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Supplementary appendix

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Appendix

Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study

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SNP Selection and Genotyping

We selected the initial 25 SNPs mapped for plasma HDL-C or LDL-C concentrations using a genome-wide association approach.[1] Each selected SNP has been associated with either HDL-C or LDL-C at a $P<5 \times 10^{-8}$.

In case-control studies, genotypes were extracted from 16 genome-wide association studies (GWAS) and directly genotyped in an additional 14 studies. Array-based genotyping was conducted using Affymetrix 500K, Affymetrix 5.0, Affymetrix 6.0, Illumina Human Hap300, Illumina HumanHap370, Illumina HumanHap610 chips as previously described.[2] Imputation for un-genotyped SNPs and quality control were conducted as previously described.[2] Direct genotyping was attempted in 13 studies using the Sequenom iPLEX MassARRAY platform or the Illumina HumanCVDBeadChip Infinium II assay.[3] Direct genotyping at deCODE was done using the Centaurus (Nanogen) platform. We only considered SNPs that exceeded stringent quality control criteria including genotyping call rate > 95% and Hardy-Weinberg equilibrium filters ($P > 10^{-6}$ for SNPs from GWAS or $P > 0.001$ for all other SNPs).

In each of six prospective cohort studies, *LIPG* Asn396Ser was directly genotyped as described in **Supplementary Table 2**.

Predicted MI Risk for *LIPG* Asn396Ser Based on Plasma HDL-C Difference

We estimated a predicted risk for *LIPG* Asn396Ser based on the relationship of this SNP with plasma HDL-C and the relationship of plasma HDL-C with MI in the population. For *LIPG* Asn396Ser, we estimated the SNP-to-HDL-C parameter estimate from four prospective cohort studies involving >25,000 participants (**Supplementary Table 3**).

We obtained the HDL-C-to-MI parameter estimates from four prospective cohort studies. In the Atherosclerosis Risk in Communities Study (ARIC), Copenhagen City Heart Study (CCHS), Framingham Heart Study (FHS) 2nd Generation participants, and Malmo Diet and Cancer Study-Cardiovascular Cohort (MDCS-CC), we constructed logistic regression models to examine the association of incident MI status with plasma LDL-C, HDL-C, or triglycerides (TG), excluding subjects who had had a prevalent MI or ischemic stroke. The predictor variable of plasma lipid fraction was modeled in standard deviation units. Covariates in the model included age and gender. As a single time point measurement of a plasma lipid fraction can underestimate the relationship between lipids and MI,[4] we adjusted the hazard ratios for regression dilution bias [5] in a manner consistent with other recent studies.[6] The overall effect of each plasma lipid fraction across the four studies was summarized using fixed-effects inverse-variance-weighted meta-analysis (**Supplementary Table 4**).

Using the SNP-to-biomarker and the biomarker-to-MI relationships as inputs, we derived predicted MI risk for *LIPG* Asn396Ser. For *LIPG* Asn396Ser, we first calculated the change in plasma HDL-C in SD units. This degree of change in plasma HDL-C was algebraically converted to an odds ratio for MI by multiplying the plasma HDL-C change (in SD units) by the beta-coefficient (representing log odds ratios) from the HDL-C-to-MI modeling described above.[6]

Instrumental Variable Analysis Using *LIPG* Asn396Ser

We performed instrumental variable analysis in the six prospective cohort studies listed in **Supplementary Table 5**. In four of the six studies (ARIC, CCHS, HPFS, and MDCS-CC), we used the qvf command, with Murphy–Topel variance, to fit the data to logistic-regression models

for MI using *LIPG* Asn396Ser as a randomized instrument.[7] For two studies, an alternate two-stage regression approach was used because of the presence of related individuals (FHS) or case-cohort design (DCH). For these two studies, in the first stage, generalized estimating equations (FHS) or a generalized linear model (DCH) was fitted with the outcome variable of plasma HDL-C and predictor variables of *LIPG* Asn396Ser genotype, age, and gender. In the second stage, a generalized linear model was used to test the association of MI status with the fitted HDL-C from the first stage. A summary instrumental variable estimate for the association of plasma HDL-C with MI risk across the six studies was generated with fixed-effects variance-weighted meta-analysis.

Mendelian randomization using multiple genetic variants as instrumental variables

It has recently been proposed that statistical power for instrumental variable analysis could be increased if multiple genetic variants in combination were used as instruments.[8] From our recently published genome-wide association study of plasma lipids traits involving >100,000 individuals,[9] we observed that 13 SNPs had statistical evidence at genome-wide levels of significance ($P < 5 \times 10^{-8}$) for plasma LDL-C and no evidence for association with triglycerides (P>0.01) or HDL-C (P>0.01). We constructed a "LDL-C genetic score" combining the LDL-C raising alleles at each of these 13 SNPs (**Supplementary Table 9**). We also observed that 14 SNPs had statistical evidence at genome-wide levels of significance ($P < 5 \times 10^{-8}$) for plasma HDL-C and no evidence for association with triglycerides (P>0.01) or LDL-C (P>0.01). We constructed a "HDL-C genetic score" combining the HDL-C raising alleles at each of these 14

SNPs (**Supplementary Table 10**). Each SNP was given a weight based on the degree of LDL-C change or HDL-C change as estimated in ~100,000 individuals.[9]

We defined genetic risk scores in the following way[10]: Using a set of *m* SNPs, for the *i*-th SNP in the *j*-th individual denote *xij* as the 0/1/2 coded genotype (for directly genotyped SNPs) or expected allele dosage (which takes real values between 0.0 and 2.0 for imputed SNPs). Using results from Teslovich et al.,[9] define the set of regression coefficients to be *w*1, *w*2, ..., *wm*. Then the risk score for subject j is defined to be

(1) $sj = s0 + w1\ x1j + w2\ x2j + ... + wm\ xmj,$

where *s*0 is the intercept. In all our analyses, we specify the coefficients *w*1, *w*2, ..., *wm* to be the effect sizes, in standard deviation units per coded allele, estimated in single SNP analyses of LDL-C or HDL-C.

We also note that, when considering multiple SNPs that are in linkage equilibrium with each other, and small effect sizes per SNP, effect sizes estimated jointly for all SNPs using a multiple regression model are effectively identical to those estimated in a series of single SNP regression models. Thus regression on the risk score can be reconstructed from regressions on each of the *m* SNPs in turn, without further access to individual-level data.

The calculations involved are of the same type as for meta-analysis; the coefficient of the risk score is a weighted mean of the per-SNP regression coefficients, where each is weighted by its corresponding *wi*. The estimated variance of the risk score is given by similarly weighting the estimated variances (squared standard errors) of each per-SNP regression coefficient. The assumption of zero LD between SNPs ensures that these contributions are independent. Importantly, as with inverse-variance weighted meta-analysis, in large samples this procedure gives valid p-values under the null, i.e. when there is no relationship between the "lookup"

phenotype and any variants at the SNPs contributing to the risk score.

Using SNP-specific results in this way, we estimated and tested the coefficient of the risk score in independent "lookup" results using logistic regression for myocardial infarction phenotype from the published Coronary ARtery DIsease Genome-wide Replication And Meta-analysis (CARDIoGRAM) consortium GWAS study.[11,12] These estimates and tests inherit the covariate adjustment performed in the original SNP-specific analysis.

The CARDIoGRAM consortium combines data from 14 GWAS in individuals with European ancestry including 22,233 cases with coronary artery disease and/or MI and 64,762 controls.[11] For all of the participating studies, genome-wide scans were performed in the years 2006-2009 using either Affymetrix or Illumina platforms followed by imputation of genotypes in most studies. Statistical methods have been standardized across the studies, and an analysis platform has been created to allow summarized analyses on coronary artery disease, MI, and related phenotypes. We restricted our analysis to the subgroup of up to 12,482 MI cases and 41,331 MI-free controls.

Descriptions of Case-Control Studies

Italian ATVB Study, Heart Attack Risk in Puget Sound, REGICOR, MGH Premature Coronary Artery Disease Study, FINRISK, Malmo Diet and Cancer Study Early-Onset MI, PennCATH, deCODE, MedSTAR, Verona Heart Study, Mid-America Heart Institute, Irish Family Study, INTERHEART, and AMI Gene Study/Dortmund Health Study: Details for the recruitment of participants for these studies have been described in detail in a recent publication.[2]

WTCCC MI and German MI Family Study I: Details for the recruitment of the WTCCC CAD and German MI Family Study I are as recently described.[13] For the present report, we limited the analysis to cases that met clinical criterion for MI.

SHEEP: Details for the recruitment of SHEEP subjects are as recently described.[14,15]

Malmo Diet and Cancer Study Later-Onset MI: The Malmö Diet and Cancer (MDCS) study is a community-based prospective epidemiologic cohort of 28,449 persons recruited for a baseline examination between 1991 and 1996.[16] All participants underwent a medical history, a physical examination, and a laboratory assessment for cardiovascular risk factors as described previously.[17] From this cohort, 1,059 persons with MI at older age (age at MI for men >50 or women >60) were studied. Fatal or non-fatal MI status was determined as described previously.[18] For each case, a random control was selected.

COROGENE: Initially a sample was collected including all consecutive Finnish patients assigned to coronary angiogram within a 20-month period (June 2006–March 2008, n=5,330) in the Helsinki University Central Hospital. Data collection included a questionnaire, information on previous medical conditions and cardiovascular risk factors, hospital records for patients' history, various laboratory measurements, ECG, echocardiography, and medication. Approximately 22% of the patients were angiographically free of coronary artery disease (CAD). Different stages of atherosclerosis were found in 75% of patients, of which 53% had acute coronary syndrome (ACS; n=2,172). These ACS patients were selected as the complete set of COROGENE cases.

The controls for COROGENE cases were selected from the FINRISK 1997, 2002 and 2007, participants from the Helsinki-Vantaa region using risk set sampling.[19] For each case independently (= with replacement), two controls (if possible) were sampled from all controls who fulfilled the following criteria. The controls had to be 1) of the same sex, 2) of the same birth cohort (within ±5 years) to reduce the effect of secular trends and 3) free of cardiovascular disease (CVD) at least until the case's age of having ACS.

The CADomics Study: CADomics (**C**oronary **A**rtery **D**isease and gen**omics**) is a German-based case-control study of CAD. It is a pooled study from the population-based Gutenberg-Heart Study (GHS) and the hospital (cath-lab)-based Atherogene Registry.[20-22]

The GHS is a population-based, prospective, observational single-center cohort study in the Rhein-Main-Region in western mid-Germany. The primary aim of GHS is to evaluate and improve cardiovascular risk stratification. The sample was drawn randomly from the governmental local registry offices that contain all citizens in the city of Mainz and the district of Mainz-Bingen. Individuals between ages 35 and 74 were enrolled and enrollment was stratified for gender, residence (urban and rural) and decade of age. Exclusion criteria were insufficient knowledge of the German language, and physical or psychological inability to participate. Cardiovascular risk factors were assessed by a computer-assisted personal interview, from laboratory analyses of a venous blood sample in a fasting state, blood pressure and anthropometric measurements.

The Atherogene Registry has been described elsewhere.[20] Briefly, between June 1999 and February 2004, patients with documented CAD referred to the Department of Medicine II of the Johannes Gutenberg-University in Mainz, Germany and the Department of Medicine of the German Federal Armed Forces Central Hospital, Koblenz, were enrolled in the AtheroGene study registry. All participants had coronary angiography. Information on cardiovascular risk factors and coronary angiography were extracted from medical records. The angiograms were scored at the time of procedure by an interventional cardiologist.

For the current analysis, 1,212 had a diagnosis of MI and were included as cases in this report. A total of 2,952 did not have a history of MI and were included as controls.

Ottawa Heart Genomics Study I and I: Details for the recruitment of subjects are as recently described.[23,24]

GRACE GENETICS: The GRACE Genetics study prospectively enrolled 683 patients with an ACS between January 2001 and December 2007 in two hospitals in Belgium (University Hospital Gasthuisberg, Leuven and Onze-Lieve-Vrouw Clinic, Aalst). To ensure enrollment of an unselected ACS population, sites recruited the first 10-20 consecutive eligible patients each month.[25] Controls comprised 656 healthy blood donors from the Red Cross Belgium recruited from January to March 2008.[26]

PROCARDIS: The PROCARDIS study is a multi-centre case-control study in which CAD cases and controls were recruited from four European countries (United Kingdom, Italy, Sweden and Germany) according to pre-specified criteria.[27] All participants provided written informed consent to a protocol that was approved by the Ethics Committees of the participating institutions. All cases had a diagnosis of CAD before age 66 years and also had a sibling with CAD before age 66 years. Among the 3146 CAD cases, 2183 had a diagnosis of MI (91% confirmed by hospital discharge or general practice records) and were included as cases in this report. Controls with no personal or sibling history of CAD before age 66 years were contemporaneously recruited using the same infrastructure.

Utrecht Cardiovascular Pharmacogenetics (UCP) Studies: Participants were enrolled from the population-based Pharmaco-Morbidity Record Linkage System (PHARMO, www.pharmo.nl). PHARMO links drug dispensing histories from a representative sample of Dutch community pharmacies to the national registration of hospital discharges (Landelijke Medische Registratie, LMR) since 1985 on a continuous basis. Currently, the base population of PHARMO covers approximately 2,000,000 community-dwelling inhabitants of several population-defined areas in the Netherlands. Approval for this study was obtained from the Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands.

Briefly, patients with a high cardiovascular risk defined as those who received a prescription for an antihypertensive drug, or a glucose lowering drug, or who had hypercholesterolemia (prescription for a cholesterol-lowering drug or total cholesterol > 5.0 mmol/l), were selected from the PHARMO database. From this cohort, patients hospitalized for acute coronary syndrome (ACS) were included as cases (acute myocardial infarction (AMI, International Classification of Diseases (ICD)-9 code 410)) or (sub)acute forms of ischemic heart disease (ICD-9 codes 411.1 and 411.8)) if they were registered in PHARMO for at least one year and were older than 18 years. The index date was defined as the date of hospitalization for the first ACS. Controls met the same eligibility criteria as the cases, but had not developed ACS.

Participants were recruited through community pharmacies, where they received a letter in which the purpose of the study was explained. They were asked to return an informed consent form and a filled-out questionnaire. After the participant had consented to participate in the study, (s)he was sent an Oragene collection kit (hypercholesterolemic and diabetic cohort), or three cotton swabs and tubes containing buffer (hypertensive cohort) to collect saliva. All participants were explicitly asked to consent for the collection, storage and genotyping of the DNA material.

EPIC-NL: The EPIC-NL cohort is the Dutch contribution to the European Prospective Investigation into Cancer and Nutrition, and consists of the Prospect cohort, a prospective population based cohort of 17,357 women between 49-70 years at recruitment participating in breast cancer screening between 1993 and 1997, and the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort, consisting of 22,654 men and women between 20-59 years at recruitment in three Dutch towns (Amsterdam, Maastricht and Doetinchem). At baseline, a general questionnaire containing questions on demographic characteristics, smoking, presence of chronic diseases and other potential risk factors was filled out by all participants. Body weight, height, waist, and hip circumference were also measured, and a n on-fasting blood sample was taken. Information on incident coronary heart disease occurrence during follow-up was obtained through linkage with the database of hospital discharge diagnoses from the Dutch National Medical Registry. For this study, 334 MI cases and 1,827 randomly-selected MI-free controls were genotyped.

AngioGOKARD/KORA: The Lübeck and Regensburg angiographic study (Angio/GOKARD) includes 1,953 patients with angiographically proven CAD who underwent cardiac catheterization at the University Hospital Schleswig-Holstein, Campus Lübeck and University Hospital Regensburg between 2005 and 2010. Patients were not selected for particular risk factors or phenotypes.[28] Controls comprise individuals from the population-based MONICA/KORA Augsburg survey F3 (n=1,564).[29]

PopGen: The PopGen CAD sample (n=2,433) comprised unrelated German MI patients with early onset of disease who were recruited in Schleswig-Holstein, through regional catheterisation laboratories in the northernmost region in Germany (University Hospital Schleswig-Holstein, Campus Kiel, local hospitals Rendsburg, Schleswig, Flensburg, Heide), that have been contacted by the population-based PopGen biobank (www.PopGen.de). 1,687 PopGen-controls of the Max-Rubner-Institute were part of the Metabolic Intervention Cohort Kiel (MICK) and selected by age from the general population via the registration register of the same region.[30]

PROMIS: Details for the recruitment of the PROMIS subjects are as recently described.[31]

Descriptions of Cohort Studies

Atherosclerosis Risk in Communities Study (ARIC): The ARIC study is a prospective population-based study in 15,792 men and women, including 11,478 non-Hispanic whites and 4,314 African-Americans, drawn from 4 U.S. communities (suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina, and Jackson, Mississippi). The baseline examination for this report extended from 1987 – 1989 and for this study, we included only non-Hispanic whites and excluded those with prevalent CVD. Among the remaining individuals, we analyzed the association of *LIPG* Asn396Ser genotype with incident fatal or non-fatal MI. The follow-up data in this study include events up to January 1, 2003. The incidence of MI was determined by contacting participants annually, by identifying hospitalizations and deaths during the previous year, and by surveying discharge lists from local hospitals and death certificates from state vital-statistics offices for potential cardiovascular events. The incidence of MI and plasma lipid measurements was determined as previously described.[32]

Copenhagen City Heart Study (CCHS): The Copenhagen City Heart Study is a prospective study of a cohort of >10,000 persons randomly selected from the population of the city of Copenhagen.[6] The baseline examination for this report extended from 1991-1994 and we excluded all individuals all individuals with prevalent CVD at the baseline exam. Among the remaining individuals, we analyzed the association of *LIPG* Asn396Ser genotype with incident fatal or non-fatal MI. The follow-up data in this study include events up to January 1, 2009. The incidence of MI and plasma lipid measurements was determined as previously described.[6]

Danish Diet, Cancer, and Health Study (DCH): The Diet, Cancer and Health (DCH) study was initiated in 1993 when a total of 160,725 inhabitants of the greater Copenhagen or Aarhus areas who were born in Denmark and aged 50 to 64 years, were invited to participate. Eligible participants were without a record of cancer in the Danish Cancer Registry at the time of invitation. In total, 27,178 men and 29,875 women participated. Participants received a detailed FFQ by mail prior to the visit to the study clinic, where they also filled in a lifestyle questionnaire, and were asked to provide a blood sample. A detailed description of the cohort has been published previously.[33] A case-cohort study was designed using incident acute coronary syndrome (ACS), including unstable angina pectoris, MI, and sudden cardiac death as the outcome.

Information on the disease endpoint was obtained by linkage with central Danish registries via the unique identification number assigned to all Danish citizens. Hospital records of potential cases were retrieved from hospitals for participants who were registered with a first-time discharge diagnosis of ACS (ICD-8 codes 410-410.99, 427.27 and ICD-10 codes I20.0, I21.x, I46.x) in The Danish National Register of Patients, which covers all hospital discharge diagnoses since 1977 and from 1995 all discharge diagnosis from out-patient clinics (until Jan 1, 2004). Cases were classified by three reviewers according to symptoms, signs, coronary biomarkers, ECGs and/or autopsy findings in accordance with the current recommendations of the American Heart Association and the European Society of Cardiology (AHA/ECS).[34] Further, linkage to the Cause of Death Register allowed for identification of participants with ACS coded as a primary or secondary cause of death (to Jan 1, 2004). In total, for this report, 933 cases of MI were identified, however some of these were later excluded because of lacking questionnaire

data. For the creation of the cohort sample, 1588 participants were selected from the entire DCH study at random.

Framingham Heart Study (FHS): Design and recruitment strategies for the Offspring cohort of the Framingham Heart Study have been described elsewhere.[35] Since the initiation of the study in 1971, participants are seen in the FHS clinic every 4 to 8 years on average. Participants included in the current study (n=1,512) are from a subset of unrelated individuals from the Framingham offspring cohort who provided blood samples for DNA extraction at the sixth examination cycle. All participants underwent continuous surveillance for incident CVD events and death. A team of 3 physicians reviews all available information, hospitalization records and physician charts to adjudicate outcome events.[36] We excluded all individuals with prevalent CVD at the sixth examination cycle. Follow-up for incident MI or fatal CHD (n=52) extended from the sixth examination cycle (considered baseline for this study) until December 31, 2007.

Health Professionals Follow-up Study (HPFS): The HPFS was initiated in 1986 when 51,529 male health professionals between 40 and 75 years of age completed a food frequency questionnaire (FFQ) and a medical history questionnaire. The participants have been followed with repeated questionnaires on lifestyle and health every 2 years and FFQ's every 4 years. Blood samples were requested between 1993 and 1996 and obtained from 18,225 participants.[37]

For a nested case-control study, 426 incident nonfatal MI or fatal CHD cases that occurred between blood draw and January 31, 2004 were collected and ascertained. Cases of MI and fatal CHD were identified primarily through review of medical records. Participants who had reported an incident CHD on the follow-up questionnaire were contacted for confirmation and permission to review medical records was requested. Medical records for deceased participants were also sought for deaths that were identified by families and postal officials and through the National Death Index. Physicians blinded to the participant's questionnaire reports reviewed all medical records.

Malmo-Diet and Cancer Study (MDC): MDC is a community-based prospective epidemiologic cohort of 28,449 persons recruited for a baseline examination between 1991 and 1996.[38] All participants underwent a medical history, a physical examination, and a laboratory assessment for cardiovascular risk factors. The final data with *LIPG* Asn396Ser genotype was available from 27,041 subjects. All participants gave written informed consent.

Cardiovascular events were ascertained through linkage of the 10-digit personal identification number of each Swedish citizen with three registries: the Swedish Hospital Discharge Register, the Swedish Cause of Death Register, and the Stroke Register of Malmö. The prespecified composite end point was defined as MI infarction and death from CHD. MI was defined on the basis of codes 410 and I21 in the *International Classification of Diseases, 9th Revision* and *10th Revision* (ICD-9 and ICD-10), respectively. Death from CHD was defined on the basis of codes 412 and 414 (ICD-9) or I22–I23 and I25 (ICD-10) in the Swedish Cause of Death Register. Follow-up extended to December 31, 2003.

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REFERENCES

1. Kathiresan S, Willer CJ, Peloso GM, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet* 2009;**41**:56-65.
2. Kathiresan S, Voight BF, Purcell S, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet* 2009;**41**:334-41.
3. Keating BJ, Tischfield S, Murray SS, et al. Concept, design and implementation of a cardiovascular gene-centric 50 k SNP array for large-scale genomic association studies. *PLoS One* 2008;**3**:e3583.
4. Davis CE, Rifkind BM, Brenner H, Gordon DJ. A single cholesterol measurement underestimates the risk of coronary heart disease. An empirical example from the Lipid Research Clinics Mortality Follow-up Study. *JAMA* 1990;**264**:3044-6.
5. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;**150**:341-53.
6. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med* 2008;**359**:1897-908.
7. Ding EL, Song Y, Manson JE, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009;**361**:1152-63.
8. Palmer TM, Lawlor DA, Harbord RM, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. *Stat Methods Med Res* 2011 epub 1/11/11.
9. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010;**466**:707-13.
10. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011; published online Sep 11. doi: 10.1038/nature10405.
11. Preuss M, Konig IR, Thompson JR, et al. Design of the Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study: A Genome-wide association meta-analysis involving more than 22 000 cases and 60 000 controls. *Circ Cardiovasc Genet* 2010;**3**:475-83.
12. Schunkert H, Konig IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 2011;**43**:333-8.
13. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007;**357**:443-53.
14. Reuterwall C, Hallqvist J, Ahlbom A, et al. Higher relative, but lower absolute risks of myocardial infarction in women than in men: analysis of some major risk factors in the SHEEP study. The SHEEP Study Group. *J Intern Med* 1999;**246**:161-74.
15. Samnegard A, Silveira A, Lundman P, et al. Serum matrix metalloproteinase-3 concentration is influenced by MMP-3 -1612 5A/6A promoter genotype and associated with myocardial infarction. *J Intern Med* 2005;**258**:411-9.
16. Berglund G, Elmstähl S, Janzon L, Larsson SA. The Malmo Diet and Cancer Study. Design and feasibility. *J Intern Med* 1993;**233**:45-51.

17. Persson M, Hedblad B, Nelson JJ, Berglund G. Elevated Lp-PLA2 levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. *Arterioscler Thromb Vasc Biol* 2007;**27**:1411-6.
18. Kathiresan S, Melander O, Anevski D, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med* 2008;**358**:1240-9.
19. Langholz B, Goldstein L. Risk set sampling in epidemiologic cohort studies. *Statist Sci* 1996;**11**:35-53.
20. Rupprecht HJ, Blankenberg S, Bickel C, et al. Impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease. *Circulation* 2001;**104**:25-31.
21. Tiret L, Godefroy T, Lubos E, et al. Genetic analysis of the interleukin-18 system highlights the role of the interleukin-18 gene in cardiovascular disease. *Circulation* 2005;**112**:643-50.
22. Erdmann J, Grosshennig A, Braund PS, et al. New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nat Genet* 2009;**41**:280-2.
23. Stewart AF, Dandona S, Chen L, et al. Kinesin family member 6 variant Trp719Arg does not associate with angiographically defined coronary artery disease in the Ottawa Heart Genomics Study. *J Am Coll Cardiol* 2009;**53**:1471-2.
24. Dandona S, Chen L, Fan M, et al. The transcription factor GATA-2 does not associate with angiographic coronary artery disease in the Ottawa Heart Genomics and Cleveland Clinic GeneBank Studies. *Hum Genet*;**127**:101-5.
25. Buysschaert I, Carruthers KF, Dunbar DR, et al. A variant at chromosome 9p21 is associated with recurrent myocardial infarction and cardiac death after acute coronary syndrome: The GRACE Genetics Study. *Eur Heart J* 2010;**31**: 1132-1341.
26. Buysschaert ID, Grulois V, Eloy P, et al. Genetic evidence for a role of IL33 in nasal polyposis. *Allergy* 2010;**65**: 616-22.
27. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;**361**:2518-28.
28. Linsel-Nitschke P, Jansen H, Aherrarhou Z, et al. Macrophage cholesterol efflux correlates with lipoprotein subclass distribution and risk of obstructive coronary artery disease in patients undergoing coronary angiography. *Lipids Health Dis* 2009;**8**:14.
29. Wichmann HE, Gieger C, Illig T. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)) 2005;**67** Suppl 1:S26-30.
30. Krawczak M, Nikolaus S, von Eberstein H, Croucher PJ, El Mokhtari NE, Schreiber S. PopGen: population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships. *Community Genet* 2006;**9**:55-61.
31. Saleheen D, Alexander M, Rasheed A, et al. Association of the 9p21.3 locus with risk of first-ever myocardial infarction in Pakistanis: case-control study in South Asia and updated meta-analysis of Europeans. *Arterioscler Thromb Vasc Biol* 2010;**30**:1467-73.
32. Chambless LE, Folsom AR, Sharrett AR, et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol* 2003;**56**:880-90.
33. Tjonneland A, Olsen A, Boll K, et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health* 2007;**35**:432-41.

34. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation* 2003;**108**:2543-9.
35. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979;**110**:281-90.
36. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;**355**:2631-9.
37. Chu NF, Spiegelman D, Yu J, Rifai N, Hotamisligil GS, Rimm EB. Plasma leptin concentrations and four-year weight gain among US men. *Int J Obes Relat Metab Disord* 2001;**25**:346-53.
38. Berglund G, Elmstahl S, Janzon L, Larsson SA. The Malmo Diet and Cancer Study. Design and feasibility. *J Intern Med* 1993;**233**:45-51.

Supplementary Table 1. Characteristics of Cases with Myocardial Infarction and Controls Free of Myocardial Infarction*

Study	Italian ATVB Study		Heart Attack Risk in Puget Sound		REGICOR		MGH Premature Coronary Artery Disease Study		FINRISK		Malmö Diet and Cancer Study Early-Onset MI	
	cases	Controls	cases	controls	cases	controls	cases	controls	Cases	controls	cases	controls
N	1,693	1,668	505	559	312	317	204	260	167	172	86	99
MI age criterion	men or women ≤ 45	--	men ≤50 or women ≤ 60	--	men ≤50 or women ≤ 60	--	men ≤50 or women ≤ 60	--	men ≤50 or women ≤ 60	--	men ≤50 or women ≤ 60	--
Genotyping platform	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0
Country of origin	Italy	Italy	U.S.	U.S.	Spain	Spain	U.S.	U.S.	Finland	Finland	Sweden	Sweden
Mean age (y) †	39.4 ± 4.9	39.3 ± 5.0	46.0 ± 6.9	45.2 ± 7.3	45.9 ± 5.8	46.0 ± 5.6	47.0 ± 6.1	53.8 ± 11.1	47.1 ± 6.2	47.1 ± 6.0	48.5 ± 4.4	48.7 ± 4.6
Female gender (%)	11.4	11.6	51.1	55.5	20.2	21.5	29.9	33.5	33.5	31.4	41.9	42.4
Study	**WTCCC MI**		**German MI Family Study I**		**German MI Family Study II**		**PennCATH**		**deCODE**		**MedSTAR**	
	cases	controls	cases	controls	cases	controls	cases	controls	Cases	controls	cases	controls
N	1,561	2,938	875	1,644	1,222	1,874	415	468	729	29,218	420	447
MI age criterion	<66 years	--	men ≤60 or women ≤ 65	--	men ≤60 or women ≤ 65	--	<66 years	--	men<50 or women <60	--	<66 years	--
Genotyping platform	Affymetrix 500K	Affymetrix 500K	Affymetrix 500K	Affymetrix 500K	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 6.0	Illumina 300/370K	Illumina 300/370K	Affymetrix 6.0	Affymetrix 6.0
Country of origin	U.K.	U.K.	Germany	Germany	Germany	Germany	U.S.	U.S.	Iceland	Iceland	U.S.	U.S.
Mean age (y) †	49.3±7.9	44.7±9.3	50.2±7.9	62.5±10.1	51.3 ± 7.6	51.2±11.9	50.2±7.5	61.7 ± 9.6	56.7 ± 10.6	48.9 ± 21.6	46.8±6.8	59.7 ± 8.9
Female gender (%)	20.2	49.2	32.5	50.5	20.3	47.9	17.6	51.7	40.8	61.3	23.8	48.8
Study	**Verona Heart Study**		**Mid-America Heart Institute**		**Irish Family Study**		**INTERHEART European Ancestry**		**AMI Gene Study / Dortmund Health Study**		**SHEEP**	
	cases	controls	cases	controls	cases	controls	cases	controls	Cases	controls	cases	controls
N	510	388	811	650	577	719	1,886	2,231	809	1,132	1,155	1,502
MI age criterion	men ≤65 or women ≤ 65	--	no age criterion	--	men ≤55 or women ≤ 65	--	no age criterion	--	men <65	--	men and women 46-70	--
Genotyping platform	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom	Sequenom
Country of origin	Italy	Italy	U.S.	U.S.	Northern Ireland	Northern Ireland	U.S. and multiple in Europe	U.S. and multiple in Europe	Germany	Germany	Sweden	Sweden
Mean age (y) †	57.0±9.1	58.9±12.1	61.5±12.7	60.7±12.4	45.9±6.7	55.7±8.0	61.2±12.1	60.5±12.0	52.2±8.2	52.6±13.7	59.2±7.2	59.8±7.1
Female gender (%)	10.6	34.8	32.1	39.0	20.1	55.2	28.9	31.3	0	53.1	29.4	32.2
Study	**Malmö Diet and Cancer Study Later-Onset MI**		**COROGENE**		**CADomics**		**Ottawa Heart Genomics Study I**		**Ottawa Heart Genomics Study II**		**GRACE Genetics**	
	cases	controls	cases	controls	cases	controls	cases	controls	Cases	controls	cases	controls
N	1,059	1,056	2,172	1,579	1,212	2,952	950	1,455	1,090	933	683	656
MI age criterion	Men >50 or women >60	--	no age criterion		no age criterion	--	men ≤55 or women ≤ 65	---	men ≤55 or women ≤ 65	---	no age criterion	
Genotyping platform	Sequenom	Sequenom	Illumina	Illumina	Affymetrix 6.0	Affymetrix 6.0	Affymetrix 500K&6.0	Affymetrix 500K&6.0	Affymetrix 6.0	Affymetrix 6.0	Sequenom	Sequenom
Country of origin	Sweden	Sweden	Finland	Finland	Germany	Germany	Canada	Canada	Canada / U.S	Canada / U.S	Belgium	Belgium
Mean age (y) †	63.7 ± 5.9	63.7 ± 5.9	66.1 ± 12.0	55.7 ± 12.2	59.3 ± 10.8	55.3 ± 10.8	47.7±7.3	75.0±5.0	47.8±7.1	74.3±5.8	65.2±11.8	41.0±13.2

Study	PROCARDIS		UCP		EPIC-NL		AngioGOCARD/KORA		PopGen		PROMIS	
	cases	controls	cases	controls	cases	controls	cases	controls	Cases	controls	cases	controls
N	2,183	3,347	830	1,139	334	1,827	1,953	1,482	2,433	1,687	1854	1897
MI age criterion	<66 years	<66 years	None	None	None	None	30-65	35-84	34-88	20-68	None	None
Genotyping platform	Illumina CVD chip	Illumina CVD chip	Illumina CVD chip	Illumina CVD chip	Illumina CVD chip	Illumina CVD chip	Sequenom	Sequenom	Sequenom	Sequenom	Illumina CVD chip	Illumina CVD chip
Country of origin	Europe	Europe	Netherlands	Netherlands	Netherlands	Netherlands	Germany	Germany	Germany	Germany	Pakistan	Pakistan
Mean age (y) †	52.9 ± 7.7	59.4 ± 9.9	63.7 ± 10.3	62.7 ± 10.7	54.9 ± 9.2	49.0 ± 12.1	55.1 ± 6.9	52.2 ± 13.3	61.2 ± 8.2	51.2 ± 14.4	54.5 ± 10.9	52.1 ± 10.3
Female gender (%)	25.3	50.9	26.4	32.5	58.8	72.2	19.1	52.1	18.9	0.0	16.0	19.0

Values with '±' are means ± s.d.

*Summary characteristics are provided for maximal number of available subjects. For any given genotype, a subset may have been studied.

†Mean age at MI for cases and age at recruitment for controls.

Supplementary Table 2. Characteristics of Participants from Prospective Cohort Studies by Myocardial Infarction Status

Prospective cohort	ARIC		CCHS		DCH		FHS		HPFS		MDCS*	
MI status	No event	MI	No event	MI	No event	MI	No event	MI	No event	MI	No event	MI
No. of individuals (%)	8,214 (93%)	558 (7%)	8,964 (93%)	655 (7%)	1,588 (63%)	933 (37%)	1,462 (97%)	50 (3%)	869 (67%)	426 (33%)	25,438 (94%)	1,606 (6%)
Women, %	56	38	58	45	38	62	53	42	0	0	63	35
Age, years	54 ± 0.1	56 ± 0.2	55 ± 0.2	66 ± 0.4	56 ± 0.1	58 ± 0.1	58 ± 0.2	63 ± 1.2	64 ± 0.3	64 ± 0.4	58 ± 0.1	62 ± 0.2
Total cholesterol, mmol/L	5.5 ± 0.01	5.8 ± 0.04	6.0 ± 0.01	6.6 ± 0.05	6.0 ± 0.03	6.4 ± 0.04	5.4 ± 0.03	5.6 ± 0.15	5.3 ± 0.03	5.5 ± 0.05	6.2 ± 0.02	6.3 ± 0.06
LDL-C, mmol/L	3.5 ± 0.01	3.9 ± 0.04	3.6 ± 0.01	4.2 ± 0.05	3.6 ± 0.02	3.9 ± 0.04	3.3 ± 0.02	3.5 ± 0.13	3.3 ± 0.03	3.5 ± 0.04	4.2 ± 0.01	4.4 ± 0.06
HDL-C, mmol/L	1.3 ± 0.01	1.1 ± 0.01	1.6 ± 0.01	1.4 ± 0.02	1.6 ± 0.01	1.4 ± 0.01	1.3 ± 0.01	1.1 ± 0.04	1.9 ± 0.01	1.1 ± 0.01	1.4 ± 0.01	1.2 ± 0.02
TG, mmol/L	1.5 ± 0.01	1.9 ± 0.06	1.8 ± 0.01	2.2 ± 0.06	1.8 ± 0.03	2.3 ± 0.04	1.7 ± 0.03	2.1 ± 0.22	1.6 ± 0.04	1.9 ± 0.05	1.4 ± 0.01	1.6 ± 0.06
Body mass index, kg/m2	27 ± 0.05	28 ± 0.2	25 ±0.05	27 ± 0.2	26 ± 0.13	27 ± 0.13	28 ± 0.13	28 ± 0.75	26 ± 0.1	26 ± 0.2	26 ± 0.03	27 ± 0.1
Genotyping method for *LIPG* Asn396Ser	Illumina CVD Chip		Taqman		Taqman		Taqman		Taqman		Taqman	

ARIC, Atherosclerosis Risk in Communities Study; CCHS, Copenhagen City Heart Study; DCH, Danish Diet, Cancer, and Health Study; FHS, Framingham Heart Study; HPFS, Health Professionals Follow-up Study; MDCS, Malmö Diet and Cancer Study

All continuous traits are given as means ± SEM. All categorical variables are shown in percentages.

*Lipid traits were available for 5,042-5,173 MDCS study participants.

Supplementary Table 3. Association of *LIPG* Asn396Ser with Plasma High-Density Lipoprotein Cholesterol in Four Prospective Cohort Studies

	ARIC	CCHS	FHS	MDCS-CC	Meta-analysis across 4 studies
N total	8,735	9,618	1,589	5,127	25,069
Number of 396Ser mutation carriers	225	232	43	133	633
Beta*	0.33	0.15	0.49	0.39	0.29
SE	0.07	0.07	0.16	0.09	0.04
P	7×10^{-7}	0.02	0.002	1×10^{-5}	8×10^{-13}

ARIC, Atherosclerosis Risk in Communities Study; CCHS, Copenhagen City Heart Study; FHS, Framingham Heart Study; MDCS-CC, Malmö Diet and Cancer Study-Cardiovascular Cohort

In each study, association results are from a linear regression model with a predictor variable of the *LIPG* 396Ser allele. The outcome variable was plasma high-density lipoprotein cholesterol residual after adjustment for age and gender and standardized to a mean of 0 and SD of 1.

*Beta represents increment change in standard deviation units for each copy of the *LIPG* 396Ser allele.

Supplementary Table 4. Association of Plasma Lipid Level and Incident Myocardial Infarction in Four Prospective Cohort Studies

Predictor	Covariate	OR per SD increase in plasma lipid level	95% CI
Atherosclerosis Risk in Communities Study			
LDL cholesterol	Age, gender, HDL-C, TG	1.65	1.48 - 1.85
HDL cholesterol	Age, gender, LDL-C, TG	0.56	0.51 – 0.62
Triglycerides	Age, gender, HDL-C, LDL-C	1.40	1.20 - 1.62
Copenhagen City Heart Study			
LDL cholesterol	Age, gender, HDL-C, TG	1.61	1.40 - 1.85
HDL cholesterol	Age, gender, LDL-C, TG	0.74	0.64 – 0.85
Triglycerides	Age, gender, HDL-C, LDL-C	1.31	1.11 - 1.55
Framingham Heart Study			
LDL cholesterol	Age, gender, HDL-C, TG	1.64	1.48 - 1.82
HDL cholesterol	Age, gender, LDL-C, TG	0.71	0.61 – 0.82
Triglycerides	Age, gender, HDL-C, LDL-C	1.88	1.65 – 2.13
Malmo Diet and Cancer Study – Cardiovascular Cohort			
LDL cholesterol	Age, gender, HDL-C, TG	1.23	1.11 - 1.35
HDL cholesterol	Age, gender, LDL-C, TG	0.55	0.46 – 0.66
Triglycerides	Age, gender, HDL-C, LDL-C	1.01	0.86 - 1.18
Meta-analysis of Four Cohort Studies			
LDL cholesterol	Age, gender, HDL-C, TG	1.54	1.45 - 1.63
HDL cholesterol	Age, gender, LDL-C, TG	0.62	0.58 – 0.66
Triglycerides	Age, gender, HDL-C, LDL-C	1.42	1.31 - 1.52

The four prospective cohort studies were: 1) ARIC, Atherosclerosis Risk in Communities Study; 2) CCHS, Copenhagen City Heart Study; 3) FHS, Framingham Heart Study; and 4) MDCS-CC, Malmö Diet and Cancer Study-Cardiovascular Cohort.

In each study for each trait, the odds ratio estimates were adjusted for regression dilution bias using a parametric approach. The test-retest correlations for LDL-C, HDL-C, and TG were the following: ARIC (0.55, 0.72, and 0.56); CCHS (0.60, 0.73, and 0.58); and Framingham Heart Study (0.72, 0.72, and 0.56).

Supplementary Table 5. Characteristics of Participants from Prospective Cohort Studies by *LIPG* 396Ser Carrier Status

Prospective cohort	ARIC		CCHS		DCH		FHS		HPFS		MDCS-CC	
LIPG 396Ser carrier status	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
No. of individuals (%)	8,510 (97.4)	225 (2.6)	9,387 (97.6)	232 (2.4)	2,458 (97.5)	63 (2.5)	6128 (97.4)	161 (2.6)	1255 (98.2)	23 (1.8)	5568 (97.4)	148 (2.6)
Women, %	55	55	57	53	38	37	55	56	0	0	58	58
Age, years	54.2 ± 0.1	54.3 ± 0.4	55.4 ± 0.2	58.0 ± 1.0	57.1 ± 0.1	56.2 ± 0.5	46.9 ± 0.2	47.6 ± 1.0	64.2 ± 0.2	64.0 ± 1.9	57.4 ± 0.1	57.8 ± 0.5
Total cholesterol, mmol/L	5.54 ± 0.01	5.76 ± 0.07	6.02 ± 0.01	6.27 ± 0.08	6.15 ± 0.02	6.11 ± 0.13	5.13 ± 0.01	5.41 ± 0.08	5.32 ± 0.03	5.32 ± 0.18	6.17 ± 0.02	6.39 ± 0.10
LDL-C, mmol/L	3.54 ± 0.01	3.62 ± 0.06	3.67 ± 0.01	3.74 ± 0.07	3.71 ± 0.02	3.59 ± 0.12	2.92 ± 0.01	3.04 ± 0.10	3.34 ± 0.02	3.41 ± 0.14	4.17 ± 0.01	4.22 ± 0.09
HDL-C, mmol/L	1.32 ± 0.01	1.46 ± 0.03	1.57 ± 0.01	1.65 ± 0.04	1.54 ± 0.01	1.58 ± 0.05	1.38 ± 0.01	1.52 ± 0.04	1.16 ± 0.01	1.19 ± 0.09	1.38 ± 0.005	1.52 ± 0.04
TG, mmol/L	1.53 ± 0.01	1.51 ± 0.06	1.79 ± 0.01	1.93 ± 0.08	1.98 ± 0.02	2.06 ± 0.13	3.41 ± 0.03	3.38 ± 0.20	1.70 ± 0.03	1.60 ± 0.19	1.37 ± 0.01	1.37 ± 0.06
Body mass index, kg/m2	27.29 ± 0.33	26.95 ± 0.05	25 ± 0.04	26 ± 0.3	27 ± 0.1	26 ± 0.5	27 ± 0.07	27 ± 0.5	26 ± 0.1	26 ± 0.6	26 ± 0.1	25 ± 0.3
Systolic blood pressure, mm/Hg	118.26 ± 0.18	118.69 ± 1.12	137 ± 0.2	141 ± 2	143 ± 0.4	143 ± 2	123 ± 0.3	126 ± 1.8	NA	NA	141 ± 0.3	141 ± 2
Fasting glucose, mg/dl	103.69 ± 0.29	102.22 ± 1.52	104 ± 0.4	105 ± 2	NA	NA	98 ± 0.5	99 ± 3	NA	NA	93 ± 0.3	93 ± 2
Active cigarette smoking, %	24	19	47	53	45	52	15	19	9	9	28	26
Type 2 diabetes, %	6	7	7	8	3	0	4	3	5	3	3	2

ARIC, Atherosclerosis Risk in Communities Study; CCHS, Copenhagen City Heart Study; DCH, Danish Diet, Cancer, and Health Study; FHS, Framingham Heart Study; HPFS, Health Professionals Follow-up Study; MDCS, Malmö Diet and Cancer Study

All continuous traits are given as means ± SEM. All categorical variables are shown in percentages.

Supplementary Table 6. Association of *LIPG* Asn396Ser with Plasma Low-Density Lipoprotein Cholesterol or Triglycerides in Four Prospective Cohort Studies

	N	Beta	SE	P
	Low-density lipoprotein cholesterol			
ARIC	8,588	0.024	0.019	0.21
CCHS	9,618	0.006	0.021	0.77
FHS	1,589	0.013	0.041	0.75
MDCS-CC	5,045	0.031	0.089	0.73
Meta-analysis	24,840	0.016	0.013	0.23
	Triglycerides			
ARIC	8,720	-0.018	0.033	0.60
CCHS	9,618	0.062	0.035	0.07
FHS	1,589	-0.016	0.091	0.86
MDCS-CC	5,175	0.001	0.088	0.99
Meta-analysis	25,012	0.016	0.02	0.47

The four prospective cohort studies were: 1) ARIC, Atherosclerosis Risk in Communities Study; 2) CCHS, Copenhagen City Heart Study; 3) FHS, Framingham Heart Study; and 4) MDCS-CC, Malmö Diet and Cancer Study-Cardiovascular Cohort

Supplementary Table 7. Association of *LIPG* Asn396Ser with Cardiovascular Risk Factors in the Malmo Diet and Cancer Study.

Risk factor	N	Beta	SE	P
Systolic blood pressure	27,868	-0.80	0.69	0.24
Body mass index	27,863	-0.19	0.15	0.20
Type 2 diabetes	2,452 cases, 23,326 non-cases	-0.05	0.13	0.70
C-reactive protein	5,110	-0.55	0.40	0.17
Small LDL particle concentration	4,466	-0.07	0.09	0.47

Linear regression modeling was utilized to test the association of *LIPG* Asn396Ser with systolic blood pressure, body mass index, C-reactive protein or small LDL particle concentration. In these models, the predictor variable was the quantitative risk factor, the predictor variable was number of copies of the *LIPG* 396Ser allele, and covariates of age and gender. For type 2 diabetes, logistic regression modeling was utilized.

*Small LDL particle concentration measured by airborne ion mobility assay.

Supplementary Table 8. Association of *LIPG* Asn396Ser with a range of cardiovascular phenotypes in the Atherosclerosis Risk in Communities (ARIC) Study

Phenotype	Beta	SE	N	P
HDL cholesterol	**5.41**	**1.01**	**8,720**	**9.6×10^{-8}**
apo-AI	**8.63**	**1.93**	**8,720**	**7.9×10^{-6}**
LDL cholesterol	2.98	2.53	8,588	0.24
apoB	1.00	1.86	8,719	0.59
Lp(a)	-4.18	6.27	8,576	0.50
Log triglycerides	-0.02	0.03	8,720	0.53
Systolic blood pressure	0.28	1.09	8,734	0.26
Diastolic blood pressure	0.75	0.66	8,734	0.26
Fasting glucose	-1.57	1.78	8,731	0.38
Type 2 diabetes	0.003	0.02	8,731	0.89
Cigarette smoking	-0.055	0.03	8,731	0.06
Waist/hip ratio	-0.0003	0.005	8,727	0.95
Fibrinogen	0.91	4.06	8,704	0.82
Log C-reactive protein	-0.05	0.08	7,032	0.51

Genotypes were coded as Serine allele carrier or non-carrier. Linear or logistic regression was performed with outcome variable being phenotype in column 1, predictor variable of Serine allele carrier status, and covariates of age and gender. Betas are unstandardized and in original units for phenotype except for triglycerides and C-reactive protein where these phenotypes were log-transformed.

Supplementary Table 9. Evaluation of an LDL genetic score for association with myocardial infarction

			Data from Global Lipid Genetic Consortium GWAS for Lipids			Data from CARDIOGRAM GWAS for MI		
Marker	**Effect Allele**	**Other Allele**	**Effect***	**SD**	**P**	**Effect**	**SD**	**P**
rs11136341	G	A	0.041	0.006	6.20E-11	-0.032	0.030	0.310
rs11220462	A	G	0.057	0.008	1.88E-14	0.040	0.029	0.555
rs1169288	C	A	0.042	0.005	2.21E-14	0.084	0.019	7.55E-05
rs12027135	T	A	0.032	0.005	5.61E-10	-0.001	0.018	0.869
rs12916	C	T	0.072	0.005	2.46E-41	0.0238	0.019	0.225
rs1800562	G	A	0.065	0.011	1.39E-08	0.016	0.037	0.674
rs217386	G	A	0.034	0.005	2.86E-10	0.029	0.019	0.125
rs2332328	T	C	0.034	0.006	6.75E-10	0.001	0.027	0.933
rs3757354	C	T	0.042	0.006	2.34E-11	0.025	0.026	0.339
rs514230	T	A	0.033	0.005	5.99E-10	0.009	0.018	0.894
rs649129	T	C	0.060	0.006	1.03E-21	0.119	0.024	6.17E-05
rs6511720	G	T	0.206	0.009	1.03E-117	0.176	0.046	2.37E-04
rs7225700	C	T	0.026	0.005	1.53E-06	0.030	0.019	0.194

The beta coefficient for association of LDL genetic score with MI was 0.756, SE of 0.119 and P= 1.8×10^{-10}

*Effect is in standard deviation units

Supplementary Table 10. Evaluation of an HDL genetic score for association with myocardial infarction

			Data from Global Lipid Genetic Consortium GWAS for Lipids			Data from CARDIOGRAM GWAS for MI		
Marker	**Effect Allele**	**Other Allele**	**Effect***	**SD**	**P**	**Effect**	**SD**	**P**
rs13107325	C	T	0.056	0.011	2.22E-07	0.004	0.053	0.912
rs1689800	A	G	0.031	0.005	1.43E-09	-0.020	0.019	0.334
rs16942887	A	G	0.085	0.007	8.62E-29	-0.038	0.028	0.125
rs181362	C	T	0.031	0.006	7.10E-07	-0.004	0.022	0.846
rs2293889	G	T	0.029	0.005	1.18E-08	0.038	0.018	0.040
rs2923084	A	G	0.027	0.006	3.21E-05	0.015	0.023	0.382
rs386000	C	G	0.055	0.007	2.92E-13	0.007	0.028	0.760
rs4082919	T	G	0.027	0.005	2.57E-07	0.005	0.019	0.667
rs4759375	T	C	0.057	0.011	6.30E-08	-0.013	0.038	0.548
rs7134594	T	C	0.030	0.005	1.26E-09	0.005	0.018	0.844
rs7255436	A	C	0.030	0.005	2.70E-08	-0.024	0.022	0.322
rs737337	T	C	0.043	0.009	3.48E-06	-0.036	0.035	0.358
rs838880	C	T	0.040	0.006	1.18E-11	0.008	0.023	0.825
rs881844	G	C	0.034	0.005	2.87E-11	0.001	0.019	0.772

The beta coefficient for association of HDL genetic score with MI was -0.077, SE of 0.159 and P= 0.63

*Effect is in standard deviation units