0.14
HDLPUFA	rs3735964	*LPL*	0.0637	0.0056	2.58E-30	8.26E-29	+++++++++	0.0655	0.0051	7.597E-38	+++++++++	38.8	0.11
HDLPUFA	rs13702	*LPL*	-0.0414	0.0038	4.10E-27	1.45E-26	--------	-0.0418	0.0035	8.568E-33	---------	30.4	0.17
HDLPUFA	rs1059611	*LPL*	-0.0635	0.0056	3.43E-30	1.22E-28	--------	-0.0653	0.0051	1.106E-37	---------	37.4	0.12
HDLPUFA	rs15285	*LPL*	0.0501	0.0047	1.21E-26	1.68E-25	+++++++++	0.0529	0.0043	1.537E-34	+++++++++	17	0.29
HDLPUFA	rs1057233	*SPI1*	0.0173	0.0038	6.03E-06	8.29E-06	+++++++++	0.0167	0.0035	0.000001624	+++++++++	11.1	0.34
HDLPUFA	rs2293577	*SLC39A13*	0.0181	0.0043	2.24E-05	3.77E-05	++++++++?	0.0165	0.0038	0.00001634	++++++++?	25.9	0.22
HDLPUFA	rs2293578	*SLC39A13*	-0.0181	0.0043	2.31E-05	3.77E-05	--------?	-0.0165	0.0038	0.00001677	--------?	25.8	0.22
HDLPUFA	rs9909	*NUP160*	0.0204	0.0037	2.32E-08	6.73E-08	+++++++++	0.0190	0.0033	1.099E-08	+++++++++	23.1	0.24
HDLPUFA	rs4246215	*FEN1*	-0.0180	0.0037	8.48E-07	1.91E-06	---+-----	-0.0193	0.0033	6.43E-09	---+-----	0	0.47
HDLPUFA	rs174545	*FADS1*	0.0196	0.0042	3.22E-06	4.90E-06	++--++++?	0.0204	0.0038	5.79E-08	++-+++++?	28.5	0.20
HDLPUFA	rs174546	*FADS1*	-0.0188	0.0037	2.71E-07	6.53E-07	---+-----	-0.0198	0.0033	2.322E-09	---+-----	18.7	0.28
HDLPUFA	rs2266788	*APOA5*	0.0397	0.0068	5.96E-09	1.09E-08	++++-++++	0.0381	0.0062	8.543E-10	+++++++++	0	0.68
HDLPUFA	rs473465	*INHBE*	-0.0171	0.0043	5.88E-05	9.88E-05	---+---+---	-0.0142	0.0039	0.000277	---+---+--	15.3	0.31
HDLPUFA	rs10773003	*SBNO1*	0.0255	0.0061	2.60E-05	4.26E-05	+++++++++	0.0287	0.0055	1.968E-07	+++++++++	0	0.99
HDLPUFA	rs3088303	*SBNO1*	0.0282	0.0068	3.72E-05	4.90E-05	++++++++?	0.0304	0.0061	7.072E-07	++++++++?	0	0.98
HDLPUFA	rs6738	*TPM1*	0.0160	0.0042	0.00014	0.000192	++++++++?	0.0190	0.0038	4.934E-07	+++-++++?	0	0.70
HDLPUFA	rs8468	*LACTB*	0.0150	0.0037	5.05E-05	7.21E-05	+-+++++++	0.0194	0.0034	1.022E-08	+-+++++++	0	0.67
HDLPUFA	rs37029	*SLC12A3*	0.0138	0.0035	9.01E-05	0.000113	+++++-+++	0.0124	0.0032	0.0001061	+++++++++	0	0.55
HDLPUFA	rs12449157	*GFOD2*	-0.0232	0.0048	1.31E-06	2.22E-06	---+-----	-0.0226	0.0044	2.457E-07	---+-----	0	0.67
HDLPUFA	rs4474673	*RANBP10*	0.0323	0.0055	4.36E-09	8.93E-09	++-++++++	0.0314	0.0050	4.162E-10	+++++++++	0	0.67
HDLPUFA	rs1109166	*SLC12A4, LCAT*	-0.0230	0.0046	6.62E-07	9.81E-07	---+-----	-0.0225	0.0042	1.029E-07	---+-----	0	0.60
HDLPUFA	rs11043	*ESRP2, NFATC3*	0.0229	0.0052	1.02E-05	1.62E-05	++-++++++	0.0234	0.0047	8.375E-07	+++++++++	0	0.83
HDLPUFA	rs6857	*NECTIN2*	-0.0298	0.0052	9.67E-09	2.01E-08	--------	-0.0349	0.0047	8.972E-14	---------	50.5	0.04
HDLPUFA	rs7679	*PCIF1*	0.0209	0.0046	4.70E-06	8.65E-06	+++++++ +	0.0218	0.0041	1.143E-07	+++++++ +	0	0.62
HDLPUFA	rs2305001	*BID*	0.0511	0.0136	0.000177	0.000234	+-++++-+?	0.0308	0.0123	0.01227	+++-++-+?	33.8	0.16

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
LDLCHO	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLCHO	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLCHO	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLCHO	rs12747251	*NSL1*	1	212903089	6	+	0.104	G/A,A	0.48	0.027
LDLCHO	rs1172294	*DNAJC27*	2	25169200	8	+	0.09507	G/A,A	0.47	0.018
LDLCHO	rs10942729	*ANKRD31*	5	74364300	3	+	1.02E-17	A/G,A	0.36	0.019
LDLCHO	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.40	0.020
LDLCHO	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLCHO	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLCHO	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLCHO	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLCHO	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLCHO	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLCHO	rs4804572	*KANK2*	19	11277074	9	+	NA	T/C,T	0.37	0.021
LDLCHO	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLCHO	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023
LDLSFA	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLSFA	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLSFA	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLSFA	rs12747251	*NSL1*	1	212903089	6	+	0.104	G/A,A	0.48	0.027
LDLSFA	rs1172294	*DNAJC27*	2	25169200	8	+	0.09507	G/A,A	0.47	0.018
LDLSFA	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.40	0.020
LDLSFA	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLSFA	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLSFA	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLSFA	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLSFA	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLSFA	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLSFA	rs4804572	*KANK2*	19	11277074	9	+	NA	T/C,T	0.37	0.021
LDLSFA	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLSFA	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
LDLCHO	rs583609	*USP1*	-0.0809	0.0601	0.0028	0.0012	1.19E-06	1.91E-06	--+--+-+?	++-+++++?
LDLCHO	rs17034539	*KIAA1324*	0.0276	0.0670	-0.0016	0.0014	0.000133	0.000181	-+++++++-	--------+
LDLCHO	rs629301	*CELSR2*	0.1429	0.0594	0.0000	0.0012	4.71E-42	6.31E-41	+++++++++	+----+--+
LDLCHO	rs12747251	*NSL1*	-0.0929	0.0575	0.0011	0.0012	0.000268	0.000392	--++--++?	++--++--?
LDLCHO	rs1172294	*DNAJC27*	-0.0769	0.0507	0.0009	0.0010	0.000928	0.001396	--+-----+	++-+++++-
LDLCHO	rs10942729	*ANKRD31*	0.1016	0.0605	-0.0014	0.0013	0.001099	0.00152	+---++++?	-+++----?
LDLCHO	rs12916	*HMGCR*	-0.0960	0.0518	0.0004	0.0011	3.75E-16	9.03E-16	-+++-----	+---+++++
LDLCHO	rs4246215	*FEN1*	-0.1108	0.0539	0.0010	0.0011	6.77E-12	1.33E-11	--+----+-	-+-+-++-+
LDLCHO	rs174545	*FADS1*	0.1137	0.0617	-0.0009	0.0013	1.60E-11	6.15E-11	++-++++-?	+-+-+--+?
LDLCHO	rs174546	*FADS1*	-0.1119	0.0541	0.0009	0.0011	2.88E-13	5.83E-13	--+----+-	-+-+-++-+
LDLCHO	rs13465	*ILF3*	0.0590	0.1157	-0.0036	0.0024	3.72E-09	9.41E-09	-+-+---++	--+-++---
LDLCHO	rs1433099	*LDLR*	-0.0473	0.0611	0.0000	0.0013	2.34E-05	2.91E-05	-+-++-+--	--+--+-++
LDLCHO	rs7188	*KANK2*	-0.0847	0.0673	0.0002	0.0014	1.29E-10	2.86E-10	?-+++--+-	?+---++-+
LDLCHO	rs4804572	*KANK2*	0.0035	0.0841	0.0011	0.0018	0.000174	0.000228	?----++-?	?++++--+?
LDLCHO	rs3810444	*SUGP2*	-0.3030	0.1031	0.0046	0.0021	7.74E-06	1.36E-05	-++--++--	+--++--++
LDLCHO	rs6859	*NECTIN2*	0.0878	0.0540	-0.0004	0.0011	4.21E-12	2.19E-11	--+-+++++	++++-----
LDLSFA	rs583609	*USP1*	0.1052	0.0440	-0.0044	0.0035	6.08E-06	8.09E-06	+++-+-++?	--++-+--?
LDLSFA	rs17034539	*KIAA1324*	-0.0262	0.0460	-0.0017	0.0036	0.000214	0.000306	------+-+	-+++++-+-
LDLSFA	rs629301	*CELSR2*	0.1461	0.0409	-0.0005	0.0032	1.57E-41	1.10E-39	+--++++++	-++---+-+
LDLSFA	rs12747251	*NSL1*	-0.0326	0.0413	-0.0006	0.0033	0.000398	0.000568	-+--+---?	--++--++?
LDLSFA	rs1172294	*DNAJC27*	-0.0126	0.0354	-0.0016	0.0028	0.001081	0.001445	+++-+-+--	---+-+--+
LDLSFA	rs12916	*HMGCR*	-0.0567	0.0362	-0.0015	0.0029	3.06E-16	1.47E-15	+-+++++--	-++-----+
LDLSFA	rs4246215	*FEN1*	-0.0621	0.0370	-0.0002	0.0029	1.23E-11	2.98E-11	--++-++--	-+--+--++
LDLSFA	rs174545	*FADS1*	0.0544	0.0443	0.0015	0.0035	2.06E-11	5.59E-11	++--+--+?	+-++-++-?
LDLSFA	rs174546	*FADS1*	-0.0550	0.0370	-0.0011	0.0029	4.40E-13	1.45E-12	--++-++--	-+--+--+-
LDLSFA	rs13465	*ILF3*	-0.1839	0.0767	0.0056	0.0060	1.64E-08	3.20E-08	-++++--+-	+----++-+
LDLSFA	rs1433099	*LDLR*	-0.0768	0.0420	0.0022	0.0033	1.03E-05	1.49E-05	--++---+-	++--+++--
LDLSFA	rs7188	*KANK2*	-0.0427	0.0423	-0.0025	0.0033	8.61E-11	1.93E-10	?--++-++--	?---+--+-
LDLSFA	rs4804572	*KANK2*	0.0544	0.0553	0.0001	0.0044	0.000282	0.000387	?++++--+?	?--+-++-?
LDLSFA	rs3810444	*SUGP2*	-0.0436	0.0734	-0.0032	0.0057	5.22E-05	7.56E-05	-------++	+++-+++--
LDLSFA	rs6859	*NECTIN2*	0.0510	0.0364	0.0014	0.0028	3.05E-12	7.82E-12	+++++--++	----+++-+

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
LDLCHO	rs583609	*USP1*	1.31E-06	-0.0734	0.0594	0.0026	0.0012	2.37E-06	--++-+-+?	++--++++?	0.34	16009
LDLCHO	rs17034539	*KIAA1324*	3.95E-05	0.0293	0.0659	-0.0016	0.0014	4.31E-05	-+++++++-	--------+	0.19	21995
LDLCHO	rs629301	*CELSR2*	2.63E-42	0.1404	0.0585	0.0000	0.0012	7.36E-43	+++++++++	+----++-+	0.59	21995
LDLCHO	rs12747251	*NSL1*	0.00022	-0.0861	0.0559	0.0010	0.0012	0.000358	--++---+?	++--++--?	0.66	16009
LDLCHO	rs1172294	*DNAJC27*	0.004369	-0.0718	0.0496	0.0009	0.0010	0.006016	--+-----+	++-+++++-	0.20	21995
LDLCHO	rs10942729	*ANKRD31*	0.000443	0.1113	0.0587	-0.0015	0.0012	0.000356	+---++++?	-+++----?	0.19	16009
LDLCHO	rs12916	*HMGCR*	2.36E-17	-0.1131	0.0505	0.0008	0.0010	5.22E-17	-+++-----	+---+++++	0.01	21995
LDLCHO	rs4246215	*FEN1*	1.82E-12	-0.1026	0.0516	0.0008	0.0011	7.67E-13	--+----+-	-+-+-++-+	0.78	21995
LDLCHO	rs174545	*FADS1*	3.29E-12	0.1024	0.0582	-0.0006	0.0012	1.14E-12	++-++++-?	+-+-+--+?	0.93	16009
LDLCHO	rs174546	*FADS1*	6.12E-14	-0.1041	0.0518	0.0007	0.0011	2.07E-14	--+----+-	-+-+-++-+	0.94	21995
LDLCHO	rs13465	*ILF3*	2.03E-09	0.0974	0.1129	-0.0044	0.0023	2.73E-09	-+-+---++	--+-++---	0.61	21994
LDLCHO	rs1433099	*LDLR*	1.98E-05	-0.0376	0.0598	-0.0002	0.0012	2.12E-05	-+-++-+--	--+--+-++	0.78	21995
LDLCHO	rs7188	*KANK2*	1.67E-12	-0.0910	0.0607	0.0004	0.0012	2.15E-12	--+++--+-	+----++-+	0.59	15418
LDLCHO	rs4804572	*KANK2*	2.38E-06	0.0061	0.0718	0.0011	0.0015	3.30E-06	-----++-?	+++++--+?	0.57	9432
LDLCHO	rs3810444	*SUGP2*	4.41E-06	-0.3202	0.1019	0.0050	0.0021	4.11E-06	-++--++--	+--++--++	0.51	21995
LDLCHO	rs6859	*NECTIN2*	2.37E-13	0.0675	0.0532	0.0000	0.0011	6.37E-13	--+-+++-+	++++---+-	0.19	21995
LDLSFA	rs583609	*USP1*	4.89E-06	0.1088	0.0430	-0.0049	0.0034	7.07E-06	+++-+-++?	--++-+--?	0.46	16009
LDLSFA	rs17034539	*KIAA1324*	8.81E-05	-0.0294	0.0447	-0.0015	0.0035	9.44E-05	------+-+	-+++++-+-	0.54	21995
LDLSFA	rs629301	*CELSR2*	4.37E-42	0.1476	0.0401	-0.0006	0.0031	1.11E-42	+--++++++	-++---+-+	0.49	21995
LDLSFA	rs12747251	*NSL1*	0.000366	-0.0380	0.0402	0.0000	0.0032	0.000564	-+--+---?	+-++--++?	0.89	16009
LDLSFA	rs1172294	*DNAJC27*	0.005163	-0.0081	0.0344	-0.0015	0.0027	0.006897	+++++-+--	---+-+--+	0.02	21995
LDLSFA	rs12916	*HMGCR*	3.09E-17	-0.0478	0.0348	-0.0022	0.0027	7.58E-17	-++-++++-	--+-----+	0.07	21995
LDLSFA	rs4246215	*FEN1*	2.83E-12	-0.0583	0.0354	-0.0006	0.0028	1.22E-12	--++-++--	-+--+--+-	0.21	21995
LDLSFA	rs174545	*FADS1*	3.90E-12	0.0552	0.0416	0.0016	0.0033	1.38E-12	++--+--+?	+-++-++-?	0.35	16009
LDLSFA	rs174546	*FADS1*	8.72E-14	-0.0527	0.0354	-0.0014	0.0028	3.04E-14	--++-++--	-+--+--+-	0.42	21995
LDLSFA	rs13465	*ILF3*	1.12E-08	-0.1909	0.0754	0.0065	0.0059	2.61E-08	-++++----	+----++-+	0.29	21994
LDLSFA	rs1433099	*LDLR*	8.56E-06	-0.0763	0.0407	0.0023	0.0032	1.03E-05	--++---+-	++--+++--	0.60	21995
LDLSFA	rs7188	*KANK2*	1.24E-12	-0.0519	0.0394	-0.0018	0.0031	1.47E-12	--++-++--	+---+--+-	0.48	15418
LDLSFA	rs4804572	*KANK2*	4.83E-06	0.0616	0.0491	-0.0002	0.0039	6.05E-06	+++++--+?	---+-++-?	0.56	9432
LDLSFA	rs3810444	*SUGP2*	5.21E-05	-0.0398	0.0708	-0.0034	0.0055	4.88E-05	-------++	+++-+++--	0.62	21995
LDLSFA	rs6859	*NECTIN2*	1.67E-13	0.0563	0.0356	0.0011	0.0028	3.94E-13	+++++--++	----+++-+	0.46	21995

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLCHO, LDLSFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
LDLCHO	rs583609	*USP1*	0.0393	0.0090	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.074E-07	+++-++++?	0	0.47
LDLCHO	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.0110	0.00002173	------+--	0	0.59
LDLCHO	rs629301	*CELSR2*	0.1445	0.0100	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.268E-47	+++++++++	28	0.20
LDLCHO	rs12747251	*NSL1*	-0.0320	0.0085	0.000163	0.000212	--------?	-0.0368	0.0093	0.00008368	------+-?	0	0.78
LDLCHO	rs1172294	*DNAJC27*	-0.0294	0.0076	0.000117	0.000141	--++-+---	-0.0233	0.0083	0.004828	--++-+---	29.7	0.18
LDLCHO	rs10942729	*ANKRD31*	0.0390	0.0099	8.42E-05	0.000106	++-+++++?	0.0390	0.0097	0.00005802	++-+++++?	0	0.78
LDLCHO	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.077E-17	--+------	58	0.01
LDLCHO	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	---------	-0.0623	0.0086	4.403E-13	---------	0	0.54
LDLCHO	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLCHO	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	---------	-0.0660	0.0086	1.404E-14	---------	0	0.76
LDLCHO	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	---------	-0.1073	0.0188	1.071E-08	----+----	38.1	0.11
LDLCHO	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	---------	-0.0468	0.0098	0.000001801	---------	0	0.64
LDLCHO	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?--------	-0.0719	0.0096	8.282E-14	---------	0	0.51
LDLCHO	rs4804572	*KANK2*	0.0496	0.0118	2.44E-05	3.53E-05	?+++++++?	0.0591	0.0115	2.493E-07	++++++++?	0	0.85
LDLCHO	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	0.00001067	------+--	12.9	0.33
LDLCHO	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-+++++++	0.0691	0.0088	5.788E-15	+-+++++++	28.1	0.19
LDLSFA	rs583609	*USP1*	0.0393	0.0090	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.074E-07	+++-++++?	0	0.47
LDLSFA	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.0110	0.00002173	------+--	0	0.59
LDLSFA	rs629301	*CELSR2*	0.1445	0.0100	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.268E-47	+++++++++	28	0.20
LDLSFA	rs12747251	*NSL1*	-0.0320	0.0085	0.000163	0.000212	--------?	-0.0368	0.0093	0.00008368	------+-?	0	0.78
LDLSFA	rs1172294	*DNAJC27*	-0.0294	0.0076	0.000117	0.000141	--++-+---	-0.0233	0.0083	0.004828	--++-+---	29.7	0.18
LDLSFA	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.077E-17	--+------	58	0.01
LDLSFA	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	---------	-0.0623	0.0086	4.403E-13	---------	0	0.54
LDLSFA	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLSFA	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	---------	-0.0660	0.0086	1.404E-14	---------	0	0.76
LDLSFA	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	---------	-0.1073	0.0188	1.071E-08	----+----	38.1	0.11
LDLSFA	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	---------	-0.0468	0.0098	0.000001801	---------	0	0.64
LDLSFA	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?--------	-0.0719	0.0096	8.282E-14	---------	0	0.51
LDLSFA	rs4804572	*KANK2*	0.0496	0.0118	2.44E-05	3.53E-05	?+++++++?	0.0591	0.0115	2.493E-07	++++++++?	0	0.85
LDLSFA	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	0.00001067	------+--	12.9	0.33
LDLSFA	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-+++++++	0.0691	0.0088	5.788E-15	+-+++++++	28.1	0.19

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Global Lipids GWAS P value	Alleles (minor/major, effect)	MAF[2]	FreqSE
LDLMUFA	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLMUFA	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLMUFA	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLMUFA	rs12747251	*NSL1*	1	212903089	6	+	0.104	G/A,A	0.48	0.027
LDLMUFA	rs1172294	*DNAJC27*	2	25169200	8	+	0.09507	G/A,A	0.47	0.018
LDLMUFA	rs10942729	*ANKRD31*	5	74364300	3	+	1.02E-17	A/G,A	0.36	0.019
LDLMUFA	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.40	0.020
LDLMUFA	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLMUFA	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLMUFA	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLMUFA	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLMUFA	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLMUFA	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLMUFA	rs4804572	*KANK2*	19	11277074	9	+	NA	T/C,T	0.37	0.021
LDLMUFA	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLMUFA	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023
LDLPUFA	rs583609	*USP1*	1	62916796	12	+	1.76E-16	C/T,T	0.34	0.025
LDLPUFA	rs17034539	*KIAA1324*	1	109747635	3	+	1.56E-21	T/C,T	0.17	0.007
LDLPUFA	rs629301	*CELSR2*	1	109818306	8	+	5.40E-241	G/T,T	0.23	0.013
LDLPUFA	rs12747251	*NSL1*	1	212903089	6	+	0.104	G/A,A	0.48	0.027
LDLPUFA	rs2254487	*LGALS8, HEATR1*	1	236714335	3	+	NA	C/T,T	0.35	0.030
LDLPUFA	rs1172294	*DNAJC27*	2	25169200	8	+	0.09507	G/A,A	0.47	0.018
LDLPUFA	rs12916	*HMGCR*	5	74656539	12	+	7.79E-78	C/T,T	0.40	0.020
LDLPUFA	rs4246215	*FEN1*	11	61564299	5		4.47E-31	T/G,T	0.35	0.022
LDLPUFA	rs174545	*FADS1*	11	61569306	13	+	7.17E-21	G/C,C	0.34	0.029
LDLPUFA	rs174546	*FADS1*	11	61569830	8	+	1.63E-39	T/C,T	0.34	0.025
LDLPUFA	rs13465	*ILF3*	19	10802792	7		3.97E-30	A/G,A	0.05	0.008
LDLPUFA	rs1433099	*LDLR*	19	11242658	6	+	2.51E-16	T/C,T	0.27	0.009
LDLPUFA	rs7188	*KANK2*	19	11275139	8	+	9.39E-31	C/A,A	0.32	0.016
LDLPUFA	rs4804572	*KANK2*	19	11277074	9	+	NA	T/C,T	0.37	0.021
LDLPUFA	rs3810444	*SUGP2*	19	19103986	7		2.60E-12	A/T,A	0.07	0.009
LDLPUFA	rs6859	*NECTIN2*	19	45382034	5	+	4.65E-88	A/G,A	0.42	0.023

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 1 GC1 SNP β	Model 1 GC1 SNP SE	Model 1 GC1 Int β	Model 1 GC1 Int SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction SNP	Model 1 Direction Int
LDLMUFA	rs583609	*USP1*	0.1400	0.0447	-0.0074	0.0036	1.84E-06	3.50E-06	++--+++-?	--++-+-+?
LDLMUFA	rs17034539	*KIAA1324*	-0.0596	0.0437	0.0011	0.0035	0.000291	0.000406	--+---+-+	++--++-+-
LDLMUFA	rs629301	*CELSR2*	0.1746	0.0406	-0.0028	0.0034	9.58E-43	3.94E-41	+--++++++	-++----+-
LDLMUFA	rs12747251	*NSL1*	-0.0431	0.0407	0.0003	0.0032	0.000477	0.000647	----+-+-?	+-++---+?
LDLMUFA	rs1172294	*DNAJC27*	-0.0511	0.0346	0.0016	0.0028	0.001163	0.001554	++-++-+--	--+--+--+
LDLMUFA	rs10942729	*ANKRD31*	-0.0120	0.0431	0.0040	0.0034	0.000893	0.001197	++++----?	----++++?
LDLMUFA	rs12916	*HMGCR*	-0.0362	0.0352	-0.0033	0.0029	1.59E-16	7.52E-16	----++++-	++++----+
LDLMUFA	rs4246215	*FEN1*	-0.0034	0.0361	-0.0052	0.0030	2.16E-12	8.48E-12	--++-++-+	----+--+-
LDLMUFA	rs174545	*FADS1*	0.0248	0.0433	0.0040	0.0034	9.49E-12	2.09E-11	++--+--+?	++++-++-?
LDLMUFA	rs174546	*FADS1*	-0.0115	0.0363	-0.0048	0.0030	1.15E-13	4.14E-13	--++-++-+	----+--+-
LDLMUFA	rs13465	*ILF3*	-0.2330	0.0764	0.0103	0.0062	1.34E-08	2.73E-08	----++---	++++--+++
LDLMUFA	rs1433099	*LDLR*	-0.0588	0.0406	0.0008	0.0034	1.48E-05	2.36E-05	-------++	++-++++--
LDLMUFA	rs7188	*KANK2*	-0.1071	0.0424	0.0029	0.0036	9.27E-11	2.18E-10	?-+--++--	?-+++----
LDLMUFA	rs4804572	*KANK2*	0.1393	0.0549	-0.0071	0.0045	7.00E-05	9.99E-05	?++++--+?	?----++-?
LDLMUFA	rs3810444	*SUGP2*	-0.0331	0.0741	-0.0040	0.0061	0.000112	0.000155	-------++	+++++++--
LDLMUFA	rs6859	*NECTIN2*	0.1507	0.0363	-0.0071	0.0030	3.53E-13	1.04E-12	+++++++++	--+--+---
LDLPUFA	rs583609	*USP1*	0.0667	0.0284	-0.0030	0.0046	1.74E-05	2.54E-05	+-+-+++-?	++-+---+?
LDLPUFA	rs17034539	*KIAA1324*	-0.1187	0.0314	0.0128	0.0053	8.77E-06	1.34E-05	-+++-----	+---+++++
LDLPUFA	rs629301	*CELSR2*	0.1546	0.0285	-0.0025	0.0049	9.69E-42	3.31E-40	+-+++++++	-++-+--+-
LDLPUFA	rs12747251	*NSL1*	-0.0161	0.0272	-0.0041	0.0044	0.00027	0.000372	---++-+-?	-++----+?
LDLPUFA	rs2254487	*LGALS8, HEATR1*	0.0195	0.0294	-0.0099	0.0048	0.000277	0.000385	+---+--+?	-+++----?
LDLPUFA	rs1172294	*DNAJC27*	-0.0047	0.0252	-0.0049	0.0043	0.000832	0.001088	+++---+--	---+++---
LDLPUFA	rs12916	*HMGCR*	-0.1071	0.0247	0.0057	0.0042	1.51E-16	5.66E-16	---+-+++-	+-+-+---+
LDLPUFA	rs4246215	*FEN1*	-0.0404	0.0254	-0.0043	0.0043	8.24E-12	2.06E-11	--++-++--	++-----++
LDLPUFA	rs174545	*FADS1*	0.0511	0.0286	0.0038	0.0046	1.62E-11	3.95E-11	++--+--+?	--+++++-?
LDLPUFA	rs174546	*FADS1*	-0.0464	0.0253	-0.0040	0.0043	3.14E-13	1.02E-12	--++-++--	++-----+-
LDLPUFA	rs13465	*ILF3*	-0.0919	0.0538	-0.0031	0.0092	1.01E-07	1.88E-07	+-------	--+++-++-
LDLPUFA	rs1433099	*LDLR*	-0.0540	0.0293	0.0009	0.0050	1.52E-05	2.22E-05	-+-+---++	--+-+++--
LDLPUFA	rs7188	*KANK2*	-0.0862	0.0304	0.0023	0.0050	1.34E-10	3.01E-10	?++----+-	?-++++--+
LDLPUFA	rs4804572	*KANK2*	0.0430	0.0364	0.0021	0.0057	0.00025	0.000343	?--+++-+?	?++-+-++?
LDLPUFA	rs3810444	*SUGP2*	-0.0952	0.0531	0.0030	0.0092	0.000171	0.000231	+---+--+-	-+++-++--
LDLPUFA	rs6859	*NECTIN2*	0.1159	0.0260	-0.0088	0.0044	8.26E-13	2.77E-12	+++++++++	--+------

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 2 P value	Model 3 SNP β	Model 3 SNP SE	Model 3 Int β	Model 3 Int SE	Model 3 P value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het P value	N
LDLMUFA	rs583609	*USP1*	1.62E-06	0.1423	0.0441	-0.0077	0.0035	1.84E-06	++--+++-?	--++-+-+?	0.65	16009
LDLMUFA	rs17034539	*KIAA1324*	0.000105	-0.0441	0.0435	-0.0003	0.0035	0.000115	--+---+-+	++-+++-+-	0.21	21994
LDLMUFA	rs629301	*CELSR2*	3.82E-43	0.1774	0.0406	-0.0030	0.0034	1.20E-43	+--++++++	-++------	0.11	21994
LDLMUFA	rs12747251	*NSL1*	0.000399	-0.0465	0.0401	0.0007	0.0032	0.000622	----+-+-?	+-++---+?	0.80	16009
LDLMUFA	rs1172294	*DNAJC27*	0.006291	-0.0477	0.0344	0.0018	0.0028	0.007935	++-++-++-	--+--+--+	0.38	21994
LDLMUFA	rs10942729	*ANKRD31*	0.000366	-0.0151	0.0423	0.0044	0.0034	0.000314	++++----?	----++++?	0.38	16009
LDLMUFA	rs12916	*HMGCR*	2.70E-17	-0.0422	0.0346	-0.0028	0.0028	6.78E-17	----+++-	++++----+	0.05	21994
LDLMUFA	rs4246215	*FEN1*	9.35E-13	-0.0112	0.0352	-0.0046	0.0029	3.34E-13	-+++-++--	----+--+-	0.28	21994
LDLMUFA	rs174545	*FADS1*	2.78E-12	0.0352	0.0419	0.0033	0.0033	9.12E-13	+---+--+?	++++-++-?	0.32	16009
LDLMUFA	rs174546	*FADS1*	4.49E-14	-0.0202	0.0354	-0.0042	0.0029	1.35E-14	-+++-++-+	----+--+-	0.41	21994
LDLMUFA	rs13465	*ILF3*	4.84E-09	-0.2496	0.0764	0.0118	0.0062	9.37E-09	----++---	++++--+++	0.27	21993
LDLMUFA	rs1433099	*LDLR*	1.09E-05	-0.0629	0.0399	0.0012	0.0033	1.22E-05	-------++	++-++++--	0.72	21994
LDLMUFA	rs7188	*KANK2*	8.94E-13	-0.1053	0.0395	0.0027	0.0033	1.20E-12	-----++--	--+++----	0.62	15417
LDLMUFA	rs4804572	*KANK2*	1.25E-06	0.1373	0.0492	-0.0065	0.0040	1.28E-06	+++++--+?	-----++-?	0.67	9432
LDLMUFA	rs3810444	*SUGP2*	8.34E-05	-0.0258	0.0728	-0.0046	0.0060	7.78E-05	---+---++	+++-+++--	0.56	21994
LDLMUFA	rs6859	*NECTIN2*	8.15E-15	0.1593	0.0356	-0.0077	0.0029	2.15E-14	++-++++++	--+-+----	0.38	21994
LDLPUFA	rs583609	*USP1*	1.32E-05	0.0611	0.0285	-0.0021	0.0046	1.80E-05	+-+-+++-?	++-+---+?	0.69	16009
LDLPUFA	rs17034539	*KIAA1324*	3.54E-06	-0.1209	0.0320	0.0131	0.0054	4.68E-06	-+++-----	+---+++++	0.83	21995
LDLPUFA	rs629301	*CELSR2*	2.96E-42	0.1600	0.0285	-0.0035	0.0048	1.03E-42	+++++++++	-++-+----	0.63	21995
LDLPUFA	rs12747251	*NSL1*	0.000197	-0.0145	0.0268	-0.0042	0.0044	0.000323	------+-?	-++-----?	0.94	16009
LDLPUFA	rs2254487	*LGALS8, HEATR1*	0.000184	0.0212	0.0290	-0.0103	0.0048	0.000154	+---+--+?	-+++----?	0.94	16009
LDLPUFA	rs1172294	*DNAJC27*	0.004163	0.0033	0.0249	-0.0053	0.0042	0.004894	+++---++-	---+++---	0.39	21995
LDLPUFA	rs12916	*HMGCR*	2.98E-17	-0.1024	0.0246	0.0049	0.0042	6.53E-17	-+-+-+++-	+-+-+---+	0.02	21995
LDLPUFA	rs4246215	*FEN1*	2.70E-12	-0.0502	0.0253	-0.0028	0.0043	1.01E-12	--++-++--	++-----++	0.17	21995
LDLPUFA	rs174545	*FADS1*	3.59E-12	0.0633	0.0283	0.0021	0.0046	1.11E-12	++--+--+?	--+++++-?	0.22	16009
LDLPUFA	rs174546	*FADS1*	8.78E-14	-0.0576	0.0252	-0.0023	0.0043	2.68E-14	--++-++--	++-----++	0.28	21995
LDLPUFA	rs13465	*ILF3*	9.98E-08	-0.0843	0.0532	-0.0040	0.0091	1.51E-07	+-------	--+++-++-	0.21	21994
LDLPUFA	rs1433099	*LDLR*	9.87E-06	-0.0527	0.0290	0.0007	0.0050	1.07E-05	-+-+---++	--+-+++--	0.50	21995
LDLPUFA	rs7188	*KANK2*	1.01E-12	-0.0769	0.0287	0.0005	0.0049	1.44E-12	-++------	--++++--+	0.49	15418
LDLPUFA	rs4804572	*KANK2*	3.36E-06	0.0523	0.0328	0.0013	0.0053	4.44E-06	+--+++-+?	-++---++?	0.63	9432
LDLPUFA	rs3810444	*SUGP2*	0.000152	-0.0900	0.0522	0.0022	0.0090	0.000135	+---+--+-	-+++-++-+	0.39	21995
LDLPUFA	rs6859	*NECTIN2*	3.04E-14	0.1194	0.0257	-0.0091	0.0044	7.95E-14	++-++++++	--+------	0.66	21995

Supplemental Table 2.1.6. Blood lipids associated miRNA-related SNPs using 2 degrees of freedom joint meta-analysis

(B) Dietary interaction analysis of CHARGE top miRNA-related SNPs associated with blood lipids: MiRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1.25 \times 10^{-3}$ (selected from CHARGE miRNA GWAS $P < 2 \times 10^{-4}$) (LDLMUFA, LDLPUFA, continued)

Phen-Diet	SNP	Gene	CHARGE GWAS Model 1 GC1 SNP β	Model 1 GC1 SE	Model 1 GC1 P value	Model 1 GC2 P value	Model 1 Direction	Model 3 SNP β	Model 3 SE	Model 3 P value	Model 3 Direction	Model 3_I^2	Model 3 Het P value
LDLMUFA	rs583609	*USP1*	0.0393	0.0090	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.074E-07	+++-++++?	0	0.47
LDLMUFA	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.0110	0.00002173	------+--	0	0.59
LDLMUFA	rs629301	*CELSR2*	0.1445	0.0100	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.268E-47	+++++++++	28	0.20
LDLMUFA	rs12747251	*NSL1*	-0.0320	0.0085	0.000163	0.000212	--------?	-0.0368	0.0093	0.00008368	-------+-?	0	0.78
LDLMUFA	rs1172294	*DNAJC27*	-0.0294	0.0076	0.000117	0.000141	--++-+---	-0.0233	0.0083	0.004828	--++-+---	29.7	0.18
LDLMUFA	rs10942729	*ANKRD31*	0.0390	0.0099	8.42E-05	0.000106	++-+++++?	0.0390	0.0097	0.00005802	++-+++++?	0	0.78
LDLMUFA	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.077E-17	--+------	58	0.01
LDLMUFA	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	---------	-0.0623	0.0086	4.403E-13	---------	0	0.54
LDLMUFA	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLMUFA	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	---------	-0.0660	0.0086	1.404E-14	---------	0	0.76
LDLMUFA	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	---------	-0.1073	0.0188	1.071E-08	----+----	38.1	0.11
LDLMUFA	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	---------	-0.0468	0.0098	0.000001801	---------	0	0.64
LDLMUFA	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?--------	-0.0719	0.0096	8.282E-14	---------	0	0.51
LDLMUFA	rs4804572	*KANK2*	0.0496	0.0118	2.44E-05	3.53E-05	?+++++++?	0.0591	0.0115	2.493E-07	++++++++?	0	0.85
LDLMUFA	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	0.00001067	------+--	12.9	0.33
LDLMUFA	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-++++++	0.0691	0.0088	5.788E-15	+-++++++	28.1	0.19
LDLPUFA	rs583609	*USP1*	0.0393	0.0090	1.23E-05	1.73E-05	+-+-++++?	0.0528	0.0099	1.074E-07	+++-++++?	0	0.47
LDLPUFA	rs17034539	*KIAA1324*	-0.0463	0.0112	3.31E-05	4.74E-05	------+--	-0.0465	0.0110	0.00002173	------+--	0	0.59
LDLPUFA	rs629301	*CELSR2*	0.1445	0.0100	8.46E-48	6.87E-46	+++++++++	0.1396	0.0097	7.268E-47	+++++++++	28	0.20
LDLPUFA	rs12747251	*NSL1*	-0.0320	0.0085	0.000163	0.000212	--------?	-0.0368	0.0093	0.00008368	-------+-?	0	0.78
LDLPUFA	rs2254487	*LGALS8, HEATR1*	-0.0358	0.0090	7.08E-05	9.06E-05	--------?	-0.0354	0.0099	0.0003505	--------?	0	0.87
LDLPUFA	rs1172294	*DNAJC27*	-0.0294	0.0076	0.000117	0.000141	--++-+---	-0.0233	0.0083	0.004828	--++-+---	29.7	0.18
LDLPUFA	rs12916	*HMGCR*	-0.0671	0.0078	1.01E-17	2.55E-17	--+------	-0.0711	0.0084	3.077E-17	--+------	58	0.01
LDLPUFA	rs4246215	*FEN1*	-0.0586	0.0087	2.11E-11	3.39E-11	---------	-0.0623	0.0086	4.403E-13	---------	0	0.54
LDLPUFA	rs174545	*FADS1*	0.0473	0.0088	8.71E-08	1.23E-07	++++++++?	0.0702	0.0098	8.48E-13	++++++++?	0	0.77
LDLPUFA	rs174546	*FADS1*	-0.0481	0.0079	1.15E-09	2.08E-09	---------	-0.0660	0.0086	1.404E-14	---------	0	0.76
LDLPUFA	rs13465	*ILF3*	-0.1073	0.0192	2.14E-08	3.81E-08	---------	-0.1073	0.0188	1.071E-08	----+----	38.1	0.11
LDLPUFA	rs1433099	*LDLR*	-0.0457	0.0091	5.95E-07	7.73E-07	---------	-0.0468	0.0098	0.000001801	---------	0	0.64
LDLPUFA	rs7188	*KANK2*	-0.0641	0.0098	6.46E-11	1.22E-10	?--------	-0.0719	0.0096	8.282E-14	---------	0	0.51
LDLPUFA	rs4804572	*KANK2*	0.0496	0.0118	2.44E-05	3.53E-05	?+++++++?	0.0591	0.0115	2.493E-07	++++++++?	0	0.85
LDLPUFA	rs3810444	*SUGP2*	-0.0798	0.0183	1.32E-05	1.78E-05	------++-	-0.0789	0.0179	0.00001067	------+--	12.9	0.33
LDLPUFA	rs6859	*NECTIN2*	0.0552	0.0084	6.14E-11	1.00E-10	+-++++++	0.0691	0.0088	5.788E-15	+-++++++	28.1	0.19

Abbreviations: Phen, phenotype; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; 2DF, 2 degrees of freedom; JMA, joint meta-analysis; GC1, single genomic control correction; GC2, double genomic control correction; Int, interaction term; β, beta coefficient; SE, standard error; I^2, heterogeneity index; Het, heterogeneity test statistic; miR, miRNA; eQTL, expression quantitative trait loci.

Additive allele mode. Basic interaction analyses (Model 1) adjusted for age, sex, total energy intake and study-specific covariates (e.g., family relationship, study site, population stratification by principal components, when applicable). Model 2 adjusted for Model 1 covariates and body mass index; and Model 3 adjusted for Model 2 covariates and diabetes mellitus status [as dichotomous variable]. Beta coefficients for SNP effect and interaction between SNP and macronutrient are shown as SNP β (SE) and Int β (SE), respectively. Int β represents the change in ln-TG, HDL-C or LDL-C (mmol/L) with each additional percentage energy of CHO, SFA, MUFA or PUFA intake, per each additional copy of the effect allele. Study order in direction: ARIC, GOLDN, GOYA, InCHIANTI, RSI/II/III, YFS and Inter99.

[1]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicates the number of the data sources.

[2]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.

Supplemental Table 2.1.7. Full list of potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis)

Phen-Diet	SNP	Gene	Chr	Position_hg19	miR score	eQTL[1]	Gene Exp Lipid Meta P value	Global Lipid GWAS P value	Alleles (minor/major,effect)	MAF[2] (SE)
TGCHO	rs7131691	*SRGAP1*	12	64540960	5	+	>0.050	0.9715	A/G,A	0.46(0.020)
TGCHO	rs944450	*DDHD1*	14	53503668	6	++	NA	0.5394	T/C,T	0.14(0.020)
TGCHO	rs10151030	*DDHD1*	14	53506409	4	++	NA	0.2885	T/C,T	0.16(0.023)
TGCHO	rs11844798	*DDHD1*	14	53507522	5	++	NA	0.75	C/T,T	0.16(0.020)
TGCHO	rs10142309	*DDHD1*	14	53507634	5	+	NA	0.5931	C/G,C	0.16(0.020)
TGCHO	rs10009	*PPIL2*	22	22051709	9	++	NA	0.9307	G/A,A	0.41(0.032)
TGCHO	rs1860	*YPEL1*	22	22055394	6		>0.050	0.9969	A/G,A	0.39(0.031)
TGSFA	rs9854618	*MASP1*	3	186936778	6		>0.050	0.537	T/C,T	0.02(0.004)
TGSFA	rs845725	*MCTP1, SLF1*	5	94040908	3	+++	0.006093837 (ANKRD32)	0.3051	G/C,C	0.27(0.033)
TGMUFA	rs12421673	*ANO3*	11	26684012	12		>0.050	0.5416	A/C,A	0.03(0.005)
TGMUFA	rs972	*ANO3*	11	26684763	7		>0.050	0.2903	T/C,T	0.03(0.006)
TGMUFA	rs17243615	*SLC5A12*	11	26689017	10		>0.050	0.4665	T/C,T	0.03(0.006)
TGPUFA	rs11934922	*TMEM33*	4	41957431	4		1.42E-06	0.8339	G/A,A	0.02(0.002)
TGPUFA	rs42377	*CDK6*	7	41957431	8	+	3.27E-11	NA	A/G,A	0.32(0.016)
TGPUFA	rs12585558	*ABHD13*	13	108886022	6		NA	NA	A/G,A	0.01(0.001)
TGPUFA	rs6566883	*ONECUT2*	18	41957431	8		>0.050	NA	G/A,A	0.02(0.019)
TGPUFA	rs17831587	*ONECUT2*	18	55147888	8		>0.050	0.7063	C/A,A	0.02(0.018)
TGPUFA	rs10503013	*ONECUT2*	18	55148861	10		>0.050	0.5855	T/A,A	0.02(0.018)
HDLCHO	rs16848494	*LAD1*	1	41957431	9		>0.050	NA	T/C,T	0.03(0.003)
HDLCHO	rs17363829	*OTULIN*	5	41957431	9		>0.050	0.8567	T/C,T	0.05(0.009)
HDLSFA	rs6436677	*COL4A3, LOC654841 (ncRNA)*	2	41957431	8		>0.050	0.9835	T/C,T	0.01(0.005)
HDLSFA	rs3011621	*MTUS2*	13	41957431	3		>0.050	0.3536	C/T,T	0.02(0.004)
HDLSFA	rs17226781	*PROSER1*	13	41957431	15		>0.050	NA	G/C,C	0.02(0.004)
HDLSFA	rs9717	*LSS*	21	41957431	10	+++	>0.050	NA	T/C,T	0.34(0.016)
HDLMUFA	rs5743372	*NOD1*	7	41957431	6		>0.050	0.1311	A/G,A	0.06(0.025)
HDLMUFA	rs301027	*METAP2*	12	41957431	5		>0.050	0.6327	A/G,A	0.12(0.017)
HDLMUFA	rs301026	*METAP2*	12	41957431	6	+	>0.050	0.6283	A/G,A	0.12(0.017)
HDLMUFA	rs9926366	*C16orf46*	16	41957431	7		>0.050	0.249	A/G,A	0.07(0.012)
HDLMUFA	rs2242437	*ABCA7*	19	41957431	8	+	2.80E-06	0.3281	G/C,C	0.25(0.010)
HDLMUFA	rs9717	*LSS*	21	41957431	10	+++	>0.050	NA	T/C,T	0.34(0.017)
HDLPUFA	rs6024853	*CSTF1*	20	41957431	10		0.03119243	0.4352	A/G,A	0.01(0.001)
LDLCHO	rs3732975	*LHFPL4*	3	41957431	5		>0.050	0.5243	T/C,T	0.18(0.016)
LDLCHO	rs10888	*CNTN4, CNTN4-AS1 (ncRNA)*	3	41957431	9		NA	0.5676	A/T,A	0.40(0.006)
LDLCHO	rs10488193	*TMEM106B*	7	41957431	7	+	>0.050	0.4686	G/A,A	0.10(0.005)
LDLCHO	rs13111	*KIF3B*	20	41957431	6		>0.050	0.5376	A/G,A	0.15(0.009)
LDLCHO	rs1056776	*PLAGL2*	20	41957431	7		>0.050	0.9091	G/C,C	0.15(0.008)
LDLSFA	rs6838203	*FGF5*	4	41957431	12		>0.050	0.9965	A/T,A	0.30(0.015)
LDLSFA	rs336969	*HAPLN1*	5	41957431	8		>0.050	NA	T/C,T	0.01(0.006)
LDLSFA	rs3739283	*ANXA13*	8	41957431	6	+	0.00786073	0.9606	C/T,T	0.29(0.026)
LDLSFA	rs7812	*DERL1*	8	41957431	5	++	>0.050	0.9424	T/C,T	0.11(0.008)
LDLSFA	rs11051966	*BICD1*	12	41957431	3		>0.050	0.9456	A/G,A	0.11(0.011)
LDLSFA	rs13861	*ATMIN*	16	41957431	9		>0.050	0.2467	A/G,A	0.03(0.021)
LDLSFA	rs16967028	*UTP6*	17	41957431	9		>0.050	0.5205	G/A,A	0.03(0.014)
LDLPUFA	rs1567487	*SPEG*	2	41957431	10		NA	NA	T/C,T	0.48(0.016)
LDLPUFA	rs9213	*SH3YL1*	2	41957431	7	+	NA	0.3952	A/G,A	0.36(0.013)
LDLPUFA	rs6710091	*SH3YL1*	2	41957431	3	+	NA	0.4292	G/C,C	0.36(0.013)
LDLPUFA	rs7031344	*TMEM2*	9	41957431	5		0.04154654	0.8848	C/A,A	0.02(0.003)
LDLPUFA	rs7202	*NUMB*	14	41957431	9	++	NA	0.6992	A/G,A	0.29(0.015)

Supplemental Table 2.1.7. Full list of potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis) (continued)

Phen-Diet	SNP	Gene	CHARGE 1DF GWIS Model 1 GC1 Int β (SE)	Model 1 GC1 *P* value	Model 1GC2 *P* value	Model 2 *P* value	Model 3 *P* value	Model 3 Direction	Model 3 I^2 (%)	Model 3 Het *P* value	N
TGCHO	rs7131691	*SRGAP1*	0.003(0.001)	9.44E-05	2.68E-04	0.000355	0.000462	++-++-++?	38	0.13	15939
TGCHO	rs944450	*DDHD1*	0.004(0.001)	5.54E-06	7.85E-06	3.81E-05	4.27E-05	++++-++-?	59.3	0.02	15939
TGCHO	rs10151030	*DDHD1*	0.004(0.001)	3.41E-06	7.85E-06	1.54E-05	1.82E-05	++++-++-?	51.6	0.04	15939
TGCHO	rs11844798	*DDHD1*	-0.004(0.001)	4.32E-05	1.77E-05	0.000151	0.000162	----+--+?	63.1	0.01	15939
TGCHO	rs10142309	*DDHD1*	0.004(0.001)	4.28E-05	1.77E-05	0.000149	0.000159	++++-++-?	63.1	0.01	15939
TGCHO	rs10009	*PPIL2*	-0.003(0.001)	1.22E-05	4.81E-05	4.34E-06	3.35E-06	--------?	0	0.85	15939
TGCHO	rs1860	*YPEL1*	0.003(0.001)	8.96E-05	2.68E-04	3.45E-05	3.49E-05	++++++++?	0	0.84	15938
TGSFA	rs9854618	*MASP1*	0.024(0.006)	1.58E-05	2.19E-05	0.001105	0.001938	+-?--++++	0	0.46	21599
TGSFA	rs845725	*MCTP1, SLF1*	-0.008(0.002)	9.87E-05	1.40E-04	0.002101	0.002057	-------+?	0	0.46	15939
TGMUFA	rs12421673	*ANO3*	-0.022(0.005)	1.50E-05	1.94E-05	0.001697	0.001716	----+---?	50	0.05	15939
TGMUFA	rs972	*ANO3*	-0.022(0.005)	1.14E-05	1.63E-05	0.001342	0.001367	----+---?	49.6	0.05	15939
TGMUFA	rs17243615	*SLC5A12*	-0.022(0.005)	1.17E-05	1.63E-05	0.001376	0.001402	----+---?	49.7	0.05	15939
TGPUFA	rs11934922	*TMEM33*	0.037(0.009)	5.45E-05	6.65E-05	7.13E-05	3.93E-05	+++++++-?	22.9	0.25	15939
TGPUFA	rs42377	*CDK6*	-0.011(0.003)	8.39E-05	1.27E-04	0.000227	0.000422	-++-----?	0	0.54	15939
TGPUFA	rs12585558	*ABHD13*	0.040(0.009)	1.82E-05	2.41E-05	1.10E-05	1.57E-05	-??-+++-?	0	0.45	15020
TGPUFA	rs6566883	*ONECUT2*	-0.052(0.013)	7.57E-05	1.03E-04	5.09E-05	4.37E-05	--??-?--?	54.8	0.07	13320
TGPUFA	rs17831587	*ONECUT2*	-0.052(0.013)	5.17E-05	7.11E-05	3.55E-05	2.89E-05	--??-?--?	48.4	0.10	13320
TGPUFA	rs10503013	*ONECUT2*	-0.052(0.013)	5.25E-05	7.11E-05	3.62E-05	2.96E-05	--??-?--?	48	0.10	13320
HDLCHO	rs16848494	*LAD1*	-0.009(0.002)	6.52E-05	6.33E-05	0.003285	0.004898	??-+----?	0	0.44	7494
HDLCHO	rs17363829	*OTULIN*	0.005(0.001)	5.10E-05	2.89E-05	9.15E-05	0.00013	+-++++++?	40.4	0.11	15988
HDLSFA	rs6436677	*COL4A3, LOC654841 (ncRNA)*	-0.026(0.006)	6.55E-05	8.57E-05	0.000251	0.000347	-+?-----?	0	0.59	15657
HDLSFA	rs3011621	*MTUS2*	0.023(0.006)	5.05E-05	6.44E-05	0.09923	0.1145	+-?--+++?	48.9	0.07	12982
HDLSFA	rs17226781	*PROSER1*	-0.031(0.008)	5.77E-05	6.85E-05	0.000168	0.000204	---?-+--?	50.9	0.06	14863
HDLSFA	rs9717	*LSS*	-0.006(0.002)	7.45E-05	8.04E-05	0.001383	0.001281	--------?	0	0.96	15988
HDLMUFA	rs5743372	*NOD1*	-0.014(0.004)	7.95E-05	1.26E-04	0.004249	0.004892	-++-----?	14.1	0.32	15988
HDLMUFA	rs301027	*METAP2*	0.010(0.002)	1.68E-05	2.79E-05	0.0014	0.001609	+++++--+?	53	0.04	15988
HDLMUFA	rs301026	*METAP2*	0.010(0.002)	1.71E-05	2.79E-05	0.001374	0.001578	+++++--+?	52.9	0.04	15988
HDLMUFA	rs9926366	*C16orf46*	-0.013(0.003)	2.72E-05	3.57E-05	0.01931	0.02286	-+++----?	75.4	0.0002	15987
HDLMUFA	rs2242437	*ABCA7*	-0.010(0.002)	3.27E-05	3.35E-05	0.1708	0.2508	+-++----?	50.7	0.05	15988
HDLMUFA	rs9717	*LSS*	-0.006(0.002)	8.90E-05	1.34E-04	0.09254	0.1023	---+----?	16.1	0.30	15988
HDLPUFA	rs6024853	*CSTF1*	-0.065(0.015)	9.13E-06	1.15E-05	0.000152	0.000133	---+---+?	57.8	0.02	9378
LDLCHO	rs3732975	*LHFPL4*	0.007(0.002)	1.67E-05	3.05E-05	1.21E-05	1.32E-05	+++-++++?	27.4	0.21	15844
LDLCHO	rs10888	*CNTN4, CNTN4-AS1 (ncRNA)*	-0.006(0.002)	7.76E-05	8.70E-05	8.67E-05	6.23E-05	--+---++?	0	0.46	15844
LDLCHO	rs10488193	*TMEM106B*	0.008(0.002)	4.16E-05	5.76E-05	6.61E-06	8.99E-06	++++++++?	15.1	0.31	15844
LDLCHO	rs13111	*KIF3B*	-0.007(0.002)	8.07E-05	8.70E-05	6.07E-05	5.62E-05	--------?	2.2	0.41	15844
LDLCHO	rs1056776	*PLAGL2*	0.007(0.002)	9.23E-05	1.10E-04	9.73E-05	9.29E-05	+-+-++++?	8.7	0.36	15844
LDLSFA	rs6838203	*FGF5*	-0.040(0.010)	4.51E-05	5.48E-05	0.0055	0.004085	+-+?--?-?	72.8	0.002	13151
LDLSFA	rs336969	*HAPLN1*	0.076(0.019)	4.69E-05	5.40E-05	0.000247	0.000297	+??+++-+?	43.7	0.11	14754
LDLSFA	rs3739283	*ANXA13*	0.016(0.004)	8.47E-05	1.16E-04	2.19E-05	4.09E-05	++++++++?	22.2	0.25	15844
LDLSFA	rs7812	*DERL1*	-0.022(0.006)	9.32E-05	9.48E-05	3.08E-05	4.13E-05	-+---+--?	27.7	0.21	15844
LDLSFA	rs11051966	*BICD1*	0.023(0.006)	8.35E-05	8.16E-05	1.13E-05	5.83E-06	++++++++?	0	0.92	15844
LDLSFA	rs13861	*ATMIN*	0.053(0.012)	1.73E-05	1.96E-05	1.55E-05	3.46E-05	++?-++++?	0	0.66	15513
LDLSFA	rs16967028	*UTP6*	-0.040(0.010)	3.69E-05	4.18E-05	3.74E-05	1.89E-05	---+----?	0	0.51	15844
LDLPUFA	rs1567487	*SPEG*	-0.023(0.005)	9.99E-06	1.37E-05	9.51E-06	9.46E-06	--------?	31.3	0.18	15844
LDLPUFA	rs9213	*SH3YL1*	-0.022(0.005)	3.12E-05	3.37E-05	8.25E-05	8.78E-05	--------?	28.1	0.20	15844
LDLPUFA	rs6710091	*SH3YL1*	0.021(0.005)	4.26E-05	5.51E-05	0.000116	0.000122	+++-++++?	35.9	0.14	15844
LDLPUFA	rs7031344	*TMEM2*	0.055(0.014)	5.53E-05	6.51E-05	1.55E-05	2.46E-05	+++-+-++?	0	0.56	15844
LDLPUFA	rs7202	*NUMB*	0.021(0.005)	9.18E-05	1.11E-04	0.000162	0.000148	++-+++++?	0	0.66	15844

Supplemental Table 2.1.7. Full list of potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis) (continued)

Phen-Diet	SNP	Gene	CHARGE 2DF GWIS Model 3 SNP β (SE)	Model 3 Int β (SE)	Model 3 *P* value	Model 3 Direction SNP	Model 3 Direction Int	Model 3 Het *P* value	CHARGE GWAS Model 3 SNP β (SE)	Model 3 *P* value	Model 3 Direction SNP	Model 3 I^2 (%)	Model 3 Het *P* value
TGCHO	rs7131691	*SRGAP1*	-0.096(0.029)	0.002(0.0006)	0.003354	--+--+--?	++-++-++?	0.38	-0.001(0.005)	0.8069	--+---++?	0	0.90
TGCHO	rs944450	*DDHD1*	-0.152(0.039)	0.0031(0.0008)	0.000542	----+--+?	++++-++-?	<0.01	-0.004(0.007)	0.5362	-++---++?	60.8	0.01
TGCHO	rs10151030	*DDHD1*	-0.161(0.038)	0.0033(0.0008)	9.06E-05	----+--+?	++++-++-?	<0.01	-0.005(0.006)	0.4749	-+----++?	60.6	0.01
TGCHO	rs11844798	*DDHD1*	0.132(0.037)	-0.0027(0.0008)	0.001775	++++-++-?	----+--+?	<0.01	0.003(0.006)	0.6525	+--+++--?	65.6	<0.01
TGCHO	rs10142309	*DDHD1*	-0.132(0.037)	0.0027(0.0008)	0.00175	----+--+?	++++-++-?	<0.01	-0.003(0.006)	0.6539	-++---++?	65.7	<0.01
TGCHO	rs10009	*PPIL2*	0.116(0.029)	-0.0025(0.0006)	0.000131	++++++++?	--------?	0.33	-0.002(0.005)	0.7229	+++---++?	20	0.27
TGCHO	rs1860	*YPEL1*	-0.104(0.029)	0.0022(0.0006)	0.001007	--------?	++++++++?	0.40	0.001(0.005)	0.8967	-+-+++--?	22.3	0.25
TGSFA	rs9854618	*MASP1*	-0.141(0.065)	0.0122(0.0052)	0.05776	-+?++----	+-?--++++	0.05	0.002(0.016)	0.9019	-+?++-+-+	60.9	0.01
TGSFA	rs845725	*MCTP1, SLF1*	0.061(0.023)	-0.0046(0.0018)	0.02861	+++++++-?	-------+?	0.56	0.001(0.005)	0.878	++--+-++?	0	0.99
TGMUFA	rs12421673	*ANO3*	0.131(0.057)	-0.0093(0.0045)	0.06275	++++-+++?	----+---?	<0.01	0.016(0.014)	0.2585	++-+--++?	25.6	0.22
TGMUFA	rs972	*ANO3*	0.134(0.057)	-0.0096(0.0045)	0.05317	++++-+++?	----+---?	<0.01	0.016(0.014)	0.2547	++-+--++?	25.4	0.23
TGMUFA	rs17243615	*SLC5A12*	0.134(0.057)	-0.0096(0.0045)	0.05379	++++-+++?	----+---?	<0.01	0.016(0.014)	0.2521	++-+--++?	25.7	0.22
TGPUFA	rs11934922	*TMEM33*	-0.204(0.05)	0.0351(0.008)	6.98E-05	-------+?	+++++++-?	0.58	-0.003(0.018)	0.8872	+---+++-?	0	0.67
TGPUFA	rs42377	*CDK6*	0.039(0.015)	-0.0072(0.0025)	0.01288	+--+++++?	-++-----?	0.34	-0.002(0.005)	0.6393	--+++-+-?	22	0.25
TGPUFA	rs12585558	*ABHD13*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
TGPUFA	rs6566883	*ONECUT2*	0.233(0.061)	-0.0448(0.0108)	0.000153	++??+?++?	--??-?--?	0.08	-0.013(0.02)	0.5289	-+?---++?	0	0.71
TGPUFA	rs17831587	*ONECUT2*	0.237(0.061)	-0.0451(0.0106)	0.000115	++??+?++?	--??-?--?	0.11	-0.011(0.02)	0.5824	-+?---++?	0	0.75
TGPUFA	rs10503013	*ONECUT2*	0.236(0.061)	-0.045(0.0106)	0.000121	++??+?++?	--??-?--?	0.11	-0.011(0.02)	0.5836	-+?---++?	0	0.75
HDLCHO	rs16848494	*LAD1*	0.24(0.111)	-0.0049(0.0024)	0.08836	??+?++++?	??-?----?	0.15	-0.003(0.017)	0.8469	??--+-+-?	0	0.51
HDLCHO	rs17363829	*OTULIN*	-0.194(0.051)	0.0039(0.0011)	0.000609	-+------?	+-++++++?	0.18	-0.007(0.009)	0.417	---+++--?	0	0.66
HDLSFA	rs6436677	*COL4A3, LOC654841 (ncRNA)*	0.336(0.077)	-0.0266(0.0061)	6.65E-05	+-?+++++?	-+?-----?	0.61	0.008(0.017)	0.6146	+--+-+-+?	26.6	0.22
HDLSFA	rs3011621	*MTUS2*	-0.052(0.075)	0.0055(0.0058)	0.4277	-+?++?-??	+-?--?+??	0.17	0.018(0.017)	0.3003	-+++++++?	0	0.83
HDLSFA	rs17226781	*PROSER1*	0.191(0.083)	-0.0179(0.0065)	0.00669	+++?+-++?	---?-+--?	<0.01	-0.032(0.02)	0.1136	+--?+--+?	42	0.11
HDLSFA	rs9717	*LSS*	0.046(0.017)	-0.0039(0.0013)	0.01533	++++++++?	--------?	0.64	0.003(0.004)	0.3858	+-++++--?	28.6	0.20
HDLMUFA	rs5743372	*NOD1*	0.016(0.014)	-0.0006(0.0008)	0.5028	+--+++++?	-++-----?	0.12	0.008(0.008)	0.3364	+--+++++?	0	0.65
HDLMUFA	rs301027	*METAP2*	-0.022(0.012)	0.0015(0.0008)	0.1512	-----++-?	+++++--+?	0.02	-0.001(0.006)	0.8929	-+-+-++-?	45.6	0.08
HDLMUFA	rs301026	*METAP2*	-0.022(0.012)	0.0015(0.0008)	0.1464	-----++-?	+++++--+?	0.02	-0.001(0.006)	0.8931	-+-+-++-?	45.7	0.07
HDLMUFA	rs9926366	*C16orf46*	0.02(0.014)	-0.0007(0.0007)	0.3586	+---++++?	-+++----?	<0.01	0.011(0.008)	0.1759	+++--++-?	0	0.83
HDLMUFA	rs2242437	*ABCA7*	0.009(0.009)	-0.0006(0.0004)	0.4309	-+--++++?	+-++----?	0.14	0.001(0.005)	0.8316	+------+?	0	0.46
HDLMUFA	rs9717	*LSS*	-0.003(0.007)	0.0001(0.0004)	0.9225	+++-++++?	---+----?	0.23	0.003(0.004)	0.3858	+-++++--?	28.6	0.20
HDLPUFA	rs6024853	*CSTF1*	0.15(0.071)	-0.0243(0.0108)	0.07925	?++-+++-?	?--+---+?	<0.01	0.029(0.025)	0.2395	+?-+++--?	0	0.51
LDLCHO	rs3732975	*LHFPL4*	-0.306(0.073)	0.0063(0.0015)	0.000151	---+----?	+++-++++?	0.34	-0.0001(0.013)	0.9927	-+---+++?	0	0.47
LDLCHO	rs10888	*CNTN4, CNTN4-AS1 (ncRNA)*	0.28(0.069)	-0.0056(0.0014)	0.000227	++-+++--?	--+---++?	0.59	0.015(0.012)	0.1993	+--++--+?	0	0.86
LDLCHO	rs10488193	*TMEM106B*	-0.386(0.093)	0.0086(0.0019)	2.25E-05	---+----?	++++++++?	0.75	0.021(0.016)	0.1909	++-+++-+?	0	0.98
LDLCHO	rs13111	*KIF3B*	0.308(0.083)	-0.0062(0.0017)	0.000917	++++++++?	--------?	0.10	0.017(0.014)	0.2304	+--+++++?	5	0.39
LDLCHO	rs1056776	*PLAGL2*	-0.286(0.077)	0.0057(0.0016)	0.000927	-+------?	+-+-++++?	0.21	-0.022(0.013)	0.09219	--+-----?	0	0.52
LDLSFA	rs6838203	*FGF5*	0.3(0.085)	-0.0223(0.0065)	0.002062	-+-?++?+?	+-+?--?-?	0.02	0.018(0.02)	0.3593	+++?--?+?	0	0.63
LDLSFA	rs336969	*HAPLN1*	-0.847(0.207)	0.0654(0.0171)	0.000215	-??---+-?	+??+++-+?	0.33	-0.044(0.051)	0.39	+??-++--?	0	0.63
LDLSFA	rs3739283	*ANXA13*	-0.135(0.048)	0.0112(0.0037)	0.01113	-+------?	++++++++?	0.04	0.006(0.011)	0.6121	-+-+--++?	3.4	0.40
LDLSFA	rs7812	*DERL1*	0.251(0.066)	-0.0181(0.0051)	0.000489	+-+++-++?	-+---+--?	0.09	0.025(0.015)	0.09827	++++++--?	29.9	0.19
LDLSFA	rs11051966	*BICD1*	-0.251(0.064)	0.0215(0.0052)	0.000128	--------?	++++++++?	0.92	0.001(0.015)	0.9335	++++----?	0	0.92
LDLSFA	rs13861	*ATMIN*	-0.49(0.147)	0.0418(0.0121)	0.002418	--?+----?	++?-++++?	0.21	-0.013(0.032)	0.6894	-+-++--+?	66	0.00
LDLSFA	rs16967028	*UTP6*	0.441(0.11)	-0.0367(0.0088)	0.000174	+++-++++?	---+----?	0.43	-0.012(0.027)	0.6684	-++---++?	0	0.55
LDLPUFA	rs1567487	*SPEG*	0.116(0.028)	-0.0188(0.0046)	0.000177	++++++++?	--------?	0.22	0.001(0.01)	0.9607	++++--++?	28	0.20
LDLPUFA	rs9213	*SH3YL1*	0.098(0.028)	-0.0154(0.0046)	0.002465	++++++++?	--------?	0.27	0.009(0.01)	0.3454	+++-+-++?	0	0.98
LDLPUFA	rs6710091	*SH3YL1*	-0.093(0.028)	0.0151(0.0046)	0.003576	---+----?	+++-++++?	0.22	-0.007(0.01)	0.4674	+--+----?	0	0.98
LDLPUFA	rs7031344	*TMEM2*	-0.217(0.082)	0.0438(0.0125)	0.001027	---+-+--?	+++-+-++?	0.50	0.066(0.035)	0.05851	++++++++?	0	0.97
LDLPUFA	rs7202	*NUMB*	-0.081(0.029)	0.0141(0.0048)	0.01299	--+-----?	++-+++++?	0.03	-0.001(0.01)	0.8919	+++----+?	52.2	0.04

Supplemental Table 2.1.7. Full list of potential miRNA-related SNPs interacted with dietary macronutrients on blood lipids at $P < 1 \times 10^{-4}$ (1 degree of freedom interaction term meta-analysis) (continued)

Abbreviations: Phen, phenotype; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; 1DF, 1 degree of freedom; GC1, single genomic control correction; GC2, double genomic control correction; Int, interaction term; β, beta coefficient; SE, standard error; I^2, heterogeneity index; Het, heterogeneity test statistic; miR, miRNA; eQTL, expression quantitative trait loci; Exp, expression.

Additive allele mode. Basic interaction analyses (Model 1) adjusted for age, sex, total energy intake and study-specific covariates (e.g., family relationship, study site, population stratification by principal components, when applicable). Model 2 adjusted for Model 1 covariates and body mass index; and Model 3 adjusted for Model 2 covariates and diabetes mellitus status [as dichotomous variable]. Beta coefficients for interaction between SNP and macronutrient are shown as Int β (SE). Int β represents the change in ln-TG, HDL-C or LDL-C (mmol/L) with each additional percentage energy of CHO, SFA, MUFA or PUFA intake, per each additional copy of the effect allele. Study order in direction: ARIC, GOLDN, GOYA, InCHIANTI, RSI/II/III, YFS and Inter99.
[1]Cis effects of miRNA SNPs on host gene expression. The number of plus signs indicate the number of the data sources.
[2]Weighted average coded allele frequency across the 9 studies. The coded allele refers to the effect allele.

Supplemental Table 2.1.8. CHARGE authors and affiliations

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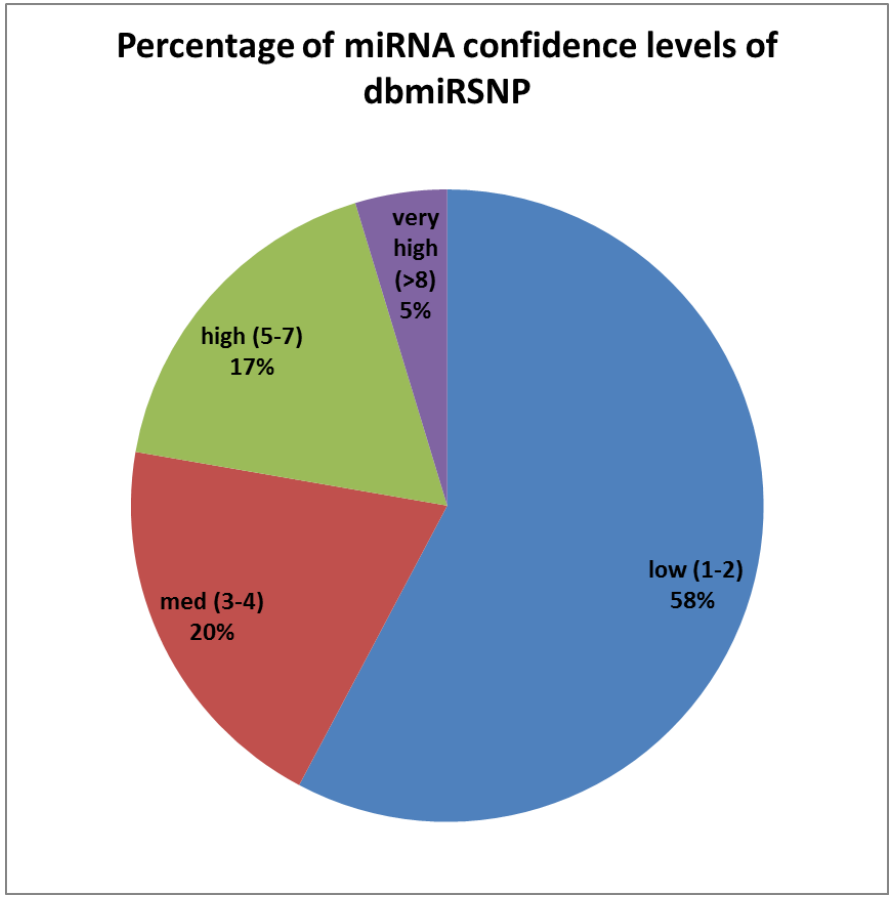
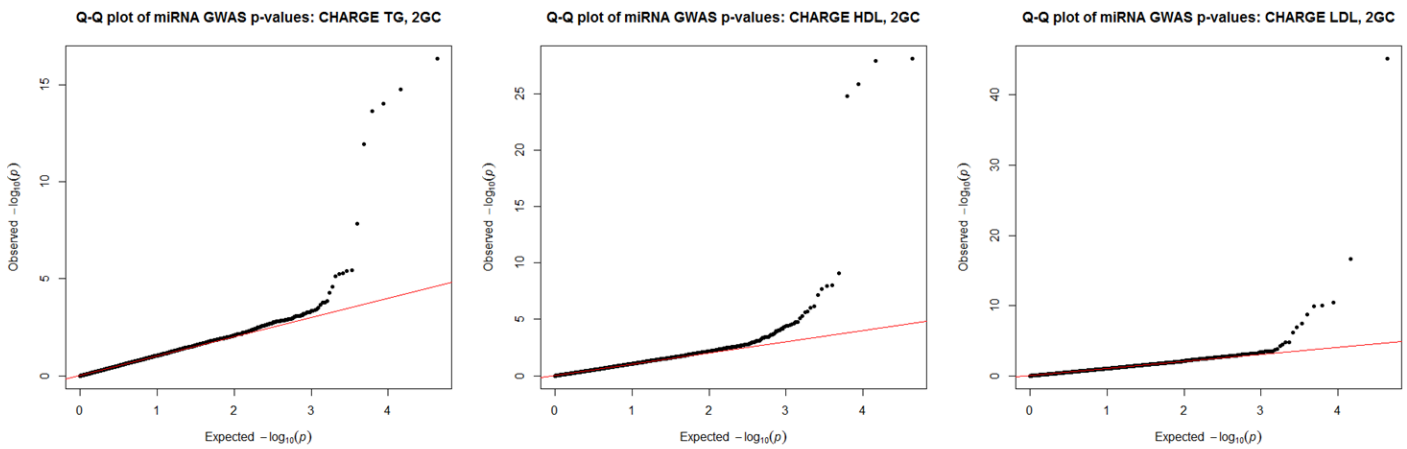
Supplemental Figure 2.1.1. Proportion of different miRNA confidence levels of dbmiRSNP



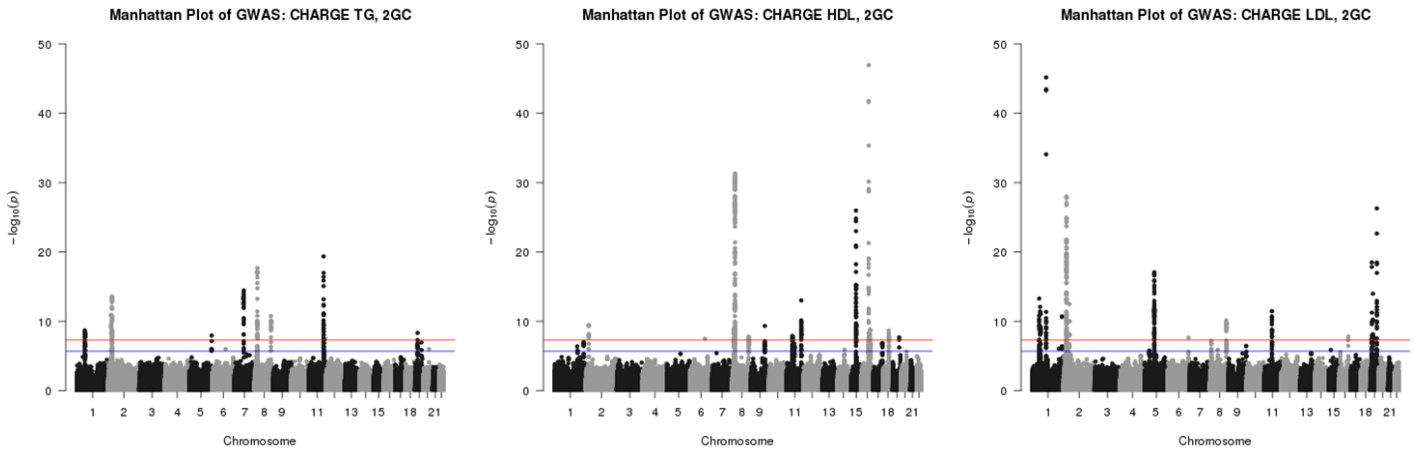
Supplemental Figure 2.1.2. QQ plots for miRNA genome-wide association meta-analysis on blood lipid levels in the CHARGE consortium



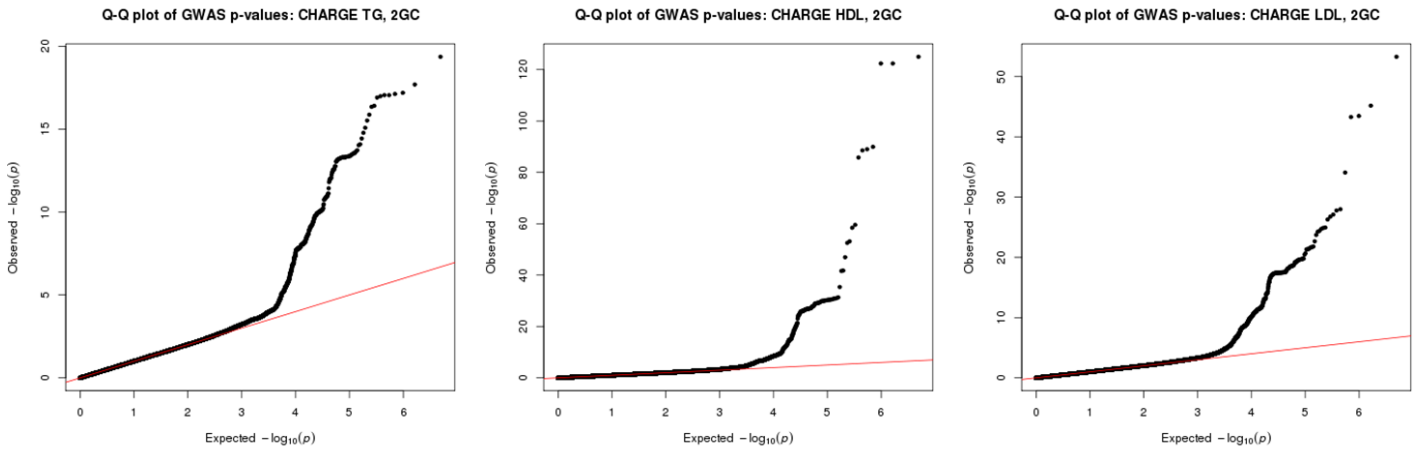
Quantile-quantile plots show observed *P*-values of miRNA GWAS meta-analysis for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex and study-specific covariates, after applying double genomic control (2GC)) vs. expected *P*-values by chance.

Supplemental Figure 2.1.3. Manhattan and QQ plots for genome-wide association meta-analysis on blood lipid levels in the CHARGE consortium

(A) Manhattan plots



(B) QQ plots

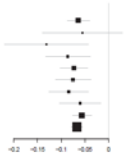


(A) Manhattan plots show the –log10(*P*-values) of ~2,500,000 SNPs from GWAS meta-analysis for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex and study-specific covariates, after applying double genomic control (2GC)) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.
(B) Quantile-quantile plots show observed *P*-values of GWAS meta-analysis for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex and study-specific covariates, after applying double genomic control (2GC)) vs. expected *P*-values by chance.

Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium

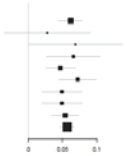
(1) LnTG: rs15285 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.064	0.012	4.61e−08	0.942	0.14
GOLDN	781	−0.055	0.043	0.2	0.937	0.15
GOYA	468	−0.131	0.045	0.00383	0.994	0.13
InCHIANTI	1125	−0.086	0.024	0.000458	0.982	0.2
RS−I	3298	−0.073	0.015	1.05e−06	0.996	0.13
RS−II	2117	−0.075	0.019	0.000108	0.996	0.14
RS−III	2046	−0.084	0.021	5.35e−05	0.997	0.13
YFS	1508	−0.06	0.022	0.00618	0.996	0.1
Inter99	6112	−0.056	0.01	2.49e−08	1	0.28
META	24065	−0.067	0.006	1.58e−32		0.18



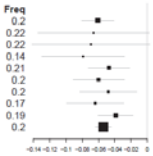
(2) LnTG: rs13702 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.062	0.009	1.68e−12	0.995	0.71
GOLDN	781	0.028	0.032	0.383	0.99	0.71
GOYA	468	0.069	0.035	0.046	0.998	0.72
InCHIANTI	1125	0.066	0.02	0.000843	0.986	0.64
RS−I	3298	0.047	0.011	2.45e−05	0.998	0.72
RS−II	2117	0.072	0.014	4.15e−07	0.998	0.7
RS−III	2046	0.049	0.015	0.00145	0.998	0.71
YFS	1508	0.049	0.015	0.00153	0.999	0.74
Inter99	6112	0.054	0.01	5.5e−08	1	0.72
META	24065	0.057	0.005	1.4e−35		0.71



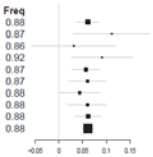
(3) LnTG: rs1051921 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.061	0.01	2.59e−09	0.949	0.2
GOLDN	781	−0.066	0.035	0.061	0.955	0.22
GOYA	468	−0.069	0.037	0.063	0.981	0.22
InCHIANTI	1125	−0.079	0.026	0.00278	0.96	0.14
RS−I	3298	−0.047	0.013	0.000211	0.978	0.21
RS−II	2117	−0.06	0.016	0.00025	0.978	0.2
RS−III	2046	−0.048	0.018	0.00812	0.976	0.2
YFS	1508	−0.064	0.018	0.000339	0.983	0.17
Inter99	6112	−0.039	0.011	0.000638	1	0.19
META	24065	−0.054	0.005	8.68e−25		0.2



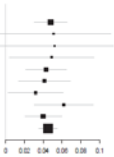
(4) LnTG: rs13232120 A/T

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.061	0.012	3.61e−07	0.999	0.88
GOLDN	781	0.111	0.041	0.00736	0.999	0.87
GOYA	468	0.031	0.045	0.493	0.966	0.86
InCHIANTI	1125	0.091	0.033	0.00582	0.965	0.92
RS−I	3298	0.057	0.015	0.000193	0.981	0.87
RS−II	2117	0.06	0.02	0.0022	0.983	0.87
RS−III	2046	0.044	0.022	0.048	0.97	0.88
YFS	1508	0.06	0.021	0.00413	0.978	0.88
Inter99	6112	0.062	0.014	7.42e−06	1	0.88
META	24065	0.061	0.006	4.43e−22		0.88



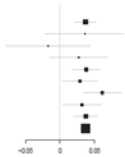
(5) LnTG: rs14415 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.048	0.009	5.16e−08	1	0.71
GOLDN	781	0.051	0.031	0.104	1	0.68
GOYA	468	0.052	0.032	0.11	0.999	0.68
InCHIANTI	1125	0.049	0.023	0.033	0.997	0.77
RS−I	3298	0.043	0.011	9.14e−05	0.999	0.7
RS−II	2117	0.041	0.014	0.00373	0.999	0.69
RS−III	2046	0.032	0.015	0.036	0.999	0.7
YFS	1508	0.062	0.016	0.000132	0.999	0.79
Inter99	6112	0.04	0.01	4.67e−05	1	0.7
META	24065	0.045	0.005	9.41e−23		0.71



(6) LnTG: rs4803 A/G

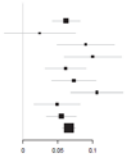
Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.037	0.008	5.57e−06	0.993	0.61
GOLDN	781	0.036	0.029	0.223	0.99	0.59
GOYA	468	−0.017	0.031	0.577	1	0.6
InCHIANTI	1125	0.027	0.021	0.194	1	0.71
RS−I	3298	0.038	0.01	0.000198	1	0.59
RS−II	2117	0.029	0.013	0.033	1	0.59
RS−III	2046	0.061	0.014	1.74e−05	1	0.58
YFS	1508	0.032	0.014	0.019	1	0.56
Inter99	6112	0.037	0.009	3.84e−05	1	0.58
META	24065	0.037	0.004	1.88e−18		0.59



Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium (continued)

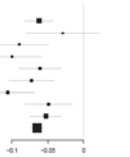
(7) HDL−C: rs3735964 A/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.062	0.01	1.3e−09	0.996	0.11
GOLDN	781	0.024	0.026	0.368	0.981	0.11
GOYA	1455	0.09	0.021	2.47e−05	0.998	0.11
InCHIANTI	1125	0.1	0.021	3.21e−06	0.983	0.15
RS−I	3347	0.061	0.015	3.18e−05	0.997	0.11
RS−II	2132	0.073	0.016	4.3e−06	0.998	0.12
RS−III	2046	0.106	0.019	5.79e−08	0.998	0.1
YFS	1508	0.049	0.017	0.00366	0.998	0.09
Inter99	6108	0.055	0.011	6.2e−07	1	0.1
META	25112	0.066	0.005	7.6e−38		0.11



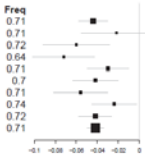
(8) HDL−C: rs1059611 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.062	0.01	1.22e−09	0.996	0.89
GOLDN	781	−0.029	0.026	0.264	0.994	0.9
GOYA	1455	−0.09	0.021	2.53e−05	0.999	0.89
InCHIANTI	1125	−0.1	0.021	3.19e−06	0.984	0.85
RS−I	3347	−0.061	0.015	3.18e−05	0.997	0.89
RS−II	2132	−0.073	0.016	4.31e−06	0.998	0.88
RS−III	2046	−0.106	0.019	5.75e−08	0.998	0.9
YFS	1508	−0.049	0.017	0.00367	0.998	0.91
Inter99	6108	−0.053	0.011	1.41e−06	1	0.89
META	25112	−0.065	0.005	1.11e−37		0.89



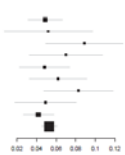
(9) HDL−C: rs13702 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.044	0.007	6.13e−10	0.995	0.71
GOLDN	781	−0.022	0.017	0.21	0.99	0.71
GOYA	1455	−0.06	0.016	0.000141	0.998	0.72
InCHIANTI	1125	−0.072	0.015	3.29e−06	0.986	0.64
RS−I	3347	−0.03	0.01	0.0023	0.998	0.71
RS−II	2132	−0.042	0.011	0.000121	0.998	0.7
RS−III	2046	−0.056	0.013	2.29e−05	0.998	0.71
YFS	1508	−0.024	0.011	0.032	0.999	0.74
Inter99	6108	−0.042	0.008	2.56e−08	1	0.72
META	25112	−0.042	0.004	8.57e−33		0.71



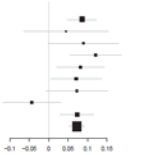
(10) HDL−C: rs15285 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.049	0.009	1.29e−07	0.942	0.14
GOLDN	781	0.052	0.023	0.025	0.937	0.15
GOYA	1455	0.089	0.02	1.3e−05	0.994	0.13
InCHIANTI	1125	0.07	0.019	0.000167	0.982	0.2
RS−I	3347	0.048	0.013	0.000296	0.996	0.13
RS−II	2132	0.062	0.015	2.86e−05	0.996	0.14
RS−III	2046	0.083	0.018	2.9e−06	0.997	0.13
YFS	1508	0.049	0.016	0.00216	0.996	0.1
Inter99	6108	0.042	0.008	1.84e−08	1	0.28
META	25112	0.053	0.004	1.54e−34		0.19



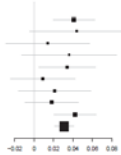
(11) HDL−C: rs3289 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.086	0.019	1.08e−05	0.975	0.97
GOLDN	781	0.045	0.055	0.416	0.968	0.98
GOYA	1455	0.09	0.046	0.049	0.992	0.98
InCHIANTI	1125	0.121	0.034	0.000408	0.925	0.95
RS−I	3347	0.082	0.031	0.00711	0.991	0.98
RS−II	2132	0.071	0.033	0.032	0.993	0.98
RS−III	2046	0.073	0.04	0.064	0.992	0.98
YFS	1508	−0.043	0.038	0.257	0.98	0.98
Inter99	6108	0.073	0.022	0.000889	1	0.98
META	25112	0.073	0.01	6.02e−13		0.97



(12) HDL−C: rs4474673 T/C

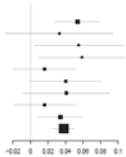
Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.041	0.011	0.000119	0.881	0.11
GOLDN	781	0.044	0.025	0.079	0.929	0.11
GOYA	1455	0.014	0.022	0.526	0.964	0.13
InCHIANTI	1125	0.036	0.025	0.161	0.945	0.1
RS−I	3347	0.034	0.015	0.018	0.94	0.11
RS−II	2132	0.009	0.017	0.592	0.937	0.11
RS−III	2046	0.021	0.019	0.268	0.943	0.11
YFS	1508	0.018	0.014	0.201	0.987	0.15
Inter99	6108	0.042	0.011	6.97e−05	1	0.11
META	25112	0.031	0.005	4.16e−10		0.12



Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium (continued)

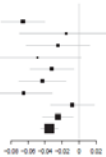
(13) HDL−C: rs2266788 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.054	0.013	2.73e−05	0.99	0.93
GOLDN	781	0.033	0.031	0.284	0.998	0.93
GOYA	1455	0.055	0.026	0.032	0.995	0.92
InCHIANTI	1125	0.059	0.025	0.018	0.974	0.91
RS−I	3347	0.016	0.018	0.368	0.98	0.93
RS−II	2132	0.04	0.021	0.053	0.974	0.93
RS−III	2046	0.041	0.025	0.096	0.979	0.93
YFS	1508	0.016	0.018	0.386	0.981	0.92
Inter99	6108	0.034	0.013	0.012	1	0.93
META	25112	0.038	0.006	8.54e−10		0.93



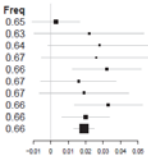
(14) HDL−C: rs6857 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.066	0.013	2.16e−07	0.489	0.15
GOLDN	781	−0.015	0.028	0.606	0.527	0.17
GOYA	1455	−0.025	0.019	0.183	0.951	0.17
InCHIANTI	1125	−0.049	0.026	0.06	0.873	0.09
RS−I	3347	−0.032	0.013	0.012	0.95	0.16
RS−II	2132	−0.043	0.014	0.00249	0.948	0.15
RS−III	2046	−0.065	0.017	1e−04	0.953	0.17
YFS	1508	−0.008	0.013	0.52	0.94	0.19
Inter99	6108	−0.025	0.009	0.00399	1	0.19
META	25112	−0.035	0.005	8.97e−14		0.17



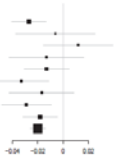
(15) HDL−C: rs9909 C/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.003	0.007	0.657	0.998	0.65
GOLDN	781	0.022	0.016	0.16	0.996	0.63
GOYA	1455	0.028	0.015	0.058	0.999	0.64
InCHIANTI	1125	0.026	0.016	0.091	1	0.67
RS−I	3347	0.032	0.01	0.000693	1	0.66
RS−II	2132	0.016	0.011	0.137	0.999	0.67
RS−III	2046	0.019	0.013	0.149	0.999	0.67
YFS	1508	0.033	0.01	0.00105	1	0.66
Inter99	6108	0.02	0.007	0.00507	1	0.66
META	25112	0.019	0.003	1.1e−08		0.66



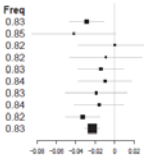
(16) HDL−C: rs174546 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.027	0.007	5.31e−05	0.999	0.33
GOLDN	781	−0.006	0.016	0.706	0.999	0.36
GOYA	1455	0.012	0.014	0.415	1	0.34
InCHIANTI	1125	−0.013	0.015	0.384	1	0.28
RS−I	3347	−0.013	0.009	0.166	1	0.34
RS−II	2132	−0.033	0.011	0.00291	1	0.32
RS−III	2046	−0.017	0.013	0.178	1	0.34
YFS	1508	−0.029	0.01	0.00347	1	0.41
Inter99	6108	−0.018	0.007	0.011	1	0.33
META	25112	−0.02	0.003	2.32e−09		0.34



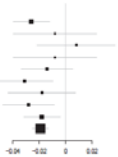
(17) HDL−C: rs1109166 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.029	0.009	0.000736	0.945	0.83
GOLDN	781	−0.042	0.022	0.053	0.952	0.85
GOYA	1455	0	0.019	0.998	0.994	0.82
InCHIANTI	1125	−0.009	0.019	0.634	0.973	0.82
RS−I	3347	−0.014	0.012	0.235	0.979	0.83
RS−II	2132	−0.01	0.014	0.486	0.953	0.84
RS−III	2046	−0.019	0.016	0.234	0.993	0.83
YFS	1508	−0.016	0.013	0.212	0.996	0.84
Inter99	6108	−0.033	0.009	0.000138	1	0.82
META	25112	−0.023	0.004	1.03e−07		0.83



(18) HDL−C: rs4246215 T/G

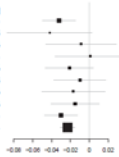
Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.026	0.007	0.00012	0.995	0.35
GOLDN	781	−0.008	0.016	0.616	1	0.37
GOYA	1455	0.008	0.015	0.584	0.935	0.36
InCHIANTI	1125	−0.008	0.016	0.612	0.901	0.3
RS−I	3347	−0.014	0.01	0.147	0.926	0.36
RS−II	2132	−0.031	0.011	0.00585	0.927	0.34
RS−III	2046	−0.018	0.013	0.169	0.931	0.36
YFS	1508	−0.028	0.01	0.00594	0.957	0.42
Inter99	6108	−0.018	0.007	0.011	1	0.35
META	25112	−0.019	0.0036	4e−09		0.36



Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium (continued)

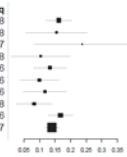
(19) HDL−C: rs12449157 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.032	0.009	0.000575	0.88	0.84
GOLDN	781	−0.042	0.023	0.073	0.9	0.86
GOYA	1455	−0.009	0.019	0.628	0.999	0.83
InCHIANTI	1125	0.001	0.019	0.949	0.994	0.84
RS−I	3347	−0.021	0.013	0.089	0.992	0.85
RS−II	2132	−0.01	0.014	0.502	0.993	0.86
RS−III	2046	−0.017	0.017	0.323	0.99	0.85
YFS	1508	−0.015	0.013	0.248	1	0.83
Inter99	6108	−0.03	0.009	0.000722	1	0.84
META	25112	−0.023	0.004	2.46e−07		0.84



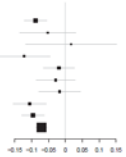
(20) LDL−C: rs629301 T/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.162	0.02	4.44e−16	0.998	0.78
GOLDN	781	0.155	0.05	0.00217	1	0.8
GOYA	466	0.237	0.078	0.00239	0.999	0.77
InCHIANTI	1125	0.104	0.048	0.03	0.99	0.8
RS−I	3265	0.134	0.026	1.64e−07	0.998	0.76
RS−II	2117	0.1	0.032	0.00217	0.998	0.76
RS−III	2045	0.117	0.035	0.000736	0.998	0.76
YFS	1508	0.083	0.029	0.00434	1	0.78
Inter99	6105	0.167	0.02	2.76e−17	1	0.76
META	23958	0.14	0.01	7.27e−47		0.77



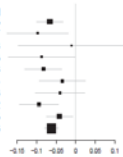
(21) LDL−C: rs12916 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.088	0.017	2.2e−07	0.98	0.61
GOLDN	781	−0.052	0.042	0.217	0.969	0.62
GOYA	466	0.017	0.069	0.811	0.974	0.58
InCHIANTI	1125	−0.122	0.039	0.00177	0.948	0.61
RS−I	3265	−0.019	0.023	0.407	0.959	0.62
RS−II	2117	−0.029	0.029	0.316	0.966	0.62
RS−III	2045	−0.017	0.031	0.589	0.966	0.62
YFS	1508	−0.106	0.025	2.05e−05	0.981	0.55
Inter99	6105	−0.096	0.017	1.68e−08	1	0.59
META	23958	−0.071	0.008	3.08e−17		0.6



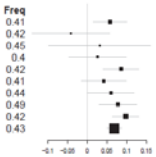
(22) LDL−C: rs4246215 T/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.066	0.017	0.000132	0.995	0.35
GOLDN	781	−0.097	0.04	0.014	1	0.37
GOYA	466	−0.01	0.07	0.887	0.935	0.38
InCHIANTI	1125	−0.087	0.043	0.043	0.901	0.3
RS−I	3265	−0.082	0.024	0.000562	0.926	0.36
RS−II	2117	−0.034	0.03	0.266	0.927	0.34
RS−III	2045	−0.04	0.032	0.214	0.931	0.36
YFS	1508	−0.094	0.025	0.000146	0.957	0.42
Inter99	6105	−0.041	0.017	0.019	1	0.35
META	23958	−0.062	0.009	4.4e−13		0.36



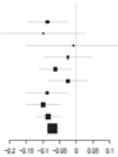
(23) LDL−C: rs6859 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.058	0.022	0.00703	0.589	0.41
GOLDN	781	−0.041	0.05	0.414	0.635	0.42
GOYA	466	0.032	0.066	0.627	0.958	0.45
InCHIANTI	1125	0.027	0.037	0.464	0.952	0.4
RS−I	3265	0.086	0.023	0.000166	0.946	0.42
RS−II	2117	0.043	0.029	0.139	0.947	0.41
RS−III	2045	0.06	0.03	0.049	0.949	0.44
YFS	1508	0.078	0.024	0.00132	0.963	0.49
Inter99	6105	0.098	0.017	1.08e−08	1	0.42
META	23958	0.069	0.009	5.79e−15		0.43



(24) LDL−C: rs7188 A/C

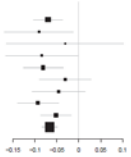
Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.086	0.03	0.00374	0.374	0.71
GOLDN	781	−0.099	0.064	0.124	0.426	0.68
GOYA	466	−0.009	0.071	0.903	0.999	0.67
InCHIANTI	1125	−0.025	0.037	0.491	0.998	0.64
RS−I	3265	−0.063	0.024	0.0072	0.999	0.68
RS−II	2117	−0.025	0.029	0.389	0.999	0.67
RS−III	2045	−0.088	0.032	0.00616	0.999	0.67
YFS	1508	−0.099	0.026	0.000173	0.999	0.71
Inter99	6105	−0.084	0.018	2.65e−06	1	0.69
META	23958	−0.072	0.01	8.28e−14		0.69



Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium (continued)

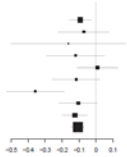
(25) LDL−C: rs174546 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.07	0.017	6.13e−05	0.999	0.33
GOLDN	781	−0.091	0.04	0.024	0.999	0.36
GOYA	466	−0.031	0.068	0.648	1	0.36
InCHIANTI	1125	−0.084	0.042	0.044	1	0.28
RS−I	3265	−0.081	0.023	0.000479	1	0.34
RS−II	2117	−0.031	0.03	0.293	1	0.32
RS−III	2045	−0.046	0.031	0.145	1	0.34
YFS	1508	−0.093	0.024	0.000138	1	0.41
Inter99	6105	−0.052	0.018	0.00324	1	0.33
META	23958	−0.066	0.009	1.4e−14		0.34



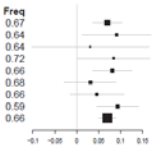
(26) LDL−C: rs13465 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.093	0.033	0.0052	0.993	0.06
GOLDN	780	−0.072	0.077	0.352	1	0.07
GOYA	466	−0.163	0.173	0.348	0.714	0.05
InCHIANTI	1125	−0.119	0.087	0.168	0.76	0.06
RS−I	3265	0.009	0.06	0.886	0.773	0.05
RS−II	2117	−0.117	0.072	0.105	0.775	0.05
RS−III	2045	−0.359	0.086	3.22e−05	0.775	0.04
YFS	1508	−0.105	0.056	0.06	0.826	0.06
Inter99	6105	−0.125	0.038	0.00108	1	0.05
META	23957	−0.107	0.019	1.07e−08		0.06



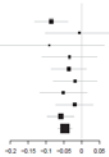
(27) LDL−C: rs174545 C/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.07	0.017	6.62e−05	0.999	0.67
GOLDN	781	0.091	0.04	0.024	0.999	0.64
GOYA	466	0.031	0.068	0.653	1	0.64
InCHIANTI	1125	0.084	0.042	0.044	1	0.72
RS−I	3265	0.081	0.023	0.000478	1	0.66
RS−II	2117	0.031	0.03	0.293	0.999	0.68
RS−III	2045	0.046	0.031	0.144	1	0.66
YFS	1508	0.093	0.024	0.000137	1	0.59
META	17853	0.07	0.01	8.48e−13		0.66



(28) LDL−C: rs1433099 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.085	0.024	0.000458	0.564	0.28
GOLDN	781	−0.006	0.049	0.907	0.791	0.27
GOYA	466	−0.091	0.079	0.25	0.999	0.25
InCHIANTI	1125	−0.034	0.039	0.385	0.996	0.29
RS−I	3265	−0.036	0.025	0.156	0.999	0.27
RS−II	2117	−0.018	0.031	0.569	0.999	0.27
RS−III	2045	−0.051	0.034	0.135	0.999	0.27
YFS	1508	−0.02	0.027	0.466	1	0.26
Inter99	6105	−0.059	0.019	0.00224	1	0.26
META	23958	−0.047	0.01	1.8e−06		0.27

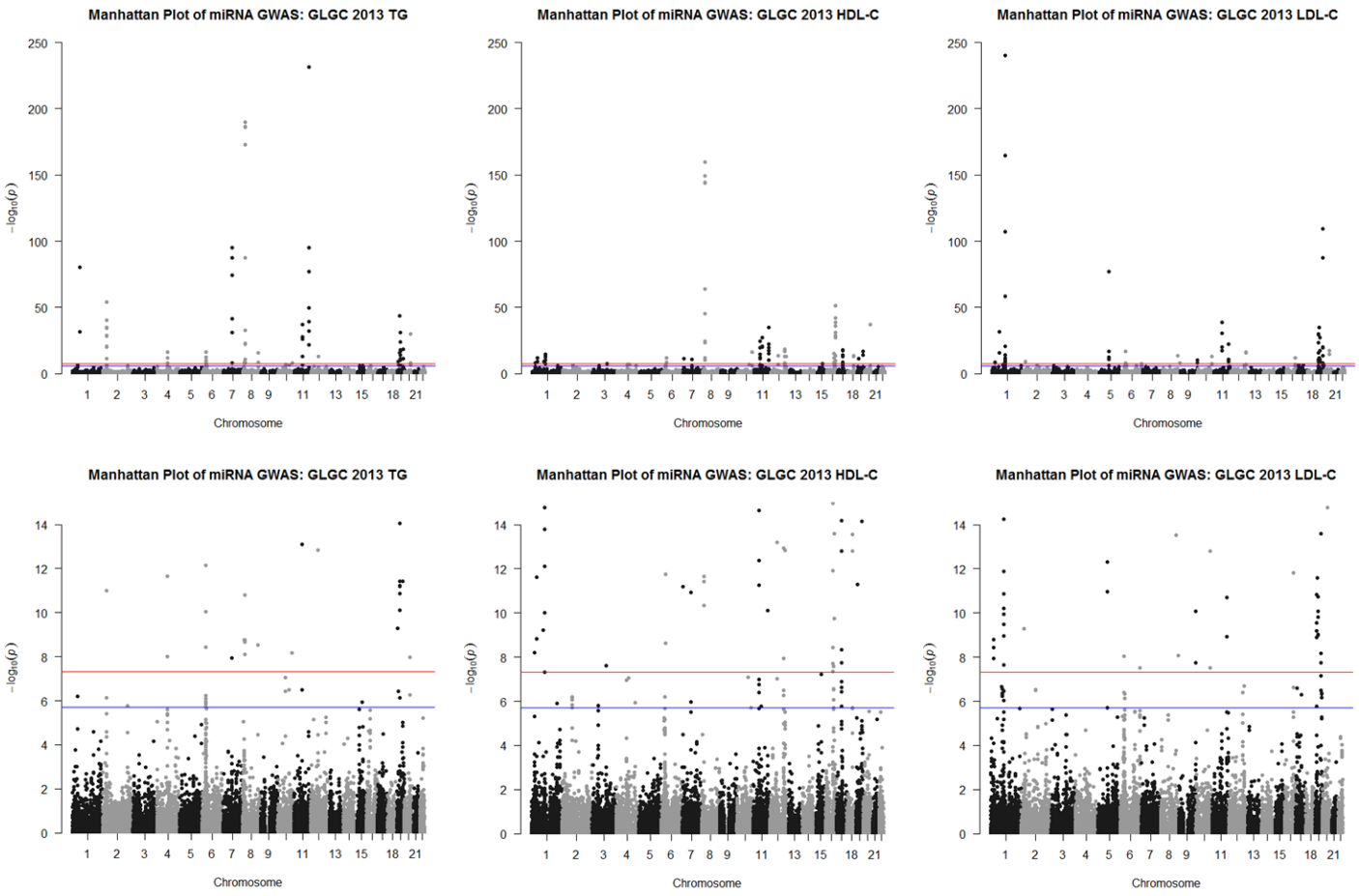


Supplemental Figure 2.1.4. Forest plots for the hits of miRNA genome-wide association meta-analysis on blood lipid levels (model 3) in the CHARGE consortium (continued)

Forest plot of associations between miRNA-related SNP and blood lipids (mmol/L) in 9 CHARGE cohort studies. The title of each plot specifies blood lipid outcome: SNP coded allele/non-coded allele. The estimate from each cohort study, indicated by a filled square, was adjusted for age, sex, study-specific covariates, BMI and diabetic status (model 3). The size of the square is proportional to the weight of the cohort study in the overall fixed-effects estimate, and the horizontal line represents the 95% CI. ARIC, Atherosclerosis Risk in Communities Study; GOLDN, Genetics of Lipid Lowering Drugs and Diet Network; GOYA, Genetics of Obesity in Young Adults; InCHIANTI, Invecchiare in Chianti; RS-I, RS-II and RS-III, Rotterdam Study baseline and extensions; YFS, Cardiovascular Risk in Young Finns Study; Inter99, Inter99 Study; N, sample size, META, meta-analysis; Beta, beta coefficient; SE, standard error; Qual, imputation quality; Freq, coded allele frequency.

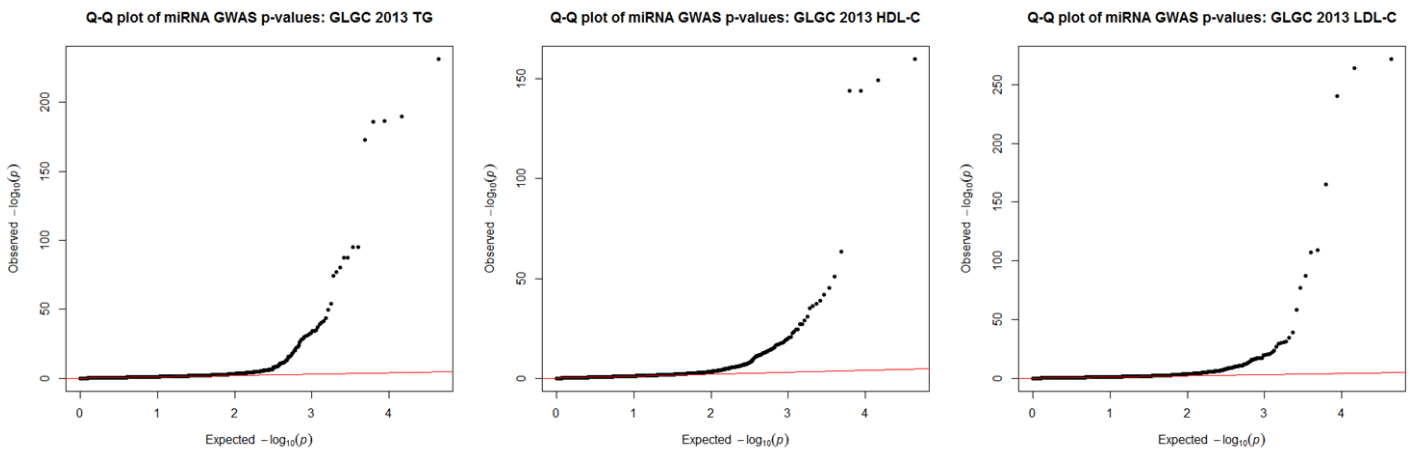
Supplemental Figure 2.1.5. Manhattan and QQ plots for miRNA genome-wide association meta-analysis from the Global Lipids Genetic Consortium 2013

(A) Manhattan plots



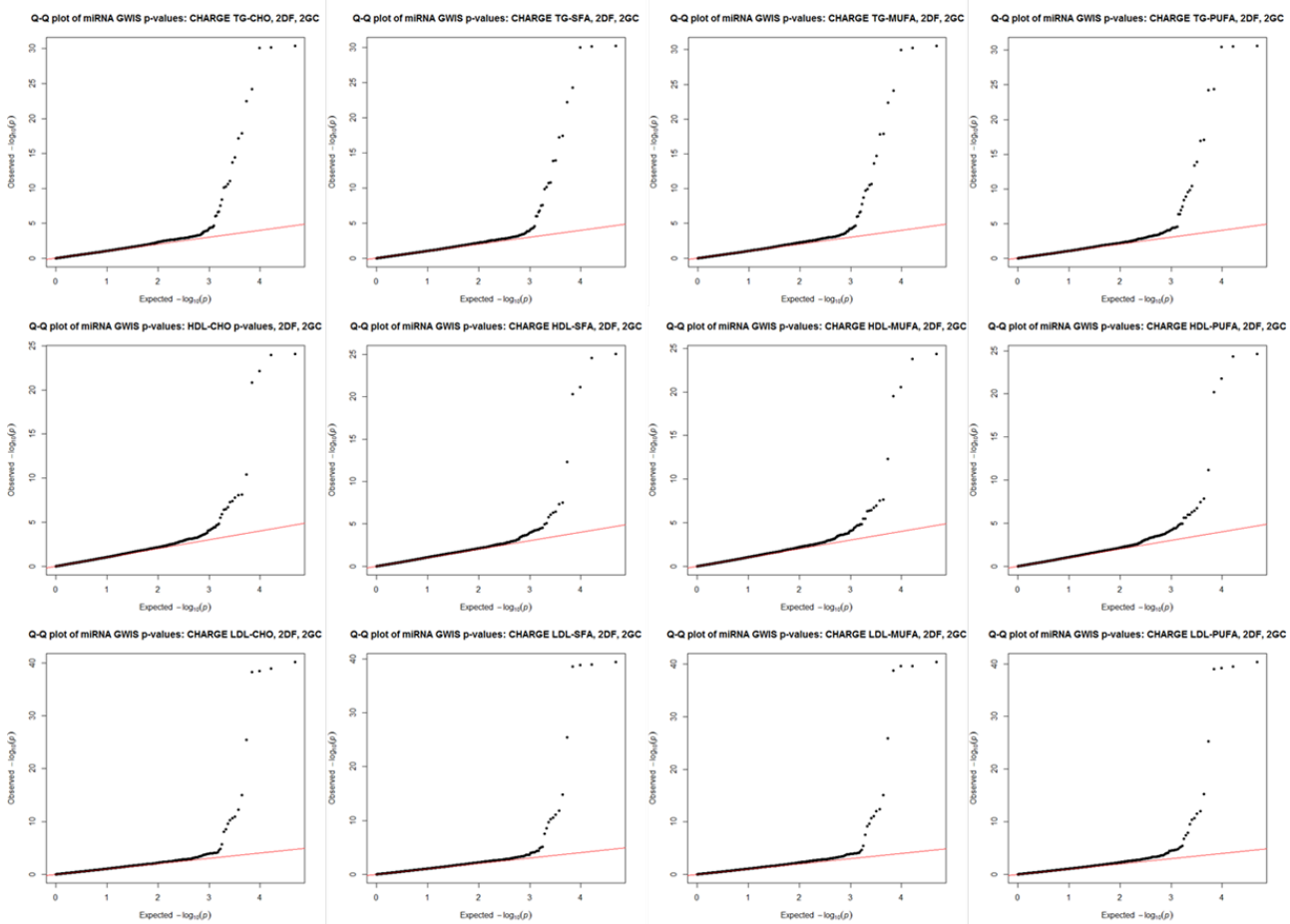
Supplemental Figure 2.1.5. Manhattan and QQ plots for miRNA genome-wide association meta-analysis from the Global Lipids Genetic Consortium 2013 (continued)

(B) QQ plots



(A) Manhattan plots show the –log10(*P*-values) of ~25,000 SNPs from miRNA GWAS meta-analysis for blood lipids using Global Lipids Genetic Consortium 2013 data with –log10(*P*) up to 250 (above) and –log10(*P*) up to 14 (below) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.
(B) Quantile-quantile plots show observed *P*-values of miRNA GWAS meta-analysis for blood lipids using Global Lipids Genetic Consortium 2013 data vs. expected *P*-values by chance.

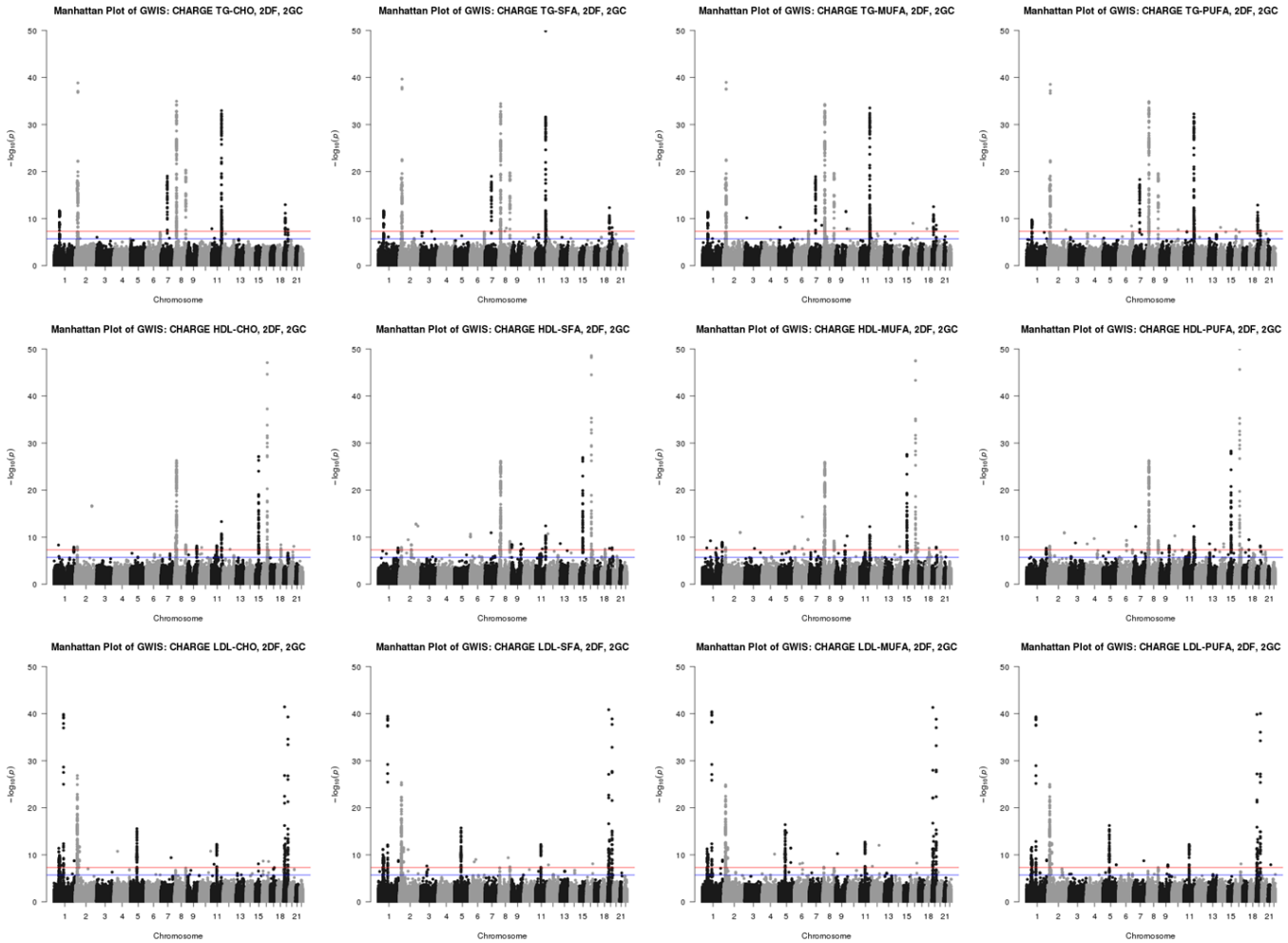
Supplemental Figure 2.1.6. QQ plots for miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels in the CHARGE consortium



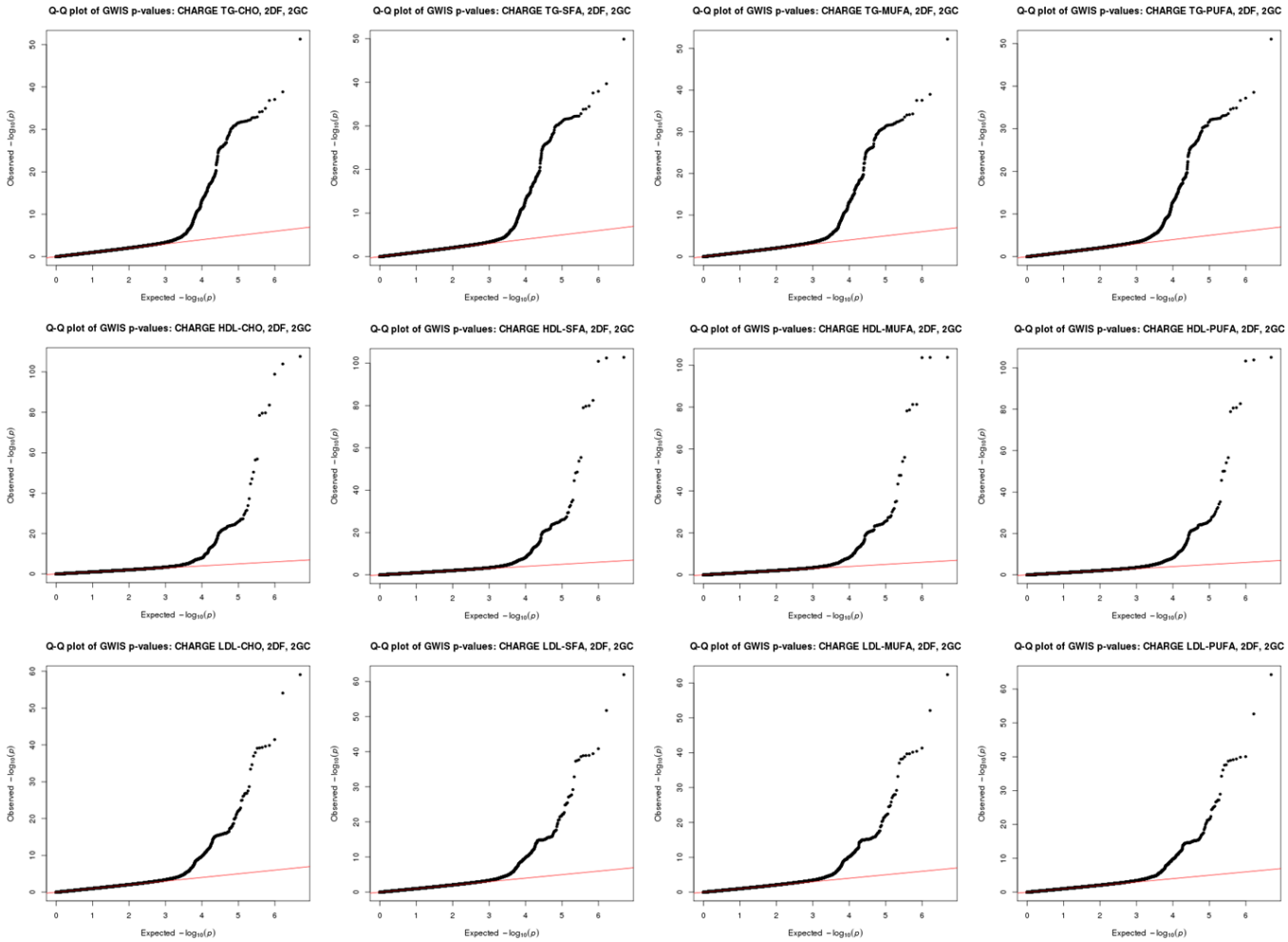
Quantile-quantile plots show observed *P*-values of miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) vs. expected *P*-values by chance.

Supplemental Figure 2.1.7. Manhattan and QQ plots for genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels in the CHARGE consortium

(A) Manhattan plots



Supplemental Figure 2.1.7. Manhattan and QQ plots for genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels in the CHARGE consortium (continued)
(B) QQ plots



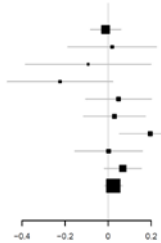
Supplemental Figure 2.1.7. Manhattan and QQ plots for genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels in the CHARGE consortium (continued)

(A) Manhattan plots show the –log10(*P*-values) of ~2,500,000 SNPs from genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.
(B) Quantile-quantile plots show observed *P*-values of genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) vs. expected *P*-values by chance.

Supplemental Figure 2.1.8. Forest plots for the selected SNPs from miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels (model 3) in the CHARGE consortium

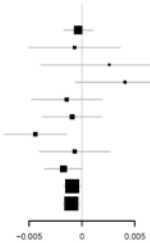
(1A) HDL−C CHO SNP: rs174546 T/C

Study	N	Qual	Freq	Beta_SNP	SE_SNP	Pval_SNP
ARIC	6610	0.999	0.33	−0.012	0.036	0.7378
GOLDN	759	0.999	0.36	0.018	0.105	0.86396
GOYA	331	1	0.34	−0.093	0.149	0.53546
InCHIANTI	1125	1	0.28	−0.224	0.125	0.07381
RS−I	2919	1	0.34	0.048	0.078	0.54019
RS−II	1167	1	0.32	0.029	0.073	0.69342
RS−III	1569	1	0.34	0.195	0.073	0.00781
YFS	1508	1	0.41	0.002	0.08	0.97518
Inter99	5987	1	0.33	0.068	0.044	0.12084
META−2DF	21975		0.34	0.024	0.021	
META−1DF	21975		0.34			



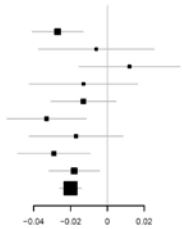
(1B) HDL−C CHO INT: rs174546 T/C

Study	Beta_Int	SE_Int	Pval_Int
ARIC	−0.00035	7e−04	0.63348
GOLDN	−7e−04	0.0022	0.74442
GOYA	0.00258	0.0033	0.43764
InCHIANTI	0.00407	0.0024	0.08465
RS−I	−0.00144	0.0017	0.40459
RS−II	−0.00093	0.0014	0.51054
RS−III	−0.00442	0.0015	0.00240
YFS	−0.00068	0.0017	0.69146
Inter99	−0.00175	9e−04	0.04517
META−2DF	−0.00094	4e−04	7.49e−10
META−1DF	−0.001	4e−04	0.0192



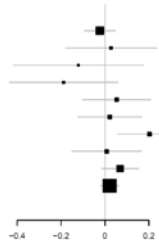
(1C) HDL−C: rs174546 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.027	0.007	5.31e−05	0.999	0.33
GOLDN	781	−0.006	0.016	0.706	0.999	0.36
GOYA	1455	0.012	0.014	0.415	1	0.34
InCHIANTI	1125	−0.013	0.015	0.384	1	0.28
RS−I	3347	−0.013	0.009	0.166	1	0.34
RS−II	2132	−0.033	0.011	0.00291	1	0.32
RS−III	2046	−0.017	0.013	0.178	1	0.34
YFS	1508	−0.029	0.01	0.00347	1	0.41
Inter99	6108	−0.018	0.007	0.011	1	0.33
META	25112	−0.02	0.003	2.32e−09		0.32



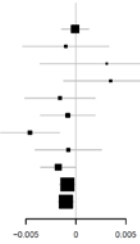
(2A) HDL−C CHO SNP: rs4246215 T/G

Study	N	Qual	Freq	Beta_SNP	SE_SNP	Pval_SNP
ARIC	6610	0.995	0.35	−0.024	0.036	0.50845
GOLDN	759	1	0.37	0.028	0.106	0.79
GOYA	331	0.935	0.36	−0.121	0.151	0.42546
InCHIANTI	1125	0.901	0.3	−0.188	0.126	0.13567
RS−I	2919	0.926	0.36	0.053	0.079	0.50659
RS−II	1167	0.927	0.34	0.022	0.074	0.76233
RS−III	1569	0.931	0.36	0.203	0.075	0.00706
YFS	1508	0.957	0.42	0.008	0.081	0.9247
Inter99	5987	1	0.35	0.069	0.043	0.10731
META−2DF	21975		0.35	0.021	0.021	
META−1DF	21975		0.35			



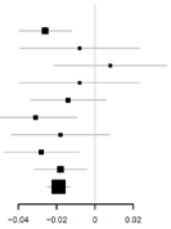
(2B) HDL−C CHO INT: rs4246215 T/G

Study	Beta_Int	SE_Int	Pval_Int
ARIC	−7e−05	7e−04	0.92382
GOLDN	−0.001	0.0022	0.64616
GOYA	0.00309	0.0034	0.36015
InCHIANTI	0.00348	0.0024	0.14289
RS−I	−0.00159	0.0018	0.36767
RS−II	−0.00081	0.0014	0.57486
RS−III	−0.00459	0.0015	0.00210
YFS	−0.00076	0.0017	0.66249
Inter99	−0.00176	9e−04	0.03872
META−2DF	−0.00086	4e−04	2.46e−09
META−1DF	−0.001	4e−04	0.02717



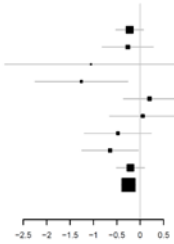
(2C) HDL−C: rs4246215 T/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.026	0.007	0.00012	0.995	0.35
GOLDN	781	−0.008	0.016	0.616	1	0.37
GOYA	1455	0.008	0.015	0.584	0.935	0.36
InCHIANTI	1125	−0.008	0.016	0.612	0.901	0.3
RS−I	3347	−0.014	0.01	0.147	0.926	0.36
RS−II	2132	−0.031	0.011	0.00585	0.927	0.34
RS−III	2046	−0.018	0.013	0.169	0.931	0.36
YFS	1508	−0.028	0.01	0.00594	0.957	0.42
Inter99	6108	−0.018	0.007	0.011	1	0.35
META	25112	−0.019	0.003	6.43e−09		0.36



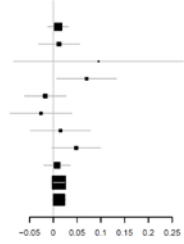
(3A) LDL−C MUFA SNP: rs13465 A/G

Study	N	Qual	Freq	Beta_SNP	SE_SNP	Pval_SNP
ARIC	6546	0.993	0.06	−0.226	0.15	0.13242
GOLDN	758	1	0.07	−0.265	0.278	0.34049
GOYA	331	0.714	0.05	−1.053	0.939	0.26338
InCHIANTI	1125	0.76	0.06	−1.255	0.506	0.0131
RS−I	2844	0.773	0.04	0.201	0.284	0.478
RS−II	1163	0.775	0.05	0.056	0.362	0.878
RS−III	1568	0.775	0.04	−0.478	0.365	0.19017
YFS	1508	0.826	0.06	−0.644	0.308	0.03667
Inter99	5983	1	0.05	−0.209	0.152	0.1704
META−2DF	21826		0.05	−0.25	0.076	
META−1DF	21826		0.05			



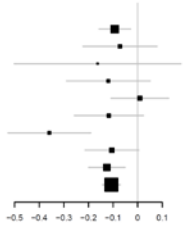
(3B) LDL−C MUFA INT: rs13465 A/G

Study	Beta_Int	SE_Int	Pval_Int
ARIC	0.01	0.011	0.36356
GOLDN	0.012	0.022	0.57761
GOYA	0.095	0.091	0.29670
InCHIANTI	0.07	0.032	0.02662
RS−I	−0.017	0.022	0.46242
RS−II	−0.026	0.033	0.43621
RS−III	0.015	0.032	0.64413
YFS	0.048	0.026	0.06494
Inter99	0.008	0.014	0.57106
META−2DF	0.012	0.006	9.37e−09
META−1DF	0.012	0.007	0.07953



(3C) LDL−C: rs13465 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.093	0.033	0.0052	0.993	0.06
GOLDN	780	−0.072	0.077	0.352	1	0.07
GOYA	466	−0.163	0.173	0.348	0.714	0.05
InCHIANTI	1125	−0.119	0.087	0.168	0.76	0.06
RS−I	3265	0.009	0.06	0.886	0.773	0.05
RS−II	2117	−0.117	0.072	0.105	0.775	0.05
RS−III	2045	−0.359	0.086	3.22e−05	0.775	0.04
YFS	1508	−0.105	0.056	0.06	0.826	0.06
Inter99	6105	−0.125	0.038	0.00108	1	0.05
META	23957	−0.107	0.019	1.07e−08		0.06

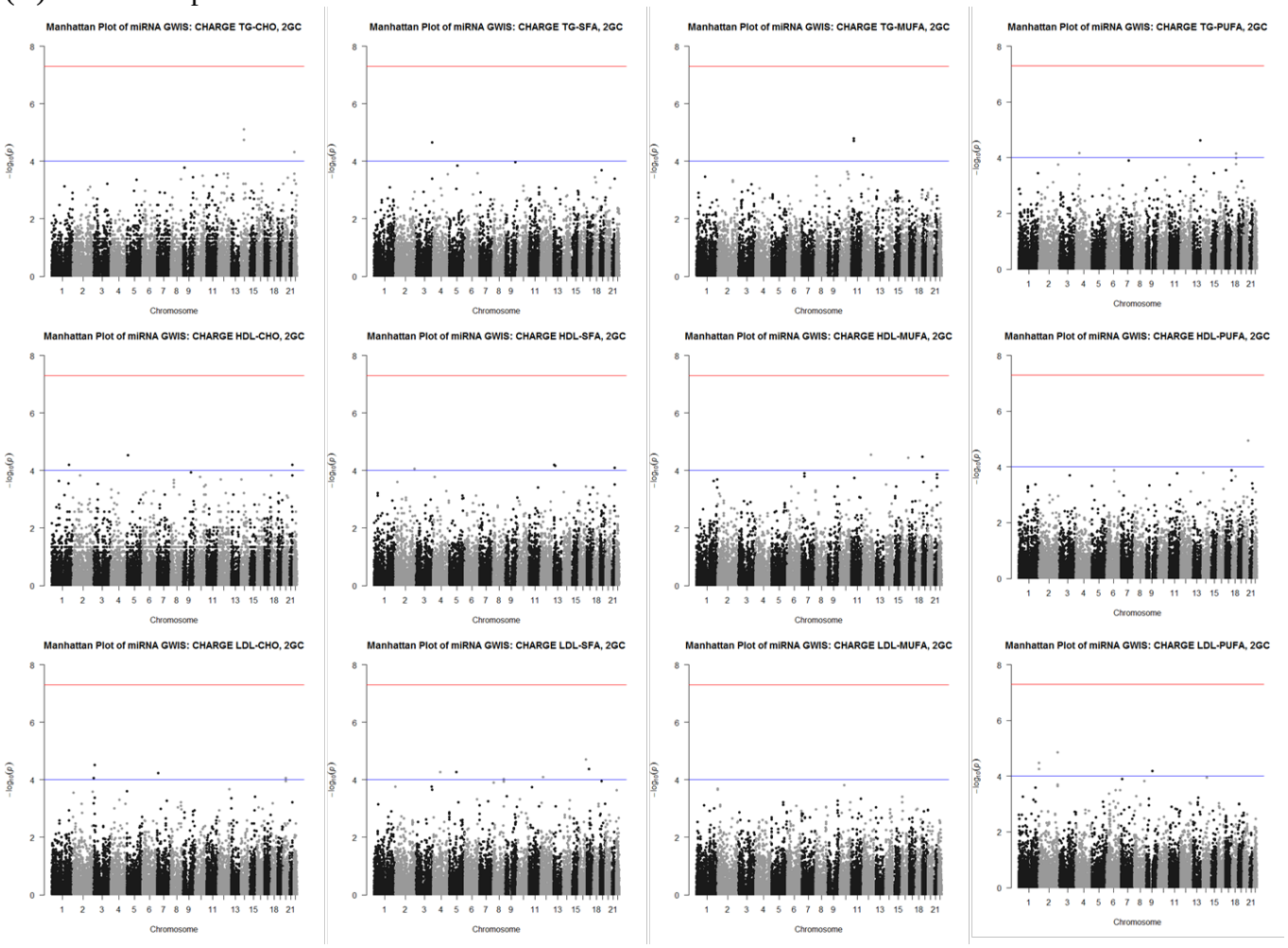


Supplemental Figure 2.1.8. Forest plots for the selected SNPs from miRNA genome-wide 2 degrees of freedom joint meta-analysis of SNP and SNP-by-dietary macronutrient interaction on blood lipid levels (model 3) in the CHARGE consortium (continued)

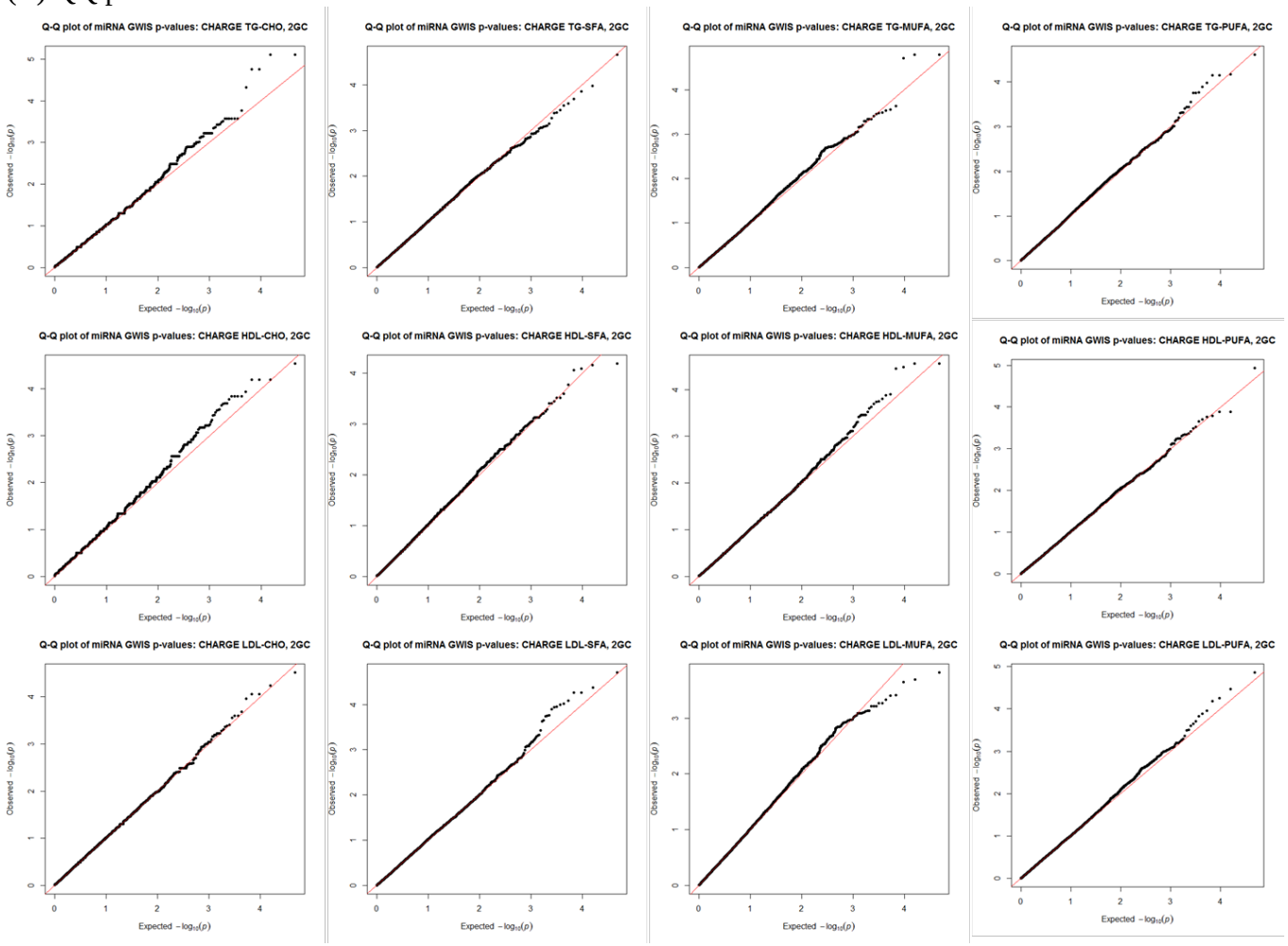
Forest plot of 2 degrees of freedom (2DF) joint meta-analysis (JMA) of SNP and SNP-by-dietary macronutrient (% energy) interaction for blood lipids (mmol/L) in 9 CHARGE cohort studies. The title of each plot specifies blood lipid outcome and macronutrient interactor: SNP coded allele/non-coded allele. The panel A (SNP) is the SNP effect (with the interaction term) at the cohort level; the panel B (INT) is the interaction effect at the cohort level; the panel C is the corresponding SNP association (without the interaction term and total energy intake) at the cohort level. The estimate from each cohort study, indicated by a filled square, was adjusted for age, sex, total energy intake, study-specific covariates, BMI and diabetic status (model 3). The size of the square is proportional to the weight of the cohort study in the overall fixed-effects estimate, and the horizontal line represents the 95% CI. The summary estimate using 2DF JMA is shown in the panel B. ARIC, Atherosclerosis Risk in Communities Study; GOLDN, Genetics of Lipid Lowering Drugs and Diet Network; GOYA, Genetics of Obesity in Young Adults; InCHIANTI, Invecchiare in Chianti; RS-I, RS-II and RS-III, Rotterdam Study baseline and extensions; YFS, Cardiovascular Risk in Young Finns Study; Inter99, Inter99 Study; META, meta-analysis; N, sample size; Qual, imputation quality; Freq, coded allele frequency, Beta, beta coefficient; SE, standard error; Int, interaction term.

Supplemental Figure 2.1.9. Manhattan and QQ plots for miRNA genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium

(A) Manhattan plots



Supplemental Figure 2.1.9. Manhattan and QQ plots for miRNA genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium (continued)
(B) QQ plots

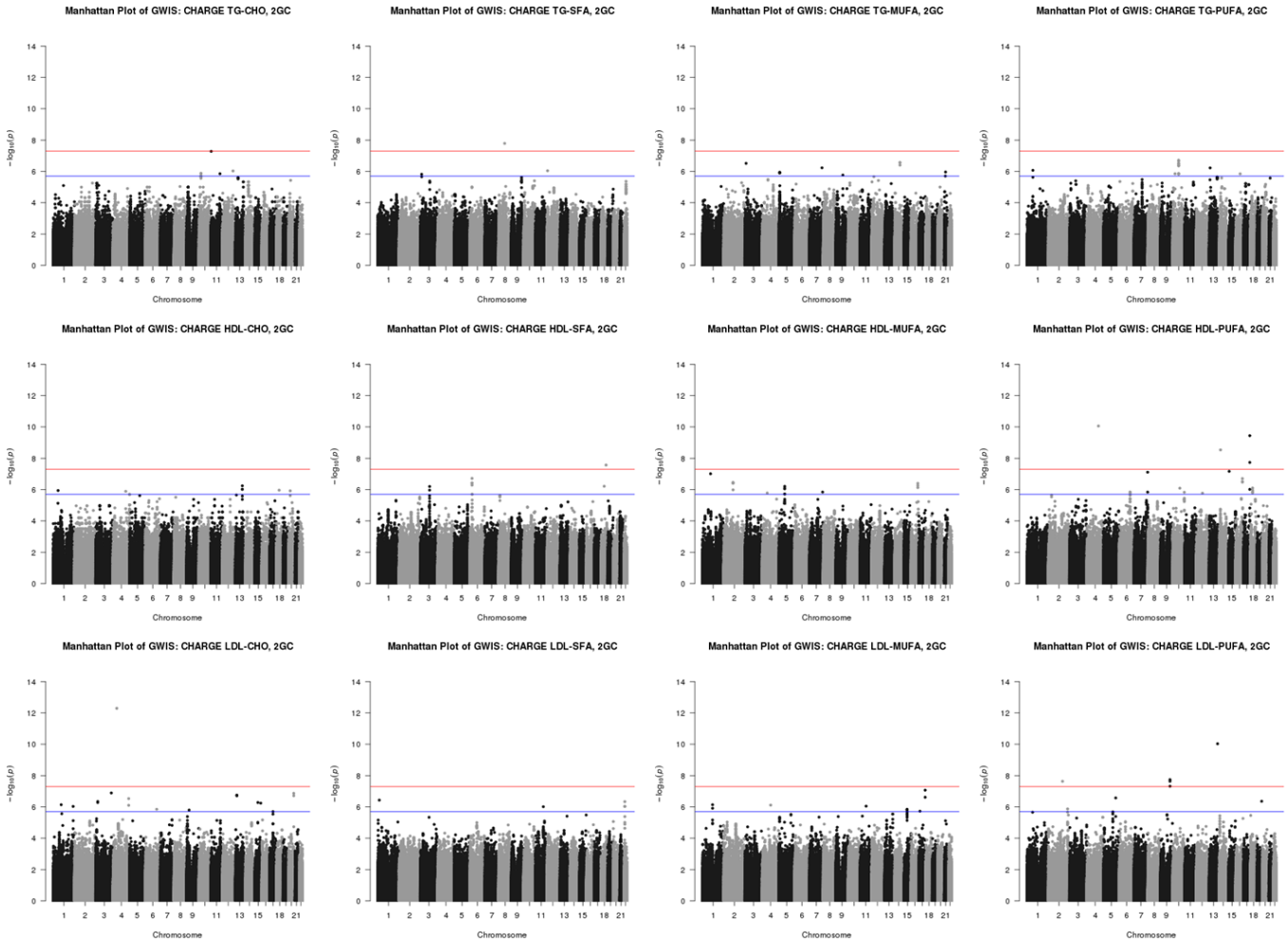


Supplemental Figure 2.1.9. Manhattan and QQ plots for miRNA genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium (continued)

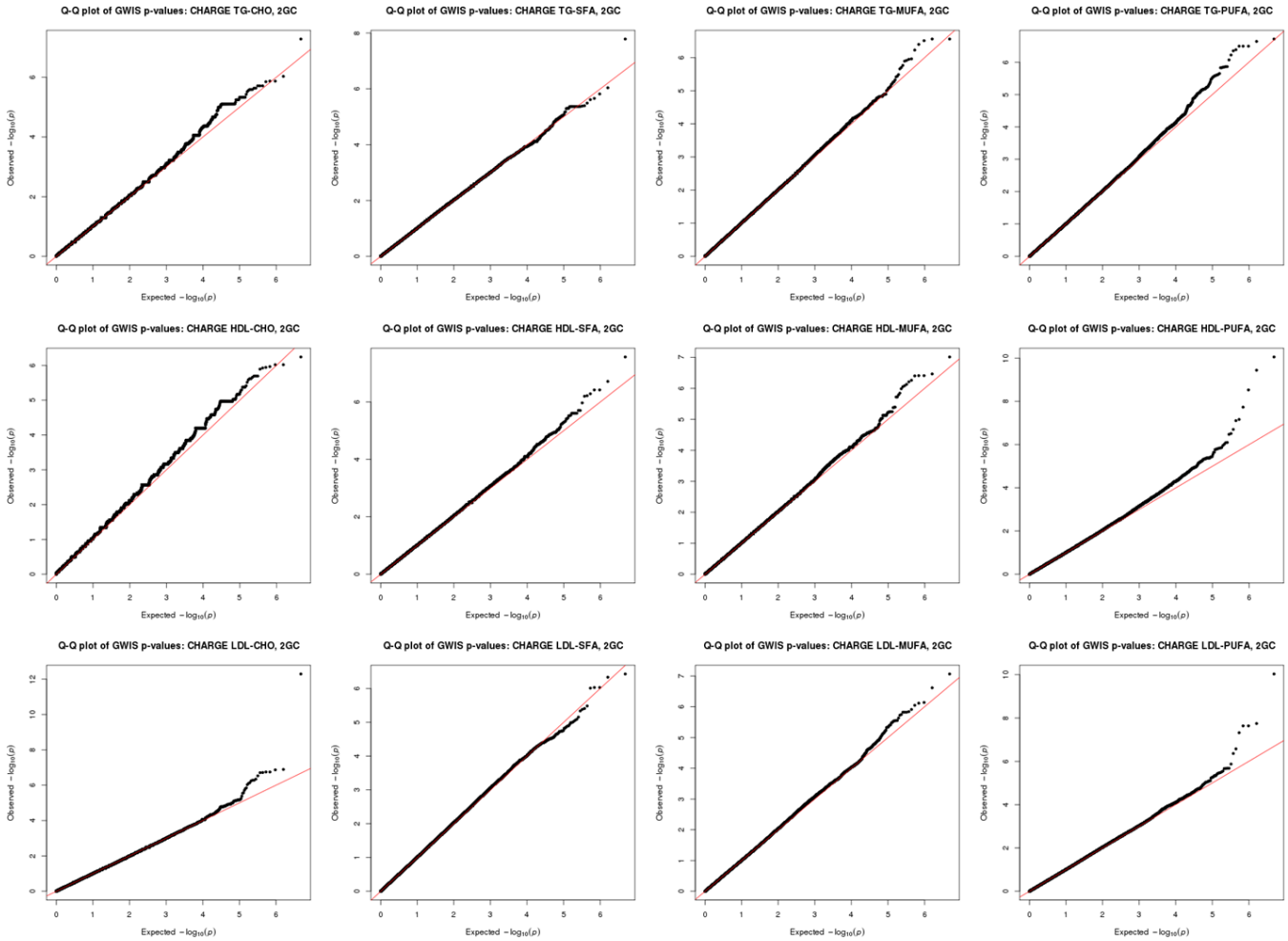
(A) Manhattan plots show the –log10(*P*-values) of ~25,000 SNPs from miRNA genome-wide interaction meta-analysis (1 degrees of freedom test, SNP-by-dietary macronutrient) for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.
(B) Quantile-quantile plots show observed *P*-values of miRNA genome-wide interaction meta-analysis (1 degrees of freedom test, SNP-by-dietary macronutrient) for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) vs. expected *P*-values by chance.

Supplemental Figure 2.1.10. Manhattan and QQ plots for genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium

(A) Manhattan plots



Supplemental Figure 2.1.10. Manhattan and QQ plots for genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium (continued)
(B) QQ plots



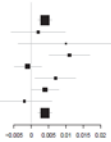
Supplemental Figure 2.1.10. Manhattan and QQ plots for genome-wide interaction meta-analysis (1 degree of freedom) with dietary macronutrients on blood lipid levels in the CHARGE consortium (continued)

(A) Manhattan plots show the –log10(*P*-values) of ~2,500,000 SNPs from genome-wide interaction meta-analysis (1 degrees of freedom test, SNP-by-dietary macronutrient) for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) ordered by their chromosomal position. Horizontal red and blue lines represent the standard genome-wide significance level $P = 5 \times 10^{-8}$ and the Bonferroni correction for miRNA functional genome-wide significance level $P = 2 \times 10^{-6}$, respectively.
(B) Quantile-quantile plots show observed *P*-values of genome-wide interaction meta-analysis (1 degrees of freedom test, SNP-by-dietary macronutrient) for blood lipids in 9 CHARGE cohort studies (with adjustment for age, sex, total energy intake, and study-specific covariates, after applying double genomic control (2GC)) vs. expected *P*-values by chance.

Supplemental Figure 2.1.11. Forest plots for the selected SNPs from miRNA genome-wide interaction meta-analysis (1 degree of freedom) with macronutrients on blood lipid levels (model 3) in the CHARGE consortium

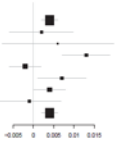
(1) SNP*CHO for LnTG: rs10151030 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.004	0.001	0.001678327	0.997	0.17
GOLDN	759	0.002	0.004	0.569704986	0.998	0.18
GOYA	331	0.01	0.007	0.158174	1	0.14
InCHIANTI	1125	0.011	0.003	0.000873353	1	0.22
RS−I	2875	−0.001	0.002	0.573454428	1	0.14
RS−II	1163	0.007	0.003	0.009579162	1	0.14
RS−III	1568	0.004	0.002	0.126590206	1	0.14
YFS	1508	−0.002	0.004	0.654246101	1	0.11
META	15939	0.004	0.001	1.82e−05		0.16



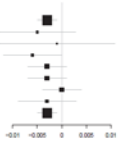
(2) SNP*CHO for LnTG: rs944450 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.004	0.001	0.003117028	0.997	0.15
GOLDN	759	0.002	0.004	0.585796802	0.998	0.16
GOYA	331	0.006	0.007	0.378389	1	0.13
InCHIANTI	1125	0.013	0.003	0.000192126	1	0.2
RS−I	2875	−0.002	0.002	0.30675103	0.999	0.12
RS−II	1163	0.007	0.003	0.011060406	0.999	0.13
RS−III	1568	0.004	0.002	0.104930887	1	0.13
YFS	1508	−0.001	0.004	0.737908741	1	0.11
META	15939	0.004	0.001	4.27e−05		0.14



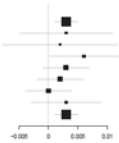
(3) SNP*CHO for LnTG: rs10009 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.003	0.001	0.000583005	0.998	0.58
GOLDN	759	−0.005	0.004	0.193318791	0.998	0.58
GOYA	331	−0.001	0.006	0.857496	0.996	0.58
InCHIANTI	1125	−0.006	0.003	0.050910161	0.994	0.58
RS−I	2875	−0.003	0.002	0.046827041	0.995	0.58
RS−II	1163	−0.003	0.002	0.154015408	0.988	0.57
RS−III	1568	0	0.002	0.798985361	0.994	0.58
YFS	1508	−0.003	0.003	0.208957228	0.998	0.73
META	15939	−0.003	0.001	3.35e−06		0.59



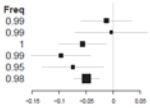
(4) SNP*CHO for LnTG: rs1860 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.003	0.001	0.002016431	0.996	0.38
GOLDN	758	0.003	0.004	0.392871849	1	0.4
GOYA	331	0.002	0.005	0.680689	0.999	0.4
InCHIANTI	1125	0.006	0.003	0.041362212	0.998	0.41
RS−I	2875	0.003	0.002	0.07528686	0.998	0.41
RS−II	1163	0.002	0.002	0.242318461	0.998	0.41
RS−III	1568	0	0.002	0.910037932	0.999	0.4
YFS	1508	0.003	0.003	0.235843395	0.998	0.26
META	15938	0.003	0.001	3.49e−05		0.39



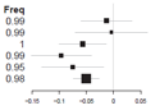
(5) SNP*PUFA for LnTG: rs17831587 A/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.013	0.024	0.600845145	1	0.99
GOLDN	759	−0.004	0.034	0.914066599	0.988	0.99
RS−I	2875	−0.057	0.022	0.01131366	0.667	1
RS−III	1568	−0.097	0.028	0.000585489	0.966	0.99
YFS	1508	−0.075	0.029	0.009623432	0.999	0.95
META	13320	−0.05	0.012	2.89e−05		0.98



(6) SNP*PUFA for LnTG: rs10503013 A/T

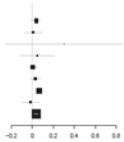
Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.013	0.024	0.600728253	1	0.99
GOLDN	759	−0.004	0.034	0.912818146	0.99	0.99
RS−I	2875	−0.057	0.022	0.011411198	0.668	1
RS−III	1568	−0.096	0.028	0.000615922	0.976	0.99
YFS	1508	−0.075	0.029	0.009634214	0.999	0.95
META	13320	−0.05	0.012	2.96e−05		0.98



Supplemental Figure 2.1.11. Forest plots for the selected SNPs from miRNA genome-wide interaction meta-analysis (1 degree of freedom) with macronutrients on blood lipid levels (model 3) in the CHARGE consortium (continued)

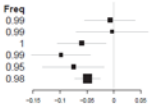
(7) SNP*PUFA for LnTG: rs11934922 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	0.039	0.022	0.074296943	1	0.99
GOLDN	759	0.009	0.042	0.825948858	1	0.98
GOYA	331	0.304	0.283	0.283411	0.998	0.98
InCHIANTI	1125	0.049	0.081	0.546174024	0.977	0.99
RS−I	2875	0.008	0.02	0.676999499	0.963	0.98
RS−II	1163	0.031	0.026	0.237932034	0.657	0.98
RS−III	1568	0.067	0.015	9.93e−06	0.992	0.98
YFS	1508	−0.016	0.041	0.704974259	0.998	0.98
META	15939	0.038	0.009	3.93e−05		0.98



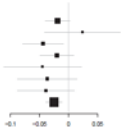
(8) SNP*PUFA for LnTG: rs6566883 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.007	0.024	0.774225948	0.974	0.99
GOLDN	759	−0.003	0.034	0.925196296	0.98	0.99
RS−I	2875	−0.06	0.023	0.009728005	0.629	1
RS−III	1568	−0.098	0.028	0.000519628	0.944	0.99
YFS	1508	−0.075	0.029	0.009603106	0.999	0.95
META	13320	−0.049	0.012	4.37e−05		0.98



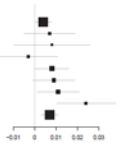
(9) SNP*SFA for HDL−C: rs6436677 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6610	−0.019	0.011	0.08637556	0.969	0.01
GOLDN	759	0.024	0.033	0.460537853	1	0.02
InCHIANTI	1125	−0.044	0.018	0.016443312	0.978	0.02
RS1	2919	−0.02	0.015	0.185104812	0.908	0.01
RS2	1167	−0.045	0.034	0.182109622	0.992	0.01
RS3	1569	−0.037	0.026	0.144224551	0.99	0.01
YFS	1508	−0.039	0.025	0.114341801	0.994	0.01
META	15657	−0.025	0.007	0.0003473		0.01



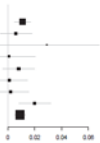
(10) SNP*CHO for LDL−C: rs3732975 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.004	0.002	0.123234304	0.917	0.19
GOLDN	759	0.007	0.006	0.19199628	0.926	0.18
GOYA	331	0.008	0.009	0.372339	0.946	0.2
InCHIANTI	1125	−0.003	0.007	0.71941752	0.934	0.16
RS−I	2844	0.008	0.004	0.051948589	0.971	0.19
RS−II	1163	0.009	0.005	0.048740563	0.97	0.19
RS−III	1568	0.011	0.005	0.020122705	0.971	0.19
YFS	1508	0.024	0.007	0.001177566	0.863	0.12
META	15844	0.007	0.002	1.32e−05		0.18



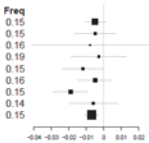
(11) SNP*CHO for LDL−C: rs10488193 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.011	0.003	0.000474729	0.99	0.91
GOLDN	759	0.006	0.006	0.355591888	0.985	0.9
GOYA	331	0.029	0.02	0.147187	0.993	0.9
InCHIANTI	1125	0.001	0.01	0.93156943	0.974	0.91
RS−I	2844	0.008	0.006	0.187443735	0.981	0.9
RS−II	1163	0.001	0.007	0.830027953	0.98	0.9
RS−III	1568	0.002	0.007	0.80495159	0.977	0.9
YFS	1508	0.02	0.006	0.000967847	0.992	0.9
META	15844	0.009	0.002	8.99e−06		0.9



(12) SNP*CHO for LDL−C: rs13111 A/G

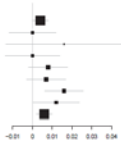
Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.005	0.003	0.06817162	0.888	0.15
GOLDN	759	−0.005	0.006	0.447755205	0.902	0.15
GOYA	331	−0.008	0.017	0.627434	0.892	0.16
InCHIANTI	1125	−0.003	0.008	0.68431814	0.89	0.19
RS−I	2844	−0.012	0.006	0.036180849	0.887	0.15
RS−II	1163	−0.005	0.005	0.368548496	0.876	0.16
RS−III	1568	−0.019	0.005	0.00027799	0.885	0.15
YFS	1508	−0.006	0.007	0.413449604	0.814	0.14
META	15844	−0.007	0.002	5.62e−05		0.15



Supplemental Figure 2.1.11. Forest plots for the selected SNPs from miRNA genome-wide interaction meta-analysis (1 degree of freedom) with macronutrients on blood lipid levels (model 3) in the CHARGE consortium (continued)

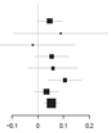
(13) SNP*CHO for LDL−C: rs1056776 C/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.004	0.002	0.07755309	0.997	0.85
GOLDN	759	0	0.006	0.974272465	0.998	0.86
GOYA	331	0.016	0.015	0.285644	1	0.84
InCHIANTI	1125	0	0.007	0.980663744	0.998	0.82
RS−I	2844	0.008	0.005	0.089938591	1	0.85
RS−II	1163	0.007	0.005	0.182489698	1	0.84
RS−III	1568	0.016	0.005	0.001293267	1	0.85
YFS	1508	0.012	0.006	0.055451029	1	0.87
META	15844	0.006	0.002	9.29e−05		0.85



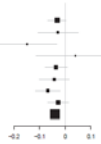
(14) SNP*SFA for LDL−C: rs13861 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.046	0.024	0.05310036	0.896	0.02
GOLDN	759	0.089	0.092	0.329324019	0.925	0.02
InCHIANTI	1125	−0.019	0.084	0.817114259	0.623	0.01
RS−I	2844	0.054	0.033	0.096589066	0.801	0.01
RS−II	1163	0.059	0.049	0.226363032	0.947	0.02
RS−III	1568	0.105	0.033	0.001425366	0.956	0.01
YFS	1508	0.034	0.024	0.143094014	0.962	0.06
META	15513	0.053	0.013	3.46e−05		0.03



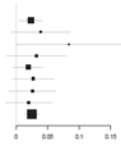
(15) SNP*SFA for LDL−C: rs16967028 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.032	0.018	0.071458537	0.999	0.98
GOLDN	759	−0.028	0.04	0.475305648	1	0.98
GOYA	331	−0.148	0.059	0.0126219	0.995	0.98
InCHIANTI	1125	0.039	0.078	0.617366904	0.998	0.98
RS−I	2844	−0.036	0.022	0.09914821	0.997	0.97
RS−II	1163	−0.043	0.03	0.146483136	1	0.98
RS−III	1568	−0.068	0.025	0.005655502	0.999	0.98
YFS	1508	−0.028	0.021	0.178100258	0.986	0.94
META	15844	−0.04	0.009	1.89e−05		0.97



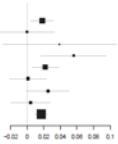
(16) SNP*SFA for LDL−C: rs11051966 A/G

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.023	0.009	0.008598265	0.995	0.11
GOLDN	759	0.039	0.024	0.104302753	0.998	0.1
GOYA	331	0.084	0.043	0.0517571	1	0.1
InCHIANTI	1125	0.032	0.024	0.180652468	0.999	0.13
RS−I	2844	0.019	0.012	0.104119147	1	0.11
RS−II	1163	0.027	0.017	0.118158763	1	0.11
RS−III	1568	0.026	0.019	0.176666961	1	0.11
YFS	1508	0.02	0.019	0.292201987	1	0.08
META	15844	0.025	0.006	5.83e−06		0.11



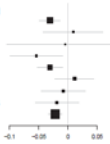
(17) SNP*SFA for LDL−C: rs3739283 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	0.018	0.007	0.017391514	0.615	0.68
GOLDN	759	0	0.017	0.989523003	0.744	0.65
GOYA	331	0.039	0.035	0.262679	0.991	0.72
InCHIANTI	1125	0.056	0.02	0.005306133	0.99	0.73
RS−I	2844	0.022	0.008	0.007366788	0.994	0.73
RS−II	1163	0.001	0.011	0.904930086	0.994	0.73
RS−III	1568	0.025	0.013	0.050210255	0.996	0.73
YFS	1508	0.004	0.012	0.735326258	0.997	0.71
META	15844	0.017	0.004	4.09e−05		0.71

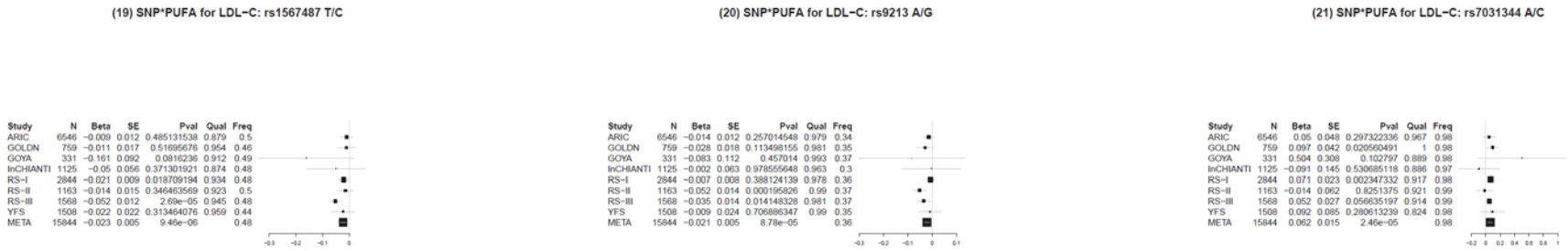


(18) SNP*SFA for LDL−C: rs7812 T/C

Study	N	Beta	SE	Pval	Qual	Freq
ARIC	6546	−0.031	0.009	0.000534988	0.999	0.11
GOLDN	759	0.009	0.026	0.717640848	1	0.11
GOYA	331	−0.005	0.051	0.923837	0.999	0.11
InCHIANTI	1125	−0.054	0.023	0.018685948	0.999	0.11
RS−I	2844	−0.031	0.011	0.007192033	0.999	0.11
RS−II	1163	0.011	0.017	0.507755798	0.998	0.11
RS−III	1568	−0.008	0.019	0.669499783	0.998	0.11
YFS	1508	−0.019	0.019	0.320236706	0.998	0.08
META	15844	−0.022	0.006	4.13e−05		0.11



Supplemental Figure 2.1.11. Forest plots for the selected SNPs from miRNA genome-wide interaction meta-analysis (1 degree of freedom) with macronutrients on blood lipid levels (model 3) in the CHARGE consortium (continued)



Forest plot of SNP-by-dietary macronutrient (% energy) interaction (1 degrees of freedom test) for blood lipids (mmol/L) in 9 CHARGE cohort studies. The title of each plot specifies an interaction test for blood lipid outcome: SNP coded allele/non-coded allele. The estimate from each cohort study, indicated by a filled square, was adjusted for age, sex, total energy intake, study-specific covariates, BMI and diabetic status (model 3). The size of the square is proportional to the weight of the cohort study in the overall fixed-effects estimate, and the horizontal line represents the 95% CI. ARIC, Atherosclerosis Risk in Communities Study; GOLDN, Genetics of Lipid Lowering Drugs and Diet Network; GOYA, Genetics of Obesity in Young Adults; InCHIANTI, Invecchiare in Chianti; RS-I, RS-II and RS-III, Rotterdam Study baseline and extensions; YFS, Cardiovascular Risk in Young Finns Study; Inter99, Inter99 Study; META, meta-analysis; N, sample size; Beta, beta coefficient; SE, standard error; Qual, imputation quality; Freq, coded allele frequency.

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2.2 Appendix: MiRNA SNP Database and Its Application (CardioG×E)

The study can be found in the published article [1], which was the extension of an earlier G×E database [2]:

[1] Parnell LD, Blokker BA, Dashti HS, Nesbeth PD, Cooper BE, Ma Y, Lee YC, Hou R, Lai CQ, Richardson K, Ordovás JM. CardioGxE, a catalog of gene-environment interactions for cardiometabolic traits. BioData Min. 2014 Oct 26;7:21. doi: 10.1186/1756-0381-7-21. eCollection 2014. PubMed PMID: 25368670; PubMed Central PMCID: PMC4217104.

[2] Lee YC, Lai CQ, Ordovas JM, Parnell LD. A Database of Gene-Environment Interactions Pertaining to Blood Lipid Traits, Cardiovascular Disease and Type 2 Diabetes. J Data Mining Genomics Proteomics. 2011 Jan 1;2(1). pii: 106. PubMed PMID: 22328972; PubMed Central PMCID: PMC3275815.

Abstract

Genetic understanding of complex traits has developed immensely over the past decade but remains hampered by incomplete descriptions of contribution to phenotypic variance. Gene-environment (G×E) interactions are one of these contributors and in the guise of diet and physical activity are important modulators of cardiometabolic phenotypes and ensuing diseases.

We mined the scientific literature to collect G×E interactions from 386 publications for blood lipids, glycemic traits, obesity anthropometrics, vascular measures, inflammation and metabolic syndrome, and introduce CardioGxE, a gene-environment interaction resource. We then analyzed the genes and SNPs supporting cardiometabolic G×Es in order to demonstrate utility of G×E SNPs and to discern characteristics of these important genetic variants. We were able to draw many observations from our extensive analysis of G×Es. 1) The CardioG×E SNPs showed little overlap with variants identified by main effect GWAS, indicating the importance of environmental interactions with genetic factors on cardiometabolic traits. 2) These G×E SNPs were enriched in adaptation to climatic and geographical features, with implications on energy homeostasis and response to physical activity. 3) Comparison to gene networks responding to plasma cholesterol-lowering or regression of atherosclerotic plaques showed that G×E genes have a greater role in those responses, particularly through high-energy diets and fat intake, than do GWAS-identified genes for the same traits. Other aspects of the CardioG×E dataset were explored.

Overall, we demonstrate that SNPs supporting cardiometabolic G×E interactions often exhibit transcriptional effects or are under positive selection. Still, not all such SNPs can be assigned potential functional or regulatory roles often because data are lacking in specific cell types or from treatments that approximate the environmental factor of the G×E. With research on metabolic related complex disease risk embarking on genome-wide G×E interaction tests, CardioG×E will be a useful resource.

Aim

In this work, we aimed to characterize G×E SNPs using miRNA SNP database.

Methods

The description of literature mining and building this dataset has been described [2]. Briefly, articles available before September, 2013 were queried at PubMed or http://www.quertle.info with search terms including genetic variation (e.g., SNP, variant, polymorphism), "interaction," or an environmental factor (e.g., diet, physical activity or exercise, alcohol, sleep, tobacco/cigarette) and, after reading and manual parsing of the data, were incorporated into the update presented here. Specifically, data fields captured included SNPs tested for GxE interactions, the assigned gene for the SNP, common aliases of the SNP, risk allele, phenotype, modifying environmental factor, population ethnicity/origin and PubMed identifier. We excluded all reports on children and adolescents, and any GxE studies examining non-alcoholic fatty liver disease and other phenotypes that are peripherally affiliated with cardiometabolic dysfunction, including atrial fibrillation, cardiomyopathies and response to lipid-lowering, glucose-homeostasis and other medications.

To demonstrate the utility of GxE SNPs within the CardioGxE dataset and interactions they represent, and to offer insight into potential mechanisms of function, we performed a series of comparisons to other biomedical genomics data. These comparisons to test for enrichment included roles in main-effect associations to disease phenotypes, transcriptional control (either via allele-specific expression, microRNA-mRNA interaction or epigenetics), adaptation, and in maintaining metabolic homeostasis in a set of pertinent tissues and cell types. To initiate these analyses, we created two separate SNP datasets based on linkage disequilibrium (LD): one for GxE SNPs and another from genome-wide association studies (GWAS) SNPs for the same cardiometabolic traits but not including any SNPs for which there is GxE evidence. Genomic coordinates (dbSNP138) for the region spanning 300 kb and centered on each SNP were determined. A bash shell script was written to retrieve iteratively all 1000 Genomes Project SNP data (accessed 04/10/2014) within this region from the CEU population using tabix and vcftools [3], pipe these data into Haploview for LD analysis using a $r^2 \geq 0.80$, and return all variants contained in the LD block of the input SNP [4]. These SNPs were used for further analysis. Significance of enrichment in a comparison between two datasets was performed by two sample *z*-test.

On the basis of our earlier microRNA (miR) target SNP database [5], we further collected human SNPs that are potentially involved in miR targeting regulation by using miR target prediction algorithms TargetScan [6], TargetScanS, miRanda [7, 8], microRNA.org [9, 10], PITA [11], PicTar [12], mirsnpscore [13, 14] and dbSMR [15]. Targets were downloaded with genome coordinates and mapped to genomic positions according to GRCh37/hg19 using the LiftOver tool from the UCSC Genome Browser and supplemented with any dbSNP137 SNPs located in predicted target sites. SNPs also were collected from published miR SNP databases: PolymiRTS [16], PolymiRTS 2.0 [17], PolymiRTS 3.0

[18], Patrocles [19], PupaSuite 3.1 [20], miRdsnp [21], miRNASNP [22], MirSNP [23] miRcode [24] and other literature resources, including predicted and experimentally validated sites. For SNPs located in miR genes, we used the UCSC Genome Browser tract wgRna_sno/miRNA and limited results to miR precursor forms then by searches for any SNPs positioned within gene regions. For genetic variants affecting miR processing machinery, SNPs were identified that mapped within genes encoding these enzymes.

GxE Allele-Specific Effects on Transcription: microRNAs

Human microRNAs (miRs) have emerged as important epigenetic regulators of cardiometabolic traits [25, 26]. Genetic variants involved in miR-mediated regulation have been shown to affect gene expression [27-29] and thus are suggested to contribute to phenotypic variation. As the environment can modulate miR levels, we hypothesized that GxE SNPs can function through miR-mediated regulation. In order to focus efforts on human SNPs likely to participate in miR targeting, we created a genome-wide miR regulatory SNP database (~900,000 SNPs) by integrating miR targeting prediction algorithms and databases from various resources. This comprehensive database allows assessment of the genetic effect of miR-mediated regulation on traits of interest. We searched GxE SNPs and their proxies against our miR SNP database to identify potential allele-specific miR-mRNA interactions and any miR-phenotype or miR-environmental factor relationships.

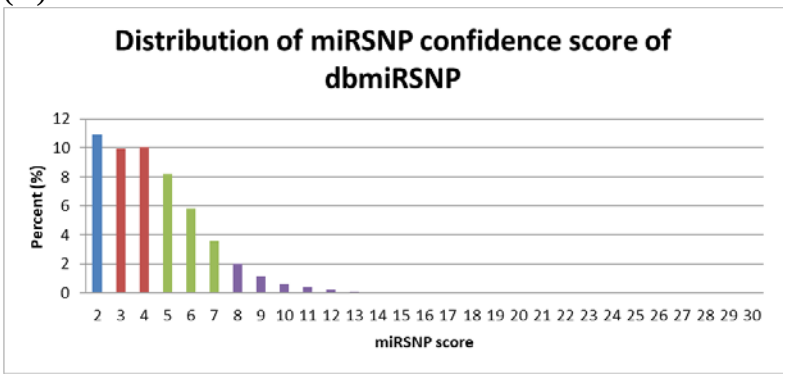
An arbitrary functional miR SNP confidence score was created by counting for each SNP the number of supported algorithms, datasets or tables supporting a genetic effect of miR-mediated regulation in order to rank the likelihood that a SNP is a miR regulatory SNP. The distribution of miR SNP confidence score in the miRSNP database is shown in **Supplemental Figure 2.1.1.** and **Figure 2.2.1**. Around 42% of miR SNPs with a miRSNP confidence score ≥ 3 (**Supplemental Figure 2.1.1.** and **Figure 2.2.1 (A)**). We did not find significant relationships between the created functional confidence score with the genetic effects (including effect sizes and *P* values) of the miRNA-related SNPs on blood lipids based on the published blood lipid GWAS data ($P < 0.005$ for association tests) from the Global Lipids Genetics Consortium (GLGC 2013) [30] ($P > 0.05$). The distribution miRSNP confidence score of the entire miRSNP database (**Figure 2.2.1 (A)**) was not statistically different from the distribution in GLGC 2013 (**Figure 2.2.1 (B)**) ($P > 0.05$).

Confidence scores for the GxE miR SNPs and their proxies ranged from 0–13. We collected all potential (predicted and experimentally validated) regulatory miRs for each SNP with a miRSNP confidence score > 3 (13 lead and 46 proxy SNPs) and identified the most frequently participating miRs among GxE miR SNPs (**Table 2.2.1**). Such commonly occurring miRs could serve as agents of a given phenotype or environmental factor preferentially. However, no easily discernible trends were noted, suggesting that miR-mediated regulation by GxE SNPs is highly specific or networked with other miRs. More research is needed to evaluate this. Our finding may be explained by the general understanding in the field that miR regulation is tissue specific and fine tunes gene expression in a precise physiological or metabolic response. Furthermore, as few common miRs have been assigned roles in GxE interactions or even in specific cellular challenges

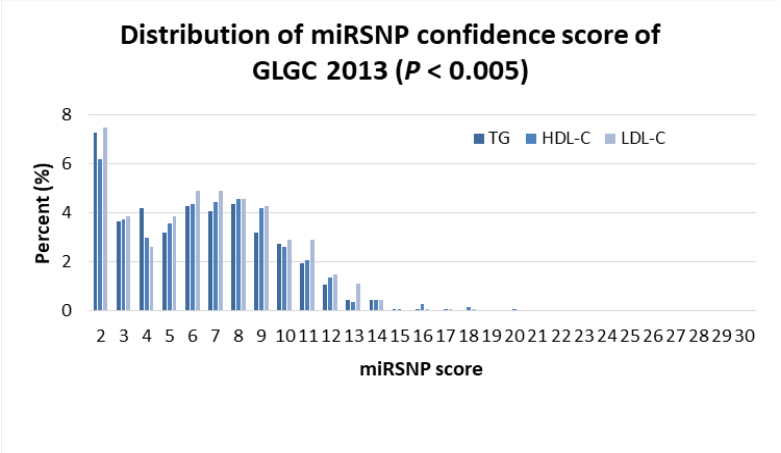
that imitate the environmental component of these GxEs, mechanistic interpretation of the participating alleles is difficult.

Figure 2.2.1. Distribution of miRNA confidence levels of dbmiRSNP

(A)



(B)



MiRSNP confidence score equals to 1 is omitted in the figures.

Table 2.2.1. Potential regulatory miRNAs involved in allele-specific miR-mRNA interactions showing G×E interactions

SNP	Lead SNP	Gene	miRSNP confidence score	Potential regulatory miRNAs*	Cardiometabolic G×E, phenotype-environmental factor
rs1063539	rs1063539	*ADIPOQ*	5	miR-593-3p	Obesity-PUFA, N-3, DHA + EPA, percent in erythrocyte membranes
rs12817689	rs2302706	*MMAB*	7	miR-33b-3p, miR-371a-3p, miR-371b-3p, miR-515-3p, miR-519e-3p	HDL-C-carbohydrate intake
rs1491235	rs1800591	*MTTP-TRMT10A*	5	miR-33b-5p	APOB-48 in VLDL-high-fat challenge; cholestanol/mol cholesterol, serum, fasting-diet; cholesterol in VLDL-high-fat challenge; ΔLDL-C-SFA, percent energy from; lathosterol/mol cholesterol, serum, fasting-diet; sitosterol/mol cholesterol, serum, fasting-diet
rs3734254	rs2076167	*PPARD*	11	miR-885-3p	ΔHDL-C-physical activity; Δwork output, max-physical activity
rs4225	rs5070	*APOC3*	6	miR-885-3p	HDL-C-fat, total intake; HDL-C-SFA intake
rs4707436	rs1049353	*CNR1*	12	miR-593-5p, miR-885-5p	Δcholesterol, total-MUFA, percent energy from; Δcholesterol, total-PUFA, percent energy from; ΔIL6, plasma-physical activity during energy restriction; ΔLDL-C-MUFA, percent energy from; ΔLDL-C-PUFA, percent energy from; Δleptin, plasma-physical activity during energy restriction; Δresistin, plasma-physical activity during energy restriction; ΔTNF, plasma-physical activity during energy restriction
rs4998	rs4994	*ADRB3*	6	miR-593-5p, miR-885-3p	BMI-energy intake; Δfat mass-physical activity; Δlean mass-physical activity; obesity-physical activity; triglyceride-low-calorie diet
rs5446	rs5443	*GNB3*	10	miR-33b-3p, miR-371a-3p, miR-371b-3p, miR-515-3p, miR-519e-3p	BMI-physical activity
rs7021	rs709592	*PSMD3*	9	miR-33b-3p, miR-371a-3p, miR-515-3p, miR-519e-3p	Glucose, fasting-carbohydrate, percent energy from; glucose, fasting-MUFA, percent energy from; insulin resistance (HOMA-IR)-carbohydrate, percent energy from

Across all miRSNP data, the maximum confidence score was 24, and for this analysis that range was 0-13, with a higher score indicating higher confidence in the miR regulatory function.
*All miRs listed contain the prefix hsa-.

Additional Methods for MiRNA SNP Database

The miRNA SNP data was originally created by the approaches described below with a particular focus on genetic variants which potentially modulate miRNA-mediated gene regulation and affect lipid and lipoprotein metabolism. However, our following work of association validation in a population-based study appeared unclear, so we then expanded the database below to a comprehensive miRNA SNP database with the goals for performing genome-wide scan for blood lipids in CHARGE consortium.

Three approaches, each employing bioinformatics tools and genomics databases, aimed to identify potential genetic variants affecting miRNA targeting and plasma lipids: (a) proxy genetic variants identified by GWAS associated with plasma lipids, (b) SNPs in candidate genes located in pathways/networks of lipid metabolism, and (c) genetic variants under positive selection. The effects of genetic variants on the expression of a target gene were then tested in publicly available databases of gene expression. Completion of Aim 1a provided a prioritized list of genetic variants for the following associations tests (Aim 1b) between genetic variants and plasma lipids in humans.

Step 1: Identification of **miRNA genes**. We formulated a list of candidate miRNAs based on literature and current knowledge. In addition, differential miRNA gene expression in lipid metabolism most relevant tissues (i.e., liver, intestine, and adipose tissues), taken from NCBI Gene Expression Omnibus (GEO), was used to select candidate miRNAs which may regulate lipid metabolism. We identified precursor miRNAs embedded in gene loci that are enriched for the annotation term “lipid metabolism.” Completing this step produced a list of candidate miRNAs with potential effects on lipid metabolism.

Step 2: Identification of **miRNA targets.** There are two major categories of computational algorithms for miRNA target prediction: the rule based (TargetScan v5.1 [31] and miRanda [8]) and the data driven approaches (PicTar [12, 32] and PITA [11]). The rule based approach derives the classifier mainly on prior biological knowledge and observations from biological experiments, whereas the data driven approach builds statistic models using the training data and makes predictions based on the model. Feature extraction (i.e., seed region match, conservation, and free energy) is a crucial element in miRNA target prediction, and it affected sensitivity and specificity of the prediction. Based on the suggestions from previous studies, we used at least two of the best programs from each approach to cover different features in order to get a comprehensive list of miRNA-mRNA interactions [33-35]. Experimentally validated targets (miRTarBase [36], TarBase v5c [37], and miR2Disease [38]) and combination databases (microRNA.org [9, 10] and miRecords [39]) were also included.

Step 3: Three major approaches [used in parallel] to identify **genetic variants**. Databases for functional SNPs in both miRNA and miRNA targets include PolymiRTS [16, 40], Patrocles [19], dbSMR [15], and MicroSNiPer [41]. There are three types of miRNA-related SNPs those affecting (1) miRNA biogenesis pathways/silencing machinery, (2) miRNA-mRNA interactions, and (3) epigenetic regulation of miRNA genes [42]. For this

study, we focused on the first two types in Aim 1. Finally, we prioritized SNPs for genetic association analysis by scoring evidence (following approaches).

GWAS (Approach a): Obtain proxy SNPs of top hits (passing genome-wide significance threshold) identified by GWAS associated with plasma lipid levels and find intersection with the genetic variants affecting miRNA regulation (above).

Candidate gene (Approach b): Use of gene ontology (GO) terms and pathway analyses related to lipid and lipoprotein metabolism narrowed the gene list. The gene list was also used to find miRNAs and continued by Step 3 and 4.

Positive selection (Approach c): Genetic modification that alters phenotypes or response to environment may be subject to selection pressure, and more than 60% of human protein-coding genes have been predicted to maintain 3'UTR pairing to miRNAs [43]. SNPs in miRNA binding sites are likely to be deleterious, so they are candidates for causal variants of human disease. However, new mutations can be advantageous in humans and reach high frequencies through the action of positive selection. In other words, SNPs showing evidence for positive adaptation may be functional and potentially influence phenotypes and disease prevalence across populations [44, 45] or may be subject to gene by environment interactions. Several measures were used to determine if above identified SNPs are under selection. Neutrality tests (Tajima' D and Fay and Wu' H) were obtained to evaluate whether the allele frequency spectrum of a given miRNA region or a miRNA target deviate from expectations under neutrality. SNP@Evolution [46] was used to obtain Heterozygosity and population differentiation (F_{ST}) [47], and evidence for recent positive selection using HapMap data was explored with Integrated Haplotype Score (iHS, Phase III), Haplotter [48] (Phase II), and composite of multiple signals [49].

Step 4: Testing cis-acting expression quantitative trait loci (eQTL) or miRNA and mRNA co-expression. The effects of genetic variants on the expression of target genes were investigated. We used databases/tools, such as GEO, GENEVAR [50], and SNPexp [51] to assess eQTL, the effects of SNPs on the expression of a target gene transcript. Main eQTL databases are: (1) human liver samples[52], downloaded from the NCBI GTEx (Genotype-Tissue Expression) eQTL browser, P value $< 1x10^{-5}$, (2) primary human liver tissue, and (3) liver, subcutaneous adipose, omental adipose tissues collected from patients of European descent who underwent Roux-en-Y gastric bypass surgery [53]. To verify miRNA-mRNA co-expression across different tissues, mimiRNA [54] was used. The main goal for this step is to validate if identified variants are associated with the level of target gene expression in relevant tissues in lipid and lipoprotein metabolism.

Additional Results Related to MiRNA SNP Database

Our research group published a genome-wide survey for SNPs altering miRNA seed sites to identify functional variants in GWAS [55]. We utilized SNP data, including 1000 Genomes Project data, to perform a genome-wide scan of SNPs that abrogate or create miRNA recognition element seed sites (MRESS). We identified 2,723 SNPs disrupting, and 22,295 SNPs creating MRESSs. We determined that 87 of these MRESS SNPs were identified in GWAS or in strong LD with a GWAS SNP, and may represent the functional variants of identified GWAS SNPs. Furthermore, 39 of these show evidence of co-expression of predicted miRNA-mRNA interactions. Previously published eQTL data also support a functional role for 4 of these SNPs shown to associate with disease phenotypes. Predicted MRESS SNPs revealed a significantly higher F_{ST} statistics (a measure of population subdivision) than non MRESS SNPs (P = 0.0004), suggesting a role for these SNPs in environmentally driven selection. For this thesis project, we expanded the previously described database further by incorporating algorithms and databases from other resources, including predicted and experimentally validated data. An expanded database, including 914,515 potential genetic variants affecting miRNA regulation (including SNPs abrogating or creating MRESS and SNPs located within miRNA genes or miRNA processing genes), has been generated. This genome-wide miRNA-related SNP database allows us to assess the genetic effect of miRNA-mediated regulation on traits of interest.

GWAS data were obtained from the NHGRI GWAS Catalog [56] and manually added from original papers of GWAS on blood lipid traits, including the most recent 95 GWAS identified loci associated with plasma lipid phenotypes [57]. 4,417 proxy SNPs were found using SNAP [58] (1,000 genomes, $r^2 \geq 0.8$). Even though no variants were found in miRNA silencing machinery, 36 SNPs found using the GWAS approach (Step3a) with higher priority assigned to SNPs supported by strong evidence of disrupting or creating a miRNA target site, are suggested to be associated with plasma lipids. Complimented with our candidate gene approach (Step3b), we have identified around 250-300 candidate SNPs using the methods described here, which are likely to be functional and can modify plasma lipids through miRNA regulation.

To expand on these findings, we have searched the SNPs available in the GOLDN Affymetrix SNP 6.0 genotype dataset against my miRNA-related SNP database and identified 8,403 SNPs with genotype data available. Based upon my genetic association analysis, the estimate variance of plasma lipids explained by all mapped miRNA SNPs combined for plasma ranges from 33% (TG) to 45% (TC) using the tool for Genome-wide Complex Trait Analysis [59-61]. MiRNA-related SNPs and their interactions with specific lifestyle factors explain a substantial part of variation of plasma lipids---“missing heritability”. Initial functional GWAS/GWIS results in GOLDN supporting the heritability estimates suggest that identified lifestyle (dietary and alcohol drinking) factors may modify genetic association through miRNA regulation. Replication study and further analysis is needed to verify which miRNA-related SNPs or miRNA-mediated environmental factors contribute to the variance of plasma lipids.

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Chapter 3 Effects of Olive Oil Consumption on miRNA Expression

3.1 Effects of 3-Months Extra Virgin Olive Oil Intervention on miRNA Expression and Cardiometabolic Traits: Randomized Controlled Trial in US Overweight and Obese Older Adults

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3.1.1 ABSTRACT

Background and Aims:
Obesity, dysregulation of metabolic traits and chronic systemic inflammation increase the risk for cardiovascular disease and other chronic diseases that accompany unhealthy aging. Epidemiological studies have shown that dietary fats influence the cardiometabolic traits and inflammation, but limited studies have evaluated the effect of olive oil consumption in overweight/obese older adults. MicroRNAs (miRNAs), small non-coding RNAs, regulate gene expression and are suggested to alter metabolic and immune function. Animal and *in vitro* studies have also demonstrated that dietary fatty acids and phytochemicals can modulate miRNA levels. We aimed to investigate the relationships between olive oil intervention and miRNA profiles in the context of cardiovascular disease biomarkers.

Methods and Results:
In this two-armed, parallel design, 3-month randomized controlled trial, 41 overweight/obese older participants (age: 72.0 ± 5.6 y; BMI: 28.8 ± 2.6 kg/m^2) were given virgin olive oil or control (soy oil/corn oil/butter) oil to replace substitutable oils/fats in their typical American diet. All cardiometabolic traits were measured at baseline and month 3. We quantified blood miRNA using miRNA microarray, quantitative RT-PCR and bioinformatics analyses. Following a 3-month intervention, systolic blood pressure (SBP) was significantly reduced in the olive oil group (P = 0.004) but not in the control group. Individuals in the olive oil group had a significantly lower SBP (P = 0.04) and marginally higher HDL-C (high-density lipoprotein cholesterol) (P = 0.06) compared with the control group at month 3. Change in hsa-miR-96-5p was correlated with changes in serum glucose and insulin levels in the olive oil group after 3 months. Furthermore, participants with impaired fasting glucose appeared to benefit from olive oil intervention by improving fasting glucose and insulin. However, the differentially expressed miRNA levels were not related to any significant effects of olive oil consumption on cardiometabolic traits.

Conclusions:
Our findings suggested that hsa-miR-96-5p may be induced by olive oil intervention and play a regulatory role in glycemic balance. How miRNAs related to olive oil consumption contributing to health benefits requires further research.

Trial registration:
ClinicalTrials.gov (ID: NCT01903304)

KEYWORDS: randomized controlled trial, olive oil, microRNA, microarrays, cardiometabolic traits, monosaturated fatty acids, aging, systolic blood pressure, glycemic traits.

ABBREVIATIONS

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VLDL-C, very-low-density lipoprotein cholesterol; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; IL-1β, interleukin 1 beta; IL-6, interleukin 6; CRP, C-reactive protein; MCP1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor alpha; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; HOMA, homeostasis model assessment; HOMA-B, HOMA of β-cell function; HOMA-IR, HOMA of insulin resistance.

3.1.2 INTRODUCTION

Aging is often accompanied by a reduced capacity for maintaining metabolic homeostasis and immunity, leading to functional decline (including metabolic dysregulation and increased chronic systemic inflammation) and increased risk for many diseases [1]. Researchers have shown that different proportions of fatty acids in the diet influence blood lipid profiles and modulate immune functions and inflammatory processes [2]. Olive oil, consisting of mainly monounsaturated fatty acids (MUFAs) and other phytonutrients such as polyphenols and squalene, has been shown to have beneficial impacts on blood lipid levels, cardiovascular diseases [3-5], antioxidant status and the inflammatory response [6]. Few studies have evaluated the role of MUFAs, especially oleic acid (C18:1, n9), the predominant fatty acids supplied by olive oil in the Mediterranean diet, on the metabolic [7] and inflammatory response in elderly. We hypothesize that high olive oil consumption will improve cardiometabolic and inflammatory biomarker profiles in overweight and obese older adults. Overall, this prospective, randomized controlled nutrition intervention trial is aimed to determine cardiometabolic impact of high olive oil consumption in elderly people.

Dietary fat intake influences plasma fatty acid profile, and altered plasma fatty acid composition has been shown to be associated with several metabolic diseases [8-10]. For instance, the most abundant plasma fatty acid, palmitic acid (C16:0), can activate inflammatory signaling to produce cytokines in macrophages [11]. The PREDIMED (PREvención con DIeta MEDiterránea) study has also shown that the changed plasma fatty acid composition derived from one year of intervention with Mediterranean diet improved metabolic syndrome [12]. However, the relationship between fatty acid composition due to diet and cardiometabolic traits are not well studied.

MicroRNAs, small non-coding RNAs, represent an epigenetic mechanism that regulates gene expression to alter metabolic function and immune response/inflammation. Epigenetic alterations are potentially reversible and can thus be modified by the environmental factors, such as dietary nutrients and the extracellular environment, for example plasma fatty acids. Animal and *in vitro* studies have demonstrated that dietary fatty acids [13-16] and phytochemicals [17, 18] can modulate miRNA levels. Gene modulation in peripheral blood cells, which include immune cells, may play an important role in inflammatory responses. In addition, miRNA regulation has been shown to mediate the age-related changes in gene expression and phenotype [19]. We hypothesize that gene regulation related to metabolic change and inflammation is mediated by miRNAs, and miRNA expression is affected by dietary fat composition, which in turn modifies plasma fatty acid profiles. We aimed to investigate the miRNA expression profiles in blood as it relates to the effects of high virgin olive oil consumption on cardiovascular disease risk factors. We also hope to reveal evidence for potential biological pathways modulated by whole blood miRNA profiles in response to olive oil consumption. To our knowledge, no intervention study has yet investigated the effect of olive oil intervention on genome-wide miRNA profiles in older adults in humans.

3.1.3 METHODS and MATERIALS

Study Design and Study Participants

This two-armed, parallel design, single-blinded randomized controlled trial was conducted between 2011 and 2013 to evaluate the effect of replacing the oils commonly used by the participants in a typical American diet with extra virgin oil in overweight and obese older adults. Participants were randomized into either the control oil or olive oil groups. All investigators and personnel involved in data collection, except for our biostatistician and the dietitian distributing the study oils, were blinded to participant group assignment. The study participants could not be blinded due to the organoleptic characteristics of the extra virgin olive oil. The assignment codes were released to all investigators who have completed sample determinations and computations of all test results obtained from participants. The intervention lasted for 3 months. **Figure 3.1.1** shows the study flow chart and design.

Subjects of both genders were included if they were 65 or older, having a BMI between 25-35 kg/m^2, consuming a typical American diet, and willing to stop using dietary supplements, olive oil, and canola oil, 30 days before and during the study. The details of inclusion and exclusion criteria were previously described [20] (also in **3.2** Appendix). The study protocol and consent forms were approved by the Tufts University/Tufts Medical Center Institutional Review Board. Study participants were recruited through direct mailing and advertising and social media. Forty-four subjects were found to be eligible following telephone, and laboratory screenings, as well as medical history and physical examination conducted by our study nurse practitioner. Participants gave consent and were enrolled in the study. Of these, 41 have completed the study. Three participants in the control group dropped out of the study (one person refused to have the delayed hypersensitivity test (DTH) plant done, one person was prescribed iron supplements by her primary care physician prior to starting the study and could not discontinue usage, and the other participant had an accident (unrelated to study participation). One subject's whole blood sample was excluded because the sample was not collected in the PAXgene Blood RNA tubes for miRNA profiling analysis

Dietary Intervention

The research dietitians provided the study oils to the participants as well as guidance on how to replace all substitutable oils/fats in their diet with the study oils and spreads. The participants were consuming and required to continue their typical American diet (before and during the study). Of those who completed the study, the least amount of olive oil used was 0.9 bottle (690 mL/bottle), and the highest amount of olive oil given was 9 bottles (this participant reported sharing the oil with his family) during the entire 3-monthe study period. The least amount of olive oil spread used was 1 container (180 g/container), and the highest amount was 6 containers. The average number of olive oil bottles used by participants was 2.8, and the average number of containers of olive oil spreads used was 3.2.

The least amount of control oil (soy oil:corn oil = 9:1) used by those who completed the 3-monthe intervention was 1.5 bottles (700 mL/bottle), and the highest amount of control oils

used was 7 bottles. The amount of control spread (butter) used ranged from 2 to 10 containers (180 g/container). The average control oil used was 3.5 bottles, and the average amount of control spread was 5.9 containers.

Assessment of Dietary Intake

Participants were given instructions on how to complete a 3-day dietary record both at baseline and at month 3. Collected dietary data from 41 participants were reviewed, entered, quality controlled and analyzed using Nutrition Data System for Research software version 2011 developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN.

Assessment of Compliance

Compliance of consuming study oil was assessed by determining the composition of fatty acids in the plasma of participants using Gas Chromatography (GC) method as previously described [21]. GC analysis was carried out using the Agilent Technologies 6890N GC (Lexington, MA) equipped with an HP-Wax 30 m x 0.25 mm column, and a flame ionization detector. Individual fatty acid retention time was determined by running standards (C14:0, C16:0, C16:1 n9, C18:0, C18:1 n9, C18:1 n7, C18:2 n6, C18:3 n6, C18:3 n3, C20:1 n9, C20:2 n6, C20:3 n6, C20:4 n6, C20:5 n3, C22:4 n6, C22:5 n6, C22:5 n3, and C22:6 n3) (NuCheck Inc, Elysian, MN). The percent of each fatty acid in the plasma sample was calculated based on total peak areas of the detectable fatty acids using ChemStation software.

Anthropometric Measurements

Anthropometric data, including standing height (to the nearest 0.5 cm), body weight (to the nearest 0.1 kg), waist and hip circumferences (to the nearest 0.5 cm) were measured by standard techniques. BMI was calculated as weight in kilograms divided by height in meters squared. Overweight and obesity were defined as BMI $\geq$ 25 and 30 respectively. Sitting systolic and diastolic blood pressures were measured using DINAMAP® ProCare Auscultatory 200 Monitor (GE Healthcare, Little Chalfont, Buckinghamshire, UK) under standardized conditions after the study participant rested 5 minutes, and the average of the two measurements (day 1 and 2) at baseline and month 3 was recorded.

Blood Collection and Processing and Biochemical Determinations

Blood samples from each participant were collected after fasting overnight. Plasma and serum were isolated by centrifugation and stored frozen at -80°C and analyzed at the same time to eliminate inter-assay variability.

Hematology profile and complete blood count (CBC)-differential (red blood cell count, white blood cell count, hematocrit, hemoglobin, mean corpuscular volume, platelet count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, lymphocytes and monocytes) were measured by electronic impedance, light scatter, double hydrodynamic sleeving system, in a HORIBA ABX Pentra C+ (ABX Diagnostics, Irvine, CA). Selected CBC values were used as covariates in the analyses for miRNA profiles.

Serum glucose was determined using an enzymatic, kinetic reaction on the Olympus AU400e with Olympus Glucose Reagents (OSCR6121) (Olympus America Inc., Melville, NY), and serum insulin was measured using the Immulite 1000 Insulin Kit (LKIN1) on the Immulite 1000 (Seimens Medical Solutions Diagnostics, Los Angeles, CA). This is a solid-phase, two-site chemiluminescent immunometric assay. Homeostasis model assessment of insulin resistance (HOMA-IR, (fasting glucose in mmol/L × fasting insulin in μIU/mL)/22.5) index was used to assess IR [22, 23], while the HOMA of β-cell function (HOMA-B, (20 x fasting insulin in μIU/mL)/(fasting glucose in mmol/L - 3.5)) index has been proposed as a good measure of β-cell function [23]. Quantitative insulin sensitivity check index (QUICKI) was used to evaluate insulin sensitivity [24]; QUICKI = 1 / ($\log_{10}$ ((fasting insulin in μU/mL) × (fasting glucose in mg/dL)) = 1/($\log_{10}$ (fasting insulin in μIU/mL) + $\log_{10}$ (fasting glucose in mg/dL)). Insulin resistance index (IR) = $\log_{10}$ (fasting insulin) + $\log_{10}$ (fasting glucose) = 1/(QUICKI).

Cholesterol was analyzed from the EDTA plasma used for the lipoprotein profile with an enzymatic endpoint reaction on the Olympus AU400e with Olympus Cholesterol Reagents (OSR6116) (Olympus America Inc., Melville, NY) [25]. High-density lipoprotein (HDL) was analyzed using EDTA plasma with the enzymatic endpoint reaction on the Olympus AU400e with Olympus HDL Reagents (OSR6195). (Olympus America Inc., Melville, NY) [25, 26]. Triglycerides measured in the EDTA plasma used for the lipoprotein profile with an enzymatic endpoint reaction on the Olympus AU400e with Olympus Triglyceride Reagents (OSR6133) (Olympus America Inc., Melville, NY) [25, 27-29]. Low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were calculated as: VLDL = triglycerides/5; LDL = cholesterol – (VLDL + HDL).

Serum levels of interleukin 1 beta (IL-1β), IL-6 and tumor necrosis factor alpha (TNF-α), were analyzed using highly sensitive technology by xMAP® Luminex® which allows detection and quantification of multiple analytes by using magnetic beads (Merck-Millipore). xPONENT MAGPIX ® software was used for data acquisition and analysis. The sensitivity for IL-1β, IL-6 and TNF-α is 0.06 pg/mL, 0.20 pg/mL and 0.18 pg/mL, respectively (minimum detectable concentration). Monocyte chemoattractant protein-1 (MCP-1) was similarly quantified in a single molecule assay (Merck-Millipore). The sensitivity was 1.9 pg/mL (minimum detectable concentration). C-reactive protein (CRP) was measured using double polyclonal antibody by enzyme-linked immunoassay (ELISA) with a sensitivity of 0.20 ng/ mL. Markers of endothelial function, serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1), were determined by immunological quantitation using magnetic beads and Luminex ® xMAP® technology. xPONENT software was used for data acquisition and analysis. The sensitivity is 0.032 ng / mL in both molecules.

Blood Collection for miRNA Profiling

Peripheral blood (2.5 ml) was collected from study participants (n = 40; one sample was not collected in PAXgene™ Blood RNA tubes) during baseline and month 3 visits in PAXgene™ Blood RNA tubes (Qiagen®, Valencia, CA), which were incubated at room temperature for 2 hours, at 4°C for 2 hours, frozen at −20°C and then transferred to −80°C within a day for long-term storage.

RNA Isolation from Whole Blood Samples

Total RNA including miRNA was isolated from whole blood collected in PAXgene™ Blood RNA tubes using the PAXgene Blood miRNA Kit (Qiagen®) following the protocol supplied by the manufacturer. RNA was collected in 80 µl of the BR5 buffer provided with the kit. Isolated RNA was stored at -80°C until use. Total RNA integrity was assessed using RNA 6000 Pico on the Bioanalyzer 2100 (Agilent Technologies, Inc., Santa Clara, CA), and quantity and purity were measured by NanoDrop 1000 Spectrophotometer (Thermo Fisher Scientific®, Waltham, MA). Small RNA was assessed by RNA 6000 Pico on the Bioanalyzer 2100 (Agilent) and miScript miRNA QC PCR Array (Qiagen®). Thirty-six RNA samples (9 samples from each intervention group at either baseline or month 3) were chosen for sample pooling based on their dietary intervention groups, sex and RNA/miRNA sample quality in whites. Due to the potential source of heterogeneity derived from ethnicity and limited quality samples in both genders available for pooling, we limited our samples at screening stage in whites.

MiRNA Profiling and identification of differentially expressed miRNAs by Quantitative Real Time-PCR (qRT-PCR)

Screening stage: We analyzed the expression levels of miRNAs in peripheral blood by using quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) in the pooled samples. We used the miScript PCR System (Qiagen®) for reverse transcription and qPCR. RNA was converted into cDNA using the miScript II Reverse Transcription Kit according to the manufacturers´ protocol. The RT-qPCR was performed with the miScript SYBR® Green PCR Kit and miScript miRNA PCR Array (miRBase v16.0 [30]; 1066 mature miRNAs) according to the manufacturers´ protocol. We normalized experimental qRT-PCR data using an average of 4 genes (small nucleolar RNA SNORD68, SNORD95, SNORD96A and the small nuclear RNA RNU6-2) as endogenous control identified by NormFinder (version 20) [31]. The normalized threshold cycle (Ct) was presented as dCt (Ct difference between a miRNA and average of control genes). This value was then converted to 2^{-dCt} for statistical analyses. Affymetrix GeneChip miRNA 4.0 Array (Affymetrix, Santa Clara, CA) was further used to confirm the findings. Two-tailed Student's *t*-test was used to evaluate expression differences of miRNAs between groups. Within-group differences for miRNA levels between baseline and post-intervention data were analyzed by paired *t*-test, while between-group differences were assessed with two-sample unpaired *t*-test. We used $P < 0.05$ without multiple testing correction as the threshold for statistical significance at the screening stage. For multiple testing correction, the False Discovery Rate (FDR) [32] and the Benjamini-Hochberg approach [33][62] approaches were used to select the miRNAs for validation.

Validation stage: We validated 6 differentially expressed miRNAs (hsa-miR-96-5p, hsa-miR-30d-5p, hsa-miR-30e-5p, hsa-miR-1910-5p, hsa-miR-598-3p and hsa-miR-3714) in 80 samples (n = 20 from baseline and month 3 in both olive oil and control groups) using qRT-PCR. We used the miScript PCR System (Qiagen®) for reverse transcription and RT-qPCR. A total of 320 ng RNA was converted into cDNA using the miScript II Reverse Transcription Kit. The RT-qPCR was performed with the miScript SYBR® Green PCR Kit. For each miScript Primer Assay, we additionally prepared a PCR negative-control with water instead of cDNA (non-template control). All suggested quality control (QC) procedures were performed. We used the average of the same 4 genes described above as the endogenous control. A Bonferroni-corrected *P* value adjusted for the number of miRNAs examined was used to determine the statistical significance.

We chose 9 potential target genes of hsa-miR-96-5p (*IRS1*, *FOXO1*, *IGF1R*, *CLOCK*, *PC*, *SLC25A1*, *INSIG2*, *CFL1* and *PFN1*) of hsa-miR-96-5p to validate using qRT-PCR in the same 80 samples. The low expressed target genes in whole blood or blood samples were excluded (determined by literature search and publicly available gene expression databases including GTEx and BioGPS). We used the RT² First Strand Kit (Qiagen®) for reverse transcription. The RT-qPCR was performed using RT² SYBR Green ROX qPCR Mastermix and Custom RT² Profiler PCR Array. All results passed the suggested QC steps. We used the average of 4 genes (*RPLP1*, *EEF1A1*, *B2M* and *RPLP0*) as the endogenous control from the whole blood samples. A Bonferroni-corrected *P* value was used to determine the statistical significance.

miRNA Bioinformatics Analysis

Differentially expressed miRNAs were analyzed through the use of GIAGEN's Ingenuity® Pathway Analysis' (IPA®; Ingenuity® Systems, QIAGEN Redwood City, www.qiagen.com/ingenuity) microRNA target filter to prioritize/choose the miRNAs measured at the validation stage.

MiRNA pathway enrichment analysis was performed using miRFocus (http://pepcyber.org/mirfocus/) and miRSystem [34] to analyze the predicted miRNA target genes for differentially expressed miRNA levels. MiRSystem uses simulation to build the null baseline probability by randomly selecting a group of miRNAs and using the default values in miRSystem to calculate the raw *P*-value for each function/pathway to identify biological functions which show enrichment for the miRNA target genes using a hypergeometric test. The empirical *P*-values of each function/pathway were determined by ranking the enriched hypergeometric probability as compared with null baseline probabilities. Weighted pathway-ranking method was used for identifying enriched biological functions. The weight for one miRNA was calculated by dividing its absolute expression value by the absolute sum of the expression values of all input miRNAs. For each functional category, the ranking score was obtained by summation of the weight of its miRNA times its enrichment −log (*P*-value) from the predicted target genes.

Statistical Analysis

For continuous variables, within-group differences between baseline and post-intervention data were analyzed by the paired *t*-test or Wilcoxon signed-rank test as appropriate, while between-group differences were assessed with two-sample unpaired *t*-tests or the Mann–Whitney U- (Wilcoxon rank-sum) test. Differences between groups at Month 3 were also tested by analysis of covariance (ANCOVA) using general linear regression models adjusting for covariates as indicated in the results. All continuous variables were examined for normal distribution if needed, and a base 10 logarithmic transformation was applied to achieve approximate normal distribution before statistical tests. For comparisons of categorical variables at baseline, we used the χ^2 test. Principal component analysis (PCA) analysis was performed to generate 3 orthogonally rotated (using VARIMAX) factors from changes (month 3 - baseline) in 7 inflammatory markers. SAS for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses, with two-sided significance set at $P < 0.05$.

We identified miRNAs differentially expressed between two groups using two-sample unpaired *t*-tests (unpaired with unequal variance) and ANCOVA (adjusting for covariates as appropriate). For multiple testing correction, the FDR approach was used [32]. We conducted further exploratory statistical analyses to relate other measures with mRNA/miRNA levels when miRNA quantification was completed. Next, we conducted bioinformatics analyses (e.g. gene set enrichment analysis and pathway analysis) to explore the potential function involved by miRNA target genes. Finally, we used Pearson's correlation and linear regression to investigate the relationships between miRNA/mRNA profiles and glycemic traits and inflammatory biomarkers. The statistical analyses were conducted using R (version 2.15.3 for Windows, 2013, R Foundation for Statistical Computing) and SAS. A two-tailed *P-value* of 0.05 was considered statistically significant.

3.1.4 RESULTS

Baseline Characteristics of the Study Participants

The baseline demographic characteristics of study participants are shown in **Table 3.1.1**. There were no significant differences in any baseline characteristics between the control and olive oil groups.

Dietary Assessment of the Intervention

During the study period, we found no significant differences in the average "amount" and "frequency" of study oil/spread consumed daily by participants between olive oil and control oil groups (**Table 3.1.2**). Due to the different fatty acid composition of the study oil/spread (**Table 3.2.1**), the consumed study olive oil provided a significantly higher amount (g) of monounsaturated fatty acids (MUFA) and significantly lower amount of polyunsaturated fatty acids (PUFA) and marginally significantly lower amount of saturated fatty acids (SFA) compared with the control group (**Table 3.1.2**). This contributed to the differences in dietary fats at month 3 between the two intervention groups in the overall dietary assessment (participants' regular diet substituted with study oils/spreads) (**Table 3.1.2**). The amount of total dietary fat supplied by the olive oil and control interventions did not differ at month 3 (**Table 3.1.2**).

Plasma fatty acid composition from the study participants reflects some degree of compliance in consuming the study oils. Oleic acid (C18:1, n9), the most abundant fatty acid in the olive oil intervention, provided ~68% of total fats, whereas it supplied only ~25% of total fats in the control oil/spread intervention (**Table 3.2.1**). Following the 3-month intervention, the olive oil group had marginally increased levels of plasma oleic acid (P = 0.08) and total MUFA (P = 0.05) and significantly reduced level of total PUFA (P = 0.01), possibly due to the marginally reduced plasma concentration of linoleic acid (C18:2 n6, P = 0.06) compared to baseline, whereas only small reduction of plasma docosapentaenoic acid (C22:5, n6), among all measured plasma fatty acids, was found in the control group (P = 0.04) (**Table 3.1.3**). At month 3, olive oil participants had significantly higher plasma oleic acid (P = 0.04) and total MUFA (P = 0.04) levels and significantly lower plasma total PUFA (P = 0.04) than control oil participants (**Table 3.1.3**).

Intervention Effect on Cardiometabolic Traits (Anthropometrics, Blood Pressure, Blood Biochemical Profiles and Inflammatory Markers)

There were no changes in anthropometric traits after 3 months of intervention in the olive oil group, while small but significant increases in body weight and BMI ($P < 0.05$) were found in the control group (**Table 3.1.4**). There were no significant differences in the anthropometric measures between groups at month 3, but participants in the olive oil group showed a trend of lower hip circumference compared with individuals in the control group (P = 0.1) (**Table 3.1.4**).

Systolic blood pressure (SBP) was significantly reduced after 3 months of intervention in the olive oil group (P = 0.004) compared to baseline, but no changes was observed in the control group ($P > 0.05$). The olive oil group had a significantly lower SBP (P = 0.04;

adjusting for age, sex, baseline SBP and use of hypertension medications) compared with the control group at month 3 (**Table 3.1.4**). Diastolic blood pressure (DBP) decreased significantly at month 3 compared to baseline in the control group ($P = 0.039$), but not in the olive oil group ($P = 0.099$).

Additionally, we observed a marginally significant higher level of HDL-C ($P = 0.06$; adjusting for age, sex and baseline HDL-C) in the olive oil compared with the control group at month 3. The levels of serum glucose, plasma inflammatory markers and CBC-differential did not change after 3 months either within or between two intervention groups (**Table 3.1.4**, data not shown for CBC). We further utilized PCA to generate 3 factors based on changes in 7 measured inflammatory biomarkers after the interventions. We found a significant difference between two study groups for rotated (varimax/orthogonal) factor 3 (loaded by sVCAM-1 and sICAM-1; $P = 0.04$) but not for factor 1 (by IL-1β, TNF-alpha and IL-6; $P > 0.05$) and factor 2 (by MCP1 and CRP; $P > 0.05$). These results remained after adjusting for age, sex and/or changes in waist. The olive oil group showed significantly lower factor 3 values than the control group ($P = 0.04$).

Initial MiRNA Microarray Screening Stage Using Pooled Samples

Differential Expression between Groups

The numbers of differentially expressed miRNAs between groups in 12 pooled samples using qRT-PCR are shown in **Figure 3.1.2** (details in **Supplemental Table 3.1.1**). We found that 127 miRNAs levels were significantly different between the two groups (control oil and olive oil) at baseline. Although the gender effect on miRNA analyses has been previously suggested [35, 36], we did not find significant differences between men and women. Therefore, three pooled samples (one male and two female) from miRNA profiling were analyzed together within each group at baseline or at month 3. Similar results were further obtained using a different microarray platform (Affymetrix GeneChip miRNA 4.0 Array; data not shown). We conducted exploratory data analyses, so statistical significance was set at P-value < 0.05 and $|\text{fold change}| \geq 1.5$ to allow more potential hits for the validation stage. Out of the pooled sample results from two different platforms, we selected 6 miRNAs differentially expressed between groups considering their expression levels and the known predicted target genes. This set contained the olive oil up-regulated miRNAs: hsa-miR-96-5p and hsa-miR-598-3p as well as the down-regulated miRNAs: hsa-miR-1910-5p, hsa-miR-3714, hsa-miR-30d-5p and hsa-miR-30e-5p.

Validation of miRNA Expression by qRT-PCR using Individual Samples

Relationship between hsa-miR-96-5p and serum glucose concentration

Selected whole blood miRNA measures were validated using qRT-PCR in individual samples. There were no significant changes at month 3 from baseline within either control oil or olive oil group (**Table 3.1.5**). The results remained after adjusting for the counts of lymphocytes and neutrophils. Among the selected miRNAs, we found that hsa-miR-96-5p level was significantly higher in the olive oil group compared with the control oil group at month 3 ($P < 0.05$) (**Table 3.1.5**). We hypothesize that the changes in miRNA levels may explain the effect of olive oil on cardiometabolic traits. However, we did not observe any significant correlation and association between the selected miRNAs (including hsa-miR-96-5p) and the changes in plasma oleic acid, SBP, HDL-C, hip circumference or

inflammatory marker factor 3 within intervention group (data not shown). In other words, the effect of olive oil consumption on SBP does not appear to be explained by the changes of plasma oleic acid and selected miRNA levels in whole blood.

Interestingly, we found the changes (from the baseline) in levels of hsa-miR-96-5p, as well as hsa-miR-30d-5p, hsa-miR-30e-5p and hsa-598-3p, in the group combined were correlated and/or associated the change in serum glucose (**Table 3.1.6**). When separated into two intervention groups, these positive associations were only observed in the olive oil group but not in the control oil group (**Figure 3.1.3; Table 3.1.6**). Similarly, change in serum glucose was also correlated with change in inflammatory biomarkers rotated factor 2 (loaded by MCP1 and CRP) from PCA in the olive oil group (Pearson partial correlation coefficients $r = -0.615$, $P = 0.025$) but not in the control group ($r = 0.413$, $P = 0.142$) when adjusting for age, sex and change in waist (**Figure 3.1.4**). As we did not see similar correlations between change of serum glucose and plasma oleic acid in either of the study groups, we hypothesize that components other than the oleic acid in olive oil contribute to the differences between the control and olive oil group.

Prediction of miRNA Targets and Over-Representation Pathway Analysis

Validation of hsa-miR-96-5p targets

We used miRSystem [34] to characterize the pathways that are potentially regulated by differentially expressed miRNAs (identified at the screening stage) based on their predicted target genes (**Supplemental Table 3.1.2**). Olive oil up-regulated miRNAs ($|\text{fold}| \geq 1.5$; $P < 0.05$) target genes enriched in functions of glucose metabolism and platelet regulation (**Supplemental Table 3.1.2 (A)**, Olive Oil Month 3 (Compared to Olive Oil Baseline). We further analyzed targets of hsa-miR-96-5p using miRFocus (Version 2.1). These targets are enriched in Gene Ontology (GO) terms: insulin receptor signaling pathway (GO:0008286), response to insulin stimulus (GO:0032868), insulin receptor binding (GO:0005158) and insulin-like growth factor receptor binding (GO:0005159) using GO categories ($P < 1 \times 10^{-5}$, 1×10^{-4}, 1×10^{-3} and 1×10^{-2} respectively), and the top enriched term is epidermal growth factor receptor signaling pathway (GO:0007173, $P < 1 \times 10^{-8}$). Among the target genes contributing to the GO terms, *IRS1* (and *FOXO1*) is a target of hsa-miR-96-5p supported by predicted algorithms and experimental evidence.

To explore, we also investigated target genes of hsa-miR-96-5p using qRT-PCR. We found a significant negative relationship between *INSIG2* expression levels and hsa-miR-96-5p only in the control group ($P < 0.05$). The expression levels are *CLOCK*, *PC* positively related to hsa-miR-96-5p ($P < 0.05$). However, these relationships did not relate to either glucose levels or plasma oleic acid ($P > 0.05$).

Effects of Olive Oil Intervention on Fasting Glycemic Traits

To further explore the relationship between olive oil intervention and glycemic traits and their potential mechanisms, we dichotomized the study participants into normal (< 100 mg/dL) and impaired diabetic status (100-125 mg/dL) using their fasting serum glucose levels at baseline. There was an interaction between fasting glucose status and study group for the changes of serum glucose and insulin (P for interaction = 0.008 and 0.09 respectively) as well as changes of insulin sensitivity (QUICKI) and resistance (1/QUICKI)

indices (*P* for interaction = 0.02 and 0.04 respectively) (**Table 3.1.7**). More specifically, the glucose level was reduced after 3 months of intervention only in the subjects with impaired fasting glucose from the olive oil group (*B* = -3.90 ± 11.14). Their insulin levels were increased less after 3 months of intervention in olive oil compared with the control oil group. Collectively, our results suggested that subjects with impaired glucose status benefited from olive oil consumption with improved glucose levels, insulin sensitivity and resistance. We also found marginally significant interactions between diabetic status and study group for the changed levels of hsa-miR-96-5p and hsa-miR-30d-5p (*P* for interaction = 0.06 and 0.07 respectively) (**Table 3.1.8**). We only observed the positive relationship between changes (after 3 months of intervention) in these miRNAs and changes in glucose levels but not the relationship between glucose and oleic acid levels. Our results suggested that the effect of olive oil consumption on glucose in subjects with impaired fasting glucose is related to hsa-miR-96-5p and hsa-miR-30d-5p levels in whole blood but not by the changes of plasma oleic acid.

3.1.5 DISCUSSION

In this study, we investigated the changes in cardiometabolic traits and explored miRNA expression profiles in a randomized controlled pilot study replacing substitutable oil/fat with olive oil compared with control oil in older adults. Several cardiovascular disease risk factors including SBP and HDL-C improved in response to the olive oil intervention. The subjects with impaired fasting glucose appeared to benefit from olive oil consumption by improving glucose levels, insulin sensitivity and resistance. We conducted miRNA profiling analysis to identify differentially expressed miRNAs in whole blood between two intervention groups. Among them, hsa-miR-96-5p level was increased in the olive oil group compared to the control group at month 3. The differentially expressed miRNA levels were not related to any traits that differed between two study groups, but changes in some identified miRNAs including hsa-miR-96-5p were positively correlated with changes in serum glucose and insulin only in the olive oil group.

Effects of Olive Oil Consumption on Cardiometabolic Traits

Our finding on the beneficial effect of olive oil intervention on SBP is consistent with many other studies [3-5]. It is still not clear which components (for example, MUFA or polyphenols) in virgin olive oil are responsible for its hypotensive effects [5, 37], and the mechanisms are not yet understood. The effects of olive oil on blood lipid profiles have also been demonstrated in many studies. Although results are inconsistent for specific blood lipid levels in the literature, olive oil showed hypocholesterolemic effects on blood lipids in general. Part of the reason for the lack of consistency in published studies may be related to different study designs with various reference/control groups and to differences in olive oil purity and composition. Similarly, it is also not clear which components (for example, MUFA or squalene) of olive oil are responsible for its hypocholesterolemic effect [38-40]. MUFAs have been shown to exert beneficial (or neutral) effects on blood lipid profile and thus reduce the risk of CVD [38, 41-43]. While the present study used a single source of olive oil and was not designed to compare refined and virgin oils, our findings suggest that further research is needed to investigate the many potential cardio-protective constitutes of virgin olive oil.

The effects of olive oil consumption on glycemic traits and markers of inflammation and endothelial function in subject with normal glucose status were unclear in the present study. However, subjects with impaired fasting glucose at baseline improved following the consumption of olive oil. The effects of increased glucose and insulin levels in the olive oil group in the whole study may not be harmful and under the normal range. The current literature does not evaluate the effects of olive oil consumption in the similar human population [44, 45], so our results of fasting glycemic traits may be metabolic or age-specific response.

Effect of Dietary Factors, Plasma Fatty Acids on miRNAs

It has been shown that miRNA can be regulated by dietary factors (including total energy intake, the proportions of dietary macronutrient and fatty acids) in animals and cell culture-based experiments. In the present study, we tested the effect of olive oil consumption on miRNA profiles. We hypothesize that different dietary fat compositions and the different

plasma fatty acid compositions arising from the different dietary interventions may contribute to different patterns/networks of miRNA-mRNA (target gene). However, due to the small effect sizes observed in our intervention, we were not able to validate a panel of miRNAs, which were specifically or differentially expressed in the olive oil group. Several factors may account for our results. First, we found that many miRNA levels differed at baseline between the two intervention groups, which may have limited our ability to detect differences at month 3 when without baseline correction. These differences in miRNA levels were not reflected in biochemical (e.g., lipids and glycemic traits) differences, suggesting that randomization could not prevent differences at the molecular levels (miRNA levels in the present study), and these differences were especially challenging in a small pilot trial. Second, the effect size of this intervention study was small for both plasma fatty acid profile (oleic acid in particular) and all of the cardiometabolic traits measured in this study. Although ~80% of the participants consumed more than 20g (~1 to 2 tablespoons, which is common in the typical American diet) of the study oil/spread, this amount was much less than the amount consumed as part of the typical Mediterranean diet (~2 to 6 tablespoons) in the literature [46, 47]. This may explain why we did not observe any significant correlation between plasma fatty acids and identified miRNA levels.

Effect of miRNAs on Cardiometabolic Traits

Previous studies have reported that miRNAs regulate up to 60% of human genes [48-50] suggesting that metabolic function and inflammation processes may be altered by miRNA-based mechanisms. In this study, we aimed to investigate the relationship between miRNA levels and the traits of interest. We examined the role of miRNAs as a mediator of the effect of olive oil on cardiometabolic traits, and we explored the underlying mechanisms using miRNA microarray and bioinformatics analyses. We identified several miRNAs that were differentially expressed between two intervention groups. Our results indicate that among the differentially expressed miRNAs, hsa-miR-96-5p is the most promising candidate for further research in target genes validation related to fasting glycemic regulation and other related functions. *MIR96* is located in the miR-183-96-182 cluster, and hsa-miR-96-5p is found to be present in hepatoma, pancreatic islets and platelets [51]. However, we did not observe any correlation between hsa-miR-96-5p and platelet counts. Further studies are needed to validate whether olive oil may affect platelet function through hsa-miR-96-5p. Recently, miR-96 (targeting *Insig2*), miR-182, and miR-183 were shown to involve in lipid metabolism by regulating nuclear SREBP levels in mice [52]. In addition, Wang *et al.* demonstrated that miR-96 regulates SR-BI expression and HDL-C uptake [53]. Although the intervention effect on serum cholesterol was small in the current study, this result still shows the potential to further assess the effect of olive oil on the roles of hsa-miR-96-5p by regulating expression levels of its potential targets in the future studies. Previous studies have also described the roles of miR-96 in the development of hepatic insulin resistance in SFA-induced obesity in mice [54], negative regulation of insulin secretion and beta cell development [55-57]. Our findings support that olive oil can regulate miR-96-5p depending on the status of fasting glucose in study subjects. With olive oil consumption, we hypothesize that miR-96-5p level is increased for normal insulin secretion in response to normal fasting glucose, while miR-96-5p level is decreased to increase insulin secretion and lower serum glucose levels in response to impaired fasting glucose.

Olive oil is a complex food comprised of many chemical constitutes that may confer cardio-protective benefits. Our study does not support the hypothesis that we suggest that olive oil lowers SBP through relationship between plasma oleic acid or selected miRNAs levels in whole blood. Similarly, we did not observe plasma oleic acid mediating the correlation between changes of hsa-miR-96-5p and serum glucose in the study oil groups. We hypothesize that components other than the oleic acid in olive oil contribute to the differences between the control and olive oil group. We also speculate that the targets of selected miRNAs are more responsive in the olive oil group, leading to the differences in relationships between miRNA and serum glucose in the two interventions. Further work to identify and quantify the metabolites of phenolic compounds in participants is needed to determine the roles of other components in olive oil on cardiometabolic phenotypes.

MiRNA Profiles in Peripheral Blood

To observe the effect of olive oil consumption on miRNA levels, we measured miRNA profiles in whole blood, which includes cell and non-cell fractions. As we used whole blood, we were unable to determine whether identified miRNAs coming from intra-cellular (blood cell) or extracellular sources. Modulation of gene expression in peripheral blood immune cells may have an important role in inflammatory responses, which can be mediated by miRNAs. Microvesicles (50-1000 nm) in plasma play a role in intercellular communication to transfer proteins, mRNAs, miRNAs, and lipids from donor cells to recipient cells [58-60]. Several hypotheses to account for the presence of tissue miRNAs in circulation have been proposed: they are passively secreted as a result of cell death and lysis [61]; tissue cells actively secrete miRNAs into their microenvironment, where they enter the circulation (whether this process is random or regulated is unknown) [59, 61, 62]; and microvesicles, containing miRNAs, stimulate cellular signaling and mediate communication between different tissues within the body [59, 63]. Further research is need to assess the responses of different sample fractions to dietary interventions because miRNA expression profile derived from peripheral blood cells may differ from that contained in microvesicles [59].

We investigated the relationships among diet, plasma fatty acids, serum biochemical measures, immune cell counts and inflammatory biomarkers followed by an exploration of which biological pathways were modulated by miRNA profiles in whole blood in response to an olive oil intervention. Based on the target and enrichment pathway analyses, the potential roles and mechanisms of hsa-miR-96-5p on serum glucose and insulin may involve the insulin-signaling pathway. However, whether evidence derived from peripheral blood is translatable to events in relevant tissues will require additional studies. Similarly, whether miRNA profiles and identified miRNAs in whole blood represent good biomarkers of the response to dietary intervention needs to be validated in separate studies.

Strengths and Limitations of the Present Study

The strengths of the present study were the randomized intervention design and examination of the effects of olive oil consumption in free-living people. The study provision of dietary oils and dietary instructions of how to replace substitutable oil/fat from participants' diet (American diet) in a real-life context, is similar to that of the PREDIMED study [64]. From a public health perspective, this unique design estimates the effectiveness

of simple dietary recommendations provided by health professionals on health promoting policies. However, several elements of the study design may also account for the small effects observed in the study. Some modifications, such as close monitoring the study participants or their caretakers, increasing sample size or increasing the intervention duration, may be needed to improve the effect size of olive oil consumption in future studies.

However, several limitations exist for this study. First, being a pilot study, small sample size reduced its statistical power. In addition, the challenge of relatively low power is exacerbated by the large variation in gene expression or even cardiometabolic traits that characterizes these older study participants as aging is a well-known contributor to variability in gene expression. Second, miRNA profiles were measured in peripheral blood samples. Although peripheral blood is easily accessible in people to facilitate evaluation of gene expression profiles, miRNA expression in blood may not reflect the profiles in the most relevant tissues for different metabolic traits. Third, providing study oils to participants is a feasible and practical design for conducting a long-term dietary intervention; however, this design may reduce investigators' ability to control the amount and frequency of study oil consumed, especially in an older population. Plasma fatty acid composition used to assess compliance showed a small but significant difference within and between groups. Fourth, there are some discrepancies of miRNA regulation between pooled samples and individual samples indicating that some unrecognized factors such as study participant race/ethnicity, differences in RNA quality, or other uncontrolled lifestyle factors may be introducing variation. Fifth, this study lacks the objective assessment of study adherence that could be obtained with biomarkers. Plasma fatty acid composition might reflect only part of the dietary compliance in this study, as olive oil is not the only dietary contributor to plasma oleic acid, and in addition, MUFAs can be endogenously synthesized from SFA, glucose or alcohol. A more controlled study should be planned in the future to include tyrosol and hydroxytyrosol (major polyphenols in olive oil) and other phenolic compounds to more precisely assess dietary compliance.

In summary, we have assessed the effect of olive oil consumption on obesity-related measures, cardiometabolic traits and inflammatory markers by investigating potential underlying mechanisms that may involve miRNA-mediated gene expression. Exploratory analyses of miRNAs and their targets may be used as a tool to generate new hypothetical molecular mechanisms that underlie the effects of intervention studies. The identified differentially expressed miRNAs in blood might be used as indicators of small effect of dietary intervention on biomarkers. Further research is needed to develop a signature pattern in miRNAs unique to olive oil (or any dietary) intervention/consumption. Hypothesis-generating results obtained for hsa-miR-96-5p suggest that the benefits associated with olive oil consumption on glycemic traits in subjects with impaired fasting glucose may be mediated through miRNA regulation. The miRNA target gene analyses further supports the possibility that olive oil consumption may regulate insulin signaling and glucose though miRNA-mediated gene regulation. The effects of olive oil consumption on miRNAs and their relationship with plasma fatty acids or other metabolites are not clear, and additional research is needed. With relevance to nutritional research, we show that miRNA research can be involved in the dietary effects on health outcomes.

AUTHOR CONTRIBUTIONS

J.M.O. contributed to study design of the genetic analyses of the study and critical manuscript revising. S.N.M. is the primary investigator of the study and contributed to study design and manuscript revising. Y-C.L. contributed to study design of miRNA/mRNA analyses, data acquisition, data quality control/analysis, results interpretation and writing of the manuscript. J.B.B., M.M. and D.W. contributed to study design and manuscript revising. M.R., L.P. and A.M. contributed data acquisition and manuscript revising. C-Q.L., R.B-R. P.F.J, S.L-F. and C.F-H. contributed to results interpretation and manuscript revising. C.E.S., A.M., Y.M. and L.D.P. contributed to manuscript revising. All authors read and approved the final manuscript.

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DISCLOSURE DECLARATION

None of the authors had a potential conflict of interest.

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Table 3.1.1. Demographic characteristics of the study participants at baseline by gender and study groups[a]

	Total	**Males**	**Females**	*P*[b]	**Control**	**Olive**	*P*[b]
n (%)	41 (100)	14 (34.15)	27 (65.85)		21 (51.22)	20 (48.78)	
Female (%)	27 (65.85)				15 (71.43)	12 (60.00)	0.520
Age (year)	72.0 ± 5.6	74.1 ± 5.5	70.9 ± 5.4	0.073	71.7 ± 5.4	72.3 ± 6.0	0.756
Race				0.300			0.572
White or Caucasian (%)	28 (68.29)	10 (71.43)	18 (66.67)		15 (71.43)	13 (65.00)	
Black or African American (%)	12 (29.27)	3 (21.43)	9 (33.33)		6 (28.57)	6 (30.00)	
Asian (%)	1 (2.44)	1 (7.14)	0		0 (0.00)	1 (5.00)	
Marriage				0.042			0.353
Education				0.709			0.563
Current Medication- Hypertension or High Blood Pressure (%)	24 (58.54)	8 (57.14)	16 (59.26)	1.000	10 (47.62)	14 (70.00)	0.208
Current Medication- High Cholesterol (%)	15 (36.59)	6 (42.86)	9 (33.33)	0.734	9 (42.86)	6 (30.00)	0.520
Current Medication- Type 2 Diabetes (%)	1 (2.44)	0 (0.00)	1 (3.70)	1.000	1 (4.76)	0 (0.00)	1.000

[a] Values are presented as mean ± SD or n (%).
[b] *P*-value between groups by independent *t*-test or chi-square test.

Table 3.1.2. Daily dietary intake of the study participants at baseline and month 3[a]

	Baseline			Month 3		
	Control oil group	**Olive oil group**	*P1*	**Control oil group**	**Olive oil group**	*P2*
n (%)	21 (51.2)	20 (48.8)		21 (51.2)	20 (48.8)	
Study oil/spread (g/d)	NA	NA	NA	39.0 ± 32.1	39.3 ± 29.4	0.967
Energy from study oil/spread (Kcal)	NA	NA	NA	326.6 ± 273.6	347.1 ± 260.2	0.782
Total Fat from study oil/spread (g/d)	NA	NA	NA	36.9 ± 30.9	39.3 ± 29.4	0.782
Total SFA from study oil/spread (g/d)	NA	NA	NA	9.9 ± 8.5	5.4 ± 4.1	0.061
Total MUFA from study oil/spread (g/d)	NA	NA	NA	8.8 ± 7.3	28.6 ± 21.5	<.001
Total PUFA from study oil/spread (g/d)	NA	NA	NA	16.4 ± 16.3	4.1 ± 3.1	0.015
Frequency of using study oil/spread	NA	NA	NA	2.0 ± 0.7	1.8 ± 0.7	0.409
Energy intake (Kcal/d)	1809.2 ± 576.6	1716.7 ± 571.9	0.609	1967.7 ± 596.3	2192.9 ± 665.7	0.260
Protein (g/d)	74.0 ± 25.9	73.4 ± 22.2	0.936	70.5 ± 23.4	82.7 ± 28.6	0.130
Carbohydrate (g/d)	221.7 ± 74.7	212.7 ± 89.0	0.727	218.0 ± 81.9	234.6 ± 95.8	0.553
Total dietary fiber (g/d)	22.5 ± 12.3	20.9 ± 11.2	0.705	21.3 ± 11.3	21.5 ± 8.2	0.939
Fat (g/d)	70.9 ± 27.4	64.4 ± 25.2	0.434	92.4 ± 40.8	103.3 ± 48.1	0.423
Total SFA (g/d)	21.1 ± 7.8	20.8 ± 9.5	0.928	28.8 ± 11.9	28.6 ± 13.2	0.867
Total MUFA (g/d)	23.5 ± 8.6	22.9 ± 9.0	0.824	28.4 ± 11.7	50.8 ± 30.0	0.001
MUFA 16:1 (g/d)	1.08 ± 0.58	1.00 ± 0.51	0.652	1.09 ± 0.51	1.62 ± 0.69	0.005
MUFA 18:1 (g/d)	22.0 ± 8.3	21.4 ± 8.6	0.813	26.6 ± 11.1	48.3 ± 28.8	0.001
Total PUFA (g/d)	18.0 ± 8.3	15.1 ± 8.1	0.269	28.4 ± 18.7	16.6 ± 6.8	0.010
Total Trans FA (g/d)	2.14 ± 1.36	1.87 ± 1.15	0.430	2.59 ± 1.22	2.05 ± 1.17	0.088
Cholesterol (mg/d)	221.6 ± 102.9	261.4 ± 133.2	0.252	267.5 ± 117.2	282.2 ± 140.5	0.692
Protein (% E)	16.9 ± 5.0	18.0 ± 4.3	0.327	14.9 ± 4.6	16.0 ± 5.0	0.472
Carbohydrate (% E)	47.7 ± 6.4	47.7 ± 8.3	0.983	42.7 ± 8.6	42.2 ± 9.6	0.851
Fat (% E)	34.0 ± 6.2	32.3 ± 7.4	0.411	40.6 ± 10.2	40.1 ± 9.2	0.903
Total SFA (% E)	10.3 ± 2.8	10.7 ± 3.8	0.728	12.9 ± 3.8	11.1 ± 2.7	0.075
Total MUFA (% E)	11.6 ± 2.3	11.5 ± 2.9	0.860	12.6 ± 2.5	19.4 ± 6.8	<.001
Total PUFA (% E)	8.6 ± 3.3	7.3 ± 2.4	0.151	12.0 ± 5.9	6.7 ± 2.1	<.001
PUFA to SFA ratio	0.92 ± 0.45	0.81 ± 0.42	0.344	0.98 ± 0.44	0.63 ± 0.22	0.003
MUFA to SFA ratio	1.22 ± 0.30	1.11 ± 0.35	0.182	1.02 ± 0.24	1.81 ± 0.61	<.001
S:M:P	1:1.2:0.9	1:1.1:0.8		1:1:1	1:1.8:0.6	

Abbreviations: SFA (or S), saturated fatty acids; MUFA (or M), monounsaturated fatty acids; PUFA (or P), polyunsaturated fatty acids; FA, fatty acids; E, energy; NA, not applicable.
[a] Values are presented as mean ± SD
P1: *P*-value between groups at baseline by independent *t*-test.
P2: *P*-value between groups at month 3 by independent *t*-test.

Table 3.1.3. Plasma fatty acid composition (% total fatty acids) of the study participants within and between study groups[a]

	Control oil group (n=20)				Olive oil group (n=20)							
	Baseline	**Month 3**	**Change**	*P1*	**Baseline**	**Month 3**	**Change**	*P2*	*P3*	*P4*	*P5*	*P6*
C14:0 Myristic acid (%)	1.35 ± 0.29	1.36 ± 0.29	0.01 ± 0.31	0.883	1.30 ± 0.22	1.42 ± 0.37	0.11 ± 0.40	0.222	0.599	0.576	0.369	0.478
C16:0 Palmitic acid (%)	22.14 ± 1.79	22.19 ± 2.12	0.05 ± 1.94	0.918	22.23 ± 1.65	22.58 ± 1.81	0.35 ± 1.62	0.351	0.872	0.536	0.598	0.514
C16:1 n9 Palmitoleic acid (%)	1.89 ± 0.74	1.99 ± 0.80	0.10 ± 0.35	0.212	1.68 ± 0.58	1.9 ± 0.99	0.21 ± 0.82	0.258	0.342	0.755	0.579	0.560
C18:0 Stearic acid (%)	7.6 ± 0.61	7.58 ± 0.91	-0.02 ± 0.73	0.899	7.63 ± 0.78	7.67 ± 0.83	0.05 ± 0.73	0.780	0.915	0.743	0.772	0.927
C18:1 n9 Oleic acid (%)	18.81 ± 2.37	18.19 ± 2.38	-0.63 ± 2.25	0.229	18.51 ± 2.26	19.99 ± 2.84	1.48 ± 3.55	0.077	0.685	**0.035**	**0.031**	**0.035**
C18:1 n7 Vaccenic acid (%)	1.62 ± 0.23	1.56 ± 0.23	-0.06 ± 0.22	0.206	1.53 ± 0.18	1.61 ± 0.23	0.08 ± 0.29	0.259	0.186	0.493	0.094	0.259
C18:2 n6 Linoleic acid (%)	31.41 ± 3.33	30.51 ± 5.39	-0.90 ± 3.77	0.299	31.81 ± 4.19	29.93 ± 4.89	-1.88 ± 4.17	0.058	0.738	0.724	0.439	0.472
C18:3 n6 Gamma Linoleic acid (%)	0.55 ± 0.17	0.63 ± 0.27	0.08 ± 0.22	0.112	0.55 ± 0.29	0.59 ± 0.27	0.03 ± 0.22	0.503	0.977	0.564	0.490	0.615
C18:3 n3 Alpha Linoleic acid (%)	0.62 ± 0.15	0.62 ± 0.19	-0.0002 ± 0.1740	0.995	0.58 ± 0.17	0.57 ± 0.21	-0.02 ± 0.18	0.703	0.518	0.445	0.783	0.447
C20:1 n9 11-Eicosenoic Gondolic acid (%)	0.13 ± 0.04	0.14 ± 0.04	0.01 ± 0.06	0.483	0.14 ± 0.06	0.14 ± 0.05	-0.002 ± 0.058	0.898	0.391	0.871	0.560	0.889
C20:2 n6 11-14 Eicosadienoic acid (%)	0.21 ± 0.09	0.19 ± 0.05	-0.02 ± 0.08	0.348	0.2 ± 0.05	0.19 ± 0.03	-0.01 ± 0.05	0.330	0.589	0.678	0.727	0.886
C20:3 n6 Homogamma Linoleic acid (%)	1.49 ± 0.37	1.43 ± 0.27	-0.07 ± 0.22	0.206	1.43 ± 0.25	1.50 ± 0.32	0.06 ± 0.28	0.333	0.570	0.456	0.120	0.106
C20:4 n6 Arachidonic acid (%)	8.94 ± 2.26	9.06 ± 2.59	0.11 ± 1.16	0.662	8.64 ± 2.15	8.30 ± 2.09	-0.34 ± 1.71	0.389	0.664	0.316	0.334	0.330
C20:5 n3 Eicosapentaenoic acid (%)	0.67 ± 0.29	0.61 ± 0.23	-0.06 ± 0.32	0.419	0.66 ± 0.37	0.73 ± 0.32	0.12 ± 0.26	0.057	0.966	0.191	0.062	0.114
C22:4 n6 Docosatetraenoic acid (%)	0.25 ± 0.05	0.25 ± 0.05	-0.001 ± 0.053	0.921	0.25 ± 0.08	0.24 ± 0.07	-0.007 ± 0.064	0.637	0.919	0.852	0.763	0.743
C22:5 n6 Docosapentaenoic acid (%)	0.16 ± 0.05	0.13 ± 0.06	-0.03 ± 0.06	**0.040**	0.16 ± 0.05	0.15 ± 0.06	-0.009 ± 0.062	0.531	0.590	0.502	0.283	0.377
C22:5 n3 Docosapentaenoic acid (%)	0.42 ± 0.17	0.45 ± 0.15	0.03 ± 0.14	0.361	0.58 ± 0.37	0.48 ± 0.21	-0.11 ± 0.38	0.226	0.075	0.667	0.145	0.739
C22:6 n3 Docosahexaenoic acid (%)	1.74 ± 0.37	1.78 ± 0.57	0.05 ± 0.39	0.614	1.96 ± 0.70	1.87 ± 0.57	-0.09 ± 0.49	0.410	0.225	0.652	0.334	0.453
Total SFA (%)	31.09 ± 1.88	31.13 ± 2.54	0.03 ± 2.66	0.954	31.16 ± 2.04	31.66 ± 2.12	0.50 ± 2.10	0.296	0.913	0.4706	0.539	0.480
Total MUFA (%)	22.32 ± 2.66	21.73 ± 2.70	-0.59 ± 2.59	0.323	21.73 ± 2.48	23.50 ± 3.46	1.77 ± 3.79	0.050	0.472	0.0794	**0.027**	**0.042**
Total PUFA (%)	46.59 ± 3.82	47.14 ± 4.61	0.55 ± 4.51	0.590	47.11 ± 3.39	44.84 ± 4.05	-2.28 ± 3.54	**0.010**	0.651	0.1004	**0.033**	**0.042**

Abbreviations: SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
[a] Values are presented as mean ± SD.
P1: *P*-value within control oil group by paired *t*-test.
P2: *P*-value within olive oil group by paired *t*-test.
P3: *P*-value between groups at baseline by independent *t*-test.
P4: *P*-value between groups at month 3 by independent *t*-test.
P5: *P*-value for changes (intervention effects) between groups by independent *t*-test.
P6: *P*-value between groups from ANCOVA adjusting for age, sex and baseline value.

Table 3.1.4. Anthropometric, blood biochemical and inflammatory measures of the study participants within and between study groups[a]

	Control oil group (n=21)				Olive oil group (n=20)								
	Baseline	**Month 3**	**Change**	*P1*	**Baseline**	**Month 3**	**Change**	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*
Weight (kg)	79.7 ± 10.6	80.3 ± 10.7	0.6 ± 1.1	**0.027**	79.6 ± 12.1	79.8 ± 12.6	0.2 ± 1.9	0.647	0.979	0.899	0.456	0.394	NA
Height (cm)	166.3 ± 9.6	166.3 ± 9.6	NA	NA	165.7 ± 8.1	165.7 ± 8.1	NA	NA	0.827	0.827	NA	0.372	NA
BMI (kg/cm^2)	28.8 ± 2.6	29.0 ± 2.7	0.2 ± 0.4	**0.029**	28.8 ± 2.4	28.9 ± 2.5	0.1 ± 0.7	0.739	0.924	0.916	0.373	0.314	NA
Waist (cm)	97.2 ± 8.1	97.1 ± 8.5	-0.1 ± 2.0	0.748	96.8 ± 11.1	96.7 ± 11.1	-0.1 ± 2.8	0.877	0.892	0.905	0.956	0.928	NA
Hip (cm)	106.4 ± 9.1	107.0 ± 9.0	0.7 ± 2.4	0.208	106.2 ± 8.7	105.7 ± 8.4	-0.5 ± 2.0	0.273	0.960	0.628	0.095	0.101	NA
Waist/hip ratio	0.92 ± 0.08	0.91 ± 0.08	-0.008 ± 0.028	0.220	0.91 ± 0.09	0.92 ± 0.10	0.004 ± 0.029	0.567	0.867	0.816	0.203	0.255	NA
SBP (mmHg)	125.5 ± 10.4	126.1 ± 13.3	0.6 ± 12.2	0.812	127.6 ± 11.5	121.5 ± 9.0	-6.2 ± 8.2	**0.004**	0.537	0.198	**0.044**	0.059	**0.036**
DBP (mmHg)	76.3 ± 7.8	73.4 ± 8.4	-2.9 ± 5.9	**0.039**	75.7 ± 6.6	73.4 ± 6.3	-2.3 ± 5.9	0.099	0.797	0.999	0.754	0.984	NA
TC (mg/dL)	217.2 ± 38.1	219.2 ± 35.8	2.0 ± 34.4	0.798	202.6 ± 31.2	207.5 ± 34.6	4.9 ± 30.8	0.489	0.194	0.301	0.784	0.876	NA
LDL-C (mg/dL)	143.6 ± 32.5	145.3 ± 33.1	1.7 ± 29.2	0.797	130.0 ± 30.5	131.5 ± 27.7	1.5 ± 28.8	0.818	0.180	0.161	0.983	0.517	NA
HDL-C (mg/dL)	53.3 ± 8.6	52.2 ± 7.8	-1.1 ± 4.3	0.286	52.4 ± 10.6	53.8 ± 11.5	1.5 ± 4.5	0.170	0.770	0.610	0.081	0.060	NA
TG (mg/dL)	103.9 ± 43.8	110.2 ± 52.2	6.3 ± 43.8	0.503	103.2 ± 38.4	112.5 ± 53.3	9.4 ± 41.8	0.473	0.979	0.895	0.823	0.685	NA
VLDL-C (mg/dL)	20.4 ± 8.7	21.7 ± 10.4	1.4 ± 8.7	0.457	20.3 ± 7.7	22.2 ± 10.7	1.9 ± 8.3	0.459	0.949	0.890	0.839	0.713	NA
Glucose (mg/dL)	101.5 ± 8.7	104.9 ± 11.3	3.5 ± 8.7	0.091	101.4 ± 9.0	103.6 ± 9.4	2.2 ± 11.4	0.399	0.986	0.695	0.699	0.745	NA
Insulin (uIU/mL)	11.9 ± 4.8	14.9 ± 8.9	3.5 ± 6.5	**0.033**	12.5 ± 6.1	17.6 ± 11.8	5.1 ± 8.3	**0.013**	0.747	0.45	0.503	0.680	NA
HOMA-IR	3.05 ± 1.37	4.03 ± 2.85	1.11 ± 2.23	**0.043**	3.18 ± 1.59	4.56 ± 3.02	1.38 ± 2.31	**0.015**	0.782	0.536	0.718	0.781	NA
HOMA-B (%)	112.6 ± 42.8	124.4 ± 49.1	15.0 ± 33.0	**0.043**	118.6 ± 63.1	157.6 ± 108.5	39.1 ± 59.6	**0.0001**	0.972	0.263	0.128	0.268	NA
QUICKI	0.33 ± 0.02	0.32 ± 0.02	-0.01 ± 0.02	**0.028**	0.33 ± 0.03	0.32 ± 0.03	-0.01 ± 0.02	**0.016**	0.770	0.555	0.503	0.436	NA
IR (1/QUICKI)	3.05 ± 0.18	3.14 ± 0.25	0.10 ± 0.18	**0.028**	3.04 ± 0.26	3.19 ± 0.27	0.14 ± 0.19	**0.004**	0.904	0.536	0.489	0.498	NA
IL-1β (pg/mL)	1.54 ± 2.76	1.81 ± 3.19	0.28 ± 1.39	0.629	3.12 ± 6.50	3.67 ± 8.16	0.37 ± 1.97	0.176	0.545	0.324	0.923	0.993	NA
IL-6 (pg/mL)	11.7 ± 15.38	17.1 ± 26.56	5.43 ± 14.39	0.154	7.7 ± 15.90	8.9 ± 19.05	1.21 ± 4.48	0.663	0.297	0.180	0.201	0.195	NA
CRP (μg/mL)	2.42 ± 1.71	1.98 ± 1.47	-0.45 ± 1.67	0.199	1.65 ± 1.35	1.50 ± 1.09	-0.16 ± 0.91	0.960	0.095	0.251	0.414	0.618	NA
MCP1 (pg/mL)	401 ± 238.4	428 ± 247.8	26.67 ± 95.13	0.214	512 ± 214.3	503 ± 185.7	-8.10 ± 202.37	0.860	0.128	0.251	0.491	0.886	NA
TNF-α (pg/mL)	6.42 ± 10.73	7.35 ± 13.69	0.93 ± 4.75	0.193	7.76 ± 12.64	10.15 ± 18.19	2.39 ± 5.89	0.103	0.930	0.929	0.413	0.568	NA
sICAM-1 (ng/mL)	326 ± 119.7	326 ± 141.7	-0.21 ± 62.23	0.988	337 ± 183.6	322 ± 157.5	-14.43 ± 73.23	0.389	0.829	0.937	0.583	0.507	NA
sVCAM-1 (ng/mL)	2883 ± 1011.2	2924 ± 925.2	42.04 ± 365.1	0.378	2581 ± 640.0	2550 ± 624.0	-31.14 ± 347	0.737	0.330	0.161	0.663	0.385	NA

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; VLDL-C, very low density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, HOMA of β-cell function; QUICKI, quantitative insulin sensitivity check index; IL-1β, interleukin 1 beta; IL-6, interleukin 6; CRP, C-reactive protein; MCP1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor alpha; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; NA, not applicable.

[a] Values are presented as mean ± SD.

P1: *P*-value within control oil group by paired *t*-test.

P2: *P*-value within olive oil group by paired *t*-test.

P3: *P*-value between groups at baseline by independent *t*-test.

P4: *P*-value between groups at month 3 by independent *t*-test.

P5: *P*-value for changes (intervention effects) between groups by independent *t*-test.

P6: *P*-value between groups from ANCOVA adjusting for age, sex and baseline value.

P7: *P*-value between groups from ANCOVA adjusting for age, sex, baseline value and use of hypertension medications.

Table 3.1.5. Selected whole blood miRNA measures of the elderly participants within and between study groups[a]

	Control oil group (n=20)				Olive oil group (n=20)								
	Baseline	**Month 3**	**Change**	*P1*	**Baseline**	**Month 3**	**Change**	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*
hsa-miR-96-5p	0.00497 ± 0.00522	0.00397 ± 0.00397	-0.00100 ± 0.00603	0.312	0.00636 ± 0.00479	0.00665 ± 0.00479	0.000292 ± 0.00636	0.452	0.309	**0.011**	**0.012**	**0.032**	**0.004**
hsa-miR-30d-5p	1.034 ± 0.564	1.0434 ± 0.525	0.00948 ± 0.380	0.912	1.175 ± 0.744	1.143 ± 0.695	-0.0325 ± 0.827	0.862	0.503	0.613	0.840	0.628	NA
hsa-miR-30e-5p	0.600 ± 0.335	0.588 ± 0.326	-0.0116 ± 0.243	0.833	0.621 ± 0.384	0.589 ± 0.358	-0.0321 ± 0.419	0.735	0.851	0.992	0.995	0.748	NA
hsa-miR-1910-5p	0.00397 ± 0.00158	0.00474 ± 0.00351	0.000773 ± 0.00370	0.845	0.00622 ± 0.00873	0.00540 ± 0.00469	-0.000830 ± 0.00991	0.880	0.647	0.651	0.550	0.557	NA
hsa-miR-598-3p	0.00166 ± 0.00112	0.00153 ± 0.00105	-0.000140 ± 0.00148	0.624	0.00160 ± 0.00120	0.00151 ± 0.000877	-0.000100 ± 0.00131	0.734	0.595	0.785	0.669	0.541	NA
hsa-miR-3714	0.000687 ± 0.000372	0.000963 ± 0.000887	0.000276 ± 0.000949	0.360	0.00132 ± 0.00191	0.00112 ± 0.00113	-0.000200 ± 0.00233	0.843	0.113	0.602	0.471	0.855	NA

NA, not applicable.
[a] Values are presented as mean ± SD of transformed normalized Ct (2^{-dCt}). Original Ct values were normalized to mean of 4 small non-coding RNAs (SNORD68, SNORD95, SNORD96A and RNU6-2).

P1: *P*-value within control oil group by paired *t*-test.
P2: *P*-value within olive oil group by paired *t*-test.
P3: *P*-value between groups at baseline by unpaired *t*-test.
P4: *P*-value between groups at month 3 by unpaired *t*-test.
P5: *P*-value for values at month 3 between groups from ANCOVA adjusting for age, sex and baseline value.
P6: *P*-value for changes (intervention effects) between groups from ANCOVA adjusting for age, sex and baseline value.
P7: *P*-value for values at month 3 between groups from ANCOVA adjusting for age, sex, baseline value and reported consumption of provided oil (g).

Table 3.1.6. Association between changes in serum glucose and selected whole blood miRNAs in study groups

	Change in Glucose (mg/dL)																	
	All						Control oil group						Olive oil group					
Change in miRNAs	**Pearson Correlation Coefficient (*r1*)**	*P1*	**Partial Correlation Coefficient (*r2*)**	*P2*	**Beta (SE)**	*P3*	**Pearson Correlation Coefficient (*r1*)**	*P4*	**Partial Correlation Coefficient (*r2*)**	*P5*	**Beta (SE)**	*P6*	**Pearson Correlation Coefficient (*r1*)**	*P7*	**Partial Correlation Coefficient (*r2*)**	*P8*	**Beta (SE)**	*P9*
hsa-miR-96-5p	0.339	**0.035**	0.400	**0.017**	7.296 (2.907)	**0.017**	0.021	0.932	0.036	0.896	0.528 (3.960)	0.896	0.636	**0.003**	0.695	**0.002**	14.738 (3.931)	**0.002**
hsa-miR-30d-5p	0.342	**0.033**	0.368	**0.030**	10.980 (4.826)	**0.030**	0.109	0.657	0.141	0.603	5.808 (10.919)	0.603	0.451	**0.046**	0.504	**0.039**	14.868 (6.586)	**0.039**
hsa-miR-30e-5p	0.270	0.096	0.306	0.074	7.932 (4.293)	0.074	-0.070	0.776	-0.128	0.637	-4.258 (8.828)	0.637	0.431	0.058	0.487	**0.048**	12.371 (5.733)	**0.048**
hsa-miR-598-3p	0.344	**0.032**	0.418	**0.013**	8.868 (3.358)	**0.013**	0.077	0.754	0.136	0.614	2.581 (5.007)	0.614	0.539	**0.014**	0.636	**0.006**	14.570 (4.570)	**0.006**

Changes in miRNA (log10 transformed 2^{-ddCt}) were treated as predictors, and change in glucose was treated as a dependent variable. Original Ct values were normalized to mean of 4 small non-coding RNAs (SNORD68, SNORD95, SNORD96A and RNU6-2) and baseline miRNA levels.

r1: Pearson Correlation Coefficients; *r2*: Partial Pearson Correlation Coefficients; Beta: regression coefficient (SE) for miRNA.
P1: *P*-value for the test for Pearson correlation coefficient in all participants.
P2: *P*-value for partial correlation adjusted for group, age, sex and change in waist in all participants.
P3: *P*-value for beta of change in miRNA was calculated by using a general linear regression model adjusted for group, age, sex and change in waist in all participants.
P4: *P*-value for the test for Pearson correlation coefficient in control oil group.
P5: *P*-value for partial correlation adjusted for age, sex and change in waist in control oil group.
P6: *P*-value for beta of change in miRNA was calculated by using a general linear regression model adjusted for group, age, sex and change in waist in control oil group.
P7: *P*-value for the test for Pearson correlation coefficient in olive oil group.
P8: *P*-value for partial correlation adjusted for age, sex and change in waist in olive oil group.
P9: *P*-value for beta of change in miRNA was calculated by using a general linear regression model adjusted for group, age, sex and change in waist in olive oil group.

Table 3.1.7. Demographic characteristics and changes in glycemic traits of the study participants between study groups by fasting glucose status[a]

CHANGES	Normal Fasting Glucose (<100 mg/dL)				Impaired Fasting Glucose (100-125 mg/dL)				
	Control Oil (n=11)	**Olive Oil (n=10)**	*P1*	*P2*	**Control Oil (n=10)**	**Olive Oil (n=10)**	*P3*	*P4*	*P5*
Female	7	4	0.279	NA	8	8	1.000	NA	NA
Age (year)	71.4 ± 5.7	72.3 ± 6.2	0.723	NA	72.1 ± 5.3	72.3 ± 6.1	0.938	NA	NA
Current Medication-									
High Cholesterol	3	4	0.537	NA	6	2	0.068	NA	NA
Type 2 Diabetes	1	0	0.329	NA	0	0	NA	NA	NA
Hypertension or High Blood Pressure	6	7	0.466	NA	4	7	0.178	NA	NA
Glucose (mg/dL)	2.4 ± 5.4	8.3 ± 8.2	0.075	0.105	4.5 ± 11.3	-3.9 ± 11.1	0.111	0.104	**0.008**
Insulin (uIU/mL)	2.6 ± 3.2	7.2 ± 10.3	0.137	0.133	4.2 ± 8.7	3.0 ± 5.5	0.357	0.887	0.088
HOMA-IR	0.77 ± 0.99	2.05 ± 2.76	0.114	0.127	1.43 ± 2.97	0.71 ± 1.63	0.479	0.695	0.137
HOMA-B (%)	11.7 ± 31.8	41.3 ± 76.3	0.133	0.158	18.0 ± 35.5	36.8 ± 40.8	0.730	0.356	0.283
QUICKI	-0.01 ± 0.01	-0.03 ± 0.02	**0.014**	**0.016**	-0.01 ± 0.02	-0.003 ± 0.02	0.436	0.639	**0.022**
IR (1/QUICKI)	0.09 ± 0.10	0.25 ± 0.17	**0.028**	**0.027**	0.11 ± 0.24	0.04 ± 0.17	0.463	0.669	**0.038**

Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, HOMA of β-cell function; QUICKI, quantitative insulin sensitivity check index; NA, not applicable.

[a] Values are presented as mean ± SD.
P1: *P*-value for changes (intervention effects) between study groups in subjects with normal fasting glucose at baseline by independent *t*-test.
P2: *P*-value for changes (intervention effects) between study groups in subjects with normal fasting glucose at baseline from ANCOVA adjusting for age, sex and change in BMI.
P3: *P*-value for changes (intervention effects) between study groups in subjects with impaired glucose at baseline by independent *t*-test.
P4: *P*-value for changes (intervention effects) between study groups in subjects with impaired glucose at baseline from ANCOVA adjusting for age, sex and change in BMI.
P5: *P*-value for interaction between fasting glucose status at baseline and study group for changes (intervention effects) from ANCOVA adjusting for age, sex and change in BMI.

Table 3.1.8. Changes of selected whole blood miRNA measures of the study participants between study groups by fasting glucose status[a]

Change	Normal Fasting Glucose (<100 mg/dL)					Impaired Fasting Glucose (100-125 mg/dL)					
	Control Oil (n=11)	**Olive Oil (n=10)**	*P1*	*P2*	*P3*	**Control Oil (n=10)**	**Olive Oil (n=10)**	*P4*	*P5*	*P6*	*P7*
hsa-miR-96-5p	0.8466 ± 0.6669	3.4760 ± 4.3860	**0.010**	**0.021**	0.084	2.3814 ± 2.6973	1.1429 ± 0.8494	0.711	0.547	0.312	0.064
hsa-miR-30d-5p	0.9995 ± 0.3571	1.9443 ± 1.2684	0.078	0.112	0.229	1.3266 ± 1.0443	1.1786 ± 1.5995	0.303	0.198	0.665	0.075
hsa-miR-30e-5p	0.9527 ± 0.3589	2.2534 ± 2.1184	0.181	0.154	0.412	1.4585 ± 1.4492	1.2290 ± 1.7965	0.387	0.272	0.687	0.138
hsa-miR-1910-5p	1.0187 ± 0.6866	2.4821 ± 2.4717	0.295	0.260	**0.047**	2.0600 ± 2.3362	0.9195 ± 0.5456	0.221	0.210	0.840	0.110
hsa-miR-598-3p	1.1662 ± 0.9836	3.0464 ± 3.7442	0.096	0.183	0.423	2.0023 ± 2.8579	1.1431 ± 1.4122	0.562	0.388	0.997	0.173
hsa-miR-3714	1.2282 ± 0.8695	2.2288 ± 2.3834	0.589	0.466	0.115	2.0585 ± 1.9742	1.0426 ± 1.1267	0.125	0.156	0.912	0.107

[a] Values are presented as mean ± SD of fold changes in miRNA (transformed 2^{-ddCt}). Original Ct values were normalized to mean of 4 small non-coding RNAs (SNORD68, SNORD95, SNORD96A and RNU6-2) and baseline miRNA levels.
P1: *P*-value for changes (intervention effects) between study groups in subjects with normal fasting glucose at baseline by independent *t*-test.
P2: *P*-value for changes (intervention effects) between study groups in subjects with normal fasting glucose at baseline from ANCOVA adjusting for age, sex and BMI.
P3: *P*-value for changes (intervention effects) between study groups in subjects with normal fasting glucose at baseline from ANCOVA adjusting for age, sex, BMI and baseline value.
P4: *P*-value for changes (intervention effects) between study groups in subjects with impaired glucose at baseline by independent *t*-test.
P5: *P*-value for changes (intervention effects) between study groups in subjects with impaired glucose at baseline from ANCOVA adjusting for age, sex and BMI.
P6: *P*-value for changes (intervention effects) between study groups in subjects with impaired glucose at baseline from ANCOVA adjusting for age, sex, BMI and baseline value.
P7: *P*-value for interaction between fasting glucose status at baseline and study group for changes (intervention effects) from ANCOVA adjusting for age, sex and change in BMI.

Figure 3.1.1. Study flow chart

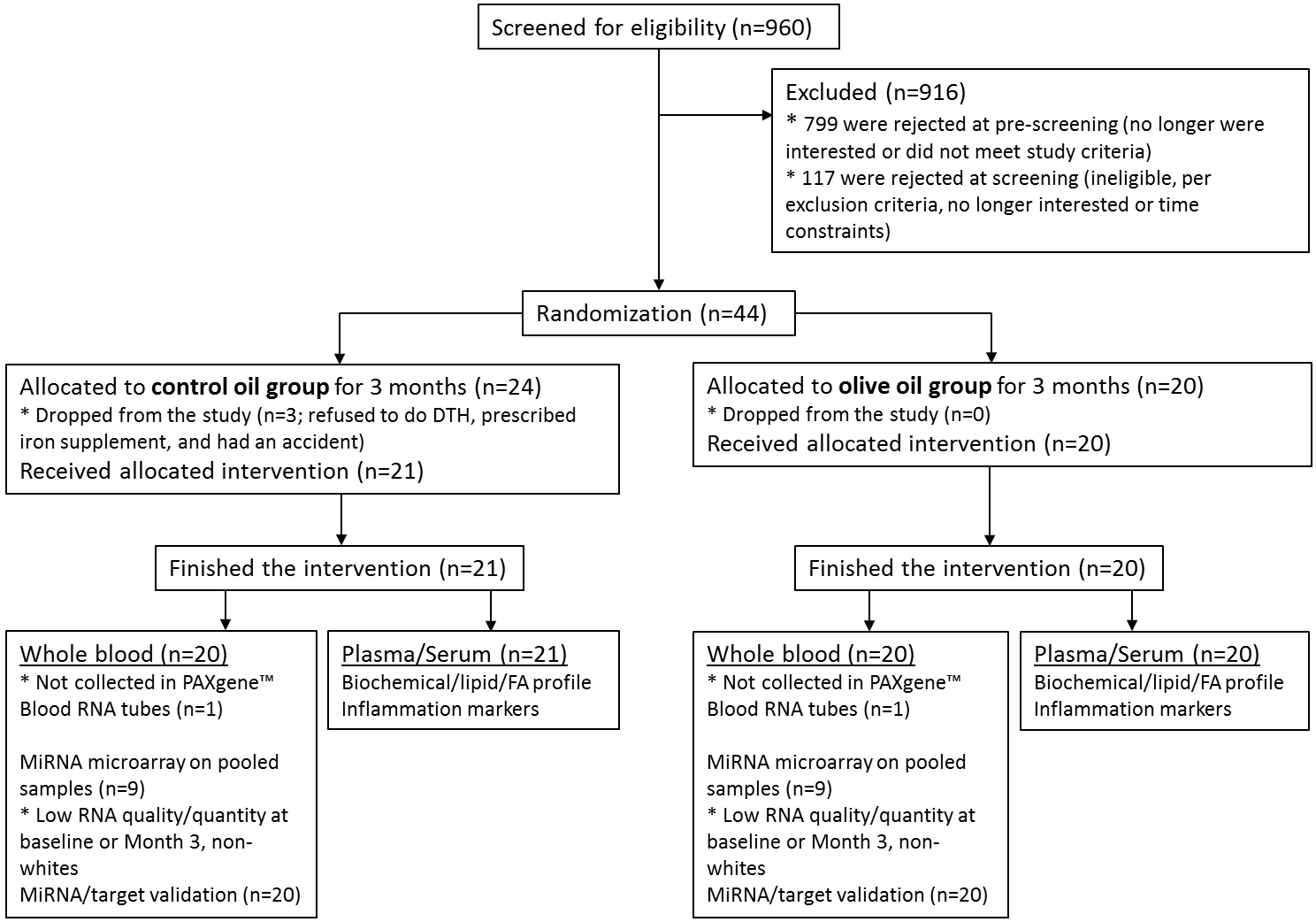
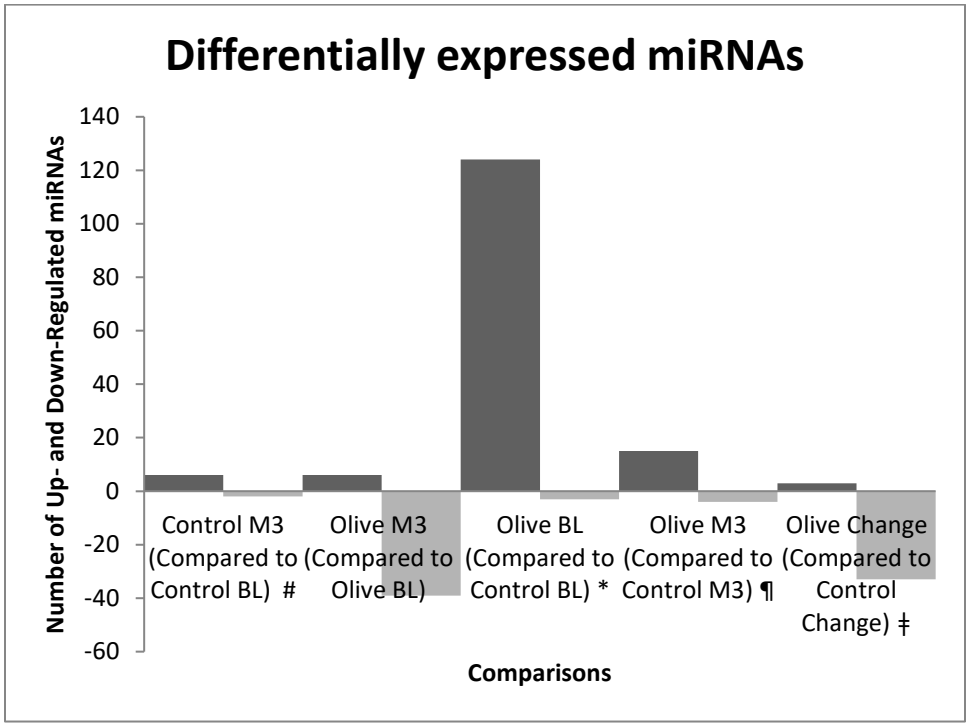


Figure 3.1.2. Number of differentially expressed miRNAs between study groups



Numbers of genes that were differentially expressed between groups were presented. Original Ct values were normalized to mean of 4 small non-coding RNAs (SNORD68, SNORD95, SNORD96A and RNU6-2).
# $P < 0.05$ within control oil group by paired *t*-test and $|fold| \geq 1.5$.
† $P < 0.05$ within olive oil group by paired *t*-test and $|fold| \geq 1.5$.
* $P < 0.05$ between groups at baseline by independent *t*-test and $|fold| \geq 1.5$.
¶ $P < 0.05$ between groups at month 3 by independent *t*-test and $|fold| \geq 1.5$.
ǂ $P < 0.05$ for changes (intervention effects) between groups by independent *t*-test and $|fold| \geq 1.5$.

Figure 3.1.3. Association between changes in serum glucose and insulin and selected whole blood miRNAs in study groups

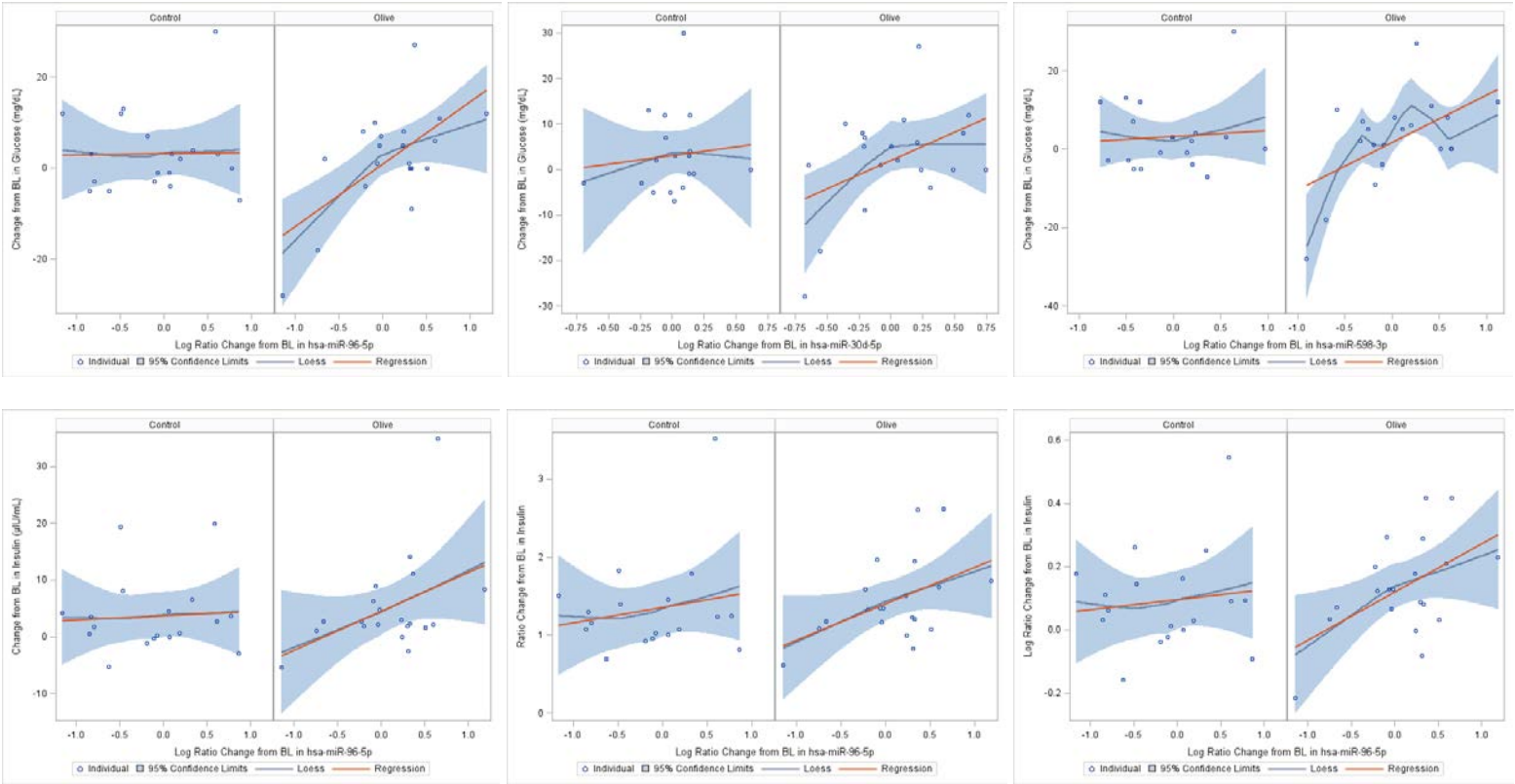
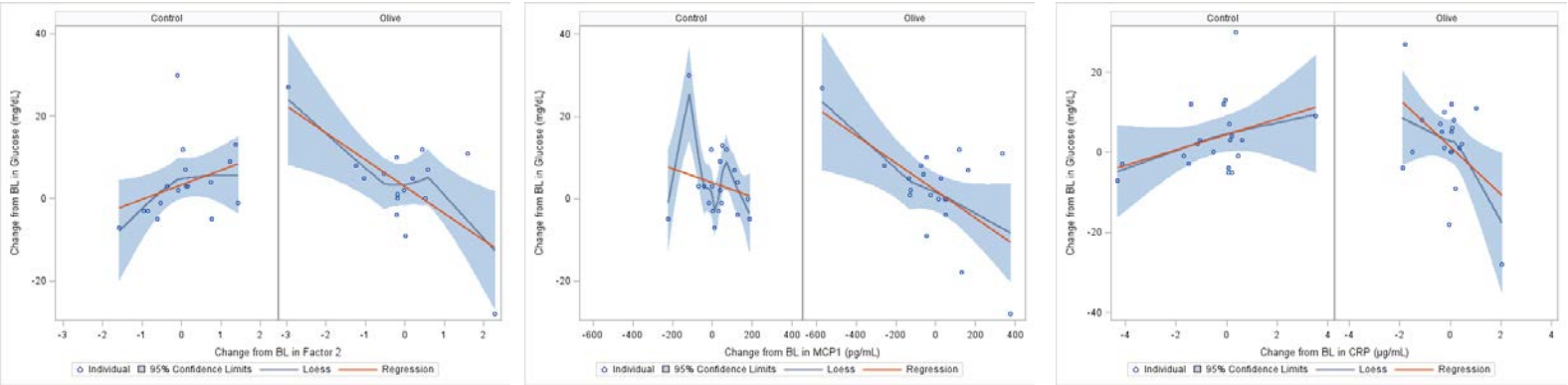


Figure 3.1.4. Association between changes in serum glucose and inflammatory markers in study groups



Supplemental Table 3.1.1. Differentially expressed miRNAs between study groups

Response	Control Oil Month 3 (Compared to Control Oil Baseline) #	Olive Oil Month 3 (Compared to Olive Oil Baseline) †	Olive Oil Baseline (Compared to Control Oil Baseline) *	Olive Oil Month 3 (Compared to Control Oil Month 3) ¶	Olive Oil Change (Compared to Control Oil Change) ǂ
Up-Regulated	6(2): hsa-miR-376b hsa-miR-651 hsa-miR-548d-5p hsa-miR-376a* hsa-miR-449b hsa-miR-488* (hsa-miR-338-3p hsa-miR-99b)	6(4): hsa-miR-542-3p **hsa-miR-96-5p** hsa-miR-139-3p hsa-miR-1290 hsa-miR-3685 hsa-miR-3676 (hsa-miR-770-5p hsa-miR-148b* hsa-miR-339-3p hsa-miR-3134)	124(1): hsa-miR-659 hsa-miR-193b hsa-miR-646 hsa-miR-548b-3p hsa-miR-575 hsa-miR-9 hsa-miR-125b hsa-miR-200a* hsa-miR-619 hsa-miR-302c hsa-miR-296-5p hsa-miR-487a hsa-miR-610 hsa-miR-134 hsa-miR-412 hsa-miR-202 hsa-miR-524-5p hsa-miR-100 hsa-miR-493 hsa-miR-518d-3p hsa-miR-623 hsa-miR-338-3p hsa-miR-613 hsa-miR-193a-5p hsa-miR-498 hsa-miR-518f* hsa-miR-520e hsa-miR-632 hsa-miR-138-1* hsa-miR-21* hsa-miR-431* hsa-miR-302b* hsa-miR-485-5p hsa-miR-1224-3p hsa-miR-593 hsa-miR-891a hsa-miR-92b* hsa-miR-1253 hsa-miR-18b* hsa-miR-1538 hsa-miR-1539 hsa-miR-1269 hsa-miR-200c* hsa-miR-3614-3p hsa-miR-3144-5p	15(0): hsa-miR-410 hsa-miR-301b hsa-miR-125b hsa-miR-579 hsa-miR-127-3p hsa-miR-100 hsa-miR-190b hsa-miR-545 hsa-miR-1203 hsa-miR-2115 hsa-miR-3136-5p hsa-miR-2355-5p hsa-miR-3685 hsa-miR-16-1* hsa-miR-3676	3(1): hsa-miR-103b hsa-miR-3685 hsa-miR-598-3p (hsa-miR-132*)

Response	Control Oil Month 3 (Compared to Control Oil Baseline) #	Olive Oil Month 3 (Compared to Olive Oil Baseline) †	Olive Oil Baseline (Compared to Control Oil Baseline) *	Olive Oil Month 3 (Compared to Control Oil Month 3) ¶	Olive Oil Change (Compared to Control Oil Change) ǂ
			hsa-miR-3180-3p hsa-miR-4315 hsa-miR-2110 hsa-miR-320e hsa-miR-4260 hsa-miR-885-3p hsa-miR-3666 hsa-miR-617 hsa-miR-3925-5p hsa-miR-483-5p hsa-miR-4304 hsa-miR-466 hsa-miR-3182 hsa-miR-34c-3p hsa-miR-548y hsa-miR-187* hsa-miR-593* hsa-miR-4293 hsa-miR-3682-3p hsa-miR-3907 hsa-miR-3943 hsa-miR-508-5p hsa-miR-3194-5p hsa-miR-1912 hsa-miR-3164 hsa-miR-490-5p hsa-miR-640 hsa-miR-764 hsa-miR-4283 hsa-miR-4311 hsa-miR-3654 hsa-miR-4282 hsa-miR-296-3p hsa-miR-548w hsa-miR-3147 hsa-miR-887 hsa-miR-4268 hsa-miR-3680 hsa-miR-3917 hsa-miR-3926 hsa-miR-1914 hsa-miR-1909* hsa-miR-4286 hsa-miR-4314 hsa-miR-3132 hsa-miR-1910-5p hsa-miR-4253 hsa-miR-214* hsa-miR-3934 hsa-miR-4257		

Response	Control Oil Month 3 (Compared to Control Oil Baseline) #	Olive Oil Month 3 (Compared to Olive Oil Baseline) †	Olive Oil Baseline (Compared to Control Oil Baseline) *	Olive Oil Month 3 (Compared to Control Oil Month 3) ¶	Olive Oil Change (Compared to Control Oil Change) ǂ
			hsa-miR-125a-3p hsa-miR-2113 hsa-miR-3622b-3p hsa-miR-1261 hsa-miR-3692 hsa-miR-2115* hsa-miR-934 hsa-miR-3622a-5p hsa-miR-4319 hsa-miR-3679-5p hsa-miR-4300 hsa-miR-4265 hsa-miR-3661 hsa-miR-2116* hsa-miR-921 hsa-miR-4303 hsa-miR-3126-5p hsa-miR-3184 hsa-miR-4267 hsa-miR-616 hsa-miR-3121-3p hsa-miR-1914* hsa-miR-3135 hsa-miR-3652 hsa-miR-3714 hsa-miR-3125 hsa-miR-4258 hsa-miR-4263 hsa-miR-4287 (hsa-miR-410)		
Down-Regulated	2(0): hsa-miR-658 hsa-miR-98	39(12): hsa-miR-619 hsa-miR-622 hsa-miR-649 hsa-miR-524-5p hsa-miR-518d-3p hsa-miR-498 hsa-miR-518f* hsa-miR-520e hsa-miR-127-5p hsa-miR-920 hsa-miR-1539 hsa-miR-3144-5p hsa-miR-2110 hsa-miR-320e hsa-miR-3670 hsa-miR-645 hsa-miR-466 hsa-miR-670 hsa-miR-187*	3(1): hsa-miR-3607-3p hsa-miR-3124-5p hsa-miR-3653 (hsa-miR-3607-5p)	4(0): hsa-miR-9* hsa-miR-556-3p hsa-miR-1266 hsa-miR-3653	33(7): hsa-miR-608 hsa-miR-564 hsa-miR-504-5p hsa-miR-484 hsa-miR-639 hsa-miR-589 hsa-miR-637 hsa-miR-218 hsa-miR-548d-5p hsa-miR-30d-5p hsa-miR-30a hsa-miR-216b hsa-miR-99b hsa-miR-297 hsa-miR-300 hsa-miR-488* hsa-miR-1207-3p hsa-miR-194* hsa-miR-20b*

Response	Control Oil Month 3 (Compared to Control Oil Baseline) #	Olive Oil Month 3 (Compared to Olive Oil Baseline) †	Olive Oil Baseline (Compared to Control Oil Baseline) *	Olive Oil Month 3 (Compared to Control Oil Month 3) ¶	Olive Oil Change (Compared to Control Oil Change) ǂ
		hsa-miR-3943 hsa-miR-3194-5p hsa-miR-640 hsa-miR-764 hsa-miR-4311 hsa-miR-548w hsa-miR-887 hsa-miR-3140-3p hsa-miR-1909* hsa-miR-1910-5p hsa-miR-214* hsa-miR-125a-3p hsa-miR-3622b-3p hsa-miR-3692 hsa-miR-3184 hsa-miR-3135 hsa-miR-3652 hsa-miR-4258 hsa-miR-4263 hsa-miR-4287 (hsa-miR-299-3p hsa-miR-504-5p hsa-miR-25 hsa-miR-26a hsa-miR-522 hsa-miR-23a hsa-miR-639 hsa-miR-139-5p hsa-miR-151-3p hsa-miR-151-5p hsa-miR-3120-3p hsa-miR-3691-5p)			hsa-miR-1266 hsa-miR-181a-2* hsa-miR-4254 hsa-miR-3182 hsa-miR-670 hsa-miR-764 hsa-miR-4283 hsa-miR-3680 hsa-miR-1910-5p hsa-miR-214* hsa-miR-1261 hsa-miR-1293 hsa-miR-3184 hsa-miR-3714 (hsa-miR-15b hsa-miR-324-5p hsa-miR-140-3p hsa-miR-361-3p hsa-miR-151-5p hsa-let-7d* hsa-miR-33a*)

The numbers and lists of miRNAs that were differentially expressed between groups were presented. Ct values were normalized by mean of 4 small RNAs (SNORD68, SNORD95, SNORD96A and RNU6-2).

# $P < 0.05$ within control oil group by paired *t*-test and $|\text{fold}| \geq 1.5$ ($|\text{fold}| \geq 1.3$).

† $P < 0.05$ within olive oil group by paired *t*-test and $|\text{fold}| \geq 1.5$ ($|\text{fold}| \geq 1.3$).

* $P < 0.05$ between groups at baseline by independent *t*-test and $|\text{fold}| \geq 1.5$ ($|\text{fold}| \geq 1.3$).

¶ $P < 0.05$ between groups at month 3 by independent *t*-test and $|\text{fold}| \geq 1.5$ ($|\text{fold}| \geq 1.3$).

ǂ $P < 0.05$ for changes (intervention effects) between groups by independent *t*-test and $|\text{fold}| \geq 1.5$ ($|\text{fold}| \geq 1.3$).

Supplemental Table 3.1.2. Top enriched pathways of the differentially expressed miRNAs by (A) functional annotation summary and (B) pathway ranking summary in miRSystem functional annotation chart

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Control Oil Month 3 (Compared to Control Oil Baseline) up-regulated

Category	Term	Total Genes of the Term	Targets in the Term	Targets in Total Genes of the Term (%)	Targets in Total Targets of Submitted miRNA(s) (%)	Union miRNAs in the Term	Raw *P*-Value[1]	Empirical *P*-Value[2]
REACTOME	REGULATION OF DNA REPLICATION	75	3	4	4.286	3	1.67E-03	9.60E-03
REACTOME	REMOVAL OF LICENSING FACTORS FROM ORIGINS	72	3	4.167	4.286	3	1.49E-03	1.00E-02
PATHWAY INTERACTION DATABASE	NOTCH SIGNALING PATHWAY	59	3	5.085	4.286	3	8.44E-04	1.44E-02
REACTOME	DNA REPLICATION	200	4	2	5.714	3	3.36E-03	1.54E-02
PATHWAY INTERACTION DATABASE	NOTCH-MEDIATED HES HEY NETWORK	48	3	6.25	4.286	3	4.64E-04	1.95E-02
PATHWAY INTERACTION DATABASE	IL23-MEDIATED SIGNALING EVENTS	37	2	5.405	2.857	2	5.96E-03	2.12E-02
PATHWAY INTERACTION DATABASE	IL2 SIGNALING EVENTS MEDIATED BY STAT5	30	2	6.667	2.857	2	3.98E-03	2.20E-02
PATHWAY INTERACTION DATABASE	AURORA A SIGNALING	31	2	6.452	2.857	2	4.24E-03	2.87E-02
REACTOME	NEUROTRANSMITTER RECEPTOR BINDING AND DOWNSTREAM TRANSMISSION IN THE POSTSYNAPTIC CELL	136	3	2.206	4.286	2	8.41E-03	2.95E-02
PATHWAY INTERACTION DATABASE	VALIDATED TRANSCRIPTIONAL TARGETS OF DELTANP63 ISOFORMS	45	2	4.444	2.857	2	8.64E-03	3.05E-02
REACTOME	CELL CYCLE MITOTIC	330	5	1.515	7.143	3	3.38E-03	3.19E-02
REACTOME	TRANSMISSION ACROSS CHEMICAL SYNAPSES	190	3	1.579	4.286	2	1.96E-02	3.66E-02
KEGG	APOPTOSIS	88	2	2.273	2.857	2	2.92E-02	3.74E-02
REACTOME	REGULATION OF APC C ACTIVATORS BETWEEN G1 S AND EARLY ANAPHASE	77	3	3.896	4.286	2	1.80E-03	3.94E-02
PATHWAY INTERACTION DATABASE	SHP2 SIGNALING	54	2	3.704	2.857	2	1.21E-02	4.09E-02
KEGG	COLORECTAL CANCER	62	2	3.226	2.857	3	1.57E-02	4.36E-02
REACTOME	APC C-MEDIATED DEGRADATION OF CELL CYCLE PROTEINS	82	3	3.659	4.286	2	2.14E-03	4.58E-02
REACTOME	REGULATION OF MITOTIC CELL CYCLE	82	3	3.659	4.286	2	2.14E-03	4.58E-02
PATHWAY INTERACTION DATABASE	E2F TRANSCRIPTION FACTOR NETWORK	73	3	4.11	4.286	3	1.55E-03	4.79E-02
REACTOME	NEURONAL SYSTEM	289	4	1.384	5.714	2	1.13E-02	4.86E-02

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Control Oil Month 3 (Compared to Control Oil Baseline) down-regulated

Category	**Term**	**Total Genes of the Term**	**Targets in the Term**	**Targets in Total Genes of the Term (%)**	**Targets in Total Targets of Submitted miRNA(s) (%)**	**Union miRNAs in the Term**	**Raw *P*-Value[1]**	**Empirical *P*-Value[2]**
REACTOME	NCAM_SIGNALING_FOR_NEURITE_OUT-GROWTH	70	11	15.714	3.064	2	1.57E-08	3.80E-03
REACTOME	NCAM1_INTERACTIONS	44	9	20.455	2.507	2	2.99E-08	5.78E-03
KEGG	PYRIMIDINE_METABOLISM	99	6	6.061	1.671	1	4.48E-03	1.19E-02
KEGG	APOPTOSIS	88	6	6.818	1.671	1	2.59E-03	1.80E-02
KEGG	PURINE_METABOLISM	161	6	3.727	1.671	1	3.21E-02	2.04E-02
KEGG	RNA_POLYMERASE	29	3	10.345	0.836	1	1.03E-02	2.34E-02
KEGG	PROTEIN_DIGESTION_AND_ABSORPTION	80	8	10	2.228	2	4.21E-05	2.47E-02
REACTOME	AMINE_LIGAND-BINDING_RECEPTORS	42	4	9.524	1.114	1	4.20E-03	2.61E-02
BIOCARTA	BIOCARTA_FAS_PATHWAY	30	4	13.333	1.114	1	1.25E-03	2.84E-02
REACTOME	SIGNALING_BY_PDGF	122	9	7.377	2.507	2	1.47E-04	3.23E-02
PATHWAY_INTERACTION_DATABASE	AP-1_TRANSCRIPTION_FACTOR_NETWORK	69	8	11.594	2.228	1	1.45E-05	3.33E-02
PATHWAY_INTERACTION_DATABASE	SYNDECAN-1-MEDIATED_SIGNALING_EVENTS	46	7	15.217	1.95	2	8.27E-06	3.55E-02
KEGG	CYTOSOLIC_DNA-SENSING_PATHWAY	56	4	7.143	1.114	1	1.10E-02	3.70E-02
KEGG	AMOEBIASIS	105	9	8.571	2.507	1	4.75E-05	3.81E-02
REACTOME	AXON_GUIDANCE	266	16	6.015	4.457	2	6.55E-06	4.15E-02
PATHWAY_INTERACTION_DATABASE	BETA1_INTEGRIN_CELL_SURFACE_INTERACTIONS	65	6	9.231	1.671	2	5.74E-04	4.46E-02
KEGG	AUTOIMMUNE_THYROID_DISEASE	52	3	5.769	0.836	1	4.27E-02	4.68E-02
KEGG	ECM-RECEPTOR_INTERACTION	84	6	7.143	1.671	2	2.08E-03	4.88E-02
KEGG	CYTOKINE-CYTOKINE_RECEPTOR_INTERACTION	275	11	4	3.064	1	3.76E-03	4.94E-02

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Olive Oil Month 3 (Compared to Olive Oil Baseline) up-regulated

Category	**Term**	**Total Genes of the Term**	**Targets in the Term**	**Targets in Total Genes of the Term (%)**	**Targets in Total Targets of Submitted miRNA(s) (%)**	**Union miRNAs in the Term**	**Raw *P*-Value[1]**	**Empirical *P*-Value[2]**
REACTOME	GLUCOSE METABOLISM	62	3	4.839	4.762	2	7.19E-04	7.28E-04
REACTOME	GLUCONEOGENESIS	31	2	6.452	3.175	1	3.46E-03	1.61E-02
REACTOME	PLATELET DEGRANULATION	78	3	3.846	4.762	2	1.38E-03	1.69E-02
REACTOME	RESPONSE TO ELEVATED PLATELET CYTOSOLIC CA2+	83	3	3.614	4.762	2	1.65E-03	1.97E-02
REACTOME	METABOLISM OF CARBOHYDRATES	126	3	2.381	4.762	2	5.19E-03	3.83E-02
BIOCARTA	BIOCARTA RHO PATHWAY	32	2	6.25	3.175	1	3.68E-03	4.57E-02

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): 2d, 3u and 3d

Category	**Term**	**Total Genes of the Term**	**Targets in the Term**	**Targets in Total Genes of the Term (%)**	**Targets in Total Targets of Submitted miRNA(s) (%)**	**Union miRNAs in the Term**	**Raw *P*-Value[1]**	**Empirical *P*-Value[2]**
NA	NA	NA	NA	NA	NA	NA	NA	NA

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Olive Oil Month 3 (Compared to Control Oil Month 3) up-regulated

Category	Term	Total Genes of the Term	Targets in the Term	Targets in Total Genes of the Term (%)	Targets in Total Targets of Submitted miRNA(s) (%)	Union miRNAs in the Term	Raw *P*-Value[1]	Empirical *P*-Value[2]
REACTOME	REGULATION OF APC C ACTIVATORS BETWEEN G1 S AND EARLY ANAPHASE	77	3	3.896	13.636	3	5.95E-05	1.65E-03
REACTOME	ACTIVATION OF APC C AND APC C CDC20 MEDIATED DEGRADATION OF MITOTIC PROTEINS	70	3	4.286	13.636	3	4.48E-05	1.69E-03
REACTOME	APC C-MEDIATED DEGRADATION OF CELL CYCLE PROTEINS	82	3	3.659	13.636	3	7.17E-05	2.46E-03
REACTOME	REGULATION OF MITOTIC CELL CYCLE	82	3	3.659	13.636	3	7.17E-05	2.46E-03
REACTOME	APC C CDH1 MEDIATED DEGRADATION OF CDC20 AND OTHER APC C CDH1 TARGETED PROTEINS IN LATE MITOSIS EARLY G1	69	3	4.348	13.636	3	4.29E-05	2.51E-03
REACTOME	DNA REPLICATION	200	3	1.5	13.636	3	9.60E-04	2.86E-03
REACTOME	MITOTIC M-M G1 PHASES	178	3	1.685	13.636	3	6.88E-04	2.90E-03
REACTOME	CDK-MEDIATED PHOSPHORYLATION AND REMOVAL OF CDC6	50	2	4	9.091	2	1.12E-03	2.35E-02
REACTOME	P53-INDEPENDENT DNA DAMAGE RESPONSE	52	2	3.846	9.091	2	1.21E-03	2.35E-02
REACTOME	P53-INDEPENDENT G1 S DNA DAMAGE CHECKPOINT	52	2	3.846	9.091	2	1.21E-03	2.35E-02
REACTOME	UBIQUITIN-DEPENDENT DEGRADATION OF CYCLIN D	50	2	4	9.091	2	1.12E-03	2.35E-02
REACTOME	UBIQUITIN-DEPENDENT DEGRADATION OF CYCLIN D1	50	2	4	9.091	2	1.12E-03	2.35E-02
REACTOME	UBIQUITIN MEDIATED DEGRADATION OF PHOSPHORYLATED CDC25A	52	2	3.846	9.091	2	1.21E-03	2.35E-02
REACTOME	VPU MEDIATED DEGRADATION OF CD4	52	2	3.846	9.091	2	1.21E-03	2.35E-02
REACTOME	VIF-MEDIATED DEGRADATION OF APOBEC3G	54	2	3.704	9.091	2	1.30E-03	2.51E-02
REACTOME	REGULATION OF ACTIVATED PAK-2P34 BY PROTEASOME MEDIATED DEGRADATION	49	2	4.082	9.091	2	1.07E-03	2.52E-02
REACTOME	ORC1 REMOVAL FROM CHROMATIN	70	2	2.857	9.091	2	2.17E-03	2.53E-02
REACTOME	SWITCHING OF ORIGINS TO A POST-REPLICATIVE STATE	70	2	2.857	9.091	2	2.17E-03	2.53E-02
REACTOME	REGULATION OF APOPTOSIS	60	2	3.333	9.091	2	1.60E-03	2.56E-02
REACTOME	DEGRADATION OF BETA-CATENIN BY THE DESTRUCTION COMPLEX	67	2	2.985	9.091	2	1.99E-03	2.59E-02
REACTOME	SIGNALING BY WNT	67	2	2.985	9.091	2	1.99E-03	2.59E-02
REACTOME	P53-DEPENDENT G1 DNA DAMAGE RESPONSE	57	2	3.509	9.091	2	1.45E-03	2.60E-02
REACTOME	P53-DEPENDENT G1 S DNA DAMAGE CHECKPOINT	57	2	3.509	9.091	2	1.45E-03	2.60E-02

Category	Term	Total Genes of the Term	Targets in the Term	Targets in Total Genes of the Term (%)	Targets in Total Targets of Submitted miRNA(s) (%)	Union miRNAs in the Term	Raw *P*-Value[1]	Empirical *P*-Value[2]
REACTOME	SCF-BETA-TRCP MEDIATED DEGRADATION OF EMI1	54	2	3.704	9.091	2	1.30E-03	2.62E-02
REACTOME	AUTODEGRADATION OF THE E3 UBIQUITIN LIGASE COP1	51	2	3.922	9.091	2	1.16E-03	2.65E-02
REACTOME	STABILIZATION OF P53	52	2	3.846	9.091	2	1.21E-03	2.65E-02
REACTOME	ANTIGEN PROCESSING-CROSS PRESENTATION	75	2	2.667	9.091	2	2.48E-03	2.69E-02
REACTOME	ER-PHAGOSOME PATHWAY	64	2	3.125	9.091	2	1.82E-03	2.69E-02
REACTOME	SCF(SKP2)-MEDIATED DEGRADATION OF P27 P21	56	2	3.571	9.091	2	1.40E-03	2.80E-02
REACTOME	G1 S DNA DAMAGE CHECKPOINTS	60	2	3.333	9.091	2	1.60E-03	2.85E-02
REACTOME	SYNTHESIS OF DNA	96	2	2.083	9.091	2	3.99E-03	2.95E-02
REACTOME	DESTABILIZATION OF MRNA BY AUF1 (HNRNP D0)	54	2	3.704	9.091	2	1.30E-03	3.00E-02
REACTOME	CELL CYCLE MITOTIC	330	3	0.909	13.636	3	3.87E-03	3.16E-02
REACTOME	APC C CDC20 MEDIATED DEGRADATION OF MITOTIC PROTEINS	69	2	2.899	9.091	2	2.11E-03	3.29E-02
KEGG	RETINOL METABOLISM	65	1	1.538	4.545	1	6.11E-02	3.43E-02
KEGG	ASCORBATE AND ALDARATE METABOLISM	26	1	3.846	4.545	1	2.54E-02	3.54E-02
REACTOME	CELL CYCLE CHECKPOINTS	117	2	1.709	9.091	2	5.83E-03	3.60E-02
REACTOME	APC C CDC20 MEDIATED DEGRADATION OF SECURIN	64	2	3.125	9.091	2	1.82E-03	3.66E-02
REACTOME	AUTODEGRADATION OF CDH1 BY CDH1 APC C	60	2	3.333	9.091	2	1.60E-03	3.66E-02
REACTOME	CYCLIN E ASSOCIATED EVENTS DURING G1 S TRANSITION	65	2	3.077	9.091	2	1.87E-03	3.68E-02
REACTOME	ASSEMBLY OF THE PRE-REPLICATIVE COMPLEX	67	2	2.985	9.091	2	1.99E-03	3.74E-02
REACTOME	CDT1 ASSOCIATION WITH THE CDC6 ORC ORIGIN COMPLEX	58	2	3.448	9.091	2	1.50E-03	3.74E-02
REACTOME	CYCLIN A CDK2-ASSOCIATED EVENTS AT S PHASE ENTRY	66	2	3.03	9.091	2	1.93E-03	3.82E-02
REACTOME	APOPTOSIS	148	2	1.351	9.091	2	9.08E-03	3.90E-02
REACTOME	DNA REPLICATION PRE-INITIATION	82	2	2.439	9.091	2	2.94E-03	4.01E-02
REACTOME	M G1 TRANSITION	82	2	2.439	9.091	2	2.94E-03	4.01E-02
KEGG	PORPHYRIN AND CHLOROPHYLL METABOLISM	43	1	2.326	4.545	1	4.13E-02	4.09E-02
REACTOME	S PHASE	112	2	1.786	9.091	2	5.36E-03	4.19E-02
REACTOME	REGULATION OF DNA REPLICATION	75	2	2.667	9.091	2	2.48E-03	4.22E-02
REACTOME	REMOVAL OF LICENSING FACTORS FROM ORIGINS	72	2	2.778	9.091	2	2.29E-03	4.22E-02
REACTOME	PEPTIDE LIGAND-BINDING RECEPTORS	186	2	1.075	9.091	2	1.39E-02	4.94E-02

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Olive Oil Month 3 (Compared to Control Oil Month 3) down-regulated

Category	**Term**	**Total Genes of the Term**	**Targets in the Term**	**Targets in Total Genes of the Term (%)**	**Targets in Total Targets of Submitted miRNA(s) (%)**	**Union miRNAs in the Term**	**Raw *P*-Value[1]**	**Empirical *P*-Value[2]**
REACTOME	REGULATION OF IFNA SIGNALING	25	1	4	10	1	1.12E-02	5.20E-03
REACTOME	INTERFERON ALPHA BETA SIGNALING	64	1	1.563	10	1	2.83E-02	7.94E-03
PATHWAY INTERACTION DATABASE	ARF6 SIGNALING EVENTS	35	1	2.857	10	1	1.57E-02	1.54E-02
KEGG	UBIQUITIN MEDIATED PROTEOLYSIS	135	2	1.481	20	1	1.60E-03	2.74E-02
REACTOME	ANTIGEN PROCESSING UBIQUITINATION PROTEASOME DEGRADATION	213	2	0.939	20	1	3.88E-03	3.21E-02
REACTOME	CLASS I MHC MEDIATED ANTIGEN PROCESSING PRESENTATION	251	2	0.797	20	1	5.32E-03	3.64E-02
REACTOME	INTERFERON SIGNALING	110	1	0.909	10	1	4.78E-02	3.94E-02
PATHWAY INTERACTION DATABASE	ARF6 TRAFFICKING EVENTS	49	1	2.041	10	1	2.18E-02	3.97E-02

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Olive Oil Change (Compared to Control Oil Change) up-regulated

Category	Term	Total Genes of the Term	Targets in the Term	Targets in Total Genes of the Term (%)	Targets in Total Targets of Submitted miRNA(s) (%)	Union miRNAs in the Term	Raw *P*-Value[1]	Empirical *P*-Value[2]
REACTOME	METABOLISM OF MRNA	218	2	0.917	22.222	1	3.28E-03	6.37E-03
REACTOME	REGULATION OF MRNA STABILITY BY PROTEINS THAT BIND AU-RICH ELEMENTS	86	2	2.326	22.222	1	5.29E-04	9.20E-03
KEGG	SELENOAMINO ACID METABOLISM	26	1	3.846	11.111	1	1.05E-02	1.93E-02
KEGG	RNA DEGRADATION	57	1	1.754	11.111	1	2.28E-02	2.22E-02
REACTOME	METABOLISM OF RNA	264	2	0.758	22.222	1	4.75E-03	2.71E-02
KEGG	PARKINSON'S DISEASE	130	1	0.769	11.111	1	5.07E-02	3.14E-02
KEGG	ALZHEIMER'S DISEASE	168	1	0.595	11.111	1	6.46E-02	4.55E-02
PATHWAY INTERACTION DATABASE	ALPHA-SYNUCLEIN SIGNALING	33	1	3.03	11.111	1	1.33E-02	4.65E-02
REACTOME	DEADENYLATION-DEPENDENT MRNA DECAY	46	1	2.174	11.111	1	1.85E-02	4.74E-02
REACTOME	AMYLOIDS	51	1	1.961	11.111	1	2.05E-02	4.79E-02

(A) Functional Annotation Chart--Functional annotation summary (Empirical *P*-Value < 0.05): Olive Oil Change (Compared to Control Oil Change) down-regulated

Category	Term	Total Genes of the Term	Targets in the Term	Targets in Total Genes of the Term (%)	Targets in Total Targets of Submitted miRNA(s) (%)	Union miRNAs in the Term	Raw *P*-Value[1]	Empirical *P*-Value[2]
GO MOLECULAR FUNCTION TIER2	PROTEIN BINDING TRANSCRIPTION FACTOR ACTIVITY	369	2	0.542	28.571	4	5.41E-03	1.94E-02
PATHWAY INTERACTION DATABASE	REGULATION OF NUCLEAR SMAD2 3 SIGNALING	82	1	1.22	14.286	2	2.55E-02	4.04E-02

(B) Functional Annotation Chart--Pathway Ranking Summary: Control Oil Month 3 (Compared to Control Oil Baseline) up-regulated

Category	Term	Total Genes of the Term	Union Targets in the Term	Union miRNAs in the Term	Score[3] (>1.302)
REACTOME	AXONGUIDANCE	266	47	4	2.966
KEGG	AXONGUIDANCE	129	28	4	2.661
REACTOME	L1CAMINTERACTIONS	94	25	4	2.332
REACTOME	DEVELOPMENTALBIOLOGY	494	65	4	2.329
PATHWAYINTERACTIONDATABASE	NOTCHSIGNALINGPATHWAY	59	17	3	2.205
KEGG	UBIQUITINMEDIATEDPROTEOLYSIS	135	24	4	2.147
KEGG	PATHWAYSINCANCER	325	45	4	1.902
PATHWAYINTERACTIONDATABASE	SIGNALINGEVENTSMEDIATEDBYHEPATOCYTEGROWTHFACTORRECEPTOR (C-MET)	77	16	4	1.642
GOMOLECULARFUNCTIONTIER2	PROTEINBINDINGTRANSCRIPTIONFACTORACTIVITY	369	41	4	1.617
KEGG	MAPKSIGNALINGPATHWAY	272	33	4	1.607
KEGG	ERBBSIGNALINGPATHWAY	87	17	4	1.58
KEGG	WNTSIGNALINGPATHWAY	150	22	4	1.481
KEGG	MELANOGENESIS	101	15	4	1.437
KEGG	PROSTATECANCER	89	16	4	1.428
PATHWAYINTERACTIONDATABASE	EPHAFORWARDSIGNALING	34	7	3	1.412
PATHWAYINTERACTIONDATABASE	C-MYBTRANSCRIPTIONFACTORNETWORK	81	16	4	1.351
REACTOME	SIGNALINGBYROBORECEPTOR	32	8	3	1.349
BIOCARTA	BIOCARTAKERATINOCYTEPATHWAY	46	13	4	1.336
BIOCARTA	BIOCARTAMAPKPATHWAY	87	14	3	1.329

(B) Functional Annotation Chart--Pathway Ranking Summary: Control Oil Month 3 (Compared to Control Oil Baseline) down-regulated

Category	Term	Total Genes of the Term	Union Targets in the Term	Union miRNAs in the Term	Score[3] (>1.302)
PATHWAYINTERACTIONDATABASE	INTEGRINSINANGIOGENESIS	74	14	2	3.206
KEGG	MAPKSIGNALINGPATHWAY	272	29	1	3.049
REACTOME	AXONGUIDANCE	266	26	2	3.012
REACTOME	NCAM1INTERACTIONS	44	10	2	2.869
REACTOME	NCAMSIGNALINGFORNEURITEOUT-GROWTH	70	12	2	2.676
REACTOME	DEVELOPMENTALBIOLOGY	494	37	2	2.588
PATHWAYINTERACTIONDATABASE	SYNDECAN-1-MEDIATEDSIGNALINGEVENTS	46	9	2	2.44
KEGG	PATHWAYSINCANCER	325	29	1	2.384
REACTOME	SIGNALINGBYPDGF	122	15	2	2.352
KEGG	CHRONICMYELOIDLEUKEMIA	73	12	1	2.215
PATHWAYINTERACTIONDATABASE	BETA1INTEGRINCELLSURFACEINTERACTIONS	65	10	2	2.208
PATHWAYINTERACTIONDATABASE	BETA3INTEGRINCELLSURFACEINTERACTIONS	43	9	1	2.093
PATHWAYINTERACTIONDATABASE	SHP2SIGNALING	54	10	1	2.088
KEGG	OLFACTORYTRANSDUCTION	388	1	1	2.075
KEGG	ECM-RECEPTORINTERACTION	84	11	2	2.063
KEGG	P53SIGNALINGPATHWAY	68	11	1	2.026
REACTOME	OLFACTORYSIGNALINGPATHWAY	377	1	1	2.007
PATHWAYINTERACTIONDATABASE	TNFRECEPTORSIGNALINGPATHWAY	46	9	1	1.989
KEGG	MELANOMA	71	11	1	1.95
KEGG	FOCALADHESION	199	18	2	1.915
KEGG	PROTEINDIGESTIONANDABSORPTION	80	10	2	1.89
BIOCARTA	BIOCARTAFASPATHWAY	30	7	1	1.817
KEGG	GLIOMA	65	10	1	1.787
KEGG	BLADDERCANCER	42	8	1	1.76
KEGG	PANCREATICCANCER	70	10	1	1.672
KEGG	HYPERTROPHICCARDIOMYOPATHY (HCM)	87	11	1	1.611
BIOCARTA	BIOCARTARACCYCDPATHWAY	26	6	1	1.578
REACTOME	CYCLINDASSOCIATEDEVENTSING1	38	7	1	1.531
REACTOME	G1PHASE	38	7	1	1.531
PATHWAYINTERACTIONDATABASE	NEUROTROPHICFACTOR-MEDIATEDTRKRECEPTORSIGNALING	61	6	2	1.524
KEGG	CELLCYCLE	124	13	1	1.512
PATHWAYINTERACTIONDATABASE	IL4-MEDIATEDSIGNALINGEVENTS	64	9	1	1.51
BIOCARTA	BIOCARTAG1PATHWAY	28	6	1	1.5
PATHWAYINTERACTIONDATABASE	C-MYBTRANSCRIPTIONFACTORNETWORK	81	10	1	1.455
KEGG	CYTOKINE-CYTOKINERECEPTORINTERACTION	275	21	1	1.445
KEGG	AXONGUIDANCE	129	11	2	1.427
PATHWAYINTERACTIONDATABASE	AP-1TRANSCRIPTIONFACTORNETWORK	69	9	1	1.409
KEGG	SMALLCELLLUNGCANCER	84	10	1	1.404
KEGG	TGF-BETASIGNALINGPATHWAY	84	10	1	1.404
REACTOME	INTEGRINCELLSURFACEINTERACTIONS	85	10	1	1.387
BIOCARTA	BIOCARTAMAPKPATHWAY	87	10	1	1.354
KEGG	AMOEBIASIS	105	11	1	1.323
KEGG	PROSTATECANCER	89	10	1	1.323
KEGG	DILATEDCARDIOMYOPATHY	90	10	1	1.308

(B) Functional Annotation Chart--Pathway Ranking Summary: Olive Oil Month 3 (Compared to Olive Oil Baseline) up-regulated

Category	Term	Total Genes of the Term	Union Targets in the Term	Union miRNAs in the Term	Score[3] (>1.302)
REACTOME	SIGNALINGBYEGFR	109	25	2	2.679
REACTOME	AXONGUIDANCE	266	37	2	2.556
REACTOME	DOWNSTREAMSIGNALINGOFACTIVATEDFGFR	100	22	2	2.311
REACTOME	DOWNSTREAMSIGNALTRANSDUCTION	93	21	2	2.263
REACTOME	L1CAMINTERACTIONS	94	19	2	2.254
REACTOME	SIGNALINGBYFGFR	114	23	2	2.244
REACTOME	NGFSIGNALLINGVIATRKAFROMTHEPLASMAMEMBRANE	136	25	2	2.238
REACTOME	DEVELOPMENTALBIOLOGY	494	49	3	2.093
REACTOME	SIGNALLINGBYNGF	221	31	2	2.069
REACTOME	SIGNALINGBYPDGF	122	21	2	1.813
KEGG	LONG-TERMPOTENTIATION	70	14	3	1.717
PATHWAYINTERACTIONDATABASE	SIGNALINGEVENTSMEDIATEDBYFOCALADHESIONKINASE	58	15	2	1.711
REACTOME	SIGNALINGBYSCF-KIT	78	16	2	1.529
BIOCARTA	BIOCARTAPYK2PATHWAY	29	10	2	1.493
REACTOME	PI3KAKTACTIVATION	37	11	2	1.431
KEGG	FOCALADHESION	199	25	2	1.41
REACTOME	GAB1SIGNALOSOME	39	11	2	1.384
REACTOME	PI-3KCASCADE	57	13	2	1.379
REACTOME	HEMOSTASIS	467	39	3	1.321

(B) Functional Annotation Chart--Pathway Ranking Summary: 2d, 3u, 3d, 4d and 5u

Category	Term	Total Genes of the Term	Union Targets in the Term	Union miRNAs in the Term	Score[3] (>1.302)
NA	NA	NA	NA	NA	NA

(B) Functional Annotation Chart--Pathway Ranking Summary: Olive Oil Month 3 (Compared to Control Oil Month 3) up-regulated

Category	Term	Total Genes of the Term	Union Targets in the Term	Union miRNAs in the Term	Score[3] (>1.302)
PATHWAYINTERACTIONDATABASE	DIRECTP53EFFECTORS	137	40	8	2.007
KEGG	PATHWAYSINCANCER	325	70	8	1.772
KEGG	OOCYTEMEIOSIS	112	31	8	1.646
PATHWAYINTERACTIONDATABASE	SIGNALINGEVENTSMEDIATEDBYHEPATOCYTEGROWTHFACTORRECEPTOR(C-MET)	77	31	7	1.563
KEGG	TGF-BETASIGNALINGPATHWAY	84	31	7	1.548
KEGG	PROGESTERONE-MEDIATEDOOCYTEMATURATION	86	19	7	1.463
BIOCARTA	BIOCARTAMAPKPATHWAY	87	37	7	1.45
PATHWAYINTERACTIONDATABASE	ALK1SIGNALINGEVENTS	25	14	6	1.428
REACTOME	AXONGUIDANCE	266	67	7	1.401
REACTOME	NGFSIGNALLINGVIATRKAFROMTHEPLASMAMEMBRANE	136	41	7	1.396
KEGG	WNTSIGNALINGPATHWAY	150	43	7	1.393
PATHWAYINTERACTIONDATABASE	IFN-GAMMAPATHWAY	42	14	6	1.352
PATHWAYINTERACTIONDATABASE	BMPRECEPTORSIGNALING	42	14	6	1.348
KEGG	MAPKSIGNALINGPATHWAY	272	67	8	1.324

(B) Functional Annotation Chart--Pathway Ranking Summary: Olive Oil Change (Compared to Control Oil Change) down-regulated

Category	Term	Total Genes of the Term	Union Targets in the Term	Union miRNAs in the Term	Score[3] (>1.302)
REACTOME	AXONGUIDANCE	266	97	12	1.435
REACTOME	DEVELOPMENTALBIOLOGY	494	137	13	1.307

Functional Annotation: KEGG, Biocata, Pathway Interaction Database (human), Reactome (human), GO molecular function (Tier 2). Hit (Target genes are shown if they are greater than or equal to the number of algorithms predicting the same miRNA-gene interaction pair. Check the "Include validated genes" item will include target genes verified by biological experiments regardless of the number of hits.): Include validated genes ; greater than or equal to 3. O/E ratio (Target genes are shown if they are greater than or equal to the number of defined O/E ratio): greater than or equal to 2. Total genes in a pathway: Only biological functions/pathways with at least 25 genes and at most 500 genes are analyzed. [1]Raw *P*-values were obtained by a hypergeometric test. [2]Empirical *P*-values were compared with 1,000 random selections. [3]Score was calculated based on the weighted pathway-ranking method.

3.2 Appendix

The details of study population and design can be found at the published article [1]:

Rozati M, Barnett J, Wu D, Handelman G, Saltzman E, Wilson T, Li L, Wang J, Marcos A, Ordovás JM, Lee YC, Meydani M, Meydani SN. Cardio-metabolic and immunological impacts of extra virgin olive oil consumption in overweight and obese older adults: a randomized controlled trial. Nutr Metab (Lond). 2015 Aug 7;12:28. doi: 10.1186/s12986-015-0022-5. eCollection 2015. PubMed PMID: 26251666; PubMed Central PMCID: PMC4527272.

Study Population

Participants for this study were recruited by the Recruitment and Volunteer Services Department at the JM USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University following invitations to individuals within the specified age and body mass index (BMI) ranges in the HNRCA recruitment database, advertisements in the various local newspapers, media sources, and at the Tufts University Boston campus, Tufts Medical Center clinics, and on public bulletin boards in the downtown Boston area and neighboring towns.

A total of 960 responses were received, of whom 799 individuals were considered ineligible following telephone pre-screening (i.e., were no longer interested or did not meet study criteria), and 117 were not eligible following laboratory screenings, assessment of medical history, and physical examination performed by a study nurse practitioner in the Metabolic Research Unit (MRU) at the HNRCA.

Inclusion Criteria: Subjects of both genders were included if they were 65 or older, having a BMI between 25-35 kg/m^2, consuming a typical American diet as determined by National Health and Nutrition Examination Survey (NHANES) [2], and willing to stop using dietary supplements (except vitamin D and calcium), including multivitamin and minerals, fish oil, olive oil, and canola oil, 30 days before and during the study.

Exclusion Criteria: Subjects were excluded if they reported being on a vegetarian diet, eating more than meals per week at a restaurant, having habitual eating disorders, HIV^+, or having autoimmune diseases or cancers (except for non-melanoma skin cancer), using chemotherapy or immunosuppressive drugs, or having any major illnesses including un-controlled CVD, liver disease, renal disease, diabetes, hypertension, asthma, history of splenectomy, being on dialysis and any conditions associated with maldigestion or malabsorption including pancreatitis, celiac disease, gastric bypass or surgery for weight loss, and diagnosis or on treatment for psychosis, and obtained a BDI-II (Beck Depression Inventory-II) score > 20 or MMSE (Mini Mental State Examination) score < 25. They were also excluded if they did not speak English, were blind or deaf, consumed more than 2 glasses of alcoholic drinks/day, had a history of smoking or using nicotine during past 6 months, were on antibiotics or had infections within the past 2 weeks, received flu vaccination within 3 weeks and tetanus immunization within 6 weeks prior to study blood draws and skin tests.

Forty-four subjects who were eligible to participate in the study signed the informed consent form, and 41 participants completed the study. Three participants dropped out from the study because one was prescribed with an iron supplement, one refused to have the delayed type hypersensitivity (DTH) skin test implant, and one had an accident not related to the study.

Study Design

We conducted a randomized, single-blinded, and placebo-controlled trial in overweight and obese older adults between 2011 and 2013 to determine the impact of replacing substitutable oils in a typical American diet with olive oil. The study protocol and consent form were approved by Tufts University/Tufts Medical Center Institutional Review Board. Eligible participants were randomized into either the control or olive oil group in a 1:1 ratio. Treatment was assigned by the study statistician, who had no contact with subjects and had no role in data collection. The study oils (control or olive oil) were labeled with the subjects' names by the study dietitian, who also held the randomization code; all other investigators and the study nurse were blinded to this information. Participants, however, could not be blinded since they might recognize the smell and taste of olive oil. The oils were provided in a bottle or as a spread. To minimize the bias, both study oils were provided to participants in the same type of bottle, and the spread in the same type of container. The control oil was a blend of 10% corn oil and 90% soybean oil and the control spread was butter; these were defined as the oils consumed in a typical American diet [3]. The olive oil used for the study was provided by Deoleo Company in Cordoba (Spain). Prior to screening, participants were asked to taste the oil/spread and provide feedback if they were willing to consume these oils while on the study. **Table 3.2.1** shows the composition of fatty acids in both the control and olive oils. As can be seen, oleic acid (C18:1 n9) comprised about 68% of olive oil compared to 23% in control oil (soybean and corn oil) and 31% in butter (control spread). Linoleic acid (C18:2 n6) comprised 10% of olive oil compared to 54% in control oil and 4% in butter, and linolenic acid (C18:3 n3) constitutes 0.7% of olive oil compared to 6% in control oil and 0.5% in butter. Participants consumed the assigned oils for 3 months. During the study, both groups continued their typical American diet and only replaced substitutable oils in their diet, such as their cooking oil, spread, and oils in their dressings, with the study oil/spread provided to them. The study oils were distributed to the participants by the dietitians at the MRU of the HNRCA.

Baseline and Month 3 Study Visits

Subjects were asked to come to the center for 4 consecutive days at the beginning (baseline) and 3 months after enrollment in the study. On day 1, vital signs (temperature, blood pressure, pulse, and respiratory rate), weight, height, and waist and hip circumferences were measured. Blood was collected after a 12-hour fast for blood chemistry, lipid profile, complete blood count (CBC) differential, fatty acids, and immune tests. On day 2, second blood sample was drawn for repeated ex vivo immune tests, and then three recall antigens detailed below and saline were implanted on front arm for the DTH skin test. On day 3 and 4, participants visited MRU for evaluation of their DTH skin response at 24-hour and 48-hour post-administration. Subjects were asked to discontinue anti-inflammatory medicines including aspirin or anti-histamine 72-hour before the blood was collected until 48-hour after DTH implantation.

Diet Intervention Visits and Assessment of Dietary Intake

Dietitians at the MRU of HNRCA provided all the instructions to the participants on how to substitute fats used in their diet with study oils and spreads. Dietary counseling was provided every two weeks or more often as needed to ensure the subjects were following the instructions and using the right diet and oil. Compliance with consuming study oils was evaluated by the dietitians using a “checklist of study oils consumed per week” as indicated by participants as they returned used containers for a new supply of study oils and spreads as well as by plasma fatty acid analysis. To assess dietary intake, participants completed a 3-day dietary record at both baseline and month 3, which were reviewed and analyzed by a dietitian using the Minnesota Nutrient Data System (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN), version 2010.

Table 3.2.1. Measured fatty acid composition (% total fatty acids) of control and olive oil/spread

	Control Oil	Control Spread (Butter)	Control Oil/Spread (3:1)	Olive Oil/Spread
Total SFA	15.40	62.73	27.23	16.32
C14:0	0.14	11.51	2.98	0.41
C16:0	10.90	36.15	17.21	13.48
C18:0	4.36	15.06	7.04	2.43
Total MUFA	24.14	32.65	26.27	73.02
C16:1	0.00	0.00	0.00	1.28
C18:1 n9	22.75	30.71	24.74	68.28
C18:1 n7	1.39	1.94	1.53	3.18
C20:1 n9	0.00	0.00	0.00	0.29
Total PUFA	60.46	4.62	46.50	10.66
C18:2 n6	54.20	4.11	41.68	10.00
C18:3 n6	0.00	0.00	0.00	0.00
C18:3 n3	6.26	0.52	4.82	0.66
C20:5 n3	0.00	0.00	0.00	0.00
C22:5 n6	0.00	0.00	0.00	0.00
MUFA to SFA ratio	1.57	0.52	1.31	4.48
PUFA to SFA ratio	3.93	0.07	2.96	0.65
S:M:P	1:1.6:3.9	1:0.5:0.07	1:1.3:3	1:4.5:0.7
S:M:P (Goal)			1:1:0.5	1:3:1
n6/n3 PUFA	8.66	7.97	8.49	15.12

3.2.1 References

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3. *U.S. Census Bureau, National Agricultural Statistics Service, USDA. Oil Crops Yearbook (Update 03/10) Stock #89002 Economic Research Service, United States. Department o f Agriculture. Fats and Oils: Oilseed Crushings and Production, Consumption, and Stocks, Appendix Table 31: Edible fats and oils: U.S. Supply and disappearance, 1997-2010.*

Chapter 4 Summary and Discussion

4.1 Summary of Main Findings

Dysregulation of metabolic traits and obesity are risk factors for cardiovascular disease (CVD), a leading cause of mortality in the US [1]. Understanding the regulation of cardiometabolic traits, by genetic variants, dietary factors and their interrelationships, can have a profound impact on CVD onset and progression. Gene-environment (G×E) interactions are hypothesized to account for a portion of the "missing heritability" of complex traits [2], but the mechanisms by which genotypes and dietary factors interact to regulate cardiometabolic traits are still largely unknown. MiRNAs regulate gene expression via targeting mRNAs and represent an epigenetic mechanism that underlies human biology and diseases, including metabolic function and CVD. Previous research has identified genetic variants involved in miRNA-mediated gene regulation, suggesting that such genetic polymorphisms also modulate cardiometabolic traits through miRNAs. It has also been demonstrated that dietary factors can modulate miRNA levels. The underlying miRNA-based mechanisms related to the effect of dietary factors on cardiometabolic traits are not well-understood. This leads us to characterize the roles of genetic variants in miRNA-mediated regulation of metabolic traits and their interactions with diet (G×E interactions). In our studies, we investigated the roles of functional genetic variants and dietary factors on microRNA-mediated gene regulation of cardiometabolic traits.

In Chapter 2, we built an in-house genome-wide miRNA-related single nucleotide polymorphism (SNP) (miRSNP) database with a particular focus on genetic variants which potentially modulate miRNA-mediate gene regulation and affect blood lipids and lipid metabolism. MiRNA target prediction algorithms, publicly available databases and bioinformatics tools were utilized in the processes. This comprehensive miRNA-related SNP database includes 914,515 SNPs located in target regulatory regions/miRNA seed sites, miRNA genes and miRNA processing machinery. This type of functional genetic variant database can be used to assess the genetic contribution of miRNA-mediated regulation on any traits of interest (*Aim 1a*).

Based on the knowledge obtained from our miRSNP database, we then identified *miRNA-related genetic associations and their interactions with diet* for blood lipid concentrations. We then performed functional genome-wide association studies (fGWAS) and genome-wide interaction studies (fGWIS) and meta-analyzed association and interaction data in 9 population-based cohort studies (n = ~21,000, European origin participants) from the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium for blood lipids using miRNA-related SNPs. We evaluated SNP-by-Diet interactions for dietary carbohydrate and saturated, monounsaturated and polyunsaturated fats. Using miRNA fGWAS and fGWIS approaches, we identified 19 loci associated with blood lipids and 17 novel loci potentially interacted with diet in determining blood lipids. Some key results including miRNA-related SNPs in *CELSR2*, *NECTIN2* (also known as *PVRL2*), *FADS1*, *SH3YL1*, *ONECUT2* and *PPIL2* were supported by multiple functional annotation

databases (*Aim 1b*). To our knowledge, this is the first genome-wide dietary interaction scan for functional genetic variants (i.e., miRNA-related SNPs).

All identified miRNA-related SNPs are situated only in miRNA seed sites or regulatory regions of target genes but not miRNA genes or miRNA processing machinery. Our finding was not consistent with a previous report showing that some miRNA genes located in proximity (<100 kb) of SNPs were associated with blood lipid levels [3]. Our smaller population size compared with the data from the Global Lipid Genetics Consortium (GLGC 2013) may have limited our power to discover significant results related to miRNA genes or miRNA processing machinery [4]. Nevertheless, our findings contribute to a deeper understanding of miRNA-mediated regulation, generating new hypotheses for its relationship to blood lipids and dietary macronutrients. We described several examples of how a genetic variant can influence the miRNA-based mechanisms on gene regulation and how a dietary factor can modulate the genetic association with blood lipids, and furthermore, how these findings of SNP-by-macronutrient interactions can be translated to the potential strategies for personalized nutrition if the proposed hypotheses are validated by mechanistic examination.

In Chapter 3, we investigated *the effect of extra virgin olive oil intervention* on miRNA profiles in the context of cardiovascular disease biomarkers. We conducted a two-armed, 3-month randomized controlled trial (RCT): 41 overweight/obese older adults were given extra virgin olive oil or control (soy oil/corn oil/butter) oil to substitute oils/fats commonly used in participants' usual American diet. We utilized miRNA microarray, quantitative RT-PCR and bioinformatics analyses to quantify blood miRNAs to elucidate the effects of olive oil on cardiometabolic traits and their relation with miRNAs. In the olive oil RCT, participants receiving extra virgin olive oil appeared to experience cardiometabolic benefits. After 3-month intervention, participants' systolic blood pressure (SBP) was significantly reduced in the olive oil group but not in the control group. Individuals in the olive oil group had a significantly lower SBP compared with the control group at month 3. Change in hsa-miR-96-5p was also correlated with changes in serum glucose and insulin levels only in the olive oil group after 3 months. Moreover, participants with impaired fasting glucose were found to benefit from olive oil intervention by improving their fasting glucose and insulin. Our findings from the olive oil RCT suggested that hsa-miR-96-5p may be induced by olive oil intervention and play a regulatory role in glycemic balance. The roles of miR-9 by targeting *IRS1* in negatively regulating insulin secretion have been previously reported [5-7]; however, our further experimental investigation of targets of selected miRNAs remained inconclusive. The regulation of miRNAs related to olive oil consumption contributing to health benefits requires further research (*Aim 2*).

4.2 Public Health Relevance

Our research from *Aim 1* have resulted in miRNA-related SNPs associated with blood lipids and potentially interacting with dietary macronutrients for blood lipids with the supporting evidence from the CHARGE Consortium and miRNA-related gene regulatory annotation information. These findings improve the understanding of the miRNA-mediated

regulation of blood lipid traits, especially how a dietary factor can mediate the genetic associations with blood lipids, and inform further replication studies and functional mechanistic examination. Once validated, our studies of nutritional genomics may eventually have an impact on public health by developing personalized dietary preventative strategies and recommendations to improve dyslipidemias and reduce CVD risk for genetically susceptible individuals.

The results from *Aim 2* suggest that olive oil's impact on improving glycemic traits may involve miRNAs. Investigating miRNA-based nutrigenomic changes induced by extra virgin olive oil may legitimate the beneficial effects of extra virgin olive oil in improving cardiometabolic traits. Successful exploratory analyses of miRNAs and their targets may be used as a tool to elucidate molecular mechanisms that underlie the effects of intervention studies. The identified differentially expressed miRNAs in blood might be used as biomarkers of dietary intervention. Our work may help elucidate possible mechanisms by which diet could affect miRNA profiles to promote public health.

4.3 Limitations and Future Directions

Limitations exist in our miRNA-related SNP database. First, the potential functional miRNA-related SNPs from our database may be biased to available data, algorithms and databases. Compiling multiple algorithms and sources data in our research were unclear regarding improving the accuracy of target predictions as previously suggested [8]. Each algorithm/tool to identify miRNA targets or SNPs has its own strengths and limitations, but the overall efficiency of identifying all potential miRNA-related SNPs was hard to summarize and evaluate. Second, the phenotypic consequences of disrupting a single true miRNA-target gene interaction can be subtle, and investigation of such an interaction may require other approaches that examine combined effects of miRNA-related SNPs.

Although the CHARGE consortium provides a great platform for collaboration to improve generalizability, sample size and statistical power for detecting significant results, the observed heterogeneity among the participating cohorts have hindered our ability to detect significant associations and interactions. The cohorts participating in our fGWAS and fGWIS meta-analyses vary in study design, genetic, geographical and cultural background and dietary assessment methodologies. These may explain the small and heterogeneous effects of SNP-by-diet interactions and the possible limited power of 2DF JMA for gene discovery observed in our studies. Our results generated from cross-sectional (i.e., single measure for plasma lipids and dietary intake) study design cannot determine causality. In addition to well-known limitations of measuring dietary intake, different assessment methods used in participating cohorts may introduce high levels of heterogeneity into meta-analysis results. Some challenges observed in our research have been also recently discussed [9, 10]. Replication of our findings is necessary to verify results obtained from our analyses. Data harmonization and validating results in large and relatively homogeneous populations with well-characterized environmental/dietary data are, therefore, suggested to be the key components for the immediate future validation. New analytic methods/tools are needed for nutritional GWIS.

In addition, other studies such as targeted dietary intervention study based on genetic information in combination with miRNA profiles and transcriptome are required to evaluate the proposed mechanisms. Different statistical methods and experiment-based follow-up functional analyses are also recommended for further investigation. Both the effect of a SNP on miRNA-mRNA interactions and the effect of a dietary treatment on expression of identified miRNA and target pairs should be verified.

Due to the nature of the olive oil pilot study, limitations include small sample size, participants' heterogeneity derived from aging, ethnicity and dietary intervention dose actually consumed. A more controlled study with adequate sample size and detailed molecular and chemical characterization and quantification of intervention olive oil and a specific sub-group of participants (to reduce variability) should be planned to better investigate the impact of diet on the relationships between miRNA and cardiometabolic traits. Effects of dietary factors on plasma fatty acids, miRNA profiles and phenotypes require detailed time-course studies in multiple tissues to determine if and how plasma fatty acid or miRNA changes are causal for changes in phenotypes.

4.4 References

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