Genetic Determinants of Major Blood Lipids in Pakistan Is Compared with Europeans

Running title: Saleheen et al.; Genetic loci for major lipids in Pakistan

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Abstract

Background Evidence is sparse about the genetic determinants of major lipids in Pakistanis.

Methods and Results 45,000 variants across 2000 genes were assessed in 3200 Pakistanis, and compared with 2450 Germans using the same gene array and similar lipid assays. We also did a meta-analysis of selected lipid-related variants in Europeans. Pakistani genetic architecture was distinct from that of several ethnic groups represented in international reference samples. 41 variants at 14 loci were significantly associated with levels of HDL-C, triglyceride or LDL-C. The most significant lipid-related variants identified among Pakistanis corresponded to genes previously shown to be relevant to Europeans, such as CETP associated with HDL-C levels (rs711752; P<10^{-13}); APOA5/ZNF259 (rs651821; P=10^{-13}) and GCKR (rs1260326; P<10^{-13}) with triglyceride levels; and CELSR2 variants with LDL-C levels (rs646776; P<10^{-9}). For Pakistanis, these 41 variants explained 6.2%, 7.1%, and 0.9% of the variation in HDL-C, triglyceride, and LDL-C, respectively. Compared with Europeans, the allele frequency of rs662799 in APOA5 among Pakistanis was higher and its impact on triglyceride concentration was greater (P<10^{-4}).

Conclusions Several lipid-related genetic variants are common to Pakistanis and Europeans, though they explain only a modest portion of population variation in lipid concentration. Allelic frequencies and effect sizes of lipid-related variants can differ between Pakistanis and Europeans.

Key words: Lipids, HDL-C, LDL-C, triglycerides, Pakistan, Gene, Population structure, GWAS, IBC-array, Meta-analysis
INTRODUCTION

Levels of major blood lipids — that is, concentrations of low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) and triglyceride — are each strongly, log-linearly, and positively (or, in the case of HDL-C, inversely) associated with the risk of coronary heart disease (CHD). \(^1\)\(^-\)\(^2\) Linkage and twin based studies suggest that more than 50% of the variation in these serum lipids is determined by genetic factors.\(^3\)\(^-\)\(^5\) Several genetic variants have been established in the regulation of lipid metabolism in people of European continental ancestry, including 40 genomic loci (represented by 152 SNPs) identified in genome wide association scans.\(^5\)\(^-\)\(^6\) In contrast with considerable evidence available on people of European ancestry, data on genetic regulation of major blood lipids in Pakistanis are limited. For example, the previous largest relevant study reported on five genetic markers in relation to a few hundred participants.\(^7\) We report the first large-scale study of the genetic determinants of LDL-C, HDL-C and triglyceride concentrations in people living in Pakistan, a country of 175 million people with a high burden of cardiovascular disease. We have assayed over 45,000 single nucleotide polymorphisms (SNPs) across 2000 candidate genes using the ITMAT-Broad-CARe (IBC) array\(^8\) in 3200 participants from the Pakistan Risk of Myocardial Infarction Study (PROMIS).\(^9\) We compared association signals observed in PROMIS with those in 2450 participants of German ancestry from the Ludwigshafen Risk and Cardiovascular Health (LURIC) prospective study, which used the same gene array.\(^10\) To place the German findings in the context of data from other populations of European ancestry, we did a meta-analysis of published studies.
MATERIALS AND METHODS

Participants This paper follows the reporting recommendations of STREGA.21 PROMIS is a case-control study of acute myocardial infarction (MI) in six centres in urban Pakistan.20 MI cases had symptoms within 24 hours of hospital presentation, typical electrocardiographic changes, and a positive troponin-I test. Controls were individuals without a history of cardiovascular disease. They were frequency-matched to cases by sex and age (in 5 year bands) and concurrently identified in the same hospitals as index cases because they were either: (1) visitors of patients attending the outpatient department (2) patients attending the outpatient department for routine noncardiac complaints or (3) nonblood related visitors of index MI cases. People with recent illnesses or infections were not eligible. Information was recorded on personal and paternal ethnicity, spoken language, dietary intake, lifestyle factors and other characteristics. Nonfasting blood samples (with the time since last meal recorded) were drawn from each participant and centrifuged within 45 minutes of venepuncture. Serum samples were stored at -80 C. Total cholesterol, HDL-C and triglyceride concentration was measured using enzymatic methods (Roche Diagnostics, USA) at the Center for Non-Communicable Diseases, Pakistan. LDL-C was calculated using Friedewald’s formula.22

LURIC is a prospective study of cardiovascular death in individuals of German ancestry resident in southwest Germany who underwent elective coronary angiography and left ventriculography between June 1997 and January 2000.21 CHD in the current analyses was defined by troponin confirmed MI (ie, acute ST or non-ST- elevation MI or based on past medical records) or presence of visible luminal narrowing of ≥50% in at least
on coronary vessel. Individuals with $\geq 20\%$ but $<50\%$ stenosis were excluded from the analyses. Individuals with stenosis $<20\%$ were regarded as controls. Fasting blood samples collected before angiography were kept frozen at $-80^\circ C$ between the day of blood draw and the day of analysis for total cholesterol, HDL-C and triglycerides (all determined enzymatically).

The studies were approved by relevant ethics committees, and participants gave informed consent.

Genotyping Genotyping for both studies was performed at the Wellcome Trust Sanger Institute using the “IBC” array of about 2000 candidate genes. Variants on the array were selected on the basis of: (1) genes with known associations for various cardiovascular, pulmonary and sleep related disorders (2) information from pathway-based tools for the identification of biologically plausible candidate genes (3) unpublished functional experiments in mice (4) findings from various genomewide scans (5) priority SNPs identified by IBC consortium investigators. 45,237 SNPs in version 1 of this array were genotyped in the PROMIS participants and were called using the Illuminus algorithm. Markers were excluded from analysis if: the call rate was $<95\%$ (372 SNPs); there was evidence of departure from Hardy-Weinberg Equilibrium at a P-value of $<10^{-3}$ (1750 SNPs); or the minor allele frequency (MAF) was $<1\%$ (11,931 SNPs, with most such omissions due to genetic markers relevant in Africans and being uninformative in Pakistanis and Europeans). LURIC participants were typed with the version 2 of the IBC array and underwent the same calling and quality control procedures. As version 2 has 4,050 additional SNPs, these SNPs were
excluded from the current analysis. After quality control, 31,883 SNPs in 3197 Pakistanis and 35,533 SNPs in 2452 Germans remained for analyses.

Statistical methods To compare the genetic structure of Pakistanis with that of several major ethnic groups, we received permission from HapMap3 investigators to conduct principal components analyses on 1124 participants in HapMap3. We selected 19,931 SNPs in common with the PROMIS sample, and excluded 11,952 A/T and C/G SNPs to avoid possible strand alignment bias, as it is difficult to reliably infer the minor allele for A/T or C/G SNPs for non-HapMap populations. To investigate genetic substructure, we classified Pakistani participants into eight self-identified ethnic and linguistic groups and calculated principal components on the matrix of identity-by-state sharing of all pairs of individuals. Quantile-quantile plots were produced by plotting the observed –log10 P-value for each lipid against the expected –log10 p value. The association between each lipid measure and genetic variants was tested using linear regression. Additive models calculated the change in lipid level per copy of the minor allele. Beta coefficients have been reported using the common allele as the reference allele in PROMIS. All analyses were done using models adjusting for age, sex, the first two principal components and case-control status. Effect estimates in LURIC were reported for the same allele taken as reference in PROMIS.

We adopted a p ≤ 10^{-6} for declaration of significance. The Bonferroni correction for the 32,000 SNPs for three traits is 10^{-7}, assuming 96000 independent tests with no prior information. We chose a more relaxed cut-off 10^{-6} owing to the likely higher prior odds of association because the array involves candidate genes and because there is a high degree of correlation between the tested SNPs. To reduce potential biases, lipid
analyses were stratified by case-control status and excluded participants on lipid-lowering medication at the time of baseline examination. Analyses used PLINK 1.06, R version 2.9.1, and STATA 10.0.

**Meta-analysis** We sought genetic association studies of lipid-related variants in people of European ancestry without a history of cardiovascular disease published between January 1970 and January 2009. We focused on SNPs (ie, rs1800775, rs708272, rs646776, rs662799) identified as top signals in the Pakistan study to enable comparison of their impact in Europeans (with the exception of rs780093, for which there were minimal previous data owing to the recency of its discovery). Electronic searches involved MEDLINE, EMBASE, BIOSIS, and Science Citation index, and combined search terms related to genes (eg, cholesteryl ester transfer protein [CETP]) and lipids (eg, HDL-C) without language restriction. These searches were supplemented by scanning reference lists, hand searching relevant journals, and correspondence with authors. Two investigators independently extracted the following information: mean and SD of lipid levels by genotype; proportion of males; fasting status; assay methods. Analyses involved only within-study comparisons. Mean levels of lipids (and differences in mean levels in comparison with the common homozygotes) were calculated using both fixed and random-effects models (as the latter makes allowances for between-study heterogeneity). P-value for difference between the effect estimates obtained in PROMIS and European participants was calculated through a $\chi^2$ test of heterogeneity.
RESULTS

The main characteristics of the Pakistani and German participants in this study are summarised in Table 1. Comparison with HapMap3 population panels shows that the Pakistani population clustered differently to that of 11 other major ethnic groups, indicated by the separate clustering on the scatter plot of principal components (Figure 1). Pakistanis appear genetically closest to, but still clearly distinct from, Gujarati Indians living in the USA, a group that is known to differ genetically from Indians living in India.24 Analysis of the 8 ethnic and linguistic groups in the Pakistani study suggested the possibility of relatively minor population substructure; the different ethnicities could not be demarcated discretely on the scatter plots involving different principal components (Figure 1 and Supplemental Figure 1). Compared with Germans, the Pakistani participants were about a decade younger and had broadly similar mean lipid values, though lower HDL-C (Table 1).

Variants with highly significant associations

Under an additive model, linear regression analysis for each lipid measure identified several SNPs deviating from the expected $\chi^2$ values as shown by the quantile-quantile plots in Figure 2. A total of 25 variants in four genomic regions were associated with lipid levels in Pakistanis ($P \leq 10^{-6}$), including 16 variants for HDL-C, 8 variants for triglycerides, and one variant for LDL-C. All 16 HDL-C-related variants were on the cholesteryl ester transfer protein (CETP) gene ($10^{-14} < P < 10^{-6}$; Figure 3a & Supplemental Table 1). Each copy of the minor allele of rs711752, the lead SNP, was associated with 0.048 mmol/l (95% CI: 0.04 to 0.06; $P < 10^{-14}$) higher HDL-C levels. MAFs and effect sizes of the CETP variants in Pakistanis were broadly similar to those
observed in this German population (Figure 3a), with overlapping genetic association signals and a similar pattern of linkage disequilibrium (LD) in this region (Figure 4). Subsidiary analyses in PROMIS cases and controls for these variants revealed qualitatively similar results, with no substantial evidence of heterogeneity (Supplemental Figures 2a-c). To further explore LD patterns in Europeans, subsidiary analyses were conducted in CEU HapMap2 data which revealed a similar pattern of LD in the CEU HapMap2 population and LURIC participants (data available on request).

As shown in Figure 5, meta-analyses of the two most extensively studied CETP variants in Europeans yielded overall increases in HDL-C concentration of 0.063 mmol/l (0.055 to 0.071; $I^2=67\%$, 55\% to 77\%) per copy of the A allele of the Taq1B variant (rs708272; 46 studies, 65,640 participants) and 0.071 mmol/l (0.066 to 0.075; $I^2=10\%$, 0\% to 43\%) per copy of the A allele of the C-629A variant (rs1800775; 26 studies, 80,184 participants). Associations of the Taq1B variant appeared of similar size in the two studies; the Taq1B variant was in strong LD with rs711752 ($I^2=0.99$), the lead variant in the Pakistani population. By contrast, the association of the C-629A variant with HDL-C appeared somewhat stronger in Europeans than in Pakistanis ($\chi^2$ test for difference $P=2 \times 10^{-4}$; Figure 5 & Supplemental Figures 3a-1b).

Eight variants in two genomic regions were highly significantly associated with log triglyceride concentration in the Pakistani participants. The most significant SNP (rs662799; $P=1.25 \times 10^{-14}$) localized to the APOA5 gene (Figure 3b & Supplemental Table 1). Each copy of the rs662799-C allele at this locus was associated with a 0.14 mmol/l higher log triglyceride concentration (Figures 3b & 4), with MAF about two times higher in the Pakistani than German participants (0.17 v 0.07). This variant was in
strong LD with several other variants in APOA5 and nearby ZNF259 that were also significantly associated with triglyceride concentration, but apparently not in LD with any of the variants in APOA1, APOC3 or APOA4. Overall, APOA5 variants appeared to have stronger LD and associations with triglyceride concentration in Pakistani than in German participants (Figure 4). Meta-analysis of rs662799 in available European studies yielded 0.20 mmol/l (0.14 to 0.26) higher triglyceride per each copy of the minor allele (18 studies, 20,963 participants: Figure 5 & Supplemental figure 3d), an effect size that was lower than that observed in the Pakistani participants (χ² for difference P=7 x 10⁻⁴; Figure 5). Three variants in the glucokinase regulatory protein (GCKR) gene highly significantly associated with triglyceride in Pakistanis (P<10⁻⁶) had broadly similar-sized effects in Germans (Figure 3b).

Only rs646776 in the cadherin, EGF LAG seven-pass G-type receptor 2 (CELSR2) gene was highly significantly associated with LDL-C concentration in the Pakistani participants (P=1.25 x 10⁻¹⁰) and was associated with a 0.16 mmol/l (-0.23 to -0.08) lower LDL-C concentration per copy of the minor allele. This variant was not significantly associated with LDL-C concentration in the German participants (n=1175) owing to limited statistical power. Analyses conducted earlier in a larger LURIC study population (n=3189) for the same locus yielded a similar association with LDL-C levels as observed in Pakistanis.²⁵ The current meta-analysis of rs646776, however, established its relevance more reliably in Europeans, yielding an overall 0.15 mmol/l (-0.17 to -0.14) lower LDL-C per each copy of the minor allele (14 studies, 48,445
participants; Figure 5), an effect size comparable to that observed in Pakistanis ($\chi^2$ test for difference $P = 0.84$; Figure 5 & Supplemental figure 3c).

No significant interactions were observed on an additive scale of the 25 top variants with lipid measures by levels of ghee or tobacco consumption or by sex (Supplemental Figure 4). Qualitatively similar results were observed in analyses of the 875 cases in PROMIS for whom information was available on time since onset of MI symptoms; furthermore, adjustment for this variable yielded largely unchanged results (available upon request).

**Variants with nominally significant associations**

Of the 152 lipid-related SNPs discovered through previous genome wide scans in European populations, 49 were covered by the gene array used in the current study (23 for HDL-C, 17 for LDL-C, and 17 for triglycerides with a few SNPs associated with two or all three traits). At a pre-specified nominal value of $P < 0.01$, 12 of the 23 established HDL-C-related variants were associated with HDL-C concentration (including 7 variants described earlier in CETP and 5 other variants in LIPG, LIPC, and DPEP2); 10 of the established 17 triglyceride-related variants were associated with triglyceride concentration (including 3 variants described earlier in APOA5 and GCKR and 7 other variants in DOCK7, TBL2, LPL, BAZ1b, and APOB); and 5 of the 17 established LDL-C-related variants were associated with LDL-C concentration (including one variant in CELSR2 described above and 4 other variants in FADS1, FADS2 and CELSR2: Supplemental Figure 5). Hence, we identified a total of 41 different variants significantly related to major lipid levels in Pakistanis (ie, 25 variants at $P < 10^{-6}$ and a further 16 variants at $P < 10^{-2}$). Analyses of these genes in PROMIS and
LURIC participants revealed a similar pattern of LD, with somewhat stronger LD blocks in \textit{APOB} and \textit{LPL} genes in Pakistanis (\textbf{Supplemental Figure 6}). Collectively, these variants explained 6.2\%, 7.1\%, and 0.9\% of the variation in HDL-C, triglyceride, and LDL-C, respectively, whereas corresponding analyses in the German participants explained 5.9\%, 7.2\% and 0.71\% of the variation in these lipids, respectively.

Subsidiary analyses yielded odds ratio for MI in Pakistanis with each of the 41 principal SNPs that were compatible with the direction of associations of each of these variants on lipid concentration, although the current study was underpowered for reliable gene-MI analyses (\textbf{Supplemental Figure 7}).

\section*{DISCUSSION}

The current study has identified a total of 41 variants at 14 loci that were significantly associated with levels of HDL-C, triglyceride or LDL-C in Pakistanis. The most highly significant lipid-related variants identified among Pakistanis corresponded to genes previously shown to be relevant to lipid metabolism in Europeans, such as \textit{CETP}, \textit{APOA5}, and \textit{CELSR2}. Even collectively, however, the top variants explained only 6.2\%, 7.1\%, and 0.9\% of the population variation in HDL-C, triglyceride, and LDL-C levels in Pakistanis, respectively (a similar proportion of lipid variation was explained by the top signals in our parallel analysis of Germans). The current study has also suggested some differing allelic frequencies and lipid effects for variants in \textit{APOA5} in Pakistanis compared with Europeans. As discussed below, however, further studies are needed to confirm whether such differences are mainly related to ethnicity rather than other characteristics.
Most of the highly significant lipid-related loci identified in Pakistani participants were related to HDL-C and triglyceride, rather than LDL-C, a finding which is consistent with a lower yield of genetic loci associated with LDL-C in previous GWA studies in Europeans.\(^5\)-\(^{16}\) For HDL-C, our most highly significant findings related to the CETP gene.\(^{26}\) HDL is believed to exert atheroprotective effects through several mechanisms, including transfer of cholesterol from peripheral tissues to liver.\(^{26}\)-\(^{27}\) CETP facilitates this process by exchanging cholesterol esters from HDL with triglycerides in apolipoprotein B-containing particles.\(^{26}\) Deficiency of this protein leads to higher HDL-C levels and other lipoprotein abnormalities.\(^{25}\)-\(^{26}\) Our meta-analysis focused on the Taq1B and C-629A variants in CETP, which alter CETP mass and activity and, consequently, increase HDL-C concentration.\(^{27}\)

For triglyceride, our most highly significant findings related to variants in APOA5, which is part of the APOA1/C3/A4/A5 gene cluster localized to chromosome 11q23.\(^{28}\)-\(^{29}\) It has been proposed that APOAV regulates lipoprotein lipase-mediated hydrolysis of triglycerides contained in VLDL particles.\(^{28}\) Further triglyceride-related variants were found in GCKR,\(^{30}\) which regulates activity of glucokinase, a key enzyme responsible for the first rate-limiting step in the glycolysis pathway, deficiency of which alters glucose and lipoprotein metabolism.\(^{31}\) For LDL-C, the sole highly significant finding related to a variant in CELSR2,\(^{32}\) a gene that expresses itself along with PSRC1 and SORT1 within a transcriptional network proposed to regulate metabolic profile and atherosclerosis,\(^{32}\)-\(^{33}\) although precise mechanisms remain unknown.

Compared with German participants we studied, the frequency of the rs662799-C allele in the APOA5 locus was higher in Pakistanis and appeared to have a greater
impact on triglyceride concentration. However, as at least part of these differences could have been due to non-ethnic factors (eg, differences in sample size and/or population sampling frameworks used), further study is needed. Evidence of ethnic-related differences is emerging from other contexts, such as suggestions that total cholesterol is a stronger risk factor among South Asians than Europeans\(^34\) and that the \(LTA4H\) haplotype has higher odds ratios for myocardial infarction in Africans than Europeans.\(^35\) The value of large ethnic-specific studies has also been illustrated by the discovery of the strongest common susceptibility locus (\(KCNQ1\)) yet for T2D,\(^36\)-\(^38\) identified in East Asians but not initially in Europeans because the allele frequency in East Asians is much higher (40% vs 5%) despite similar odds ratios in both populations.\(^36\)-\(^38\).

For reasons of feasibility, we used existing genetic tools based on catalogues of genetic variation mostly discovered in Europeans, East Asians and West Africans, even though we were aware that these tools may not adequately capture genetic variation in Pakistanis (or other South Asians).\(^39\)-\(^40\) For example, the recent discovery of a 7-fold relative risk for heart failure with the 25 bp deletion allele in the \(MYBPC3\) gene would have remained undetected using conventional platforms because this variant is present only in South Asians.\(^41\) Further study in Pakistanis is, therefore, needed involving better population-specific tools for genetic mapping. Larger replication studies should also help to quantify and control any over-estimation in hypothesis-generating estimates (“winner’s curse”). Such studies should aim to involve fine mapping of relevant loci (eg, \(APOA5\)) and functional studies.\(^42\) Future studies may also yield stronger (or novel) genetic signals by direct assay of LDL-C rather than, as in the
current study, calculation of LDL-C using Friedewald’s formula. However, as a large prospective study has shown that associations of major lipids with CHD risk are at least as extreme in non-fasted participants as in fasted participants, use of nonfasting samples in the current study seems unlikely to have influenced materially the findings here.

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**References**


Table 1: Some characteristics of the participants from PROMIS and LURIC studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROMIS</th>
<th>LURIC</th>
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<tbody>
<tr>
<td></td>
<td>n= 3195</td>
<td>n = 2452</td>
</tr>
<tr>
<td>Age (y)</td>
<td>53.2 (10)</td>
<td>62 (10)</td>
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<tr>
<td>Women (%)</td>
<td>17.5</td>
<td>29.5</td>
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<td>Self-reported history of diabetes mellitus (%)</td>
<td>17.2</td>
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<td>Family history of MI (%)</td>
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<td>10%</td>
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<td>Body mass index (kg/m²)</td>
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<td>27.4 (4.0)</td>
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<td>Total cholesterol (mmol/l)</td>
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<td>5.0 (1.0)</td>
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<td>Low density lipoprotein cholesterol (mmol/l)</td>
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<td>2.96 (0.85)</td>
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<td>High density lipoprotein cholesterol (mmol/l)</td>
<td>0.82 (0.24)</td>
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<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.56 (0.22 0.95)</td>
<td>0.49 (0.21 0.81)</td>
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Data are mean (SD), median (IQR), or %.

Figure Legends

Figure 1: (a) Scatter plot of the first two principal components identified by principal component analysis of the identity-by-state matrix. The colors of points refer to the self reported-ethnicities in PROMIS control participants and HAPMAP (These ethnicities were not used in the PCA). (b) Scatter plot of the first two principal components and self reported ethnicities in PROMIS control participants.

Figure 1 (a-b) PAK: Pakistani from the PROMIS controls; YRI: Yoruba in Ibadan Nigeria, LWK: Luhya in Webuye Kenya, ASW: African ancestry in Southwest USA, MKK: Maasai in
Kinyawa Kenya, GIH: Gujarati Indians in Houston, CEU: Utah residents with Northern and Western European ancestry from the CEPH collection, TSI: Toscani in Italia, MEX: Mexican ancestry in Los Angeles, California, JPT: Japanese in Tokyo, Japan, CHD: Chinese in Metropolitan Denver, Colorado Texas, CHB: Han Chinese in Beijing, China. C1: First principal component; C2: Second principal component

Figure 2: λ: Genomic inflation factor

Figures 3 (a-b): Estimates represent the per-minor allele increase in lipid levels, adjusted for age, sex, the first two principal components and case-control status. The P-value for difference between studies corresponds to a test of nullity of interaction term between study and the SNP of interest. Boxes are proportional to the inverse of the variance of study estimates. Chr: chromosome, SNP: Single Nucleotide Polymorphism, MAF: minor allele frequency

Figure 4: (a) PROMIS (blue) and Luric (red) (b) LD plot (D') LURIC (c) LD plot (D') PROMIS. LD plots have been drawn using 1595 PROMIS control and 1475 LURIC control participants. Similar analyses for CELSR2 gene in PROMIS and LURIC were not possible as the current gene array has only few SNPs in this gene.

Figure 5: Estimates represent the per-minor allele increase in lipid levels. PROMIS estimates are derived fitting a regression, adjusting for age, sex, case-control status and the first two components of PCA. Estimates in Whites are derived from a random effect meta-analysis of additive estimates. Individual plots for each meta-analysis are presented in Webfigures 2a-2d. The p-value of heterogeneity derives from a heterogeneity test between the overall estimates in Whites and the estimate in PROMIS. Boxes are proportional to the inverse of the variance of study estimates. The mean difference is in mmol/l. Scales differ between lipids.
(a) PROMIS compared to HAPMAP3

(b) PCA of PROMIS ethnicities alone
Pakistani Participants (PROMIS)

HDL

\[ \lambda = 1.04 \]

LDL

\[ \lambda = 1.01 \]

TG

\[ \lambda = 1.03 \]

German Participants (LURIC)

HDL

\[ \lambda = 1.02 \]

LDL

\[ \lambda = 1.02 \]

TG

\[ \lambda = 1.03 \]
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Chr: Chromosome
SNP: Single Nucleotide Polymorphism
Gene: Associated Gene
Minor allele of participants: The less common allele amongst participants
Number of participants: The number of participants in the study
P-value for difference between studies: The significance of the difference between studies
Mean difference: The average difference between the groups
MAF: Minor Allele Frequency
P-value for association: The significance of the association with the trait

For more information, please refer to the original publication in *Circulation*.
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Genetic Determinants of Major Blood Lipids in Pakistan Is Compared with Europeans


Circ Cardiovasc Genet. published online June 22, 2010;

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"SUPPLEMENTAL MATERIAL."
Supplemental Figure 1: Scatter plot of additional principal components and self reported ethnicities in PROMIS control participants
**Supplemental Table 1:** Association of major lipid traits in PROMIS and comparison with the LURIC participants of SNPs significantly associated in PROMIS (P < 10^{-6})

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**Association with HDL-C levels (mmol/l)**

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<td>1.49E-03</td>
<td>0.15</td>
</tr>
<tr>
<td>11</td>
<td>rs2072560</td>
<td>111617036</td>
<td>APOAS</td>
<td>A</td>
<td>3195</td>
<td>0.16</td>
<td>0.142</td>
<td>0.019</td>
<td>2.13E-14</td>
<td>2450</td>
<td>0.07</td>
<td>0.077</td>
<td>0.026</td>
<td>3.34E-03</td>
<td>0.11</td>
</tr>
<tr>
<td>11</td>
<td>rs2266788</td>
<td>111615896</td>
<td>APOAS</td>
<td>G</td>
<td>3195</td>
<td>0.07</td>
<td>0.129</td>
<td>0.017</td>
<td>6.94E-14</td>
<td>2452</td>
<td>0.07</td>
<td>0.073</td>
<td>0.025</td>
<td>3.83E-03</td>
<td>0.17</td>
</tr>
<tr>
<td>11</td>
<td>rs2075290</td>
<td>111615856</td>
<td>ZNF259/APOAS</td>
<td>G</td>
<td>3189</td>
<td>0.19</td>
<td>0.132</td>
<td>0.018</td>
<td>8.77E-14</td>
<td>2452</td>
<td>0.07</td>
<td>0.077</td>
<td>0.025</td>
<td>2.15E-03</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>rs1260326</td>
<td>27584444</td>
<td>GCKR</td>
<td>T</td>
<td>5500</td>
<td>0.26</td>
<td>0.078</td>
<td>0.012</td>
<td>1.09E-10</td>
<td>2451</td>
<td>0.44</td>
<td>0.078</td>
<td>0.014</td>
<td>7.19E-09</td>
<td>0.86</td>
</tr>
<tr>
<td>2</td>
<td>rs780093</td>
<td>27596107</td>
<td>GCKR</td>
<td>T</td>
<td>3194</td>
<td>0.26</td>
<td>0.075</td>
<td>0.016</td>
<td>2.35E-06</td>
<td>2445</td>
<td>0.44</td>
<td>0.080</td>
<td>0.014</td>
<td>3.41E-09</td>
<td>0.64</td>
</tr>
<tr>
<td>2</td>
<td>rs780094</td>
<td>27594741</td>
<td>GCKR</td>
<td>T</td>
<td>3185</td>
<td>0.26</td>
<td>0.074</td>
<td>0.016</td>
<td>2.63E-06</td>
<td>2449</td>
<td>0.44</td>
<td>0.080</td>
<td>0.014</td>
<td>3.86E-09</td>
<td>0.69</td>
</tr>
</tbody>
</table>

**Association with triglyceride levels (mmol/l)**

Genotyping was done in further 2555 PROMIS individuals for variants associated with lipid traits at a P < 10^{-6}

Chr: chromosome, A1: minor allele, N: number of individuals, maf: minor allele frequency, beta: per-minor allele increase in lipid levels, adjusted for age, sex, the first two principal components and case-control status. For LDL, the LURIC dataset was restricted to participants not on lipid lowering drugs. The P-value for difference between studies corresponds to a test of nullity of interaction term between study and the SNP of interest.
**Supplemental Figure 2(a):** Association with HDL-C in PROMIS cases and controls for SNPs significantly associated with HDL-C levels in all PROMIS participants (P < 10^-6)

<table>
<thead>
<tr>
<th>SNP_id/Chr.</th>
<th>Status</th>
<th>Mean difference (95% CI)</th>
<th>P-value het.</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11076175 16</td>
<td>case control</td>
<td>-0.05 (-0.07, -0.02)</td>
<td>.128</td>
</tr>
<tr>
<td>rs11076176 16</td>
<td>case control</td>
<td>-0.04 (-0.06, -0.01)</td>
<td>.288</td>
</tr>
<tr>
<td>rs11508026 16</td>
<td>case control</td>
<td>0.05 (0.03, 0.07)</td>
<td>.554</td>
</tr>
<tr>
<td>rs12708967 16</td>
<td>case control</td>
<td>-0.06 (-0.08, -0.03)</td>
<td>.969</td>
</tr>
<tr>
<td>rs12720922 16</td>
<td>case control</td>
<td>-0.05 (-0.07, -0.02)</td>
<td>.118</td>
</tr>
<tr>
<td>rs1532624 16</td>
<td>case control</td>
<td>0.05 (0.03, 0.07)</td>
<td>.491</td>
</tr>
<tr>
<td>rs1532625 16</td>
<td>case control</td>
<td>0.05 (0.03, 0.08)</td>
<td>.902</td>
</tr>
<tr>
<td>rs17231506 16</td>
<td>case control</td>
<td>0.06 (0.04, 0.09)</td>
<td>.609</td>
</tr>
<tr>
<td>rs1800775 16</td>
<td>case control</td>
<td>-0.04 (-0.06, -0.02)</td>
<td>.049</td>
</tr>
<tr>
<td>rs1864163 16</td>
<td>case control</td>
<td>-0.07 (-0.10, -0.04)</td>
<td>.196</td>
</tr>
<tr>
<td>rs3764261 16</td>
<td>case control</td>
<td>0.06 (0.04, 0.09)</td>
<td>.570</td>
</tr>
<tr>
<td>rs5880 16</td>
<td>case control</td>
<td>-0.08 (-0.12, -0.04)</td>
<td>.609</td>
</tr>
<tr>
<td>rs708272 16</td>
<td>case control</td>
<td>0.05 (0.03, 0.08)</td>
<td>.327</td>
</tr>
<tr>
<td>rs711752 16</td>
<td>case control</td>
<td>0.06 (0.03, 0.08)</td>
<td>.362</td>
</tr>
<tr>
<td>rs7499892 16</td>
<td>case control</td>
<td>-0.05 (-0.07, -0.02)</td>
<td>.327</td>
</tr>
<tr>
<td>rs9939224 16</td>
<td>case control</td>
<td>-0.04 (-0.07, -0.02)</td>
<td>.119</td>
</tr>
</tbody>
</table>
**Supplemental Figure 2(b):** Association with log-triglyceride in PROMIS cases and controls for SNPs significantly associated with triglyceride levels in all PROMIS participants (P < 10^-6)

<table>
<thead>
<tr>
<th>SNP_id/chr</th>
<th>Status</th>
<th>Mean Difference</th>
<th>P-value het.</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1260326 2</td>
<td>case</td>
<td>0.08 (0.04, 0.12)</td>
<td>.908</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.08 (0.03, 0.12)</td>
<td></td>
</tr>
<tr>
<td>rs2072560 11</td>
<td>case</td>
<td>0.15 (0.10, 0.20)</td>
<td>.608</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.13 (0.08, 0.18)</td>
<td></td>
</tr>
<tr>
<td>rs2075290 11</td>
<td>case</td>
<td>0.14 (0.09, 0.19)</td>
<td>.561</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.12 (0.07, 0.17)</td>
<td></td>
</tr>
<tr>
<td>rs2266788 11</td>
<td>case</td>
<td>0.13 (0.08, 0.18)</td>
<td>.972</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.13 (0.08, 0.18)</td>
<td></td>
</tr>
<tr>
<td>rs651821 11</td>
<td>case</td>
<td>0.15 (0.10, 0.20)</td>
<td>.732</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.13 (0.08, 0.19)</td>
<td></td>
</tr>
<tr>
<td>rs662799 11</td>
<td>case</td>
<td>0.15 (0.10, 0.20)</td>
<td>.734</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.13 (0.08, 0.19)</td>
<td></td>
</tr>
<tr>
<td>rs780093 2</td>
<td>case</td>
<td>0.07 (0.03, 0.11)</td>
<td>.909</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.08 (0.03, 0.12)</td>
<td></td>
</tr>
<tr>
<td>rs780094 2</td>
<td>case</td>
<td>0.07 (0.03, 0.11)</td>
<td>.838</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>0.08 (0.03, 0.12)</td>
<td></td>
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</table>
Supplemental Figure 2(c): Association with LDL-C in PROMIS cases and controls for SNPs significantly associated with LDL-C levels in all PROMIS participants

Supplemental Figures 2 (a-c): Estimates represent the per-minor allele increase in lipid levels, adjusted for age, sex, the first two principal components. P_value het. is the P-value for heterogeneity for effect estimates obtained in cases and controls. Chr: chromosome.
**Supplemental Figure 3(a): Meta-analysis of previously published studies in Europeans for the association of rs1800775 (C-629A) variant, located in the CETP gene, with HDL-C levels**

<table>
<thead>
<tr>
<th>Author (Name of Study)</th>
<th>Year</th>
<th>Number of participants</th>
<th>ES (95% CI)</th>
<th>% Weight (D+L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam study</td>
<td>2007</td>
<td>1435</td>
<td>0.08 (0.06, 0.11)</td>
<td>2.94</td>
</tr>
<tr>
<td>Autchenko (ENGAGE consortium)</td>
<td>2009</td>
<td>5840</td>
<td>0.06 (0.05, 0.08)</td>
<td>9.33</td>
</tr>
<tr>
<td>Barzilai N (Longevity)</td>
<td>2003</td>
<td>743</td>
<td>0.07 (0.03, 0.11)</td>
<td>1.17</td>
</tr>
<tr>
<td>Bauerfeind</td>
<td>2002</td>
<td>185</td>
<td>0.07 (-0.01, 0.15)</td>
<td>0.32</td>
</tr>
<tr>
<td>Bernstein MS</td>
<td>2003</td>
<td>1720</td>
<td>0.05 (0.02, 0.09)</td>
<td>1.50</td>
</tr>
<tr>
<td>Blankenberg S (AtheroGene)</td>
<td>2004</td>
<td>574</td>
<td>0.08 (0.03, 0.13)</td>
<td>0.84</td>
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<tr>
<td>Chasman (WGHS)</td>
<td>2008</td>
<td>6195</td>
<td>0.09 (0.08, 0.10)</td>
<td>8.28</td>
</tr>
<tr>
<td>Dachel C (ECTIM)</td>
<td>1999</td>
<td>688</td>
<td>0.08 (0.04, 0.12)</td>
<td>1.11</td>
</tr>
<tr>
<td>Duflaart (PREVEND)</td>
<td>2007</td>
<td>8141</td>
<td>0.06 (0.05, 0.08)</td>
<td>9.87</td>
</tr>
<tr>
<td>Eiriksdottir Reykjavik</td>
<td>2001</td>
<td>745</td>
<td>0.08 (0.05, 0.11)</td>
<td>2.38</td>
</tr>
<tr>
<td>Freeman DJ (WGSCOPS)</td>
<td>2003</td>
<td>1107</td>
<td>0.06 (0.04, 0.08)</td>
<td>4.20</td>
</tr>
<tr>
<td>Girelli (Verona Heart Project)</td>
<td>2007</td>
<td>1187</td>
<td>0.07 (0.04, 0.10)</td>
<td>2.24</td>
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<tr>
<td>Heidema (CDRFMP)</td>
<td>2007</td>
<td>1071</td>
<td>0.07 (0.04, 0.10)</td>
<td>2.14</td>
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<tr>
<td>Home (HICS)</td>
<td>2007</td>
<td>1309</td>
<td>0.05 (-0.00, 0.11)</td>
<td>0.59</td>
</tr>
<tr>
<td>Kakko (OPERA)</td>
<td>2001</td>
<td>481</td>
<td>0.05 (0.01, 0.09)</td>
<td>1.17</td>
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<tr>
<td>Kathiresan (FINNREISK97)</td>
<td>2008</td>
<td>7940</td>
<td>0.06 (0.05, 0.08)</td>
<td>7.79</td>
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<tr>
<td>Kathiresan (MDC-CC)</td>
<td>2008</td>
<td>5519</td>
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<td>7.79</td>
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<tr>
<td>Kathiresan (DGI)</td>
<td>2008</td>
<td>2758</td>
<td>0.07 (0.05, 0.09)</td>
<td>4.43</td>
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<tr>
<td>Kathiresan (NORDIL)</td>
<td>2008</td>
<td>5095</td>
<td>0.08 (0.05, 0.10)</td>
<td>3.88</td>
</tr>
<tr>
<td>McCaskie (CUDAS/BPHS/CUPID)</td>
<td>2007</td>
<td>1059</td>
<td>0.07 (0.04, 0.11)</td>
<td>1.73</td>
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<tr>
<td>Sabati (NFBC1966)</td>
<td>2009</td>
<td>4531</td>
<td>0.07 (0.05, 0.09)</td>
<td>3.79</td>
</tr>
<tr>
<td>Schouw (PROSPECT/EPIC)</td>
<td>2007</td>
<td>1519</td>
<td>0.08 (0.05, 0.11)</td>
<td>2.32</td>
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<tr>
<td>Thompson JF</td>
<td>2007</td>
<td>2087</td>
<td>0.05 (0.03, 0.07)</td>
<td>5.44</td>
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<td>Tobin MD</td>
<td>2004</td>
<td>182</td>
<td>0.08 (-0.00, 0.15)</td>
<td>0.32</td>
</tr>
<tr>
<td>Ridker (WGHS)</td>
<td>2009</td>
<td>18000</td>
<td>0.06 (-0.01, 0.13)</td>
<td>0.38</td>
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</tbody>
</table>

**Overall random effect** 1-squared = 10% (95% CI 0% - 43%), p = 0.318

**Overall fixed effect** 0.07 (0.07, 0.08) 190.00

**NOTE:** Weights are from random effects analysis
Supplemental Figure 3(b): Meta-analysis of previously published studies in Europeans for the association of rs708272 (Taq1B) variant, located in the CETP gene, with HDL-C levels

<table>
<thead>
<tr>
<th>Author (Name of Study)</th>
<th>Year</th>
<th>Number of Participants</th>
<th>ES (95% CI)</th>
<th>% Weight (D+L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arca</td>
<td>2001</td>
<td>180</td>
<td>0.10 (0.01, 0.18)</td>
<td>0.76</td>
</tr>
<tr>
<td>Barzilai N (Longevity)</td>
<td>2003</td>
<td>373</td>
<td>0.12 (0.05, 0.18)</td>
<td>1.21</td>
</tr>
<tr>
<td>Bauerleind</td>
<td>2002</td>
<td>184</td>
<td>0.06 (-0.02, 0.14)</td>
<td>0.86</td>
</tr>
<tr>
<td>Blankenberg S (Atherogene)</td>
<td>2004</td>
<td>571</td>
<td>0.06 (0.03, 0.13)</td>
<td>1.62</td>
</tr>
<tr>
<td>Carr</td>
<td>2002</td>
<td>120</td>
<td>0.10 (0.01, 0.19)</td>
<td>0.89</td>
</tr>
<tr>
<td>Corella D</td>
<td>2000</td>
<td>514</td>
<td>0.11 (0.07, 0.14)</td>
<td>3.04</td>
</tr>
<tr>
<td>Cucchel (NORM &amp; CATH)</td>
<td>2002</td>
<td>224</td>
<td>0.06 (-0.02, 0.13)</td>
<td>0.96</td>
</tr>
<tr>
<td>Deguchi (SVTFR)</td>
<td>2004</td>
<td>49</td>
<td>0.02 (-0.10, 0.15)</td>
<td>0.40</td>
</tr>
<tr>
<td>Dullaart (PREVEND)</td>
<td>2007</td>
<td>8289</td>
<td>0.06 (0.05, 0.08)</td>
<td>5.00</td>
</tr>
<tr>
<td>Eiriksdottir (Reyjavik)</td>
<td>2001</td>
<td>745</td>
<td>0.07 (0.03, 0.10)</td>
<td>2.85</td>
</tr>
<tr>
<td>Freeman DJ</td>
<td>1994</td>
<td>320</td>
<td>0.10 (-0.03, 0.17)</td>
<td>1.03</td>
</tr>
<tr>
<td>Freeman DJ (WOSCOPS)</td>
<td>2003</td>
<td>1105</td>
<td>0.05 (-0.02, 0.07)</td>
<td>3.98</td>
</tr>
<tr>
<td>Fumeron F (ECTIM)</td>
<td>1985</td>
<td>724</td>
<td>0.08 (0.04, 0.13)</td>
<td>2.35</td>
</tr>
<tr>
<td>Girili (Vienna Heart Project)</td>
<td>2006</td>
<td>296</td>
<td>0.02 (-0.03, 0.07)</td>
<td>1.87</td>
</tr>
<tr>
<td>Gudson (EARS)</td>
<td>1998</td>
<td>767</td>
<td>0.07 (0.05, 0.09)</td>
<td>3.98</td>
</tr>
<tr>
<td>Hall</td>
<td>2006</td>
<td>116</td>
<td>0.06 (-0.02, 0.15)</td>
<td>0.55</td>
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<tr>
<td>Hannuksela</td>
<td>1994</td>
<td>82</td>
<td>0.10 (0.00, 0.20)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hedema (CORFIMP)</td>
<td>2007</td>
<td>1075</td>
<td>0.07 (0.04, 0.10)</td>
<td>3.11</td>
</tr>
<tr>
<td>Home (HCS)</td>
<td>2007</td>
<td>1288</td>
<td>0.06 (0.01, 0.11)</td>
<td>1.38</td>
</tr>
<tr>
<td>Juoninen-T</td>
<td>1995</td>
<td>91</td>
<td>0.20 (0.03, 0.37)</td>
<td>0.20</td>
</tr>
<tr>
<td>Kauma H</td>
<td>1996</td>
<td>524</td>
<td>0.08 (0.02, 0.15)</td>
<td>2.22</td>
</tr>
<tr>
<td>Keaveney</td>
<td>2004</td>
<td>4665</td>
<td>0.06 (0.04, 0.07)</td>
<td>4.93</td>
</tr>
<tr>
<td>Kio K (CARDIA)</td>
<td>2007</td>
<td>1586</td>
<td>0.06 (0.04, 0.08)</td>
<td>3.66</td>
</tr>
<tr>
<td>Kordon I</td>
<td>1989</td>
<td>146</td>
<td>0.11 (0.02, 0.20)</td>
<td>0.65</td>
</tr>
<tr>
<td>Kurvetnoven JA (The Monitoring Project)</td>
<td>1997</td>
<td>238</td>
<td>0.12 (0.06, 0.18)</td>
<td>1.28</td>
</tr>
<tr>
<td>Liu (PHS)</td>
<td>2002</td>
<td>384</td>
<td>0.05 (0.01, 0.09)</td>
<td>2.14</td>
</tr>
<tr>
<td>McCluskey (CUDAs/BPHS/CUPID)</td>
<td>2007</td>
<td>1058</td>
<td>0.07 (0.03, 0.10)</td>
<td>2.75</td>
</tr>
<tr>
<td>M complicated</td>
<td>2004</td>
<td>95</td>
<td>0.03 (-0.05, 0.11)</td>
<td>0.64</td>
</tr>
<tr>
<td>Mitchell</td>
<td>1994</td>
<td>112</td>
<td>0.12 (0.02, 0.21)</td>
<td>0.86</td>
</tr>
<tr>
<td>Nadelton (ARIC)</td>
<td>2006</td>
<td>6764</td>
<td>0.07 (0.06, 0.09)</td>
<td>4.36</td>
</tr>
<tr>
<td>Noone E</td>
<td>2000</td>
<td>83</td>
<td>0.02 (-0.12, 0.15)</td>
<td>0.33</td>
</tr>
<tr>
<td>Orlov (Framingham)</td>
<td>2007</td>
<td>2016</td>
<td>0.06 (0.04, 0.08)</td>
<td>4.34</td>
</tr>
<tr>
<td>Pal J (PHFS)</td>
<td>2004</td>
<td>513</td>
<td>-0.11 (-0.15, -0.07)</td>
<td>2.29</td>
</tr>
<tr>
<td>Pal J (NHIS)</td>
<td>2004</td>
<td>480</td>
<td>0.11 (0.06, 0.17)</td>
<td>1.39</td>
</tr>
<tr>
<td>Plat</td>
<td>2003</td>
<td>112</td>
<td>0.04 (0.01, 0.15)</td>
<td>0.67</td>
</tr>
<tr>
<td>Riems</td>
<td>1999</td>
<td>32</td>
<td>-0.00 (-0.11, 0.11)</td>
<td>0.47</td>
</tr>
<tr>
<td>Sandholzer (Salzburg Atherosclerosis Prevention)</td>
<td>1998</td>
<td>1503</td>
<td>0.08 (0.03, 0.09)</td>
<td>3.24</td>
</tr>
<tr>
<td>Schouw (PROSPECT-EPIC)</td>
<td>2006</td>
<td>549</td>
<td>0.06 (0.03, 0.09)</td>
<td>3.06</td>
</tr>
<tr>
<td>Soli</td>
<td>2002</td>
<td>1727</td>
<td>0.05 (0.01, 0.09)</td>
<td>2.53</td>
</tr>
<tr>
<td>Tatuatu (NPHS)</td>
<td>1991</td>
<td>108</td>
<td>0.04 (0.07, 0.18)</td>
<td>0.46</td>
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<tr>
<td>Thompson JR</td>
<td>2007</td>
<td>2105</td>
<td>0.05 (0.02, 0.07)</td>
<td>4.41</td>
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<tr>
<td>Thompson JF</td>
<td>2003</td>
<td>93</td>
<td>0.07 (0.02, 0.17)</td>
<td>0.59</td>
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<tr>
<td>Voll MC</td>
<td>1999</td>
<td>182</td>
<td>0.06 (0.02, 0.09)</td>
<td>2.88</td>
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<tr>
<td>Wettiger (SAPHRIR)</td>
<td>2004</td>
<td>1017</td>
<td>0.09 (0.05, 0.13)</td>
<td>2.72</td>
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<tr>
<td>Ridler (WGHS)</td>
<td>2009</td>
<td>18245</td>
<td>0.07 (0.07, 0.08)</td>
<td>5.58</td>
</tr>
</tbody>
</table>

Overall Random Effect I-squared = 67.0% (95% CI 55% - 78%), p = <0.001

I-V Overall 0.06 (0.05, 0.07) 100.00

NOTE: Weights are from random effects analysis
**Supplemental Figure 3(c):** Meta-analysis of previously published studies in Europeans for the association of rs646776 variant, located in the CELSR2 gene, with LDL-C levels

<table>
<thead>
<tr>
<th>Author (name of study)</th>
<th>Year</th>
<th>No. of participants</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aulchenko (Meta-analysis 15 studies)</td>
<td>2009</td>
<td>12685</td>
<td>-0.14 (-0.17, -0.11)</td>
<td>24.53</td>
</tr>
<tr>
<td>Kathiresan (DGI)</td>
<td>2008</td>
<td>2758</td>
<td>-0.19 (-0.25, -0.13)</td>
<td>5.74</td>
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<tr>
<td>Kathiresan (FINRISK 97)</td>
<td>2008</td>
<td>7940</td>
<td>-0.14 (-0.18, -0.10)</td>
<td>15.29</td>
</tr>
<tr>
<td>Kathiresan (MDC-CC)</td>
<td>2008</td>
<td>5519</td>
<td>-0.15 (-0.19, -0.11)</td>
<td>13.80</td>
</tr>
<tr>
<td>Kathiresan (NHS98 China)</td>
<td>2008</td>
<td>2891</td>
<td>-0.20 (-0.30, -0.10)</td>
<td>2.21</td>
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<tr>
<td>Kathiresan (NHS98 India)</td>
<td>2008</td>
<td>587</td>
<td>-0.19 (-0.31, -0.07)</td>
<td>1.53</td>
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<tr>
<td>Kathiresan (NHS98 Malaysia)</td>
<td>2008</td>
<td>781</td>
<td>-0.29 (-0.49, -0.09)</td>
<td>0.55</td>
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<td>Sabatti (NFBC1966)</td>
<td>2009</td>
<td>4507</td>
<td>-0.16 (-0.20, -0.11)</td>
<td>8.83</td>
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<tr>
<td>Sandhu (1958 British Birth Cohort)</td>
<td>2008</td>
<td>1330</td>
<td>-0.13 (-0.21, -0.05)</td>
<td>3.45</td>
</tr>
<tr>
<td>Sandhu (Ely study)</td>
<td>2008</td>
<td>1686</td>
<td>-0.15 (-0.21, -0.09)</td>
<td>6.13</td>
</tr>
<tr>
<td>Sandhu (EPIC-Norfolk Obese)</td>
<td>2008</td>
<td>993</td>
<td>-0.18 (-0.28, -0.08)</td>
<td>2.21</td>
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<tr>
<td>Sandhu (EPIC-Norfolk Replication)</td>
<td>2008</td>
<td>3293</td>
<td>-0.18 (-0.24, -0.12)</td>
<td>6.13</td>
</tr>
<tr>
<td>Sandhu (EPIC-Norfolk subcohort)</td>
<td>2008</td>
<td>2014</td>
<td>-0.17 (-0.23, -0.11)</td>
<td>6.13</td>
</tr>
<tr>
<td>Wallace (Twins UK)</td>
<td>2008</td>
<td>1481</td>
<td>-0.08 (-0.16, -0.00)</td>
<td>3.45</td>
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<tr>
<td>Overall random effect</td>
<td></td>
<td></td>
<td>-0.15 (-0.17, -0.14)</td>
<td>100.00</td>
</tr>
<tr>
<td>Overall fixed effect</td>
<td></td>
<td></td>
<td>-0.15 (-0.17, -0.14)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
**Supplemental Figure 3(d):** Meta-analysis of previously published studies in Europeans for the association of variant rs662799 (T1131C), located in the ApoA5 gene, with triglyceride levels

<table>
<thead>
<tr>
<th>Author (name of study)</th>
<th>Year</th>
<th>No. of participants</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klos (CARDIA)</td>
<td>2005</td>
<td>3415</td>
<td>0.08 (0.03, 0.14)</td>
<td>10.80</td>
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<tr>
<td>Grallert (KORA &amp; SAPHIR)</td>
<td>2007</td>
<td>3264</td>
<td>0.11 (0.01, 0.21)</td>
<td>9.05</td>
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<tr>
<td>Talmud (NPHSII)</td>
<td>2002</td>
<td>2537</td>
<td>0.18 (0.06, 0.31)</td>
<td>7.98</td>
</tr>
<tr>
<td>Vaessen (EPIC-Norfolk)</td>
<td>2006</td>
<td>1800</td>
<td>0.27 (0.15, 0.39)</td>
<td>8.18</td>
</tr>
<tr>
<td>Lai (Framingham Offspring)</td>
<td>2004</td>
<td>1725</td>
<td>0.42 (0.25, 0.58)</td>
<td>6.23</td>
</tr>
<tr>
<td>Hubacek (Female)</td>
<td>2004</td>
<td>1368</td>
<td>0.14 (0.03, 0.25)</td>
<td>8.40</td>
</tr>
<tr>
<td>Hubacek (Male)</td>
<td>2004</td>
<td>1191</td>
<td>0.27 (0.05, 0.49)</td>
<td>4.55</td>
</tr>
<tr>
<td>Evans</td>
<td>2003</td>
<td>1094</td>
<td>0.94 (0.39, 1.50)</td>
<td>1.06</td>
</tr>
<tr>
<td>Martinelli (Verona Heart Project)</td>
<td>2007</td>
<td>913</td>
<td>0.19 (0.04, 0.34)</td>
<td>6.88</td>
</tr>
<tr>
<td>Lee</td>
<td>2004</td>
<td>438</td>
<td>0.48 (0.04, 0.93)</td>
<td>1.56</td>
</tr>
<tr>
<td>Szalai</td>
<td>2004</td>
<td>310</td>
<td>0.18 (0.01, 0.35)</td>
<td>6.25</td>
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<tr>
<td>Vaverkova</td>
<td>2004</td>
<td>267</td>
<td>0.33 (-0.22, 0.88)</td>
<td>1.07</td>
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<tr>
<td>Acuizelat</td>
<td>2003</td>
<td>198</td>
<td>0.25 (0.05, 0.44)</td>
<td>5.33</td>
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<tr>
<td>Lee (Japanese American Family)</td>
<td>2004</td>
<td>154</td>
<td>0.30 (0.04, 0.57)</td>
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<tr>
<td>Farall (PROCARDIS)</td>
<td>2006</td>
<td>2956</td>
<td>0.23 (0.12, 0.34)</td>
<td>8.40</td>
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<tr>
<td>Helgadottir (PennCATH)</td>
<td>2007</td>
<td>476</td>
<td>0.06 (0.00, 0.12)</td>
<td>10.64</td>
</tr>
</tbody>
</table>

Overall random effect: R² = 66 (95% CI 43%-80%), p < 0.001
Overall fixed effect: 0.20 (0.14, 0.26) 100.00

**NOTE:** Weights are from random effects analysis.
References for Supplemental figures 3a-3d

Supplementary references for the SNP rs1800775 (C-629A) and SNP rs708272 (Taq1B)


Supplementary references for the SNP rs646776 located in the CELSR2 gene


Supplementary reference for SNP rs662799 (T1131C) located in the ApoA5 gene


polymorphism modulates levels of triglyceride, HDL cholesterol and FERHDL but is not a risk factor for coronary artery disease. Atherosclerosis. 2004;176:165-72


78. Lee KW, Ayyobi AF, Frohlich JJ, Hill JS. APOA5 gene polymorphism modulates levels of triglyceride, HDL cholesterol and FERHDL but is not a risk factor for coronary artery disease. Atherosclerosis. 2004;176:165-72


Supplemental Figure 4: Effect modification of genetic effects by gender, ghee consumption and tobacco consumption in Pakistanis

<table>
<thead>
<tr>
<th>Lipid trait</th>
<th>SNP</th>
<th>Genotype</th>
<th>Gender</th>
<th>Oil type</th>
<th>Tobacco</th>
</tr>
</thead>
</table>
| Lipid level (mmol/L) and 95% confidence intervals

Analyses are presented only for the lead SNPs at loci that showed highly significant associations with lipid traits (P < 10^-6)
Size of data markers are proportional to the inverse of the variance of the minor allele effect. P-values were derived from F tests of the interaction terms fitted in linear regression models of each lipid trait, adjusted for age, gender, the first two principle components and case-control status.
Supplemental Figure 5(a): Association with HDL-C (mmol/l) in PROMIS and LURIC participants of SNPs discovered in previous genome wide association studies in association with HDL-C levels.
**Supplemental Figure 5(b): Association with LDL-C (mmol/l) in PROMIS and LURIC participants of SNPs discovered in previous genome wide association studies in association with LDL-C levels**

<table>
<thead>
<tr>
<th>Chr</th>
<th>SNP</th>
<th>Gene</th>
<th>Minor allele</th>
<th>Number of participants</th>
<th>Mean difference (95% CI)</th>
<th>MAF</th>
<th>P-value for association</th>
<th>P-value for difference between studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs646776</td>
<td>CELSR2</td>
<td>G</td>
<td>3014</td>
<td>-0.15 (-0.23, -0.08)</td>
<td>0.25</td>
<td>3.4e-05</td>
<td>0.05</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.01 (-0.09, 0.06)</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>rs599839</td>
<td>CELSR2</td>
<td>G</td>
<td>3013</td>
<td>-0.16 (-0.23, -0.08)</td>
<td>0.25</td>
<td>2.7e-05</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>-0.02 (-0.09, 0.06)</td>
<td>0.34</td>
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<tr>
<td>2</td>
<td>rs6803</td>
<td>APOB</td>
<td>T</td>
<td>3015</td>
<td>0.01 (-0.06, 0.07)</td>
<td>0.27</td>
<td>8.9e-01</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.03 (-0.04, 0.09)</td>
<td>0.46</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>rs7575840</td>
<td>(intergenic)</td>
<td>A</td>
<td>3015</td>
<td>0.01 (-0.08, 0.09)</td>
<td>0.16</td>
<td>8.6e-01</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
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<td>0.06 (-0.01, 0.13)</td>
<td>0.30</td>
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<tr>
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<td>rs12654264</td>
<td>HMGCR</td>
<td>A</td>
<td>3014</td>
<td>-0.03 (-0.09, 0.04)</td>
<td>0.42</td>
<td>4.0e-01</td>
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</tr>
<tr>
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<td>-0.01 (-0.07, 0.06)</td>
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<td>HMGCR</td>
<td>T</td>
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<td>-0.02 (-0.08, 0.04)</td>
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<td>-0.00 (-0.07, 0.06)</td>
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<td>6</td>
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<td>0.01 (-0.07, 0.06)</td>
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<td>-0.04 (-0.11, 0.03)</td>
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<td>rs174570</td>
<td>FADS2</td>
<td>T</td>
<td>3013</td>
<td>-0.16 (-0.27, -0.05)</td>
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<td>0.02</td>
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<tr>
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<td>-0.04 (-0.13, 0.06)</td>
<td>0.13</td>
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<td>11</td>
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<td>G</td>
<td>3009</td>
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<td>-0.04 (-0.11, 0.03)</td>
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<tr>
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<td>LDLR</td>
<td>T</td>
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<td>0.07 (-0.02, 0.17)</td>
<td>0.14</td>
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</table>
Supplemental Figure 5(c): Association with log triglycerides (mmol/l) in PROMIS and LURIC participants of SNPs discovered in previous genome wide association studies in association with triglyceride levels

Table showing the association of SNPs with log triglycerides in PROMIS and LURIC participants:

<table>
<thead>
<tr>
<th>Chr</th>
<th>SNP</th>
<th>Minor allele</th>
<th>Number of participants</th>
<th>Mean difference (95% CI)</th>
<th>MAF</th>
<th>P-value for association</th>
<th>P-value for difference between studies</th>
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</thead>
<tbody>
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<tr>
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<td>(DOCK7)</td>
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<td>-0.02 (-0.08, 0.01)</td>
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<td></td>
<td></td>
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<tr>
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<td>.17</td>
<td>4.6e-02</td>
<td>2.5e-01</td>
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<tr>
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<td>(intergenic)</td>
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<td></td>
<td>-0.02 (-0.08, 0.01)</td>
<td></td>
<td></td>
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</tr>
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<td>9.1e-02</td>
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WebFigures 4 (a-b): Estimates represent the per-minor allele increase in lipid levels, adjusted for age, sex, the first two principal components and case-control status. The P-value for difference between studies corresponds to a test of nullity of interaction term between study and the SNP of interest. Boxes are proportional to the inverse of the variance of study estimates. Chr: chromosome, SNP: Single Nucleotide Polymorphism, MAF: minor allele frequency.
Supplemental Figure 6(a): Comparison of linkage disequilibrium in PROMIS and LURIC participants for genes with nominally significant associations with HDL-C concentration.
Supplemental Figure 6(b): Comparison of linkage disequilibrium in PROMIS and LURIC participants for genes with nominally significant associations with triglyceride concentration
Supplemental Figure 6(c): Comparison of linkage disequilibrium in PROMIS and LURIC participants for genes with nominally significant associations with LDL-C concentration.
Supplemental Figure 7(a): Association with MI for SNPs associated with high density cholesterol in PROMIS

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odds ratio
**Supplemental Figure 7(b):** Association with MI for SNPs associated with low density cholesterol in PROMIS

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**Supplemental Figure 7c:** Association with MI for SNPs associated with triglycerides in PROMIS

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Odds ratio
Acknowledgements

We would like to acknowledge the contributions of the following individuals:


**Data management:** Sarfaraz Sher Ali, Touqeer Ahmed, Fariha Nadeem, Matthew Walker, Sarah Watson and Mohammed J.R. Ghorai.

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**Administration:** Kashif Saleheen and Hannah Sneath.