SUPPLEMENTAL MATERIAL

Methods

Overview of participating studies

This study includes 66,430 men and women between 18-80 years of age from 11 European-ancestry population studies that are part of the CHARGE Gene-Lifestyle Interactions Working Group [1]. The participating studies include the Atherosclerosis Risk in Communities (ARIC) study, the Coronary Artery Risk Development in Young Adults (CARDIA) study, the Framingham Heart Study (FHS), the Netherlands Epidemiology of Obesity (NEO) study, the Women's Health Initiative (WHI) study, the Cleveland Family Study (CFS), the Cardiovascular Health Study (CHS), the Family Heart Study (FamHS), the Genetic Epidemiology Network of Arteriopathy (GENOA) study, the Multi-Ethnic Study of Atherosclerosis (MESA), and the Women's Genome Health Study (WGHS). Additional detail for these studies is provided later in the study description. Each study obtained informed consent from participants and approval from the appropriate institutional review boards. A total of 34,153 participants from five studies participated in the discovery phase (ARIC, FHS, NEO, WHI and CARDIA), and six studies involving 32,277 participants were used for replication (WGHS, CFS, CHS, FamHS, GENOA and MESA) (Supplemental Figure 1).

Plasma lipids and alcohol consumption

Three fasting (≥ 8 hours) lipid measures were analyzed separately. HDL-C and TG were directly assayed, while LDL-C was either directly assayed (WGHS, FamHS if TG > 400 mg/dL) or estimated using the Friedewald equation [2] (ARIC, FHS, NEO, WHI, CARDIA, CFS, CHS, FamHS, GENOA, MESA) in samples with TG ≤ 400 mg/dL. LDL-C levels were adjusted for use of statins: if LDL-C levels were directly assayed, LDL-C levels were adjusted for lipid-

lowering medication use by dividing the original levels by 0.7, otherwise, LDL-C levels were adjusted by first dividing total cholesterol by 0.8, which estimates the effect of statins on total cholesterol values [3], and then using the corrected total cholesterol level in the Friedewald equation. When information on statin-specific use was unavailable, LDL-C levels were adjusted for use of unspecified lipid-lowering medication in the same scheme as for statins, but only if lipid measurements were performed after 1994 when statin use becomes common [3]. No adjustments were made to HDL or triglycerides for medication use. Due to their skewed distributions, HDL-C and TG were natural log transformed prior to analyses (Supplemental Figure 3).

Alcohol consumption was assessed using two dichotomized self-reported alcohol consumption variables: "current drinker" status, defined as any recurrent drinking behavior (yes/no), and "regular drinker" status, as the subset of current drinkers who consume at least two drinks per week (yes/no) [4]. For this study, definition of "a drink" corresponds to approximately 13g of pure ethanol, and this measure was used to standardize the definitions across studies.

Genotyping and quality control

Genotyping was performed using the Illumina Human Exome or OmniExpress and Exome array. To improve accurate calling of rare variants, genotyped data from 10 CHARGE Consortium studies were jointly called [5]. Using the curated clustering files from the CHARGE joint calling effort, several cohorts within our study re-called their genotypes. For the remainder of participating studies, genotypes were determined using either BeadStudio or Zcall [6]. Detailed information regarding the genotyping platform for each study is presented in Supplemental Table 1. All studies performed the following sample-level quality control steps and removed samples with call rate <95%, autosomal heterozygosity outliers, gender discordance, GWAS discordance

(if GWAS data available), and ethnic outliers in a principal components analysis. Variants were removed by filtering for Hardy-Weinberg equilibrium test *p*-value (pHWE) < 5×10^{-6}, call rate <95%, and poorly clustering variants.

Study-specific association analyses

Statistical analyses were performed within each individual study using the gene-based rareGE R package [7], and were performed for each lipid/alcohol consumption combination for a total of six combinations. Two types of analyses were considered: 1) a G×E test that considers the genetic main effects as random effects, and 2) a joint analysis of the genetic main and the G×E interaction effects. In the GxE test, genetic main effects were modeled as random effects to reduce the number of parameters and maintain well controlled type I error rates as recommended[7]. Rare and low-frequency (MAF ≤ 5%) functional variants (i.e. frameshift, nonsynonymous, stop/gain, stop/loss, and splicing) were aggregated within genes. Genes with 0 or only 1 rare and low-frequency variant, or genes with a cumulative minor allele count ≤ 10 were not analyzed within each study. Models were adjusted for age, sex, principal components (PCs) and additionally study-specific covariates as presented in Supplemental Table 1. For studies with related subjects, we accounted for relatedness in families using generalized linear mixed effect model approach with a random effect for modeling sample relatedness (kinship matrix).

Meta-analyses

A weighted Z-test using square root of sample sizes as weights was used to meta-analyze study-specific *p*-values for genes present in at least 2 discovery studies [8]. In total, we analyzed 10,094 genes in the discovery phase. A Bonferroni corrected p-value threshold would be 0.05/10094= 5×10^{-6}. We choose to set the discovery phase significance threshold at 1 order of

magnitude lower (p-value $<5\times10^{-5}$) given our study design which involved a very restricted independent discovery and replication approach, as well as Bonferroni correction in the replication phase to minimize the possibility of reporting false positive signals. Among these 31 findings with $p < 5\times10^{-5}$, the equivalent false discovery rate is estimated to be $5\times10^{-5}\times10094/31 = 0.016$. Genes of interest from the discovery phase with a p-value $< 5\times10^{-5}$ were pursued for replication. For these select genes, we used the same approaches as in discovery studies to perform meta-analysis of the replication studies. Significance was determined using a Bonferroni correction for the number of gene-lipid pairs taken forward to replication (p-value $< 0.05/30 = 0.0017$ for analysis of the joint test of genetic main and interaction effects, p-value $<0.05/4 = 0.0125$ for analysis of the interaction effects).

Additional analyses: conditional and single variant tests

For each replicated gene-lipid pair, additional analyses were conducted following the flowchart shown in **Figure 1**. For genes +/-500kb bp from previously reported lipid loci [9], conditional analyses were performed to identify aggregated rare and low-frequency variants associated with lipids independent of the previously reported common index SNPs [9]. Results from study-specific conditional analyses were meta-analyzed using a weighted Z-test, separately in discovery and replication studies. For novel genes and known genes that remained significant after conditional analyses, we performed single variant tests for each variant (MAF $\leq$ 5% and minor allele count $\geq$ 5) that was included in the aggregate test in order to identify the driving variants within these genes. We obtained robust estimates of covariance matrices and robust standard errors from each study and implemented METAL to jointly meta-analyze the genetic main and interaction effects [10, 11], and to meta-analyze the interaction coefficients alone using inverse-variance weighted meta-analysis for each single variant within selected genes.

Method References:

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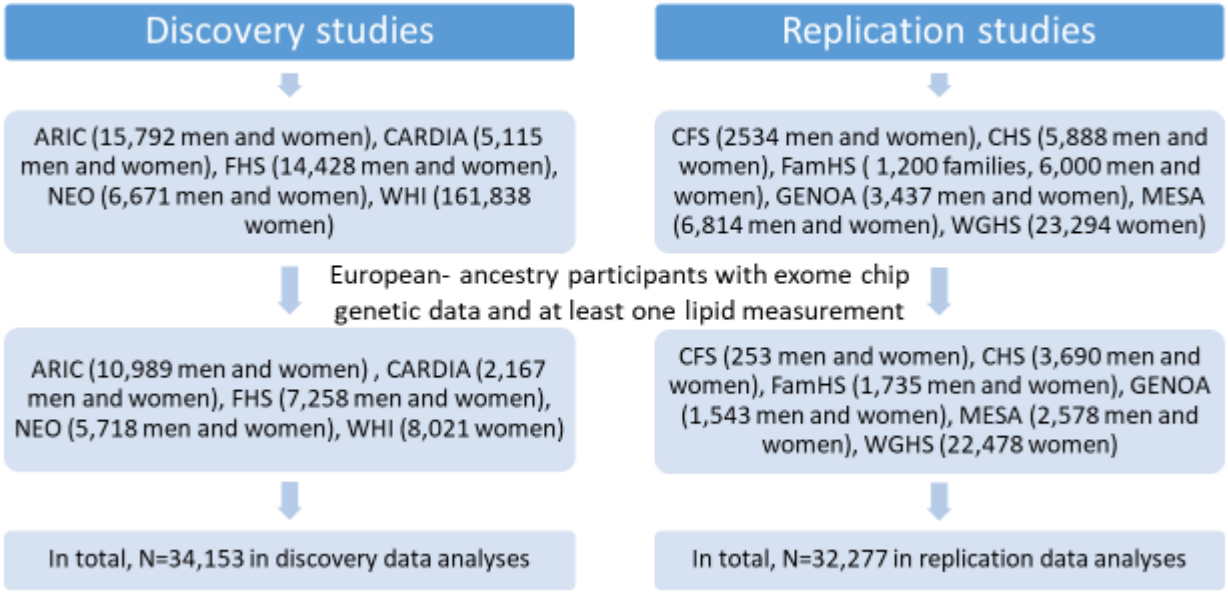
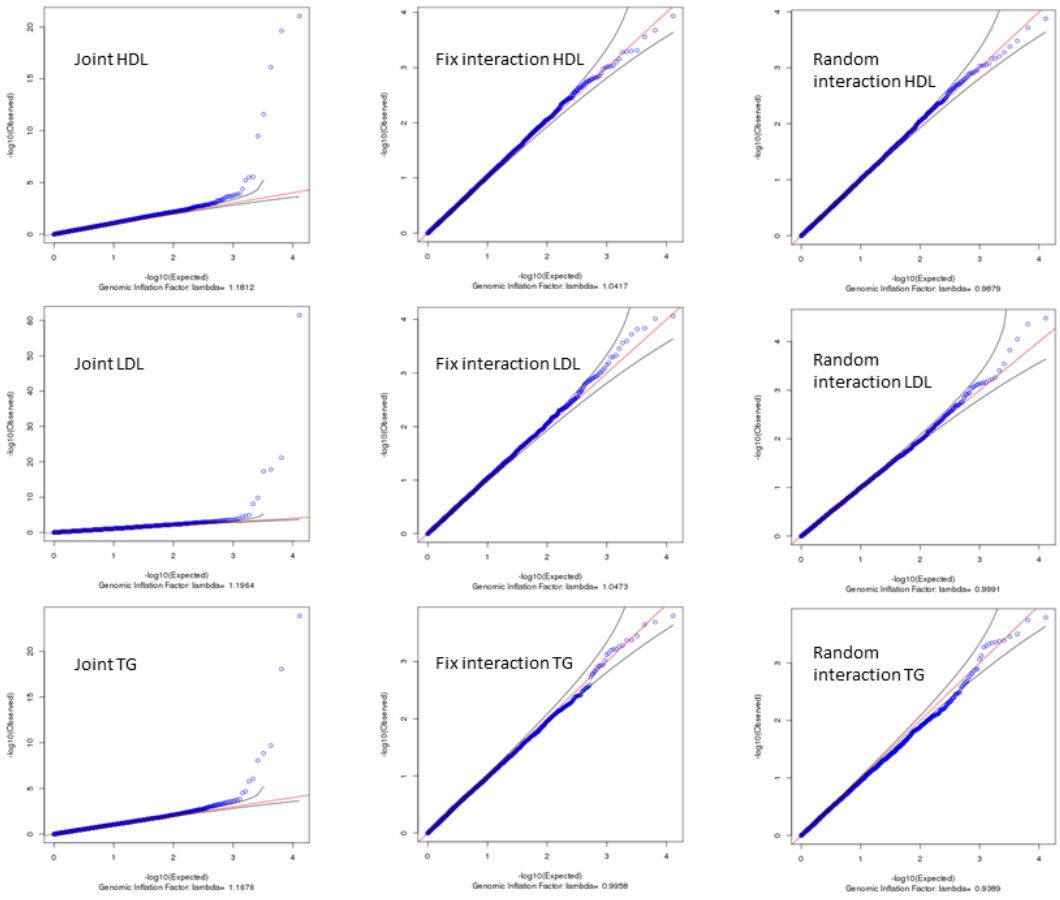
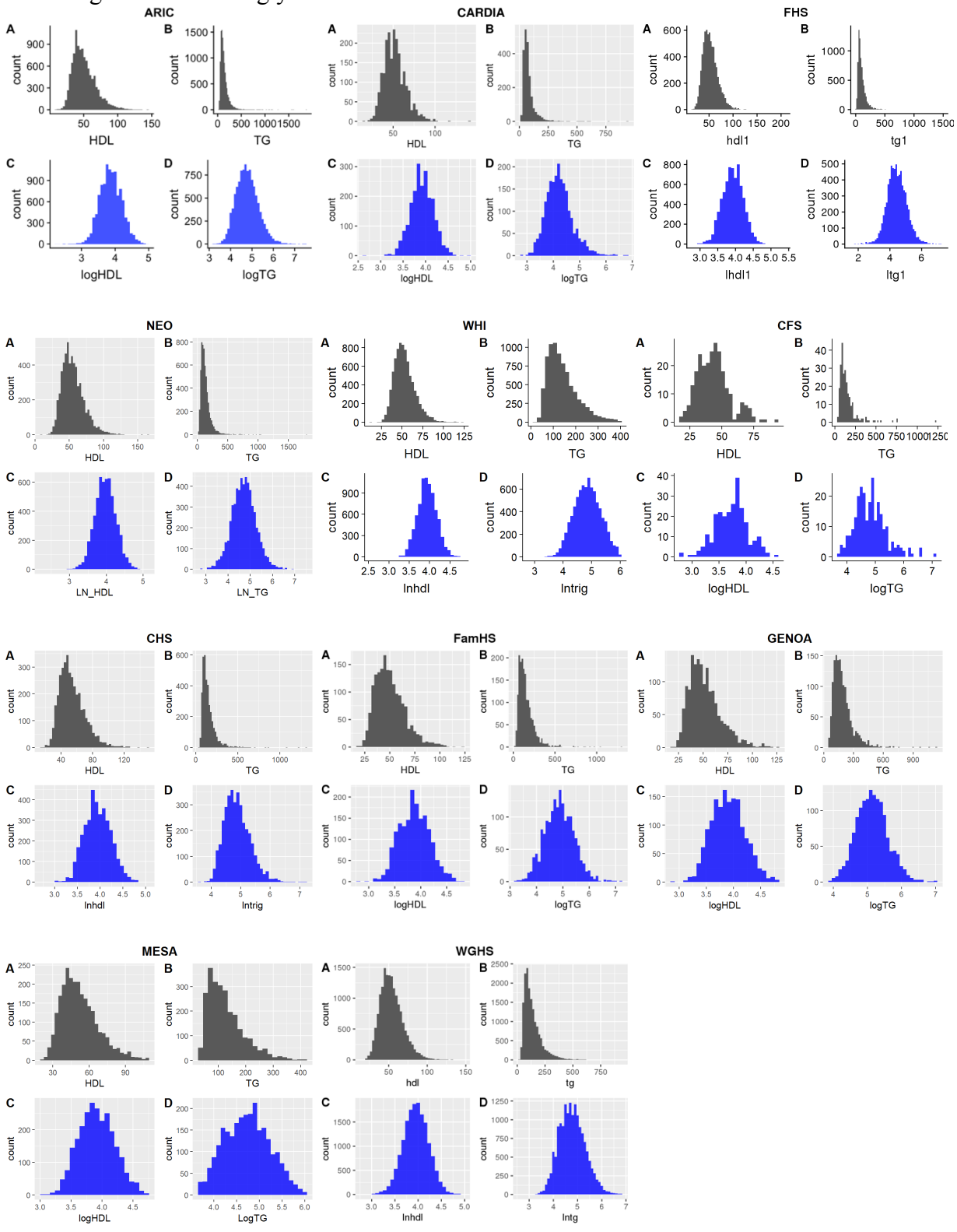
Supplemental Figure 1. Participant flow chart



Supplemental Figure 2. Quantile-quantile (QQ) plots for meta-analyzing discovery studies using different methods of rareGE



Supplemental Figure 3. Distribution of HDL-C and triglyceride levels before and after the ln-transformation in each participating study. A) histogram of raw HDL-C levels; B) histogram of raw triglyceride levels; C) histogram of nature log transformed HDL-C levels; D) histogram of nature log transformed triglyceride levels



Discovery Study Description:

ARIC (Atherosclerosis Risk in Communities): The ARIC study is a population-based prospective cohort study of cardiovascular disease sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45-64 years at baseline (1987-89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations and a fifth exam in 2011-2013. The ARIC study has been described in detail previously (1). We only analyzed the European Americans for this project.

CARDIA (Coronary Artery Risk Development in Young Adults): CARDIA is a prospective multicenter study with 5,115 adults Caucasian and African American participants of the age group 18-30 years, recruited from four centers at the baseline examination in 1985-1986. The recruitment was done from the total community in Birmingham, AL, from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The details of the study design for the CARDIA study have been previously published. Nine examinations have been completed since initiation of the study, respectively in the years 0, 2, 5, 7, 10, 15, 20, 25, and 30. Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions. We only analyzed the European Americans for this project.

FHS (Framingham Heart Study): FHS began in 1948 with the recruitment of an original cohort of 5,209 men and women (mean age 44 years; 55 percent women). In 1971 a second

generation of study participants was enrolled; this cohort (mean age 37 years; 52% women) consisted of 5,124 children and spouses of children of the original cohort. A third generation cohort of 4,095 children of offspring cohort participants (mean age 40 years; 53 percent women) was enrolled in 2002-2005 and are seen every 4 to 8 years. Details of study designs for the three cohorts are summarized elsewhere. At each clinic visit, a medical history was obtained with a focus on cardiovascular content, and participants underwent a physical examination including measurement of height and weight from which BMI was calculated.

NEO (The Netherlands Epidemiology of Obesity study): The NEO was designed for extensive phenotyping to investigate pathways that lead to obesity-related diseases. The NEO study is a population-based, prospective cohort study that includes 6,671 individuals aged 45–65 years, with an oversampling of individuals with overweight or obesity. At baseline, information on demography, lifestyle, and medical history have been collected by questionnaires. In addition, samples of 24-h urine, fasting and postprandial blood plasma and serum, and DNA were collected. Genotyping was performed using the Illumina HumanCoreExome chip, which was subsequently imputed to the 1000 genome reference panel. Participants underwent an extensive physical examination, including anthropometry, electrocardiography, spirometry, and measurement of the carotid artery intima-media thickness by ultrasonography. In random subsamples of participants, magnetic resonance imaging of abdominal fat, pulse wave velocity of the aorta, heart, and brain, magnetic resonance spectroscopy of the liver, indirect calorimetry, dual energy X-ray absorptiometry, or accelerometry measurements were performed. The collection of data started in September 2008 and completed at the end of September 2012.

Participants are currently being followed for the incidence of obesity-related diseases and mortality.

WHI (Women's Health Initiative): WHI is a long-term national health study that focuses on strategies for preventing common diseases such as heart disease, cancer and fracture in postmenopausal women. A total of 161,838 women aged 50–79 years old were recruited from 40 clinical centers in the US between 1993 and 1998. WHI consists of an observational study, two clinical trials of postmenopausal hormone therapy (HT, estrogen alone or estrogen plus progestin), a calcium and vitamin D supplement trial, and a dietary modification trial.(2) Study recruitment and exclusion criteria have been described previously. Recruitment was done through mass mailing to age-eligible women obtained from voter registration, driver's license and Health Care Financing Administration or other insurance list, with emphasis on recruitment of minorities and older women.(3) Exclusions included participation in other randomized trials, predicted survival < 3 years, alcoholism, drug dependency, mental illness and dementia. For the CT, women were ineligible if they had a systolic BP > 200 mm Hg or diastolic BP > 105 mm Hg, a history of hypertriglyceridemia or breast cancer. Study protocols and consent forms were approved by the IRB at all participating institutions. Socio-demographic characteristics, lifestyle, medical history and self-reported medications were collected using standardized questionnaires at the screening visit. Physical measures of height, weight and blood pressure were measured at a baseline clinical visit.(3) BP was measured by certified staff using standardized procedures and instruments.(4) Two BP measures were recorded after 5 minutes rest using a mercury sphygmomanometer. Appropriate cuff bladder size was determined at each

visit based on arm circumference. Diastolic BP was taken from the phase V Korotkoff measures. The average of the two measurements, obtained 30 seconds apart, was used in analyses.

Replication Study Description

CFS (Cleveland Family Study): The Cleveland Family Study is a family-based, longitudinal cohort study with the objective of examining the genetic and familial basis of sleep apnea. It consists of 2534 African- and European-American individuals from 356 families. Index probands with confirmed sleep apnea were recruited from northern Ohio sleep centers. Up to four visits were made from 1990 to 2006, and a final laboratory visit at a clinical research center between 2000 and 2006. Blood samples were obtained from 1447 participants from the final two exams, and DNA was extracted from samples that passed quality control. In this analysis, we subsetted to only European Americans who had a lab visit, and were 18 or older at the time of visit.

CHS (Cardiovascular Health Study): CHS is a population-based cohort study of risk factors for cardiovascular disease in adults 65 years of age or older conducted across four field centers (5). The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists and an additional predominately African-American cohort of 687 persons was enrolled in 1992-93 for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. CHS was approved by institutional review committees at each site and individuals in the present analysis gave informed consent including consent to use of genetic information for the study of cardiovascular disease. We only analyzed the European Americans for this project.

FamHS (Family Heart Study): The NHLBI FamHS study design, collection of phenotypes and covariates as well as clinical examination have been previously described (https://dsgweb.wustl.edu/fhscc/) (6). In brief, the FamHS recruited 1,200 families (approximately 6,000 individuals), half randomly sampled, and half selected because of an excess of coronary heart disease (CHD) or risk factor abnormalities as compared with age- and sex-specific population rates. The participants were sampled from four population-based parent studies: the Framingham Heart Study, the Utah Family Tree Study, and two centers for the Atherosclerosis Risk in Communities study (ARIC: Minneapolis, and Forsyth County, NC). These individuals attended a clinic exam (1994-1996) and a broad range of phenotypes were assessed in the general domains of CHD, atherosclerosis, cardiac and vascular function, inflammation and hemostasis, lipids and lipoproteins, blood pressure, diabetes and insulin resistance, pulmonary function, diet, education, socioeconomic status, habitual behavior, physical activity, anthropometry, medical history and medication use. Approximately 8 years later, study participants belonging to the largest pedigrees were invited for a second clinical exam (2002-04). The most important CHD risk factors were measured again, including lipids, parameters of glucose metabolism, blood pressure, anthropometry, and several biochemical and hematologic markers. In addition, a computed tomography examination provided measures of coronary and aortic calcification, and abdominal and liver fat burden. Medical history and medication use was updated. A total of 2,756 European ancestry subjects in 510 extended random and high CHD risk families were studied.

GENOA (Genetic Epidemiology Network of Arteriopathy): GENOA is one of four networks in the NHLBI Family-Blood Pressure Program (FBPP) (7, 8). GENOA's long-term objective is to elucidate the genetics of target organ complications of hypertension, including both atherosclerotic and arteriolosclerotic complications involving the heart, brain, kidneys, and peripheral arteries. The longitudinal GENOA Study recruited European-American and African-American sibships with at least 2 individuals with clinically diagnosed essential hypertension before age 60 years. All other members of the sibship were invited to participate regardless of their hypertension status. Participants were diagnosed with hypertension if they had either 1) a previous clinical diagnosis of hypertension by a physician with current anti-hypertensive treatment, or 2) an average systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg based on the second and third readings at the time of their clinic visit. Exclusion criteria were secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. During the first exam (1995-2000), 1,583 European Americans from Rochester, MN and 1,854 African Americans from Jackson, MS were examined. Between 2000 and 2005, 1,241 of the European Americans and 1,482 of the African Americans returned for a second examination. We only analyzed the European Americans for this project.

MESA (Multi-Ethnic Study of Atherosclerosis): The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA consisted of a diverse, population-based sample of an initial 6,814 asymptomatic men and women aged 45-84. 38 percent of the recruited participants were white, 28 percent African American, 22 percent Hispanic, and 12 percent Asian, predominantly of

Chinese descent. (9) Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California - Los Angeles. Participants are being followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; for cardiovascular disease interventions; and for mortality. The first examination took place over two years, from July 2000 - July 2002. It was followed by four examination periods that were 17-20 months in length. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality. We only analyzed the European Americans for this project.

WGHS (Women's Genome Health Study): WGHS is a prospective cohort of female North American health care professionals representing participants in the Women's Health Study (WHS) trial who provided a blood sample at baseline and consent for blood-based analyses. Participants in the WHS were 45 years or older at enrollment and free of cardiovascular disease, cancer or other major chronic illness. The current data are derived from 23,294 WGHS participants for whom whole genome genotype information was available at the time of analysis and for whom self-reported European ancestry could be confirmed by multidimensional scaling analysis of 1,443 ancestry informative markers in PLINK v. 1.06. At baseline, BP and lifestyle habits related to smoking, consumption of alcohol, and physical activity as well as other general clinical information were ascertained by a self-reported questionnaire, an approach which has been validated in the WGHS demographic, namely female health care professionals.

Discovery Study Acknowledgement

ARIC (Atherosclerosis Risk in Communities): The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services (contract numbers HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700004I and HHSN268201700005I). The authors thank the staff and participants of the ARIC study for their important contributions. Funding support for "Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium" was provided by the NIH through the American Recovery and Reinvestment Act of 2009 (ARRA) (5RC2HL102419).

CARDIA (Coronary Artery Risk Development in Young Adults): The CARDIA Study is conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the University of Alabama at Birmingham (HHSN268201300025C & HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging. Exome Chip genotyping was supported from grants R01-HL093029 and U01- HG004729 to MF.

FHS (Framingham Heart Study): This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators

participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract Nos. N01-HC-25195 and HHSN268201500001I) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. This research was partially supported by grant R01-DK089256 from the National Institute of Diabetes and Digestive and Kidney Diseases (MPIs: Michael Province, L. Ching-Ti Liu, Kari North) and training grant T32GM074905-14 from NIH/National Institute of General Medical Sciences.

NEO (The Netherlands Epidemiology of Obesity study): The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank the NEO study group, Pat van Beelen, Petra Noordijk and Ingeborg de Jonge for the coordination , lab and data management of the NEO study. The genotyping in the NEO study was upported by the Centre National de Génotypage (Paris, France), headed by Jean Francois Deleuze. The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. Dennis Mook Kanamori is supported by Dutch Science Organization (ZonMW) VENI Grant 916.14.023). Diana van Heemst and Raymond Noordam were supported by the European Commission funded project HUMAN (Health-2013-INNOVATION-1-602757)

WHI (Women's Health Initiative): The WHI program is funded by the National Heart, Lung, and Blood Institute through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. We thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

Replication Study Acknowledgement

CFS (Cleveland Family Study): The CFS was supported by NHLBI R35HL135818, R01HL113338, R01HL098433, R01HL46380.

CHS (Cardiovascular Health Study): This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants R01HL068986, U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and U01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease

Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

FamHS (Family Heart Study): The FamHS was funded by R01HL118305 and R01HL117078 NHLBI grants, and 5R01DK07568102 and 5R01DK089256 NIDDK grant.

GENOA (Genetic Epidemiology Network of Arteriopathy): Support for GENOA was provided by the National Heart, Lung and Blood Institute (HL119443, HL118305, HL054464, HL054457, HL054481, HL071917 and HL087660) of the National Institutes of Health. Genotyping was performed at the Mayo Clinic (Stephen T. Turner, MD, Mariza de Andrade PhD, Julie Cunningham, PhD). We thank Eric Boerwinkle, PhD and Megan L. Grove from the Human Genetics Center and Institute of Molecular Medicine and Division of Epidemiology, University of Texas Health Science Center, Houston, Texas, USA for their help with genotyping. We would also like to thank the families that participated in the GENOA study.

MESA (Multi-Ethnic Study of Atherosclerosis): MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-

HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001420, UL1-TR-001881, and DK063491.

WGHS (Women's Genome Health Study): The WGHS is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467) and the National Cancer Institute (CA047988 and UM1CA182913), with funding for lipid fractions provided by the Donald W. Reynolds Foundation, and funding for genotyping provided by Amgen.

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Supplemental Table 1. Study characteristics and analysis details and methods for rare variant gene alcohol interactions

			Discovery						Replication				
	Item	Description	ARIC	FHS	NEO	CARDIA	WIH	WGHS	CFS	CHS	FamHS	GENOA	MESA
	1	Cohort name	The Atherosclerosis Risk in Communities Study	Framingham Heart Study	The Netherlands Epidemiology o	Coronary Artery Risk Develop	Women's Health Initiative	Women's Genome Health Study	Cleveland Family Study	Cardiovascular Health Study	Family Heart Study	Genetic Epidemiology Network of Arteriopathy	Multi-Ethnic Study of Atherosclerosis
	2	Cohort Abbreviation	ARIC	FHS	NEO	CARDIA	WIH	WGHS	CFS	CHS	FamHS	GENOA	MESA
	3	Country	United States	United States	The Netherlands	United States	United States	United States	United States	United States	United States	United States	United States
STUDY INFORMATION	4	*Study design*	Unrelated	Family-based	Unrelated	Unrelated	Unrelated	Unrelated	Family-based	Unrelated	Family-based	Family-based	Unrelated
	5	Ascertainment method of alcohol consumption (eg, self-administered vs interview-led questionnaires; food frequency questionnaires vs dietary recall surveys)	interviewer-administered dietary questionnaire	interviewer-administered dietary questionnaire	self-resported dietary questionnaire	interviewer-administered dietary questionnaire	Interviewer_administered dietary questionnaire	self-report by food frequency questionnaire	interview-led questionnaires	Interviewer_administered dietary questionnaire	Interviewer_administered dietary questionnaire	Interviewer-administered questionnaire	Interviewer_administered Personal History questionnaire
ALCOHOL CONSUMPTION	6	Questions used to determine alcohol consumption group	Participants were asked "Do you presently drink alcoholic beverages?" and "Have you ever consumed alcoholic beverages?". Participants who answered yes to the first question (current drinkers) were further evaluated according to their answers to the following questions: "How many glasses of wine do you usually have per week (4-ounce glasses)?", "How many bottles or cans of beer do you usually have per week (12-ounce bottles or cans)?", and "How many drinks of hard liquor do you usually have per week (1.5-ounce shots)?". Current drinkers cosuming drinks ≥2 drinks per week were clasified as regular drinkers.	Participants were asked about their beer intake (bottles/cans/glasses per week), wine intake (glasses per week), cocktail intake (drinks per week), then the variable alcohol was created by summing up these three types of alcohol intake. Curdrink = 0 if alcohol = 0, curdrink = 1 if alcohol > 0. Regdrink = 0 if 0 ≤ alcohol < 2, regdrink = 1 if alcohol ≥ 2	Participants were asked about their beer intake, wine intake, cocktail intake, and other alcohol-containing beverages.	Detailed information about the CARDIA alcohol questionnaire are provided in https://www.cardia.dopm.uab.edu/images/more/pdf/D10008.PDF	Participants were asked 'Drank 12 alcoholic beverages ever?'. If yes then asked "Do you still drink alcohol?" (current drinkers). Alcohol servings per week were estimated from questions above and FFQ for wine, beer and liquor servings. Number of servings per week of beer, wine and/or liquor based on a medium serving size whichis 12oz of beer, 6oz of wine and 1.5 oz of liquor. If all three variables are missing, set to missing.	Participants were asked to record their average consumption, over the last year, of beer (1 glass or bottle or can), red wine (4 oz glass), white wine (4 oz glass), liquor (1 drink, shot). Participants had to choose among the following consumption frequency categories: "Never or < 1 month", "1-3/month", "1/week","2-4/week", "5-6/week", "1/day", "2-3/day", "4-5/day", "6+/day". This information was then used to classify "current drinkers" (rare or no alcohol use) and "regular drinkers" (> 2 drinks / week)	Participants were asked 'In a typical week during the past year, on how many days did you consume an alcoholic beverage of any type ?' Individuals reporting >0 day a week drinking alcohol were determinted as current drinkers.	Participants were asked "Do you ever drink beer?"/"Do you ever drink wine?"/"Do you ever drink liquor?". If yes then asked "How often?" and "How many 12 ounce cans or bottles/6 ounce glasses/drinks equal to one shot do you usually drink on one occasion?" (2nd question for beer/wine/liquor respectively). Answers for how often include daily, weekly, monthly, yearly, rarely/never. From these, number of drinks per week was calculated.	Participants were asked 'Do you currently drink alcoholic beverages?' and 'Have you ever consumed alcoholic beverages?'. Participants who answered yes to the first question (current drinkers) were further asked about the number of drinks of each type (wine,beer and spirits) of alcoholic beverage consumed per week. Current drinkers cosuming drinks ≥2 drinks per week were clasified as regular drinkers.	Participants were asked "Would you describe yourself as a person who never drinks alcoholic beverages of a person who sometimes drinks alcoholic beverages?". Participants who answered "Sometimes" (current drinkers) were further evaluated according to their answers to the following questions: "Do you drink any of the following beverages at least once per month? Beer, Wine Cooler, Wine, Hard Liquor?" Next they were asked "For each beverage that you drink at least once per month, what is the average number of servings you drink in a typical week or month?" Participants respond to the last question for only a typical week or month.	Participants were asked 'Do you currently drink alcoholic beverages?' and 'Have you ever consumed alcoholic beverages?'. Participants who answered yes to the first question (current drinkers) were further asked about the number of drinks of each type (wine,beer and spirits) of alcoholic beverage consumed per week. Current drinkers cosuming drinks ≥2 drinks per week were clasified as regular drinkers.
	7	when was alcohol consumtion information collected (initial survey? The same time as lipids collected?)	ARIC visit 1 (1987-1989), same time as lipids collected	Exam 1 (1971-1975) for offsprings, Exam 1 (2002-2005) for gen3 cohorts	Information about alcohol intake was collected durinf the NEO baseline visit (2008-2012) at which also fasting blood was	CARDIA baseline examination (1985-1987). Lipids collected at the same time.	WIH baseline visit (1993-1998) for lipid measures and alcohol data	Initial survey (1992-1995). Lipid collected at same time	Alcohol and lipids data were collected at Visit 5 (2001-2005)	Baseline for alcohol and lipids data (1989-1990 for cohort 1, 1992-1993 for cohort 2)	Alcohol and lipids data were collected at Visit 1 (1994-1996)	GENOA Phase 1, the same time as measurement of lipids	Alcohol and lipids data were collected at Exam 1 (2000-2002)
	8	Total number of participants (After exclusions) [N]	10989	7258	5718	2167	8021	22478	253	3690	1735	1543	2578
	9	Percentage of female participants (%)	54.4	53.3	51.8	52.8	100	100	46.3	57.2	56.2	55.5	52.04
	10	Age (years) [Mean (SD)]	54.3 (5.7)	38 (9.3)	56.0 (5.9)	25.5 (3.4)	67.0 (6.4)	54.2(7.0)	47.6 (15.8)	71.5 (4.1)	53.5 (12.5)	55.2 (10.7)	62.19(9.66)
	11	Natural log HDL-C [Mean (SD)]	3.8 (0.3)	3.9 (0.3)	4.0 (0.3)	3.9 (0.3)	3.9 (0.2)	3.9(0.3)	3.7 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)
	12	Medication-adjusted LDL-C	137.9 (38.2)	119.9 (34.7)	145.4 (36.1)	108.8 (29.8)	158.2 (38.6)	124.4 (34.5)	108 (34.0)	132.0 (36.9)	128.8 (38.3)	129.3 (37.5)	125.7 (32.0)
PARTICIPANTS: INCLUDED IN ANALYSIS	13	Natural log TG [Mean (SD)]	4.8 (0.5)	4.4 (0.6)	4.7 (0.5)	4.2 (0.5)	4.9 (0.5)	4.8(0.5)	4.8 (0.6)	4.9 (0.4)	4.9 (0.6)	5.1 (0.5)	4.7 (0.5)
	14	Genotyping Platform (including version)	Illumina Human Exome BeadChip v1.0	Illumina Human Exome BeadChip v1.0	Illumina HumanCoreExome 24V1-0_A	Illumina Human Exome BeadChip v1.0	Illumina Human Exome BeadChip v1.0	Illumina Human Exome BeadChip v1.1A	OmniExpress and Exome v1.2	Illumina Human Exome BeadChip v1.0	Illumina Exome Chip v1.0	Illumina ExomeChip 12v1.1 Beadchip	Illumina Human Exome BeadChip v1.0
GENOTYPING	15	Genotyping calling algorithm	Jointly called with CHARGE cohorts (PMID: 23874508), Illumina GenomeStudio2011.1	Jointly called with CHARGE cohorts (PMID: 23874508), Illumina GenomeStudio2011.1	GenCall	Jointly called with CHARGE cohorts (PMID: 23874508), Illumina GenomeStudio2011.1	GenCall	Genome Studio (v. 1.6.2) and zCall	zCall (for MAF <=1%) and Autocall (for MAF > 1%)	Jointly called with CHARGE cohorts (PMID: 23874508), Illumina GenomeStudio2011.1	Jointly called with CHARGE cohorts (PMID: 23874508), Illumina GenomeStudio2011.1	Illumina GenomeStudio v2011.1	Jointly called with CHARGE cohorts (PMID: 23874508), Illumina GenomeStudio2011.1
	16	Jointly called with CHARGE cohorts ?	Yes	No	Yes	No	No	No	No	Yes	Yes	No	yes
	17	Heterozygosity [filter details]	-	Removed if heterozygosity F value > 10	Removed if heterozygosity out of the range 0.35-0.45	-	-	-	Removed if heterozygosity F values greater than or equal to 3*standard deviation from the mean.	-	-	>6sd from mean of heterozygosity	-
	18	Sample call rate [filter details (%)]	< 89.9 %	<95%	<98%	<95%	<98%	<95%	<95%	<97%	<98.5%	< 95%	<95%
SAMPLE QC	19	Other exclusions	Sex mismatches, Low P10GC call; Outliers on first 10 ancestry-specific PCs; outliers with high levels of IBD; Cryptically related individuals	Removed samples with disconcordance with FHS GWAS SNP > 10% or sex mismatched or duplicated samples	Sex mismatches	Sex mismatch, Low P10GC call; Outliers on first 10 ancestry-specific PCs; mismatch in ancestry between PCs and self-report; outliers with high levels of IBD; Cryptically related individuals	Concordance rate <99% across intentional duplicates; Outlier samples on the principal-component plots were excluded, as were samples that were determined to be contaminated via relatedness analysis	Variants were excluded with a manually-validated statistical model that used the following parameters: cluster separation in GenomeStudio, the GenomeStudio R value for the major homozygote genotypes, the minor allele frequency from GenomeStudio, and the number of missing genotypes that remained not called by zCall	Removed outliers on principal component plots, individuals with pairwise IBD values that were contradictory to pedigree data, and Mendel errors	Sex mismatch; Low P10GC call; Outliers on first 10 ancestry-specific PCs; mismatch in ancestry between PCs and self-report; outliers with high levels of IBD; Cryptically related individuals	p10GC < 0.38	Unexpected duplicate; Gender inconsistency; >6sd from mean of inbreeding coefficient; >6sd from mean of singleton count; >6sd from PCA	-
	20	pIHWE [filter detail]	<1x10-6	<1x10-6	≤1x10-6	<1x10-6	<1x10-6	<1x10-4	<1x10-6	-	Reported, not excluded	-	<1x10-6
	21	Call rate by variant	<95%	≤97%	<98%	<95%	<99%	90%	<95%	<95%	<99%	< 95%	<95%
	22	Other SNP QC filters applied after genotyping? [filter detail]	-	-	Removed SNPs not on Exome chip and remove AT/CG pairs and	-	-	-	-	-	SNPs with excessive Mendel error rate	Low concordance rate with GWAS data (<90%); Replicate errors > 2	-
NP QC: GENOTYPE FILTERING BEFORE ANALYSI	23	Other filtering ?	Concordance rate <80% when compared to GWAS data	Discordance rate > 10% with GWAS data	-	-	-	-	-	Genotype QC and sample / variant counts are combined across CHS samples of both ethnicities. An additional 345 samples an 19875 variants were removed across both ancestries in the CHARGE joint QC effort (PMID:23874508).	-	-	-
Data analysis	24	Collapsed & single variants analysis : covariates	Age, sex, PC1-3	Age, sex, idtype, significant associated PCs	Age, sex, PC1-4	Age, sex, PC1-3	Age, recruitment region, PC1-2	age, PC1,PC2,PC5,PC6,PC10 (no sex since all women)	age, sex, PC1-5	Age, sex, centre, PC1-5	Age, sex, PC1-3, field center	Age, sex, PC1-3	Age, sex, sites, PC1-3

Supplemental Table 2. Genes discovered by the joint test or interaction only test using either regular drinker or current drinker

					Discovery							**Replication**						
Gene	CHR	Traits	Alcohol_variable	Test	N.cohort.discovery	p.discovery	p.fhs	p.aric	p.neo	p.whi	p.cardia	.cohort.replicatio	p.replicatior	p.wghs	p.chs	p.famhs	p.genoa	p.mesa	p.cfs
LPL	8	HDL	CurDrink	Joint	5	1.50E-19	0.001428	1.68E-11	0.000159	2.38E-05	0.064756	5	1.20E-20	1.14E-13	0.00177	0.000454	0.019993	0.000858	NA
LPL	8	HDL	RegDrink	Joint	5	8.76E-22	0.002211	1.56E-13	6.38E-05	2.40E-06	0.135437	5	4.25E-21	6.35E-14	0.00204	0.0003456	0.016712	0.000616	NA
IDNK	9	HDL	CurDrink	Interaction	3	3.58E-05	NA	0.010396	NA	4.39E-05	0.634867	1	NA	NA	0.87588	NA	NA	NA	NA
IDNK	9	HDL	CurDrink	Joint	3	1.96E-06	NA	0.021151	NA	1.74E-05	0.030553	1	NA	NA	0.59193	NA	NA	NA	NA
RPP38	10	HDL	RegDrink	Joint	5	4.26E-05	0.129512	0.003892	0.15253	0.007426	0.122374	6	0.320963	0.642598	0.33847	0.5837819	0.063429	0.038825	0.950833
APOC3	11	HDL	CurDrink	Joint	3	4.64E-06	0.000362	0.006864	NA	0.02583	NA	2	2.51E-05	0.002757	3.84E-05	NA	NA	NA	NA
APOC3	11	HDL	RegDrink	Joint	3	2.82E-06	0.000297	0.002901	NA	0.040549	NA	2	4.62E-06	0.001136	9.23E-06	NA	NA	NA	NA
CCDC33	15	HDL	CurDrink	Joint	5	8.52E-06	0.001177	0.001982	0.203994	0.049571	0.287732	5	0.586313	0.660912	0.65907	0.553517	0.78698	0.044356	NA
CCDC33	15	HDL	RegDrink	Joint	5	3.15E-06	0.00218	0.000795	0.213334	0.035076	0.191655	5	0.074637	0.316037	0.03814	0.4884832	0.702449	0.024602	NA
CD300LG	17	HDL	CurDrink	Joint	5	8.62E-12	0.002748	0.000213	8.41E-05	0.00311	0.010802	6	1.70E-09	2.64E-08	0.00248	0.8555972	0.055323	0.102769	0.682241
CD300LG	17	HDL	RegDrink	Joint	5	2.64E-12	0.002419	3.51E-05	0.000249	0.002971	0.010419	6	5.94E-10	3.58E-08	0.00271	0.7388682	0.033829	0.059303	0.700298
LIPG	18	HDL	CurDrink	Joint	5	9.87E-18	6.50E-06	3.40E-11	0.000386	0.030059	0.021605	5	1.03E-10	3.46E-08	0.00372	0.0536644	0.228681	0.084424	NA
LIPG	18	HDL	RegDrink	Joint	5	7.65E-17	5.88E-06	2.03E-11	0.000241	0.132333	0.016805	5	4.09E-11	2.39E-08	0.00235	0.0806716	0.112532	0.096507	NA
ANGPTL4	19	HDL	CurDrink	Joint	5	7.81E-20	1.53E-06	1.23E-08	4.11E-07	0.000581	0.285876	5	1.45E-10	1.47E-07	0.00017	0.1658017	0.144696	0.119513	NA
ANGPTL4	19	HDL	RegDrink	Joint	5	2.34E-20	4.02E-07	5.91E-09	6.49E-07	0.000735	0.274644	5	5.53E-09	4.46E-07	0.00161	0.577987	0.161017	0.066783	NA
C19orf80	19	HDL	CurDrink	Joint	5	4.81E-05	8.34E-07	0.001135	0.433181	0.361049	0.8311	3	0.756878	0.694925	0.56539	0.7632185	NA	NA	NA
HNF4A	20	HDL	CurDrink	Joint	5	9.38E-10	0.002535	0.183623	0.000817	1.95E-07	0.037485	5	1.15E-07	1.81E-07	0.19711	0.1118041	0.141615	0.367157	NA
HNF4A	20	HDL	RegDrink	Joint	5	3.37E-10	0.002024	0.161374	0.001049	4.01E-08	0.04857	5	3.20E-07	1.57E-06	0.08449	0.0272957	0.471475	0.313104	NA
MOCS3	20	HDL	RegDrink	Joint	5	6.30E-06	0.106932	8.27E-05	0.007051	0.308207	0.053663	5	0.441876	0.561326	0.45904	0.7846511	0.782972	0.016328	NA
CELSR2	1	LDL	CurDrink	Joint	5	1.78E-11	0.000709	0.000121	0.011815	1.47E-05	0.320381	6	2.64E-08	9.65E-09	0.02757	0.4515195	0.204854	0.775338	0.135906
CELSR2	1	LDL	RegDrink	Joint	5	1.63E-10	0.000493	0.000121	0.014193	0.000278	0.314377	6	3.21E-08	1.32E-08	0.0227	0.3741236	0.279505	0.725911	0.329852
MYBPHL	1	LDL	CurDrink	Joint	5	1.26E-08	0.001453	0.000468	3.15E-05	0.092125	0.414972	6	8.28E-05	0.000317	0.20405	0.2131678	0.433924	0.114609	0.222097
MYBPHL	1	LDL	RegDrink	Joint	5	7.26E-09	0.001147	0.00047	1.39E-05	0.099136	0.406923	6	6.49E-06	0.000303	0.01893	0.219785	0.396136	0.109338	0.008239
PCSK9	1	LDL	CurDrink	Joint	5	1.08E-61	5.32E-11	4.44E-23	9.94E-14	1.41E-16	3.33E-05	6	5.81E-11	0.000251	4.33E-08	0.0014034	0.002432	0.032461	0.795596
PCSK9	1	LDL	RegDrink	Joint	5	3.16E-62	7.97E-12	7.10E-23	3.44E-13	7.16E-17	3.25E-05	6	9.06E-11	0.00026	7.64E-08	0.001135	0.004932	0.028912	0.810161
APOB	2	LDL	CurDrink	Joint	5	3.26E-18	0.022652	1.42E-09	0.000577	2.99E-07	0.011877	6	2.53E-13	5.38E-13	0.00215	0.2923326	0.621638	0.414161	0.025353
APOB	2	LDL	RegDrink	Joint	5	5.33E-18	0.019036	1.19E-09	0.001198	2.66E-07	0.015656	6	1.20E-15	1.95E-13	0.00152	0.3151466	0.460562	0.082978	0.000147
LPA	6	LDL	RegDrink	Joint	5	2.28E-05	0.000136	0.005581	0.044209	0.628106	0.037119	6	0.000373	0.000255	0.90392	0.4171261	0.088502	0.195677	0.000104
PAG1	8	LDL	RegDrink	Joint	2	3.42E-05	0.006802	0.000888	NA	NA	NA	2	0.568261	0.612437	0.40072	NA	NA	NA	NA
OR8J3	11	LDL	CurDrink	Interaction	3	1.56E-05	0.012901	0.002956	NA	0.013946	NA	3	0.913678	0.919535	0.432	0.745236	NA	NA	NA
FBRSL1	12	LDL	RegDrink	Interaction	5	3.32E-05	0.001909	0.175468	0.01691	0.010199	0.304119	5	0.43918	0.278959	0.65528	0.6071971	0.239675	0.850541	NA
APOH	17	LDL	CurDrink	Joint	5	1.87E-05	0.102863	0.01697	0.092873	0.000484	0.233659	6	1.54E-05	6.07E-05	0.03858	0.6195677	0.074725	0.297601	0.632715
APOH	17	LDL	RegDrink	Joint	5	1.11E-05	0.111027	0.015422	0.082637	0.000229	0.24557	6	1.18E-05	5.47E-05	0.31706	0.0931785	0.045189	0.286847	0.491169
BCAM	19	LDL	CurDrink	Joint	5	7.93E-20	0.041726	3.80E-05	1.07E-08	1.89E-10	0.006753	6	1.17E-37	1.16E-29	1.49E-08	0.0662495	0.053199	0.000779	0.864847
BCAM	19	LDL	RegDrink	Joint	5	1.49E-18	0.040785	0.000234	2.50E-08	2.27E-10	0.006668	6	1.77E-37	2.08E-29	2.63E-08	0.0676827	0.057994	0.000189	0.956716
CBLC	19	LDL	CurDrink	Joint	5	2.13E-22	0.000144	5.44E-05	9.04E-10	9.42E-09	0.010526	6	9.58E-36	2.67E-27	1.14E-08	0.0995384	0.014669	0.003194	0.467735
CBLC	19	LDL	RegDrink	Joint	5	7.48E-22	0.000106	0.000155	2.29E-09	4.97E-09	0.011418	6	1.64E-35	5.76E-27	1.03E-08	0.1008981	0.010594	0.002724	0.59953
FAM73A	1	TG	RegDrink	Joint	5	2.08E-05	0.001161	0.028114	0.00263	0.242929	0.286807	5	0.430684	0.932022	0.05139	0.0029084	0.9188	0.123023	NA
LPL	8	TG	CurDrink	Joint	5	1.04E-17	0.001298	2.72E-09	1.99E-06	5.90E-05	0.438883	5	8.22E-16	6.40E-12	0.00011	0.0349381	0.297429	0.031796	NA
LPL	8	TG	RegDrink	Joint	5	8.55E-19	0.001327	4.31E-10	2.00E-06	2.38E-05	0.418145	5	7.30E-16	2.95E-12	0.0002	0.03697	0.293841	0.035742	NA
SMC5	9	TG	CurDrink	Interaction	4	6.65E-06	0.380445	4.68E-06	0.060019	0.028444	NA	4	0.013489	0.036153	0.22048	NA	0.187687	0.260359	NA
SMC5	9	TG	CurDrink	Joint	4	3.96E-05	0.578407	5.38E-06	0.072443	0.046387	NA	4	0.047878	0.075567	0.32958	NA	0.308428	0.2841	NA
A1CF	10	TG	CurDrink	Joint	5	1.25E-05	0.14173	0.000595	0.335097	0.000728	0.259098	5	0.296065	0.46769	0.36002	0.4133805	0.199986	0.4021	NA
A1CF	10	TG	RegDrink	Joint	5	3.11E-05	0.47438	0.001179	0.073366	0.000224	0.591255	5	0.602612	0.439749	0.92807	0.7712697	0.022583	0.643442	NA
APOA4	11	TG	CurDrink	Joint	5	9.72E-09	0.001696	0.005683	6.53E-05	0.006331	0.414015	6	5.84E-08	3.49E-07	0.26611	0.0224348	0.665737	0.03088	0.092492
APOA4	11	TG	RegDrink	Joint	5	8.83E-09	0.00188	0.004644	0.000105	0.004807	0.4236	6	3.77E-09	7.03E-07	0.03716	0.0099589	0.600743	0.03628	0.032532
APOA5	11	TG	CurDrink	Joint	5	1.21E-06	0.205076	3.07E-07	0.539344	0.00337	0.168407	5	0.000293	0.000206	0.21827	0.5018635	0.409491	0.188341	NA
APOA5	11	TG	RegDrink	Joint	5	8.93E-07	0.20737	8.39E-07	0.207198	0.002223	0.537779	5	0.000229	0.000177	0.17122	0.4602134	0.37746	0.261966	NA
APOC3	11	TG	CurDrink	Joint	3	4.08E-10	0.00084	1.82E-06	NA	0.003292	NA	3	3.58E-07	3.15E-05	0.00389	NA	NA	0.077452	NA
APOC3	11	TG	RegDrink	Joint	3	2.09E-10	0.000865	9.41E-07	NA	0.002899	NA	3	7.92E-08	1.39E-05	0.00139	NA	NA	0.081342	NA
REM2	14	TG	CurDrink	Interaction	4	1.85E-05	0.006657	0.003661	0.175001	0.024242	NA	2	0.159921	0.219235	0.24569	NA	NA	NA	NA
REM2	14	TG	CurDrink	Joint	4	2.98E-05	0.014817	0.00747	0.040625	0.051021	NA	2	0.32167	0.384942	0.32131	NA	NA	NA	NA
MAP1A	15	TG	CurDrink	Joint	5	5.67E-07	0.061082	0.003459	0.003835	0.016651	0.025533	6	1.84E-05	3.81E-05	0.15734	0.3097119	0.085053	0.589194	0.010855
MAP1A	15	TG	RegDrink	Joint	5	1.70E-06	0.065485	0.002823	0.004624	0.008675	0.268489	6	4.30E-05	0.000114	0.25987	0.3011135	0.077638	0.411677	0.013057
CD300LG	17	TG	CurDrink	Joint	5	1.56E-09	0.005	0.029555	5.66E-05	7.09E-05	0.183396	6	3.24E-08	1.01E-07	0.01193	0.3344483	0.089969	0.573824	0.25986
CD300LG	17	TG	RegDrink	Joint	5	1.39E-09	0.004188	0.022094	9.29E-05	8.93E-05	0.182848	6	5.26E-08	1.29E-07	0.01469	0.3806353	0.085562	0.56389	0.270826
ANGPTL4	19	TG	CurDrink	Joint	5	1.09E-24	3.01E-07	1.81E-10	5.94E-06	5.74E-06	0.046065	5	2.90E-15	5.94E-09	8.58E-07	0.9705168	0.004758	1.03E-05	NA
ANGPTL4	19	TG	RegDrink	Joint	5	1.33E-24	2.79E-07	1.02E-10	8.87E-06	7.93E-06	0.047752	5	3.56E-15	3.91E-09	3.25E-06	0.9416172	0.007078	1.54E-05	NA

Note: in total 31 gene-lipid pairs revealed though joint test or joint and interaction test, 2 additional gene-lipid pairs revealed though interaction test only

Supplemental Table 3. Conditional analyses

Trait	Gene	CHR	Alcohol	N.discovery	cMAF Range lower bound	cMAF Range higher bound	p.cond.disc	N.replication	p.cond.rep
HDL-c	***LPL***	8	Both	5	0.036	-0.04	6.34E-18	5	1.19E-18
HDL-c	***APOC3***	11	Both	4	0.001	-0.001	1.53E-06	3	1.37E-05
HDL-c	***LIPG***	18	Both	5	0.014	-0.019	6.11E-16	5	1.09E-10
HDL-c	***ANGPTL4***	19	Both	5	0.024	-0.031	5.67E-19	5	7.58E-08
LDL-c	***PCSK9***	1	Both	5	0.05	-0.055	6.06E-58	5	1.73E-10
LDL-c	*MYBPHL*	1	Both	5	0.044	-0.051	0.25	5	0.25
LDL-c	*CELSR2*	1	Both	5	0.079	-0.093	0.27	5	0.6
LDL-c	***APOB***	2	Both	5	0.174	-0.226	2.36E-14	5	7.36E-09
LDL-c	***LPA***	6	RegDrink	5	0.096	-0.147	1.91E-05	5	0.000331
LDL-c	*CBLC*	19	Both	5	0.084	-0.104	0.09	4	0.004
LDL-c	*BCAM*	19	Both	5	0.12	-0.166	0.01	4	0.02
TG	***LPL***	8	Both	5	0.036	-0.04	8.57E-16	5	7.18E-14
TG	***APOC3***	11	Both	4	0.001	-0.001	3.89E-11	3	1.12E-06
TG	*APOA5*	11	Both	5	0.025	-0.033	0.001	5	0.18
TG	*APOA4*	11	Both	5	0.019	-0.024	0.07	5	0.22
TG	*MAP1A*	15	Both	5	0.129	-0.166	0.12	5	0.03
TG	***CD300LG***	17	Both	5	0.031	-0.055	1.75E-09	5	7.18E-14

Supplemental Table 4. Single variant joint test

Traits	Gene	Alcohol	Leading SNPs	functional annotation	CADD phred score	Discovery			Replication		
						N.cohort	MAC range	P-value	N.cohort	MAC range	P-value
HDL-c	*LPL*	Both	rs1801177	missense	17	5	63 – 379	3.83E-08	5	67 – 766	8.02E-12
		Both	rs268	missense	15.1	5	80 – 444	2.45E-17	4	50 – 819	4.86E-12
	CD300LG	both	rs72836561	missense	22.2	4	138 – 682	6.19E-16	4	104 – 1384	9.60E-11
	HNF4A	Both	rs1800961	missense	24.7	3	130 – 700	7.35E-05	4	107 – 1319	4.71E-09
	LIPG	Both	rs77960347	missense	23.8	4	56 – 280	5.29E-14	5	24 – 568	1.28E-11
		Regdrink	rs117623631	missense	35	2	6 – 60	9.92E-13	2	15 – 22	9.48E-11
		RegDrink	rs142545730	missense	19.3	2	6 – 6	1.52E-238	2	5 – 22	6.66E-45
	ANGPTL4	Both	rs116843064	missense	35	4	83 – 440	1.53E-15	5	64 – 955	3.00E-11
		Regdrink	rs140744493	missense	33	3	9 – 64	8.38E-07	5	5 – 153	6.24E-53
	APOC3	Both	rs147210663	missense	23.6	3	6 - 11	1.65E-11	3	8 – 16	9.20E-64
LDL-c	*APOB*	Both	rs533617	missense	24.1	5	148 – 910	4.48E-20	5	129 – 1781	2.23E-08
		Both	rs41288783	missense	29.9	4	5 – 21	5.40E-08	2	8 – 54	7.92E-07
		Reg	rs12713843	missense	23.4	4	15 – 89	1.16E-06	5	14 – 209	1.51E-08
		Reg	rs1042023	missense	5.3	3	42 – 245	1.77E-04	5	43 – 493	6.82E-04
		Reg	rs1801702	missense	0.2	4	108 – 380	5.84E-04	5	61 – 905	1.00E-04
	LPA	Cur	rs139145675	missense	27.4	3	6 – 19	8.41E-117	3	5 – 46	5.71E-33
		Reg	rs41267813	missense	23.3	3	6 -- 51	6.55E-29	3	5 – 75	1.83E-03
		Both	rs3798220	missense	16.7	4	71 – 339	6.80E-10	5	50 – 820	1.15E-04
	PCSK9	Both	rs11591147	missense	17.1	5	64 – 321	3.11E-75	4	40 – 108	6.77E-19
		Reg	rs505151	missense	0.003	5	156 -- 791	6.90E-06	5	116 – 1726	1.35E-04
TG	*ANGPTL4*	Both	rs116843064	missense	35	4	83 – 424	3.11E-25	5	61 – 676	3.08E-21
	APOC3	Both	rs147210663	missense	23.6	3	6 – 11	1.06E-78	3	9 – 11	1.91E-26
	CD300LG	Both	rs72836561	missense	22.2	4	138 – 663	1.42E-09	5	104 – 988	4.72E-09
	LPL	Both	rs76708715	missense	20.2	4	10 -- 25	1.75E-19	4	7 – 45	3.63E-120
		Both	rs268	missense	15.1	5	80 – 437	1.46E-16	4	49 – 583	1.08E-12
		Both	rs1801177	missense	17	5	63 – 368	4.23E-07	5	67 – 565	3.66E-08