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Meta-analysis of genome-wide association studies of HDL cholesterol response to statins

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Abstract

Background: In addition to lowering low density lipoprotein-cholesterol (LDL-C), statin therapy also raises high density lipoprotein-cholesterol (HDL-C) levels. Inter-individual variation in HDL-C response to statins may be partially explained by genetic variation.

Methods and Results: We performed a meta-analysis of genome-wide association studies (GWAS) to identify variants with an effect on statin-induced HDL-C changes. The 123 most promising signals with $P<1x10^{-4}$ from the 16,769 statin-treated participants in the first analysis stage were followed up in an independent group of 10,951 statin-treated individuals, providing a total sample size of 27,720 individuals. The only associations of genome-wide significance ($P<5x10^{-8}$) were between minor alleles at the *CETP* locus and greater HDL-C response to statin treatment.

Conclusion: Based on results from this study that included a relatively large sample size, we suggest that *CETP* may be the only detectable locus with common genetic variants that influence HDL-C response to statins substantially in individuals of European descent. Although *CETP* is known to be associated with HDL-C, we provide evidence that this pharmacogenetic effect is independent of its association with baseline HDL-C levels.

Keywords: Pharmacogenetics, HDL-Cholesterol, Statins, Genome-wide association study

Introduction

The drug class of 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, better known as "statins", are widely prescribed and effective for the prevention and management of cardiovascular disease (CVD).[1] While the major CVD benefit of statins is due to reduction in plasma low density lipoprotein cholesterol (LDL-C)[2], statins also produce moderate increases, ranging from 4 to 10%, in levels of high density lipoprotein cholesterol (HDL-C).[3 ,4] This is of particular interest since HDL-C levels are inversely related to CVD risk in the general population and in patients treated with statins.[5 ,6] However, a causal role of low HDL-C as a determinant of increased CVD risk is controversial.[7]

The increase in HDL-C after statin therapy varies among individuals.[3] This might be partly due to genetic variation. Previous studies that have investigated associations between genotype and statin-induced changes in HDL-C[8-10] have focused primarily on variants within the *CETP* gene that are known to affect circulating HDL-C levels[11] and risk of coronary artery disease.[12] To address whether additional loci have an effect on statin-induced changes in HDL-C levels, we conducted a large-scale meta-analysis of genome-wide association studies (GWAS) using datasets from both randomized controlled trials (RCTs) and cohort studies in the large Genomic Investigation of Statin Therapy (GIST) consortium that previously identified four loci associated with LDL-C response to statins.[13]

Methods

Study populations

The GIST consortium assembled data from seven RCTs and eleven prospective population-based studies. The initial analysis (first stage) was performed in 16,769 statin-treated individuals; 8,506 individuals from six RCTs (ASCOT UK, CARDS, CAP, PRINCE, PROSPER, and TNT) and 8,263 statin-treated individuals from ten observational studies (AGES, ARIC, ASCOT UK-observational, BioVU, CHS, FHS, Health ABC, HVH, MESA, and the Rotterdam Study). Further investigation (second stage) was performed in 10,951 statin-treated individuals from two RCTs (ASCOT Scandinavia and JUPITER) and two observational studies (ASCOT Scandinavia – observational and GoDARTS), which were used to test for replication of findings from the first stage. Details of the first and second stage studies, including their genotyping and quality control (QC) information, can be found in the **Supplementary Notes 1, 2 and 3** and **Supplementary tables 1 and 2**.

Subjects

Response to statin treatment was principally studied in statin-treated individuals only. Those treated with placebo were excluded from the analyses of RCTs and those not treated with statins were excluded from observational studies. HDL-C measurements were obtained before and after start of statin treatment. Only subjects with non-missing phenotypes and covariates were included. Those of reported or suspected non-European ancestry were excluded.

Outcome measurements

The response to statin treatment was defined as the difference between the natural log-transformed on- and off-treatment HDL-C levels (ln (on-treatment HDL-C) – ln (off-treatment HDL-C)). The corresponding linear regression coefficients thus reflect the fraction of differential HDL-C increase (relative increase) per copy of the coded allele in the additive genetic model. For observational studies, on-treatment HDL-C levels were calculated for all different prescribed statins, at any dosage,

for any indication, and for any treatment episode extending at least four weeks prior to on-treatment HDL-C measurement. Characteristics of on- and off-treatment HDL-C levels and statins used in each study are shown in **Supplementary Table 2**. For each individual, at least one off-treatment HDL-C measurement and at least one on-treatment measurement were required. Subjects with missing on- or off-treatment measurements were excluded, with the exception of the GoDARTS study for which missing off-treatment HDL-C levels were estimated using imputation methods, as described previously.[14] In RCTs, when multiple on- or off-treatment measurements were available, the mean of the measurements was used.

Genotyping and imputation

Genotyping, quality control, data cleaning and imputation were performed independently in each study using different genetic platforms and software as outlined in **Supplementary Table 3**. In all studies, genotyping was performed using either Illumina, Affymetrix, or Perlegen genotyping arrays. Genotype data from each study had been imputed to the HapMap phase 2 reference panel [15] , except for JUPITER which was imputed to the 1000genomes pilot data, using either MACH, Impute, or BIMBAM software [16-18], resulting in a total of approximately 2.5 million SNPs for analysis.

GWAS analysis

Each study independently performed the GWAS on the difference between natural log-transformed on- and off-treatment HDL-C levels, according to a common, central analysis protocol. To reduce confounding by possible association with off-treatment HDL-C levels, analyses were adjusted for the natural log-transformed off-treatment HDL-C levels. Linear regression was used, with SNPs represented by an additive genetic model and with imputed SNPs represented by expected allele dosage. Analyses were additionally adjusted for age, sex, and study specific covariates (e.g ancestry principal components (PCs), site, or country). FHS made use of a linear mixed effects model considering the kinship matrix in the analysis, hereby accounting for familial correlations within FHS.

Analyses in the observational studies were, if the information was available, additionally adjusted for the time interval between on- and off-treatment HDL-C measures (mean follow-up times per study are provided in **Supplementary Table 2**) and for the natural logarithm of the statin dose equivalent, as defined in **Supplementary Table 4**. This table shows the dose for different statins for the LDL-C response; dividing the statin dosage for an individual drug by its dose equivalent shown in **Supplementary Table 4** gives the standardized statin dosage.

Quality control and Meta-analysis

Within each study, SNPs with minor allele frequency <1% or imputation quality <0.3 were excluded from the analysis. QQ-plots were assessed for each study to check that there were no between study differences nor evidence for systematic bias within studies (**Supplementary Figure 1**). The software package METAL was used to perform the meta-analysis.[19] A fixed effects, inverse variance weighted approach was used. To correct for possible inflation of the test statistic, e.g. due to small amounts of potential population sub-structure, genomic control was performed by adjusting the within-study findings and the meta-analysis results for the genomic inflation factor.

Second stage

SNPs with p-values $<1x10^{-4}$ in the first stage meta-analyses were selected for further investigation in the second stage. A maximum of two SNPs per locus (with a maximum 100 kB distance between SNPs) were selected, with the choice based on statistical significance. A total of 123 SNPs in 83 loci were selected for the second stage, which was performed in the GoDARTS study, the JUPITER trial, and the RCT and observational arm of the ASCOT Scandinavia study. GWAS data and response to statin treatment were available for these studies. Analysis was performed as for the first stage. Results of the first and second stage were combined using a fixed effects, inverse variance weighted meta-analysis using METAL.

Interaction analysis

The interaction effect of the lead *CETP* SNP rs247616 with the binary treatment indicator for statin versus placebo allocation was assessed in five of the participating RCTs (ASCOT Scandinavia, ASCOT UK, CARDS, JUPITER, and PROSPER). For these analyses, placebo treated individuals in the RCTs were included. The total sample size was 17,857, with 8,978 statin treated individuals and 8,879 placebo treated individuals. Regression models were applied to the combined population of statin and placebo treated subjects by adding to the model extra terms including treatment (statin (=1) or placebo (=0)) allocation and the product of treatment allocation with SNP minor allele dose.[20] Interaction coefficients of the five studies were combined in a fixed effects, inverse variance weighted meta-analysis using METAL. In addition, we also performed our main analysis for the *CETP* SNP rs247616 in only the placebo users of the five RCTs included in the interaction analysis.

Effect of genetic determinants of HDL-C levels on statin-induced HDL-C response

We performed a look-up in our GWAS results for all known genome-wide significant genetic variants associated with HDL-C levels, obtained from the most recent Global Lipids Genetics Consortium (GLGC) paper.[11] Of the 80 variants, 78 were available in our GWAS on statin induced HDL-C response. Subsequently, we examined whether a multi-SNP genotypic risk score constructed from these GLGC variants was associated with the level of statin induced HDL-C response, using publicly available summary level data from the GLGC (http://csg.sph.umich.edu//abecasis/public/lipids2013/). The joint effect of the 78 genetic variants on statin-induced HDL-C response was examined by means of a data-driven inverse-variance weighted approach, described previously by Dastani *et al*,[21] and accomplished through the gtx-package[22] (Genetics ToolboX, http://cran.r-project.org/web/packages/gtx) in the R statistical software environment.[23] Analogous to deriving a pooled estimate from the results of individual studies in conventional meta-analysis, this approach combines the causal estimates of multiple genetic variants, defined as the ratio of their association with statin response to their association with HDL-C levels.

Conditional analysis

Conditional analysis were performed in two of the participating studies, ASCOT UK (both RCT and observational – genotype data available for n=3,804) and CARDS (genotype data available for n=1194). Conditional analysis was conducted within GCTA software[24], using the *–cojo* method, which performs conditional and joint analysis with model selection. The genome-wide meta-analysis summary statistics from the combined analysis of both first-stage and second-stage data were used as the input data. Analysis was restricted to chromosome 16, containing the only genome-wide significant result from the meta-analysis, in order to determine whether the *CETP* region contains more than one independent signal of association. Within the GCTA analysis, MAF was restricted to ≥1% and a p-value cut-off of $5x10^{-7}$ was used as the selection threshold. LD was calculated between pairwise SNPs, but any SNPs further than 10 Mb apart were assumed to be in linkage equilibrium.

Variance explained

Two secondary analyses were performed to investigate the heritability of this pharmacogenetic trait. Firstly, the genome-wide heritability was calculated in GCTA[24] by estimating h^2 using GREML analysis, according to all HapMap SNPs with MAF ≥ 1%, with reference to the genomic relatedness matrix generated within GCTA. Secondly, the percentage variance explained for the HDL-C response to statins adjusted for baseline HDL-C was calculated specifically for the lead *CETP* SNP rs247616 using R software[23] by including the dosage data for this SNP as a continuous predictor variable within the model. Firstly, the HDL-C response trait was regressed against all non-genetic covariates. The residuals from this model were used as the residual trait. In a second stage linear regression analysis the residual trait was regressed against the lead SNP and PCs. The R^2 calculated from this second fitted linear regression model was used to estimate the percentage of the trait variance explained. Both analyses were performed using the ASCOT-UK dataset, as individual level raw

genotype data are required. The combination of both the RCT and observational sub-cohorts of ASCOT-UK gave a total sample size of N = 2,055 statin-treated participants. The explained variance analysis in R was additionally performed in the CARDS study, including 1,194 statin-treated participants. The linear regression models used exactly the same data and covariates as from the primary GWAS analysis.

Results

First-stage meta-analysis

In the first stage of this analysis, six randomized controlled trials (n=8,506 statin recipients) and ten observational studies (n=8,263 statin recipients) were included (**Supplementary Notes 1 and 2** and **Supplementary Tables 1 and 2**). Three SNPs at the *CETP* locus (chromosome 16) were identified as genome-wide significant ($P<5x10^{-8}$) for their association with HDL-C response to statin treatment (**Figures 1 and 2** and **Table 1**). The most significant association was for SNP rs247616 (MAF=0.324, β=0.011, SE=0.002, $P=5.95x10^{-10}$) (**Figure 3**), indicating that carriers of the minor allele of this SNP respond to statins with a 1.1% greater per-allele increase in HDL-C compared with non-carriers. The average increase in HDL-C during statin treatment across all studies was 0.045 mmol/L. This additional 1.1% per-allele increase in HDL-C is equivalent to a 0.046 mmol/L increase for carriers of one copy of the CETP SNP. We found no other loci associated with HDL-C response to statin treatment at a genome-wide significant level at this first stage.

Second-stage meta-analysis

We selected 123 SNPs from 83 loci with $P<1x10^{-4}$ in the first stage meta-analysis for further investigation in the second stage, which included 10,951 statin-treated individuals from two RCTs and two observational studies (**Supplementary Note 3** and **Supplementary Tables 1 and 2**). The second stage meta-analysis confirmed the significant association between genetic variants within the *CETP* loci and HDL-C response from the first stage meta-analysis (rs247616: MAF=0.327, β=0.005, SE=0.001, $P=1.59x10^{-5}$) as $P<6x10^{-4}$, the Bonferroni p-value threshold for testing 123 SNPs (**Table 1**, **Figure 2**, and **Supplementary Table 5**). The combined effect from the first and second stage meta-analysis for the *CETP* rs247616 SNP was genome-wide significant (MAF=0.326, β=0.007, SE=0.001, $P=8.52x10^{-13}$) (**Table 1**, **Figure 2**, and **Supplementary Table 5**). No other locus reached statistical significance ($P<4x10^{-4}$) in the second stage meta-analysis or in the combined meta-analysis ($P<5x10^{-}$

[8]) for association with HDL-C response to statin treatment (**Figure 1** and **Supplementary Table 5**). Indeed, **Supplementary Table 5** (ordered by the combined meta-analysis p-values) shows that the three SNPs within *CETP* which were genome-wide significant in the first stage, were the only SNPs that reached Bonferroni significance in the second stage and genome-wide significance in the combined meta-analysis

Interaction analysis

To exclude the possibility of confounding in the association between *CETP* and HDL-C response to statin treatment, two analyses were performed. First the main analysis for the *CETP* SNP rs247616 was repeated in the placebo users using data from five of the participating RCTs. In addition, in the same studies we tested for interaction between the *CETP* lead SNP rs247616 and randomized statin or placebo allocation. **Supplementary Figure 2** shows the results for the association between HDL-C change during follow-up and rs247616 stratified for placebo and statin users. **Table 2** shows a significant P-value for interaction in the meta-analysis combining the five studies ($P\text{-}3.52x10^{-3}$, β=0.007, SE=0.002) for the *CETP* SNP, indicating that genetic effects of *CETP* on baseline HDL-C contribute at most only in part to genetic effects on HDL-C response in the statin-treated group, as the genetic effect is modified by the use of statin treatment.

Effect of genetic determinants of HDL-C levels on statin-induced HDL-C response

SNPs previously shown to be associated with HDL-C levels (n=78)[11] were assessed for their association with statin-induced HDL-C response in our meta-analysis. After Bonferroni correction, rs3764261 (*CETP)* was the sole genetic variant associated with statin-induced HDL-C response amongst the 78 examined variants (**Supplementary Table 5**). Joint analysis of the HDL-C associated variants demonstrated that predisposition to high HDL-C levels is associated with increased statin-induced HDL-C response (**Figure 4**). This amounted to a 2.9% fractional increase (β=0.029, SE=0.003, $P=1x10^{-19}$) in statin-induced HDL-C response per SD increase in genetically raised HDL-C levels.

Excluding the *CETP* SNP (rs3764261) from the model did not materially change the results (β=0.029, SE=0.005, P=1x10^{-8}). Testing for heterogeneity did not reveal any indication of pleiotropic effects(P=0.64).

Conditional analysis

The conditional analysis within GCTA resulted in only one remaining SNP selected in the model, namely the lead SNP rs247616 within the *CETP* locus, with a joint p-value of 9.96x10^{-10} and joint β=0.0104, equal to its unconditional effect size estimate. As can be seen from the locus zoom plot in **Figure 3**, the other two genome-wide significant hits are in high LD with the lead SNP, and after conditioning on the lead SNP, the GCTA conditional analysis results show that no other SNPs within chromosome 16 have significant residual association, with the minimum conditional p-value being p~3x10^{-5}. Hence we conclude that there is only one independent signal within the *CETP* association.

Variance explained

From genome-wide data of the ASCOT-UK datasets, the trait heritability for HDL-C response to statins was estimated as h^2 = 17.8% (SE = 0.154) although this was non-significant (p=0.125). There was insufficient power to run the GCTA analysis in the CARDS dataset, due to smaller sample size. The trait variance explained by the lead *CETP* SNP rs247616 alone was calculated to be 0.04% from ASCOT-UK and 0.01% from CARDS, both non-significant (p=0.38 and p=0.54, respectively).

Discussion

In this study we have performed a meta-analysis of GWAS including over 27,700 statin-treated individuals, investigating genetic variants associated with variation in HDL-C response to statin treatment. We identified three genetic variants in the *CETP* locus that were highly significantly associated with a larger HDL-C response to statin treatment. No other SNPs met the genome-wide criterion for association of HDL-C change with statin use.

CETP plays an important role in HDL-C metabolism by promoting the exchange of cholesteryl esters in HDL particles with triglycerides in apolipoprotein B-containing particles, leading to increased HDL catabolism and lower HDL-C levels. Increases in HDL-C levels after statin treatment are probably partly the result of a reduction in CETP mediated lipid transfer[25], as was also shown in mice expressing human CETP.[26] Statin treatment decreases CETP activity up to 30%.[27 ,28] Previously it has been shown that genetic variants within *CETP* are associated with differences in CETP concentration.[29] The three SNPs associated with HDL-C response to statins in the present study are located 2.5-7 kb upstream of the *CETP* gene and are in high linkage disequilibrium (**Figure 3**).[30] The minor alleles of these SNPs have been shown to be associated with lower *CETP* mRNA expression levels in liver tissue and with higher HDL-C levels.[30 ,31]

Previous studies investigating the association between SNPs in the *CETP* locus and the HDL-C response to statin treatment have yielded inconsistent results. Several studies showed associations with a greater HDL-C response [8 ,10], whereas others showed no significant associations.[12 ,32-34] These discrepancies could be explained by limited sample sizes and by the investigation of different genetic variants in these studies. An alternative explanation could be the fact that the effect of statins on HDL-C response is relatively small and depends on statin dose and type.[3 ,4] Since the power to detect genetic effects on these small variations is low in single studies, the results from the present large meta-analysis, with replication, provide strong evidence that genetic variation at the *CETP* locus is associated with HDL-C response.

The results of six randomized clinical trials and ten observational studies were combined in the first stage of the current study. Different statins were investigated in the trials and used within the observational studies, resulting in combining several types of statins in our analysis. This and the variation in statin dosages during follow-up for an individual are a limitation of the current study, since the pharmacogenetic impact might be dependent on specific statin types and dose. To address this possible limitation, the individual study analyses were adjusted for statin equivalent dose based on effect on LDL-C levels, making the different statin types likely more comparable with respect to clinical effectiveness on HDL-C levels. Combining RCTs and observational cohort might also result in heterogeneity between the study types. To reduce the possibility of large heterogeneity we aimed to mimic the design of a RCT in the observational studies, by including only new statin-users. Comparing heterogeneity of the RCTs and observational studies included in the first stage showed no evidence of large heterogeneity (p=0.761, data not shown).

Another possible limitation of the current study is the association of the identified genetic variant with baseline HDL-C concentration. As shown in previous large GWAS studies, the *CETP* SNP rs3764261 is strongly associated with HDL-C levels.[11 ,31] In pharmacogenetic studies investigating lipid responses to drug exposure, it is important to eliminate the effect of the association between baseline lipid levels and the investigated genetic variants.[13] To reduce the impact of these possible confounding effects, our response to treatment analyses were adjusted for baseline HDL-C levels. In addition, interaction analyses in five of the RCTs, with direct modeled comparison with a random assignment to a placebo group, suggested little or no influence of the association between the *CETP* SNPs and baseline HDL-C levels on the genetic effect on HDL-C response to statin treatment. It is, however, possible that mechanisms underlying the effects of CETP on HDL-C levels are also involved in mediating statin effects on HDL-C.

All genetic data in the current study was imputed to up to 2.5 million autosomal SNPs based on data from the HapMap project.[15] In addition, in our analysis we excluded genetic variants with a minor

allele frequency <1%, restricting our analysis to common genetic variants. Imputation based on the more recent 1000 Genomes project could reveal more associations with rare genetic variants.[35] Future studies using exome sequencing data and investigating rare variants may identify additional associations between genetic variants and statin-induced HDL-C response. However, the non-significant estimate of heritability attributable to common variation in our analysis may indicate that the observed increase in HDL-C levels after statin-treatment may be mainly due to environmental rather than genetic effects.

The implications of the present findings regarding genetic effects on the efficacy of statins for reductions in risk of CVD are uncertain. Based on the strong inverse relationship of HDL-C with CVD, the greater statin-induced increase in HDL-C among carriers of the minor vs. major alleles of the three *CETP* SNPs reported here may confer a greater protective effect of statins on CVD in patients carrying the minor allele. However, a recent study employing Mendelian randomization found that genotypes associated with plasma HDL-C levels were not associated with the impact on CVD risk that would be predicted by the magnitude of the genotypic effects on HDL-C.[7] Moreover, two large clinical trials have failed to show reduction of CVD events by nicotinic acid-induced increases in HDL-C in patients with well-controlled LDL-C levels.[36 ,37] Hence, whether greater genetically-mediated HDL-C increases with statin treatment confer increased protection from CVD remains unknown.

In conclusion, this study is the largest meta-analysis of GWAS for HDL-C response to statin treatment conducted to date. The findings suggest that *CETP* may be the only locus in which common genetic variants are significantly associated with a substantial HDL-C response to statin treatment in individuals of European descent.

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PARC

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TNT

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AGES

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Author contributions

Writing and analysis group: IP, HRW, ST, BJA, DIC, HAD, XL, RAJS, DIC, GKH, PBM, MJC, HMC, LAC, GH, CNAP, BMP, CMS, JWJ, JIR, RMK.

IP and ST performed quality control on the individual study summary results.

IP and ST performed meta-analysis.

IP, HRW, and RAJS performed additional analyses.

All analysis and writing group authors extensively discussed the analysis, results, interpretation and presentation of results.

All authors contributed to the research and reviewed the manuscript.

Study concept and design of contributing studies: (PROSPER) JWJ, DJS, BMB, IF, NS, RGJW; (ASCOT) MJC, PS, NP, AS, DCS, EO; (CARDS) HAD, HMC, PMM, JB, PND, AD, GH; (PARC) XL, YDIC, JIR, RMK; (TNT) JJPK; (AGES) LJL, TBH, VG; (ARIC) CLA, EAW, TS, EB, CMB; (BioVU) QF, WW, CMS, RAW, JCD; (CHS, HVH) NS, KR, TL, BMP; (FHS) LAC, VR; (HABC) SRC, YL; (MESA) XG, SRH, WP, JIR, SSR; (Rotterdam Study) CEK, BHS, AGU, AH, FR; (JUPITER) DIC, BJB, FN, PMR; (GoDARTS) CNAP, HMC.

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Figure legends

Figure 1. Results of the GWAS meta-analysis. Manhattan plot presenting the $-\log_{10}$ P-values from the combined stage 1 and 2 meta-analysis on HDL-C response to statin treatment. The top (red) line represents the genome-wide significant P-value $5x10^{-8}$, the second (blue) line represents the P-value $1x10^{-4}$, the threshold used for selecting SNPs to take forward to the second stage. Hence the results of these SNPs come from the lager combined meta-analysis, whereas all other results are taken from the stage 1 discovery meta-analysis.

Figure 2. Forest plot showing the association in each study and overall association of the lead *CETP* SNP rs247616 with HDL-C response to statin treatment. Beta represents fractional HDL-C change for each copy of the minor allele.

Figure 3. Regional association plot of the *CETP* region that was genome-wide significant for association with HDL-C response to statin treatment, using the results of the combined meta-analysis (generated using LocusZoom [39]). The color of each SNP is based on the LD (r^2) with the lead SNP rs247616 (shown in purple). The RefSeq genes in the region are shown in the lower panel.

Figure 4. Plot of the per-allele association of genetic variants with HDL-C levels (x-axis, per allele in SD units, as reported by Willer *et al.* [11]) against the association with HDL-C response to statin treatment (y-axis, percentage) (generated using [22]). The regression line shows the linear relationship between these two variables, with 95% confidence boundaries.

Table 1. Association of *CETP* SNP rs247616 (chromosome 16, bp 55547091) with HDL-C response after statin treatment in the stage 1, stage 2, and combined GWAS meta-analyses.

Phase	N	Coding allele	Non-coding allele	Frequency coding allele	Beta*	SE	% extra increase[#]	P-value
Stage 1	14693	T	C	0.324	0.011	0.002	1.1	5.95×10^{-10}
Stage 2	10961	T	C	0.327	0.005	0.001	0.5	1.59×10^{-5}
Combined	25654	T	C	0.326	0.007	0.001	0.7	8.52×10^{-13}

*Beta for difference between the natural log transformed on- and off-treatment HDL-C levels, adjusted for natural log transformed off-treatment HDL-C, age, sex, and study specific covariates. The beta reflects the fraction of differential HDL-C lowering in carriers vs. non-carriers of the SNP; a positive beta indicates a better statin response (larger HDL-C increase).

[#]This percentage reflects the % extra HDL-C increase in carriers vs. non-carriers of the SNP.

Table 2. Interaction between *CETP* rs247616 and statin vs. placebo allocation on HDL-C response. Meta-analysis of data from 5 RCTs.

SNP	N	Coding allele	Non-coding allele	Frequency coding allele	Interaction Beta	Interaction SE	Interaction P-value
rs247616	17857	T	C	0.341	0.007	0.002	3.52×10^{-3}

Interaction beta and SE refer to statistics from linear regression modelling the difference between the natural log transformed on- and of-treatment HDL-C levels adjusted for natural log transformed off-treatment HDL-C, age, sex, and study specific covariates, and including an interaction term between SNP and statin or placebo allocation. The interaction p-value refers to the significance of the SNP-by-statin or placebo allocation interaction term in the regression model.

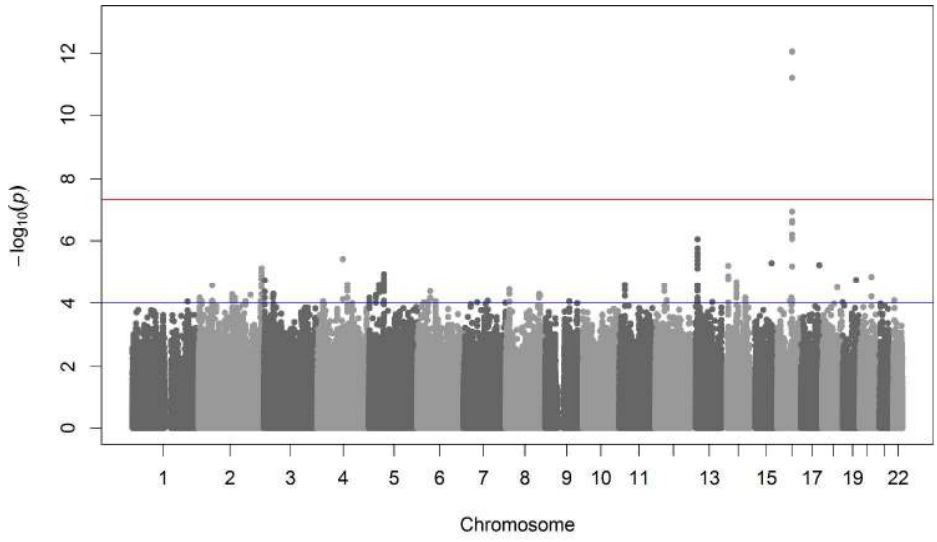

Figure 1. Results of the GWAS meta-analysis. Manhattan plot presenting the –log10 P-values from the combined stage 1 and 2 meta-analysis on HDL-C response to statin treatment. The top (red) line represents the genome-wide significant P-value 5x10-8, the second (blue) line represents the P-value 1x10-4, the threshold used for selecting SNPs to take forward to the second stage. Hence the results of these SNPs come from the lager combined meta-analysis, whereas all other results are taken from the stage 1 discovery meta-analysis.
Figure 1

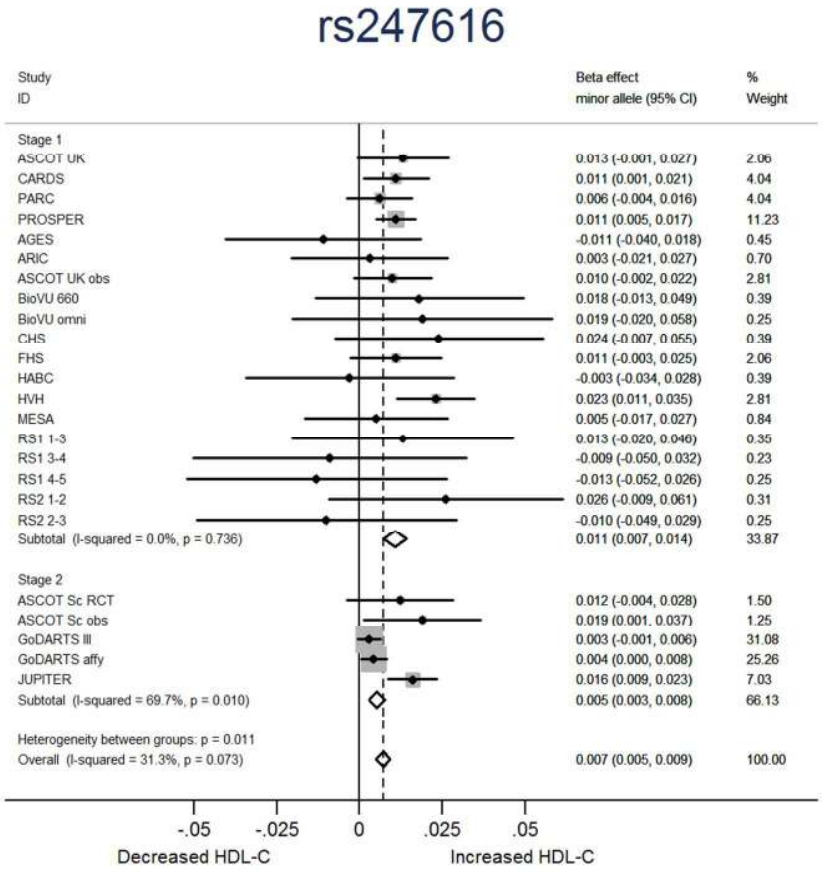

Figure 2. Forest plot showing the association in each study and overall association of the lead CETP SNP rs247616 with HDL-C response to statin treatment. Beta represents fractional HDL-C change for each copy of the minor allele.

Figure 2
384x372mm (72 x 72 DPI)

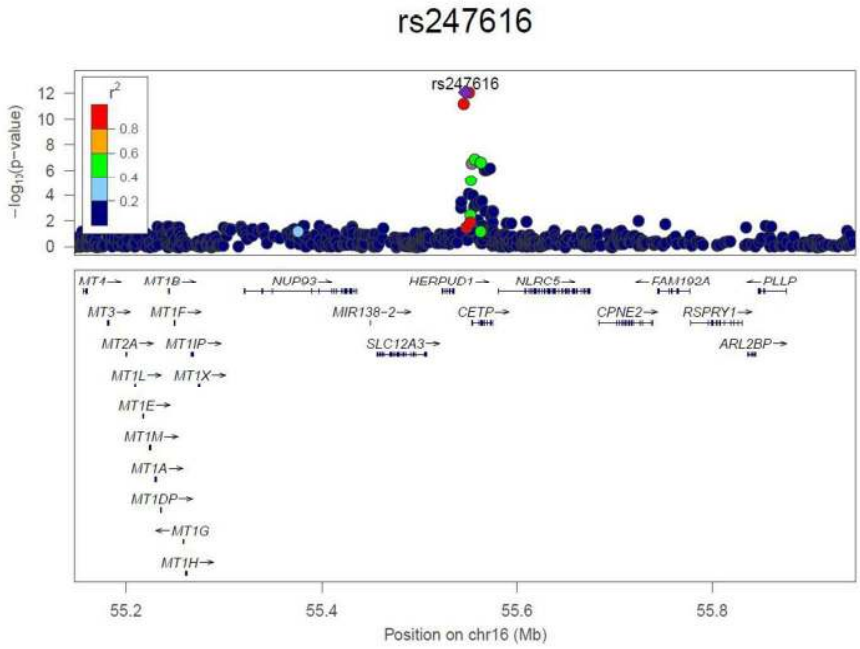

Figure 3. Regional association plot of the CETP region that was genome-wide significant for association with HDL-C response to statin treatment, using the results of the combined meta-analysis (generated using LocusZoom [39]). The color of each SNP is based on the LD (r2) with the lead SNP rs247616 (shown in purple). The RefSeq genes in the region are shown in the lower panel.

Figure 3
254x190mm (121 x 121 DPI)

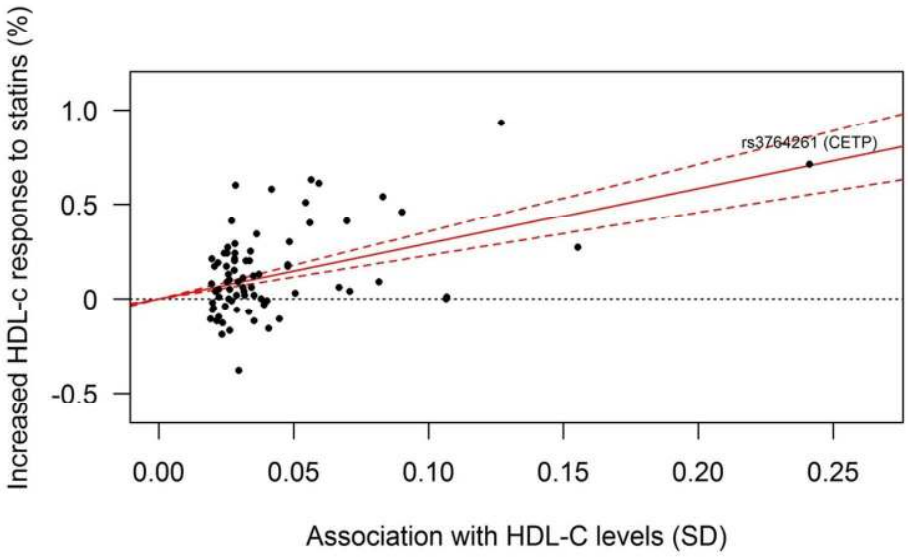

Figure 4. Plot of the per-allele association of genetic variants with HDL-C levels (x-axis, per allele in SD units, as reported by Willer et al. [11]) against the association with HDL-C response to statin treatment (y-axis, percentage) (generated using [22]). The regression line shows the linear relationship between these two variables, with 95% confidence boundaries.
Figure 4
101x67mm (300 x 300 DPI)

Supplementary information

Meta-analysis of genome-wide association studies of HDL cholesterol response to statins

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Table of Content

Supplementary Table 1: Participating study characteristics of the statin users only.

Study sample	Participants	Male, N (%)	Age*, mean ± SD	Age*, range	Body mass index, kg/m^2, mean ± SD	Diabetes, N (%)	Hypertension, N (%)
Randomized controlled trials	***N Overall***						
PROSPER	2550	1228 (48)	75.4 (3.4)	70.2-83.3	26.8 (4.1)	256 (10.0)	1592 (62.4)
ASCOT UK	978	864 (88)	64.0 (8.1)	41.0-90.0	29.1 (5.1)	215 (22.0)	978 (100.0)
CARDS	1194	632 (53)	61.6 (8.2)	40-76	28.7 (3.6)	1194 (100)	1038 (87)
PRINCE	1348	1040 (77.2)	64.8 (13.0)	26-100	29.0 (5.3)	271 (20.1)	551 (40.9) †
CAP	591	312 (52.8)	54.5 (12.6)	30-88	27.7 (5.5)	21 (3.6) ‡	108 (18.3) †
TNT	1845	1521 (82.4)	62.4 (8.4)	36.4-76.0	29.1 (4.7)	411 (22.3)	631 (34.2)
Observational studies	***N Overall***						
AGES	281	123 (43.8)	74.4 (4.8)	66-92	27.5 (4.1)	58 (20.6)	237 (84.3)
ARIC	1163	601 (52)	55 (5.3)	45-64	27.7 (4.6)	172 (14.8)	434 (37.6)
ASCOT UK	1067	894 (84)	63.4 (8.0)	40.0-80.0	29.1 (4.7)	244 (22.9)	1067 (100.0)
BioVU	435	231(53)	67.0 (14.5)	21-99	29.1 (5.8)	119 (27.4)	412 (94.7)
CHS	315	117 (37.1)	69.5 (3.1)**	65-87	26.6 (4.2)	23 (7.3)	91 (28.9)
FHS	1395	774 (55.5)	57 (9.9)	23-85	28.7 (5.1)	205 (14.7)	477 (34.2)
Health ABC	310	175 (56%)	73.4 (2.7)	69 - 80	27.2 (4.1)	60 (19%)	183 (59%)
HVH	1896	789 (41.6)	66.3 (9.5)**	32-89	31.0 (6.7)	428 (22.6)	1431 (75.5)
MESA	360	180 (50.0)	66.9 (9.3)	47-87	28.9 (5.4)	48 (13.4)	191 (53.1)
Rotterdam Study I	744	351 (47.2)	63.2 (5.0)	55.0-81.5	27.4 (3.9)	110 (14.8)	234 (31.5)
Rotterdam Study II	297	166 (55.9)	62.2 (5.5)	55.2-86.5	28.1 (3.9)	53 (17.8)	120 (41.0)
Second stage studies	***N Overall***						
ASCOT Scandinavia RCT	725	575 (79)	61.0 (8.8)	40.0-80.0	28.6 (5.0)	156 (21.5)	725 (100.0)
ASCOT Scandinavia observational	611	447 (73)	60.3 (8.5)	40.0-79.0	28.6 (4.2)	124 (20.3)	611 (100.0)
GoDARTS	6133	4293 (70)	66.0 (11.2)	40-95	30.6 (5.3)	6133 (100)	NA
JUPITER	3417	2346 (69)	65.9 (7.6)	50-93	29.5 (5.7)	12 (0.3)	1900 (55.6)

*Age at DNA collection

** Age at baseline

† Defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

‡ Defined as fasting glucose ≥126 mg/dl (diabetes on treatment were excluded from the trial).

Supplementary Table 2: High-density lipoprotein characteristics of the statin users only.

Study sample	Participants	Type of statin	Statin dose (mg/day)	HDL-C off-treatment (mmol/L) Mean ± SD	HDL-C on-treatment (mmol/L)* Mean ± SD	Follow-up time (months) Mean ± SD
RCTs	***N Overall***					
PROSPER	2550	Pravastatin	40	1.29 (0.36)	1.40 (0.38)	29.5 (9.2)
ASCOT UK	978	Atorvastatin	10	1.27 (0.33)	1.27 (0.33)	First year used
CARDS	1194	Atorvastatin	10	1.39 (0.31)	1.42 (0.39)	46.8 (4.7)
PRINCE	1348	Pravastatin	40	0.94 (0.26)	0.99 (0.27)	12 weeks
CAP	591	Simvastatin	40	1.38 (0.42)	1.44 (0.45)	6 weeks
TNT	1845	Atorvastatin	10	1.20 (0.26)	1.17 (0.26)	2.0 (0.2)
Observational studies	***N Overall***					
AGES	281	mixed	mixed	1.51 (0.42)	1.53 (0.44)	61.8 (2.5)
ARIC	1163	A, Ce, F, L, P, S, Ch	Not available	1.13 (0.34)	1.17 (0.34)	36.1 (3.1)
ASCOT UK	1067	A (N=775), F (N=9), P (N=28), R (N=11), S (N=244)	12.4 (7.5), 28.9 (20.3), 28.9 (12.2), 14.1 (9.7), 28.6 (14.0)	1.24 (0.33)	1.33 (0.35)	11.7 (4.3)
BioVU	435	A, S, F, P, L, R	5,10,20,40,80	1.29 (0.43)	1.29 (0.39)	108.6 (46.0)[1]
CHS	315	A, P, L, S, F, Ce	14.1 (8.5), 20.8 (9.3), 21.4 (8.9), 16.5 (10.6), 35.0 (23.7), 0.37 (0.08)	1.36 (0.34)	1.34 (0.36)	43.4 (43.2)[2]
FHS	1395	mixed	mixed	1.21 (0.36)	1.30 (0.38)	63.6 (22.8)
Health ABC	310	mixed	mixed	1.28 (0.37)	1.32 (0.37)	51.17 (17.22)
HVH	1896	A, P, L, S, R	34.6 (24.0), 20.8 (4.9), 33.5 (9.8), 36.7 (15.2), 20.0	1.31 (0.40)	1.33 (0.41)	3.6 (5.0)[2]
MESA	360	mixed	mixed	1.30 (0.36)	1.35 (0.41)	19.9 (3.2)
Rotterdam Study I	744	S (N=430), P (N=88), F (N=54), A (N=158), R (N=14)	18.3 (10.6), 21.8 (11.4), 33.3 (17.8), 16.6 (9.3), 7.9 (4.3)	1.30 (0.30)	1.40 (0.40)	71.4 (11.0)[3] 125.1 (53.7)[4]
Rotterdam Study II	297	S (N=166), P (N=32), F (N=7), A (N=70), R (N=22)	20.7 (6.3), 31.3 (11.8), 62.9 (49.6), 17.6 (9.8), 9.3 (4.2)	1.30 (0.30)	1.40 (0.30)	64.6 (14.7)[3] 92.7 (38.5)[4]
Second stage studies	***N Overall***					
ASCOT SC RCT	725	Atorvastatin	10	1.33 (0.38)	1.32 (0.36)	First year used
ASCOT SC observational	611	A (N=458), F (N=11), L (N=4), R (N=12), S (N=126)	13.4 (8.3), 56.4 (23.4), 40.0 (28.3), 10.1 (4.3), 25.4 (14.0)	1.27 (0.37)	1.33 (0.38)	10.8 (4.3)
GoDARTS	6133	mixed	mixed	1.33 (0.35)	1.44 (0.38)	49.6 (12)
JUPITER	3417	Rosuvastatin	20	1.40 (0.40)	1.44 (0.42)	12 months

*Mean of multiple on-treatment measurements

[1]Median HDL within 18 months after treatment used for analysis. [2]Case-Control and cohort studies - time listed is time from statin initiation to HDL measurement. [3]Mean time between off- and on-treatment HDL-C measurement. [4]Mean time between start RS and on-treatment HDL-C measurement.

Abbreviations: A, Atorvastatin; Ce, Cerivastatin; F, Fluvastatin; L, Lovastatin; P, Pravastatin; S, Simvastatin; Ch, Cholestin; R, Rosuvastatin

Supplementary Table 3: Genotyping characteristics

Study sample	Participants	Genotyping platform	Calling algorithm	NCBI build	Imputation software	Analysis software	Exclusion criteria used
RCTs	***N Overall***						
PROSPER	2550	Illumina Human 660_Quadv1	Beadstudio	36.22	MACH v1.0 16	ProbABEL	Sample call rate>=97.5%, SNP call rate >=98%, SNP MAF>0.01
ASCOT UK	978	Illumina Human 370CNV	Beadstudio	36.22	MACH v1.0 16	ProbABEL	Sample call rate <=95%, SNP call rate <=97%, HWE<=10E-7, relatedness
CARDS	1194	Perlegen 6	Perlegen 6	36.22	Impute2	SNPTEST	Sample call rate>=98% SNP call rate>=98% MAF>0.01
PRINCE	1348	Illumina Human 317K and 610_Quad	Illumina	36.23	Bimbam v0.99	SNPTEST	Imputation information>0.30, SNP MAF>0.01
CAP	591	Illumina Human 317K and 610_Quad	Illumina	36.23	Bimbam v0.99	SNPTEST	Imputation information>0.30, SNP MAF>0.01
TNT	1845	Perlegen 322K	Perlegen	36.3	IMPUTE 2 v2.1.0, GTOOL v 0.6.6	Plink v 1.07	Sample call rate>=98%, SNP call rate >=98%
Observational	***N Overall***						
AGES	281	Illumina HU370CNV	Beadstudio	36	MACH v1.0 16	ProbABEL	Pre imputation exclusions: MAF >0.01, HWE p 10-6, callrate 0.97. Call rate 0.95
ARIC	1163	Affymetrix 6.0	Birdseed	36	MACH v1.0.16	ProbABEL	MAF <1%, call rate <95%, HWE<10E-5
ASCOT UK	1067	Illumina Human 370CNV	Beadstudio	36.22	MACH v1.0 16	ProbABEL	Sample call rate <=95%, SNP call rate <=97%, HWE<=10E-7, relatedness
BioVu	435	Illumina 660K, Illumina OMNI	Illumina	36(660K), 37.1(OMNI)	MACH v1.0.16	R	Sample call rate>=98%, SNP call rate >=98%, SNP MAF>0.01
CHS	315	Illumina Human 370CNV	BeadStudio	36	BIMBAM	R	Samples excluded for sex mismatch, discordance with prior genotyping, or call rate < 95% SNPs excluded for: call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap.
FHS	1395	Affymetrix 250K Sty, 250K Nsp & MIPS 50K	BRLMM	36.22	MACH v1.0.15	R 2.6.1 with	Sample call rate ≤ 97%, SNP call rate ≤ 95%, SNP >1000 Mendelian errors,

Study sample	Participants	Genotyping platform	Calling algorithm	NCBI build	Imputation software	Analysis software	Exclusion criteria used
		Gene Centric				Imekin	Heterozygosity 5 SD from Mean (<25.758% or >29.958%)
Health ABC	310	Illumina Human1M-Duo BeadChip	BeadStudio	36.22	MACH v1.0.16	R	Sample call rate>=97%, SNP call rate >=97%, SNP MAF>0.01
HVH	1896	Illumina Human 370CNV	BeadStudio	36	BIMBAM	R	Samples excluded for sex mismatch or call rate < 95%. SNP exclusions: call rate < 97%, HWE P < 10^{-5}, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap, inconsistencies across genotyping batches.
MESA	360	Affymetrix Genome-Wide Human SNP Array 6.0	Affymetrix	36.24	IMPUTE v2.1.0	SNPTEST	SNP call rate >=95%, Imputation information>0.30, SNP MAF>0.01
Rotterdam Study	1041	Illumina HumanHap 550K	Illumina GenomeStudio	36.22	MACH v1.0.15	ProbABEL	Call rate <98%, HWE P<10^{-6}, or MAF<1%
Second stage							
ASCOT SC	RCT: 725 OBS: 611	Illumina Human Omni Exome Express v8.1	BeadStudio, followed by zCall	37	MACH v1.0.18	R	GWAS: Exclude samples with: Discrepant sex, repeat samples, <95% genotyping success rate. Excluded SNPs with: <0.5% MAF, <95% call rate, HWE p<$5x10^{-7}$
GoDARTS	6133	Affymatrix 6.0, Human Omni Express	CHIAMO, Illumina	37	IMPUTE	SNPTEST	Standard GWAS criteria
JUPITER	3417	Illumina Omni Quad 1M	Illumina GenomeStudio	36	MACH v1.0.16	R	Sample call rate < 90%, SNP call rate <98%

Supplementary Table 4: Statin dose adjustments in observational studies, based on a modified version of a table in Drugs 1998; 56: Suppl 1: 25-31[1].

Statin	Dose range (mg)	Typical starting dose (PDR)	Dose % equivalent	Reduction LDL (%)	Reduction TC (%)
Atorvastatin	10-80	10-20	10	35	29
Cerivastatin	0.2-0.4	0.2-0.3	0.3	30	-
Fluvastatin	10-80	40	60	31	23
Lovastatin	10-80	20	40	32	23
Pravastatin	10-40	40	40	30	25
Simvastatin	10-80	20-40	20	36	28
Rosuvastatin	5-40	10	5	45	33
Pitavastatin	2-4	2	2	37	-

Supplementary table 5: First stage, second stage, and combined results of all SNPs investigated in the second stage.

					Stage 1					Stage 2					Combined				
SNP	CHR	position	A1	A2	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	StdErr	P-value	N
rs247616	16	55,547,091	t	c	0.324	0.0106	0.0017	5.95E-10	14693	0.327	0.0053	0.0012	1.59E-05	10961	0.326	0.0071	0.0010	8.52E-13	25654
rs3764261	16	55,550,825	a	c	0.324	0.0105	0.0017	8.61E-10	14695	0.330	0.0053	0.0012	1.28E-05	10990	0.328	0.0071	0.0010	8.82E-13	25685
rs173539	16	55,545,545	t	c	0.326	0.0105	0.0018	6.94E-09	14161	0.325	0.0054	0.0012	1.48E-05	10814	0.325	0.0071	0.0010	5.90E-12	24975
rs12916361	15	79,025,100	t	c	0.912	0.0143	0.0032	9.10E-06	14318	0.931	0.0102	0.0103	3.24E-01	4854	0.914	0.0139	0.0031	5.11E-06	19172
rs5112	19	50,122,120	c	g	0.441	-0.0104	0.0025	3.61E-05	12805	0.451	-0.0089	0.0081	2.74E-01	1331	0.442	-0.0103	0.0024	1.73E-05	14136
rs1445311	12	33,171,126	t	c	0.933	-0.0116	0.0028	3.89E-05	16520	0.935	-0.0046	0.0023	4.24E-02	11063	0.934	-0.0074	0.0018	2.89E-05	27583
rs7973897	12	33,173,955	t	c	0.936	-0.0119	0.0029	4.61E-05	16524	0.935	-0.0045	0.0023	4.63E-02	11063	0.935	-0.0073	0.0018	4.15E-05	27587
rs17330251	4	94,500,553	t	g	0.082	-0.0136	0.0031	1.32E-05	12774	0.081	-0.0039	0.0027	1.48E-01	7933	0.082	-0.0080	0.0020	7.64E-05	20707
rs1560694	19	6,218,827	a	g	0.403	0.0066	0.0016	4.20E-05	14641	0.411	0.0020	0.0011	7.42E-02	11049	0.409	0.0036	0.0009	1.22E-04	25690
rs9912353	17	53,222,039	a	c	0.859	0.0095	0.0024	8.47E-05	14696	0.864	0.0034	0.0021	1.06E-01	7986	0.861	0.0061	0.0016	1.28E-04	22682
rs3751413	13	112,902,716	t	c	0.796	0.0086	0.0021	4.77E-05	12758	0.766	0.0019	0.0036	6.03E-01	4854	0.788	0.0069	0.0018	1.39E-04	17612
rs7557776	2	33,431,296	a	g	0.072	-0.0128	0.0032	7.13E-05	14695	0.060	-0.0041	0.0025	9.18E-02	10848	0.064	-0.0074	0.0020	1.61E-04	25543
rs1378394	3	35,450,087	t	c	0.924	0.0119	0.0029	4.61E-05	14697	0.933	0.0035	0.0023	1.17E-01	11018	0.929	0.0067	0.0018	1.73E-04	25715
rs12421631	11	100,709,979	a	g	0.688	-0.0071	0.0018	8.97E-05	14603	0.653	-0.0019	0.0031	5.46E-01	4854	0.679	-0.0058	0.0016	1.97E-04	19457
rs6424961	1	182,875,556	a	t	0.957	0.0297	0.0072	4.20E-05	10268	0.946	0.0059	0.0093	5.23E-01	4854	0.953	0.0208	0.0057	2.58E-04	15122
rs1186925	5	57,230,380	t	g	0.058	-0.0164	0.0041	7.13E-05	12758	0.013	-0.0033	0.0057	5.65E-01	7202	0.043	-0.0119	0.0033	3.40E-04	19960
rs10132919	14	55,013,890	t	c	0.884	-0.0106	0.0025	2.55E-05	14695	0.889	-0.0024	0.0018	1.73E-01	11051	0.887	-0.0052	0.0015	3.43E-04	25746
rs17577246	4	68,420,188	a	g	0.204	-0.0089	0.0020	9.92E-06	14694	0.184	-0.0011	0.0021	6.05E-01	7679	0.194	-0.0051	0.0014	3.64E-04	22373
rs17116225	15	23,617,694	t	c	0.962	0.0225	0.0047	2.00E-06	12758	0.967	0.0032	0.0033	3.36E-01	7495	0.965	0.0097	0.0027	3.74E-04	20253
rs243874	20	13,019,871	a	c	0.242	0.0100	0.0023	1.58E-05	14562	0.259	-0.0017	0.0040	6.69E-01	4854	0.246	0.0071	0.0020	3.74E-04	19416
rs2791634	2	125,426,327	a	c	0.478	0.0076	0.0017	9.03E-06	12757	0.485	0.0015	0.0011	1.87E-01	11038	0.483	0.0033	0.0009	3.74E-04	23795
rs2595427	11	6,808,473	a	t	0.721	-0.0077	0.0019	5.72E-05	14693	0.714	0.0001	0.0035	9.85E-01	4854	0.720	-0.0059	0.0017	3.89E-04	19547
rs1229470	7	81,381,822	a	g	0.134	0.0121	0.0030	6.20E-05	11120	0.147	0.0032	0.0020	1.22E-01	7986	0.143	0.0060	0.0017	3.92E-04	19106
rs2602647	2	125,380,491	a	g	0.486	0.0076	0.0017	9.03E-06	12758	0.478	0.0014	0.0011	2.09E-01	10958	0.481	0.0033	0.0009	4.42E-04	23716
rs11834039	12	41,320,636	t	g	0.161	-0.0087	0.0021	3.89E-05	14697	0.161	-0.0020	0.0015	1.92E-01	11058	0.161	-0.0043	0.0012	5.02E-04	25755

					Stage 1					Stage 2					Combined				
SNP	CHR	position	A1	A2	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	StdErr	P-value	N
rs17033144	3	35,427,890	a	g	0.078	-0.0122	0.0030	5.39E-05	14696	0.065	-0.0028	0.0023	2.20E-01	11035	0.070	-0.0063	0.0018	5.57E-04	25731
rs6952465	7	150,522,574	a	g	0.957	-0.0174	0.0043	5.87E-05	10493	0.957	-0.0039	0.0037	2.94E-01	7986	0.957	-0.0096	0.0028	6.01E-04	18479
rs12861586	13	41,808,464	a	c	0.090	-0.0128	0.0031	4.13E-05	12433	0.089	-0.0028	0.0020	1.63E-01	10805	0.090	-0.0058	0.0017	6.08E-04	23238
rs11181609	12	41,325,764	t	c	0.841	0.0091	0.0022	4.00E-05	14697	0.839	0.0020	0.0015	1.96E-01	11043	0.839	0.0043	0.0012	6.49E-04	25740
rs946066	14	55,002,625	a	c	0.117	0.0108	0.0025	1.79E-05	14689	0.109	0.0018	0.0018	3.12E-01	11038	0.112	0.0049	0.0015	7.81E-04	25727
rs302567	6	39,759,450	a	g	0.064	0.0123	0.0029	2.54E-05	16536	0.056	0.0020	0.0024	4.06E-01	11061	0.059	0.0062	0.0019	8.19E-04	27597
rs2446644	6	39,734,657	a	t	0.064	0.0123	0.0029	2.54E-05	16530	0.056	0.0019	0.0024	4.19E-01	11063	0.059	0.0062	0.0018	8.74E-04	27593
rs6552126	4	68,421,259	t	g	0.792	0.0085	0.0019	8.90E-06	14697	0.805	0.0002	0.0020	9.30E-01	7767	0.798	0.0046	0.0014	9.24E-04	22464
rs11886534	2	3,815,178	a	g	0.570	0.0063	0.0016	9.23E-05	14636	0.575	0.0014	0.0011	2.26E-01	11021	0.573	0.0031	0.0009	1.05E-03	25657
rs7130440	11	110,922,989	a	g	0.627	-0.0069	0.0017	5.57E-05	12758	0.638	-0.0014	0.0012	2.39E-01	10947	0.634	-0.0032	0.0010	1.05E-03	23705
rs12283768	11	74,130,306	t	g	0.037	0.0156	0.0039	7.13E-05	16509	0.034	0.0031	0.0031	3.26E-01	11026	0.035	0.0080	0.0024	1.09E-03	27535
rs17507421	2	3,815,450	a	g	0.582	0.0063	0.0016	9.23E-05	14639	0.582	0.0014	0.0011	2.37E-01	11008	0.582	0.0030	0.0009	1.13E-03	25647
rs4906637	15	23,643,990	t	c	0.945	0.0156	0.0038	4.57E-05	14160	0.944	0.0029	0.0025	2.42E-01	10985	0.944	0.0067	0.0021	1.23E-03	25145
rs1444212	3	3,875,591	a	g	0.636	-0.0071	0.0016	1.05E-05	14643	0.641	-0.0009	0.0012	4.57E-01	11049	0.639	-0.0030	0.0009	1.29E-03	25692
rs10134660	14	88,578,272	t	c	0.806	-0.0076	0.0019	7.13E-05	14697	0.791	-0.0014	0.0014	2.96E-01	11043	0.796	-0.0036	0.0011	1.38E-03	25740
rs13355303	5	100,939,572	t	c	0.782	-0.0081	0.0020	5.78E-05	14670	0.802	-0.0014	0.0014	3.11E-01	11061	0.796	-0.0037	0.0012	1.55E-03	25731
rs17274136	4	94,610,507	a	g	0.161	-0.0100	0.0023	1.58E-05	14642	0.135	-0.0005	0.0022	8.15E-01	7826	0.147	-0.0049	0.0016	1.66E-03	22468
rs12500707	4	183,396,389	a	g	0.327	-0.0079	0.0019	3.65E-05	12175	0.329	-0.0009	0.0016	5.75E-01	7930	0.328	-0.0038	0.0012	1.87E-03	20105
rs897266	8	13,269,177	a	g	0.582	0.0059	0.0014	2.85E-05	16483	0.582	0.0006	0.0011	5.87E-01	11021	0.582	0.0027	0.0009	2.04E-03	27504
rs12290339	11	74,138,810	a	g	0.031	0.0176	0.0044	7.13E-05	16514	0.034	0.0029	0.0031	3.52E-01	11040	0.033	0.0078	0.0025	2.17E-03	27554
rs983884	5	146,219,161	t	g	0.119	0.0087	0.0021	3.89E-05	16531	0.109	0.0008	0.0018	6.54E-01	11057	0.114	0.0042	0.0014	2.30E-03	27588
rs11151789	18	68,526,072	a	c	0.307	-0.0067	0.0017	9.09E-05	14641	0.305	-0.0011	0.0012	3.77E-01	10930	0.306	-0.0031	0.0010	2.36E-03	25571
rs11723806	4	26,692,841	c	g	0.350	0.0072	0.0018	7.13E-05	14679	0.314	-0.0041	0.0035	2.44E-01	4854	0.342	0.0049	0.0016	2.38E-03	19533
rs501955	2	134,984,330	a	c	0.354	0.0063	0.0016	9.23E-05	14641	0.327	0.0009	0.0012	4.46E-01	10973	0.337	0.0029	0.0010	2.74E-03	25614
rs13265604	8	13,572,172	t	c	0.831	0.0092	0.0022	3.29E-05	14652	0.845	0.0010	0.0016	5.37E-01	10955	0.840	0.0037	0.0013	3.37E-03	25607
rs622418	9	89,775,863	a	g	0.507	-0.0072	0.0017	2.60E-05	12757	0.490	-0.0003	0.0015	8.50E-01	7862	0.497	-0.0032	0.0011	3.78E-03	20619
rs10518102	4	73,487,738	t	g	0.057	-0.0131	0.0033	8.08E-05	14697	0.061	-0.0016	0.0024	4.87E-01	11063	0.060	-0.0055	0.0019	4.04E-03	25760

					Stage 1					Stage 2					Combined				
SNP	CHR	position	A1	A2	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	StdErr	P-value	N
rs8181581	11	20,949,701	t	c	0.085	-0.0124	0.0029	2.18E-05	14697	0.083	-0.0010	0.0020	6.18E-01	11051	0.083	-0.0048	0.0017	4.12E-03	25748
rs13134793	4	181,685,248	t	c	0.961	0.0163	0.0041	7.89E-05	14696	0.953	0.0022	0.0027	4.08E-01	11063	0.956	0.0064	0.0022	4.18E-03	25759
rs2963078	5	146,225,801	t	c	0.882	-0.0089	0.0022	5.89E-05	16519	0.890	-0.0007	0.0018	7.13E-01	11063	0.887	-0.0040	0.0014	4.27E-03	27582
rs7960253	12	128,585,576	t	c	0.847	0.0088	0.0022	7.13E-05	14697	0.850	0.0010	0.0016	5.44E-01	11047	0.849	0.0036	0.0013	4.61E-03	25744
rs9511450	13	24,273,026	a	g	0.701	-0.0074	0.0015	9.64E-07	15999	0.720	0.0005	0.0013	6.64E-01	11060	0.712	-0.0027	0.0010	4.73E-03	27059
rs2335478	7	157,763,026	a	g	0.055	0.0175	0.0044	7.83E-05	11290	0.046	0.0022	0.0028	4.41E-01	10728	0.049	0.0066	0.0024	5.23E-03	22018
rs7074609	10	123,176,624	t	c	0.653	0.0069	0.0017	5.57E-05	14643	0.655	0.0007	0.0012	5.69E-01	11057	0.654	0.0027	0.0010	5.38E-03	25700
rs4909170	7	157,781,459	t	c	0.039	0.0169	0.0043	9.51E-05	13504	0.042	0.0020	0.0028	4.83E-01	11057	0.041	0.0064	0.0023	6.26E-03	24561
rs11626215	14	94,365,382	t	c	0.645	-0.0067	0.0017	9.09E-05	14668	0.632	-0.0002	0.0015	9.05E-01	7986	0.637	-0.0030	0.0011	7.33E-03	22654
rs11025857	11	20,963,785	t	g	0.084	-0.0128	0.0030	2.27E-05	14697	0.082	-0.0006	0.0021	7.52E-01	11056	0.083	-0.0045	0.0017	7.52E-03	25753
rs9507417	13	24,299,909	t	c	0.715	-0.0070	0.0015	3.59E-06	16532	0.719	0.0006	0.0013	6.47E-01	11027	0.718	-0.0025	0.0010	8.31E-03	27559
rs1051942	5	38,971,001	a	t	0.172	0.0090	0.0021	2.08E-05	14696	0.169	0.0003	0.0015	8.64E-01	11030	0.170	0.0032	0.0012	8.61E-03	25726
rs1488455	3	3,844,513	a	t	0.334	0.0071	0.0017	3.37E-05	14643	0.331	0.0003	0.0012	8.12E-01	10888	0.332	0.0026	0.0010	8.66E-03	25531
rs7506639	18	5,819,190	t	c	0.344	-0.0074	0.0017	1.54E-05	14641	0.348	-0.0002	0.0012	8.81E-01	10962	0.347	-0.0026	0.0010	8.85E-03	25603
rs10886934	10	123,170,221	a	g	0.247	-0.0075	0.0019	8.87E-05	14163	0.244	-0.0005	0.0013	6.80E-01	11054	0.245	-0.0028	0.0011	9.95E-03	25217
rs1559474	2	50,766,521	a	g	0.220	0.0072	0.0017	2.60E-05	16522	0.237	-0.0001	0.0013	9.39E-01	11051	0.230	0.0027	0.0010	1.10E-02	27573
rs264011	1	45,233,419	a	g	0.573	0.0060	0.0015	7.13E-05	16443	0.578	0.0001	0.0012	9.64E-01	10748	0.576	0.0023	0.0009	1.30E-02	27191
rs10060696	5	39,044,888	a	g	0.834	-0.0087	0.0021	3.89E-05	14697	0.830	-0.0001	0.0015	9.25E-01	11055	0.831	-0.0030	0.0012	1.34E-02	25752
rs4432938	5	2,157,506	a	t	0.476	0.0063	0.0016	9.23E-05	14108	0.473	0.0003	0.0011	8.11E-01	10987	0.474	0.0023	0.0009	1.35E-02	25095
rs11702628	21	21,205,295	t	c	0.514	-0.0065	0.0016	5.48E-05	14643	0.501	0.0007	0.0015	6.62E-01	7873	0.507	-0.0027	0.0011	1.41E-02	22516
rs2187488	8	123,435,673	t	c	0.475	-0.0063	0.0014	7.88E-06	16469	0.470	0.0006	0.0011	6.01E-01	11056	0.472	-0.0021	0.0009	1.59E-02	27525
rs4797232	18	5,822,745	t	c	0.649	0.0073	0.0017	2.01E-05	14640	0.648	-0.0001	0.0012	9.07E-01	10894	0.648	0.0023	0.0010	1.78E-02	25534
rs171500	20	13,018,489	a	g	0.312	0.0067	0.0017	9.09E-05	14634	0.263	-0.0002	0.0014	8.69E-01	11060	0.283	0.0025	0.0011	1.92E-02	25694
rs2822884	21	15,037,883	t	c	0.779	-0.0079	0.0019	3.65E-05	14696	0.719	0.0000	0.0013	9.99E-01	11063	0.738	-0.0025	0.0011	2.00E-02	25759
rs7565375	2	174,405,548	a	c	0.570	-0.0063	0.0016	9.23E-05	14639	0.563	0.0000	0.0011	9.93E-01	10994	0.565	-0.0021	0.0009	2.20E-02	25633
rs1316566	12	93,647,288	a	g	0.372	0.0066	0.0016	4.20E-05	14643	0.372	-0.0013	0.0016	3.96E-01	7930	0.372	0.0026	0.0011	2.23E-02	22573
rs10901371	10	126,933,686	a	g	0.628	0.0063	0.0016	9.23E-05	14642	0.627	-0.0001	0.0012	9.23E-01	10811	0.628	0.0022	0.0010	2.28E-02	25453

					Stage 1					Stage 2					Combined				
SNP	CHR	position	A1	A2	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	StdErr	P-value	N
rs17299838	22	24,908,221	c	g	0.880	-0.0103	0.0026	8.36E-05	14647	0.920	0.0007	0.0022	7.37E-01	10830	0.904	-0.0038	0.0017	2.29E-02	25477
rs10187654	2	234,478,798	t	c	0.200	0.0079	0.0018	1.31E-05	16526	0.190	-0.0009	0.0014	5.47E-01	11047	0.194	0.0026	0.0011	2.31E-02	27573
rs2708027	12	86,694,952	a	c	0.626	0.0056	0.0014	7.13E-05	16487	0.612	-0.0004	0.0012	7.24E-01	11062	0.618	0.0020	0.0009	2.32E-02	27549
rs698842	2	50,743,600	a	t	0.226	0.0081	0.0019	2.30E-05	14695	0.239	-0.0003	0.0013	8.40E-01	11047	0.235	0.0025	0.0011	2.35E-02	25742
rs2247050	12	86,694,771	t	c	0.626	0.0055	0.0014	9.58E-05	16480	0.612	-0.0004	0.0012	7.32E-01	11062	0.618	0.0020	0.0009	2.56E-02	27542
rs17045203	2	53,848,324	t	c	0.063	0.0135	0.0033	4.86E-05	14697	0.059	-0.0005	0.0024	8.45E-01	11061	0.060	0.0043	0.0019	2.58E-02	25758
rs12463008	19	49,598,068	a	c	0.947	-0.0157	0.0040	9.72E-05	12448	0.953	0.0000	0.0028	1.00E+00	10833	0.951	-0.0051	0.0023	2.59E-02	23281
rs11710922	3	33,997,987	a	t	0.928	0.0126	0.0032	9.23E-05	14680	0.930	-0.0001	0.0022	9.65E-01	11054	0.929	0.0041	0.0018	2.66E-02	25734
rs9458393	6	162,175,525	t	g	0.402	0.0068	0.0017	7.13E-05	14636	0.390	0.0000	0.0011	9.74E-01	11062	0.394	0.0021	0.0009	2.74E-02	25698
rs1965629	2	234,489,470	a	g	0.803	-0.0087	0.0020	1.56E-05	14697	0.809	0.0007	0.0014	6.10E-01	11055	0.807	-0.0025	0.0012	3.32E-02	25752
rs3843917	6	154,682,502	c	g	0.638	0.0070	0.0017	4.34E-05	14684	0.629	-0.0003	0.0012	8.17E-01	11017	0.632	0.0020	0.0010	3.37E-02	25701
rs831652	5	56,536,183	t	c	0.718	0.0078	0.0018	1.69E-05	14678	0.734	-0.0006	0.0013	6.47E-01	11060	0.729	0.0022	0.0010	3.40E-02	25738
rs9944321	16	64,959,463	a	g	0.039	-0.0310	0.0072	1.91E-05	9152	0.018	0.0010	0.0046	8.21E-01	10695	0.024	-0.0082	0.0039	3.42E-02	19847
rs2287340	2	53,846,363	t	g	0.937	-0.0129	0.0032	6.25E-05	14697	0.940	0.0008	0.0024	7.27E-01	11063	0.939	-0.0040	0.0019	3.45E-02	25760
rs6996401	8	123,417,419	a	g	0.526	0.0067	0.0016	3.21E-05	14643	0.530	-0.0005	0.0011	6.77E-01	11062	0.529	0.0019	0.0009	3.89E-02	25705
rs2822878	21	15,033,311	t	c	0.222	0.0079	0.0019	3.65E-05	14697	0.216	-0.0006	0.0014	6.42E-01	11033	0.218	0.0023	0.0011	4.02E-02	25730
rs187621	5	56,632,446	a	g	0.706	0.0074	0.0017	1.54E-05	14681	0.709	-0.0010	0.0012	4.19E-01	10921	0.708	0.0019	0.0010	5.47E-02	25602
rs1354037	3	195,069,994	t	c	0.114	0.0098	0.0025	9.92E-05	14693	0.117	-0.0007	0.0017	6.70E-01	10978	0.116	0.0027	0.0014	5.78E-02	25671
rs883273	6	154,672,233	a	c	0.323	-0.0071	0.0017	3.37E-05	14695	0.328	0.0007	0.0012	5.35E-01	11042	0.326	-0.0018	0.0010	5.91E-02	25737
rs2975920	9	71,845,911	a	g	0.098	-0.0101	0.0025	6.03E-05	16537	0.091	0.0016	0.0020	4.19E-01	10934	0.094	-0.0029	0.0016	6.10E-02	27471
rs4048532	4	172,809,757	a	g	0.170	0.0087	0.0022	8.61E-05	14696	0.158	-0.0009	0.0016	5.60E-01	10564	0.162	0.0024	0.0013	6.17E-02	25260
rs12685948	9	118,942,952	c	g	0.833	-0.0084	0.0021	7.13E-05	14697	0.819	0.0007	0.0015	6.11E-01	11054	0.823	-0.0022	0.0012	6.31E-02	25751
rs1551900	18	11,597,467	a	g	0.612	-0.0070	0.0017	4.34E-05	12980	0.620	0.0007	0.0012	5.54E-01	11058	0.617	-0.0018	0.0010	6.46E-02	24038
rs6054839	20	7,164,999	c	g	0.863	0.0133	0.0033	6.28E-05	10547	0.550	-0.0001	0.0017	9.40E-01	7927	0.615	0.0027	0.0015	7.54E-02	18474
rs8066615	17	5,760,921	t	g	0.067	0.0150	0.0034	1.18E-05	14697	0.067	-0.0020	0.0022	3.83E-01	11039	0.067	0.0032	0.0019	8.80E-02	25736
rs12602671	17	5,768,371	a	g	0.058	0.0142	0.0034	3.37E-05	13292	0.057	-0.0022	0.0024	3.69E-01	11047	0.057	0.0033	0.0020	9.22E-02	24339
rs243963	4	111,510,330	c	g	0.689	-0.0072	0.0017	2.60E-05	14109	0.698	0.0012	0.0012	3.21E-01	11058	0.695	-0.0017	0.0010	9.39E-02	25167

					Stage 1					Stage 2					Combined				
SNP	CHR	position	A1	A2	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	SE	P-value	N	Freq A1	Beta*	StdErr	P-value	N
rs4833651	4	121,689,810	a	c	0.220	-0.0084	0.0020	3.04E-05	12758	0.209	0.0014	0.0014	3.33E-01	10902	0.212	-0.0019	0.0012	1.04E-01	23660
rs243937	4	111,525,259	a	t	0.310	0.0080	0.0018	1.02E-05	12758	0.303	-0.0014	0.0012	2.63E-01	11063	0.305	0.0016	0.0010	1.14E-01	23821
rs10494937	1	209,711,952	a	g	0.943	-0.0224	0.0057	9.53E-05	10547	0.957	0.0011	0.0029	7.17E-01	10880	0.954	-0.0039	0.0026	1.39E-01	21427
rs604109	11	6,773,971	t	c	0.762	-0.0079	0.0020	8.77E-05	12758	0.766	0.0013	0.0013	3.44E-01	11026	0.764	-0.0015	0.0011	1.63E-01	23784
rs6908357	6	73,176,992	t	g	0.909	-0.0119	0.0028	2.44E-05	15335	0.916	0.0030	0.0020	1.38E-01	11059	0.914	-0.0021	0.0016	2.01E-01	26394
rs10180461	2	143,979,503	t	c	0.613	0.0065	0.0016	5.48E-05	14642	0.619	-0.0015	0.0011	1.79E-01	11014	0.617	0.0012	0.0009	2.02E-01	25656
rs11628114	14	24,577,112	t	c	0.121	0.0111	0.0024	4.38E-06	14697	0.119	-0.0032	0.0017	6.88E-02	11041	0.120	0.0017	0.0014	2.19E-01	25738
rs13409451	2	143,974,109	a	g	0.612	0.0066	0.0016	4.20E-05	14642	0.620	-0.0018	0.0012	1.23E-01	10833	0.617	0.0011	0.0009	2.36E-01	25475
rs17109529	14	24,581,567	t	c	0.128	0.0113	0.0025	7.18E-06	14697	0.121	-0.0031	0.0017	7.49E-02	11059	0.123	0.0015	0.0014	2.74E-01	25756
rs490124	8	23,751,083	a	g	0.386	0.0063	0.0016	9.23E-05	14635	0.367	-0.0019	0.0012	1.10E-01	10921	0.374	0.0010	0.0010	2.83E-01	25556
rs7652290	3	46,274,769	a	g	0.686	0.0067	0.0017	9.09E-05	14286	0.705	-0.0020	0.0012	9.99E-02	11060	0.698	0.0010	0.0010	3.26E-01	25346
rs4609435	1	221,058,314	a	g	0.767	0.0180	0.0045	7.13E-05	4144	0.765	-0.0003	0.0013	8.21E-01	11045	0.765	0.0012	0.0013	3.55E-01	15189
rs4413345	3	46,285,925	t	c	0.751	0.0083	0.0019	1.44E-05	14639	0.768	-0.0030	0.0013	2.48E-02	10943	0.763	0.0008	0.0011	4.86E-01	25582
rs17013203	4	129,521,541	a	g	0.176	-0.0084	0.0021	7.13E-05	14697	0.164	0.0031	0.0015	3.94E-02	11011	0.168	-0.0008	0.0012	4.93E-01	25708
rs463918	4	39,453,011	a	g	0.058	-0.0165	0.0042	9.58E-05	10674	0.060	0.0039	0.0024	1.06E-01	11046	0.059	-0.0011	0.0021	5.98E-01	21720
rs12603905	17	40,560,117	a	t	0.789	-0.0079	0.0020	8.77E-05	14568	0.786	0.0035	0.0014	1.10E-02	10912	0.787	-0.0002	0.0011	8.74E-01	25480
rs2922236	1	11,404,200	c	g	0.087	-0.0392	0.0098	7.13E-05	3209	0.492	0.0006	0.0011	6.21E-01	10998	0.487	0.0000	0.0011	9.75E-01	14207

*Beta for difference between the natural log transformed on- and off-treatment HDL-C levels adjusted for natural log transformed off-treatment HDL-C, age, sex, and study specific covariates. The beta reflects the fraction of differential HDL-C lowering in carriers vs. non-carriers of the SNP; a positive beta indicates a better statin response (larger HDL-C increase).

Supplementary table 6: Summary statistics for all known genome-wide significant genetic variants associated with plasma HDL-c levels

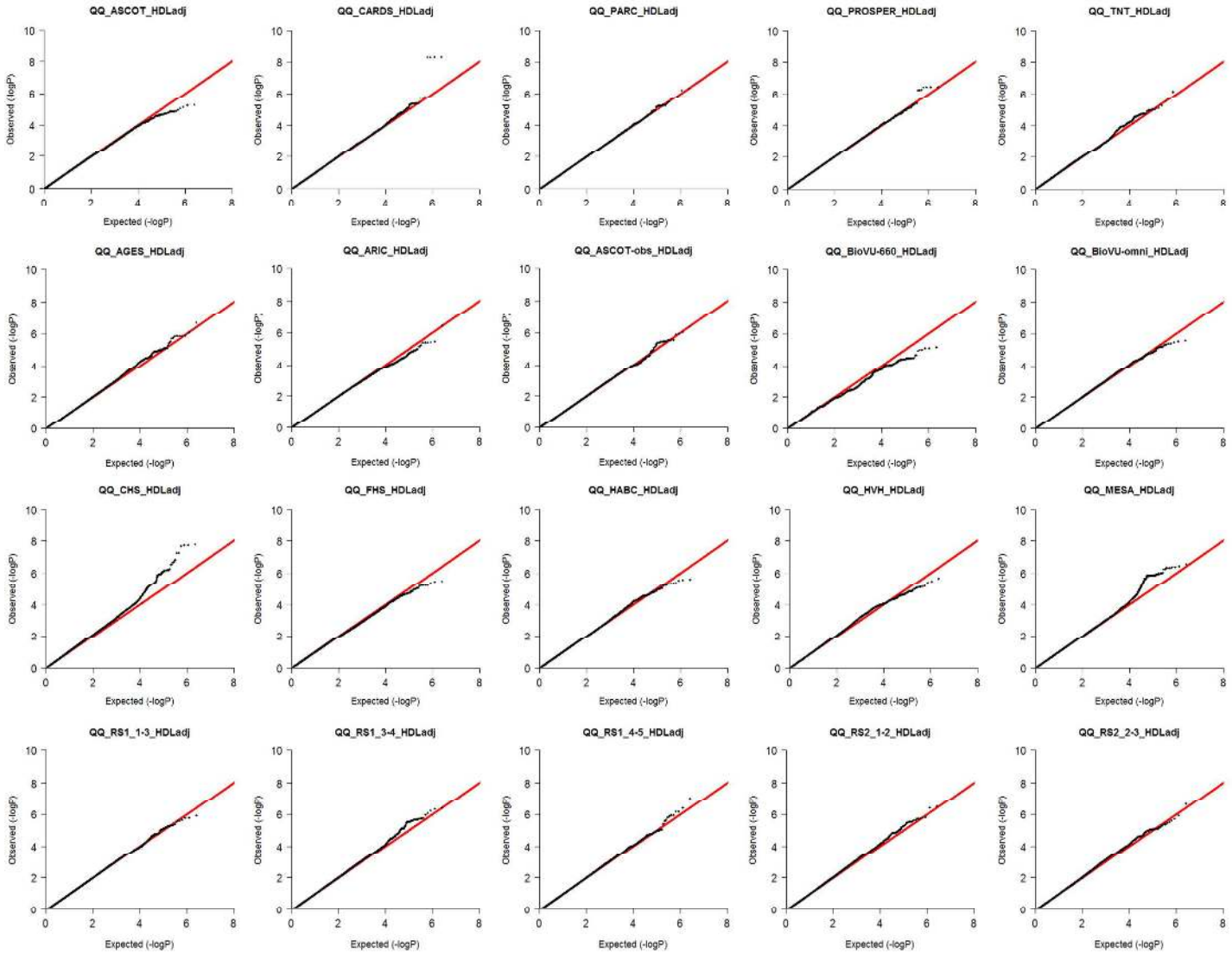
#	SNP	Chr	Locus	GLGC		GIST		
				Effect allele	Beta*	Beta†	SE	P-value
1	rs3764261	16	CETP	a	0.2412	0.0071	0.001	8.82E-13
2	rs6065906	20	PLTP	t	0.0594	0.0061	0.002	0.002391
3	rs581080	9	TTC39B	c	0.0419	0.0058	0.0021	0.00596
4	rs2652834	15	LACTB	a	0.0285	0.006	0.0022	0.006618
5	rs7241918	18	LIPG	t	0.0902	0.0046	0.0019	0.01593
6	rs16942887	16	LCAT	a	0.0831	0.0054	0.0023	0.0194
7	rs1800961	20	HNF4A	t	0.127	0.0093	0.0041	0.02392
8	rs1883025	9	ABCA1	t	0.0698	0.0041	0.0019	0.03167
9	rs3136441	11	LRP4	t	0.0545	0.0051	0.0024	0.03436
10	rs737337	19	ANGPTL8	t	0.0565	0.0063	0.003	0.03654
11	rs2290547	3	SETD2	a	0.0297	-0.0038	0.0021	0.07159
12	rs10019888	4	C4orf52	a	0.027	0.0041	0.0023	0.07591
13	rs838880	12	SCARB1	t	0.0484	0.003	0.0017	0.07891
14	rs2013208	3	RBM5	t	0.0254	0.0024	0.0014	0.08785
15	rs702485	7	DAGLB	a	0.0243	0.0024	0.0016	0.1353
16	rs2972146	2	IRS1	t	0.0323	0.002	0.0015	0.1843
17	rs4983559	14	ZBTB42-AKT1	a	0.0197	0.0021	0.0016	0.1913
18	rs2923084	11	AMPD3	a	0.0256	0.0027	0.0021	0.2005
19	rs605066	6	CITED2	t	0.0281	0.002	0.0016	0.2133
20	rs4142995	7	SNX13	t	0.0263	-0.0017	0.0014	0.2266
21	rs4759375	12	SBNO1	t	0.056	0.004	0.0033	0.2275
22	rs13076253	3	ACAD11	a	0.0283	0.0029	0.0024	0.2289
23	rs9686661	5	MAP3K1	t	0.0283	0.0024	0.002	0.2322
24	rs2255141	10	GPAM	a	0.0337	0.002	0.0017	0.2414
25	rs4765127	12	ZNF664	t	0.0324	0.002	0.0017	0.2414
26	rs4846914	1	GALNT2	a	0.0479	0.0018	0.0016	0.2627
27	rs731839	19	PEPD	a	0.022	0.0019	0.0017	0.2658
28	rs11613352	12	LRP1	t	0.0281	0.0021	0.0019	0.2711
29	rs17173637	7	TMEM176A	t	0.0363	0.0034	0.0032	0.2901
30	rs3822072	4	FAM13A	a	0.0251	0.0017	0.0016	0.2901
31	rs7134375	12	PDE3A	a	0.0207	0.0017	0.0016	0.2901
32	rs11246602	11	OR4C46	t	0.034	0.0025	0.0024	0.2997
33	rs12678919	8	LPL	a	0.1554	0.0027	0.0027	0.3194
34	rs12801636	11	KAT5	a	0.0235	-0.0019	0.002	0.3442
35	rs4148008	17	ABCA8	c	0.028	0.0015	0.0016	0.3506
36	rs386000	19	LILRA3	c	0.0479	0.0017	0.002	0.3974
37	rs4129767	17	PGS1	a	0.0237	-0.0013	0.0016	0.4185
38	rs442177	4	KLHL8	t	0.0215	-0.0012	0.0016	0.4552
39	rs7134594	12	MVK	t	0.0354	-0.0012	0.0016	0.4552
40	rs970548	10	MARCH8-ALOX5	a	0.0258	0.0013	0.0018	0.4721
41	rs2925979	16	CMIP	t	0.0351	0.0012	0.0017	0.4822
42	rs17145738	7	MLXIPL	t	0.0408	-0.0016	0.0023	0.4885
43	rs2602836	4	ADH5	a	0.0192	-0.0011	0.0016	0.4936
44	rs11065987	12	BRAP	a	0.0222	-0.001	0.0017	0.5581
45	rs645040	3	MSL2L1	t	0.0312	0.0011	0.0019	0.5643
46	rs2814982	6	C6orf106	t	0.0371	0.0013	0.0024	0.5897
47	rs4731702	7	KLF14	t	0.0294	9.00E-04	0.0017	0.5981
48	rs6450176	5	ARL15	a	0.0254	9.00E-04	0.0017	0.5981
49	rs12967135	18	MC4R	a	0.0262	0.001	0.0019	0.6003

#	SNP	Chr	Locus	GLGC		GIST		
				Effect allele	Beta*	Beta†	SE	P-value
50	rs1121980	16	FTO	a	0.0196	8.00E-04	0.0016	0.6186
51	rs12328675	2	COBLL1	t	0.0447	-0.0011	0.0022	0.6186
52	rs1936800	6	RSPO3	t	0.02	-6.00E-04	0.0016	0.7089
53	rs2293889	8	TRPS1	t	0.0312	6.00E-04	0.0016	0.7089
54	rs629301	1	SORT1	t	0.0334	-7.00E-04	0.0019	0.7137
55	rs1689800	1	ZNF648	a	0.0344	6.00E-04	0.0017	0.7253
56	rs17695224	19	HAS1	a	0.029	-6.00E-04	0.0018	0.74
57	rs9987289	8	PPP1R3B	a	0.0817	9.00E-04	0.0027	0.74
58	rs12145743	1	HDGF-PMVK	t	0.0203	-5.00E-04	0.0017	0.7696
59	rs4917014	7	IKZF1	t	0.0222	5.00E-04	0.0018	0.7821
60	rs499974	11	MOGAT2-DGAT2	a	0.0263	5.00E-04	0.0019	0.7933
61	rs4650994	1	ANGPTL1	a	0.021	4.00E-04	0.0016	0.8034
62	rs7255436	19	ANGPTL4	a	0.0316	4.00E-04	0.0016	0.8034
63	rs2606736	3	ATG7	t	0.0246	-4.00E-04	0.0017	0.8148
64	rs4420638	19	APOE	a	0.0669	6.00E-04	0.0028	0.831
65	rs174546	11	FADS1-2-3	t	0.0391	-3.00E-04	0.0016	0.8519
66	rs13107325	4	SLC39A8	t	0.0708	4.00E-04	0.0029	0.8908
67	rs6805251	3	GSK3B	t	0.02	-2.00E-04	0.0016	0.901
68	rs11869286	17	STARD3	c	0.0319	2.00E-04	0.0017	0.9068
69	rs4660293	1	PABPC4	a	0.0353	2.00E-04	0.0017	0.9068
70	rs12748152	1	PIGV-NR0B2	t	0.0506	3.00E-04	0.0029	0.918
71	rs13326165	3	STAB1	a	0.0289	2.00E-04	0.002	0.9207
72	rs1532085	15	LIPC	a	0.1068	1.00E-04	0.0015	0.9471
73	rs2954029	8	TRIB1	a	0.0401	-1.00E-04	0.0016	0.9504
74	rs7941030	11	UBASH3B	t	0.027	-1.00E-04	0.0016	0.9504
75	rs1367117	2	APOB	a	0.0223	1.00E-04	0.0019	0.9582
76	rs181362	22	UBE2L3	t	0.038	0	0.002	>0.99
77	rs964184	11	APOA1	c	0.1065	0	0.0025	>0.99
78	rs998584	6	VEGFA	a	0.026	0	0.0018	>0.99

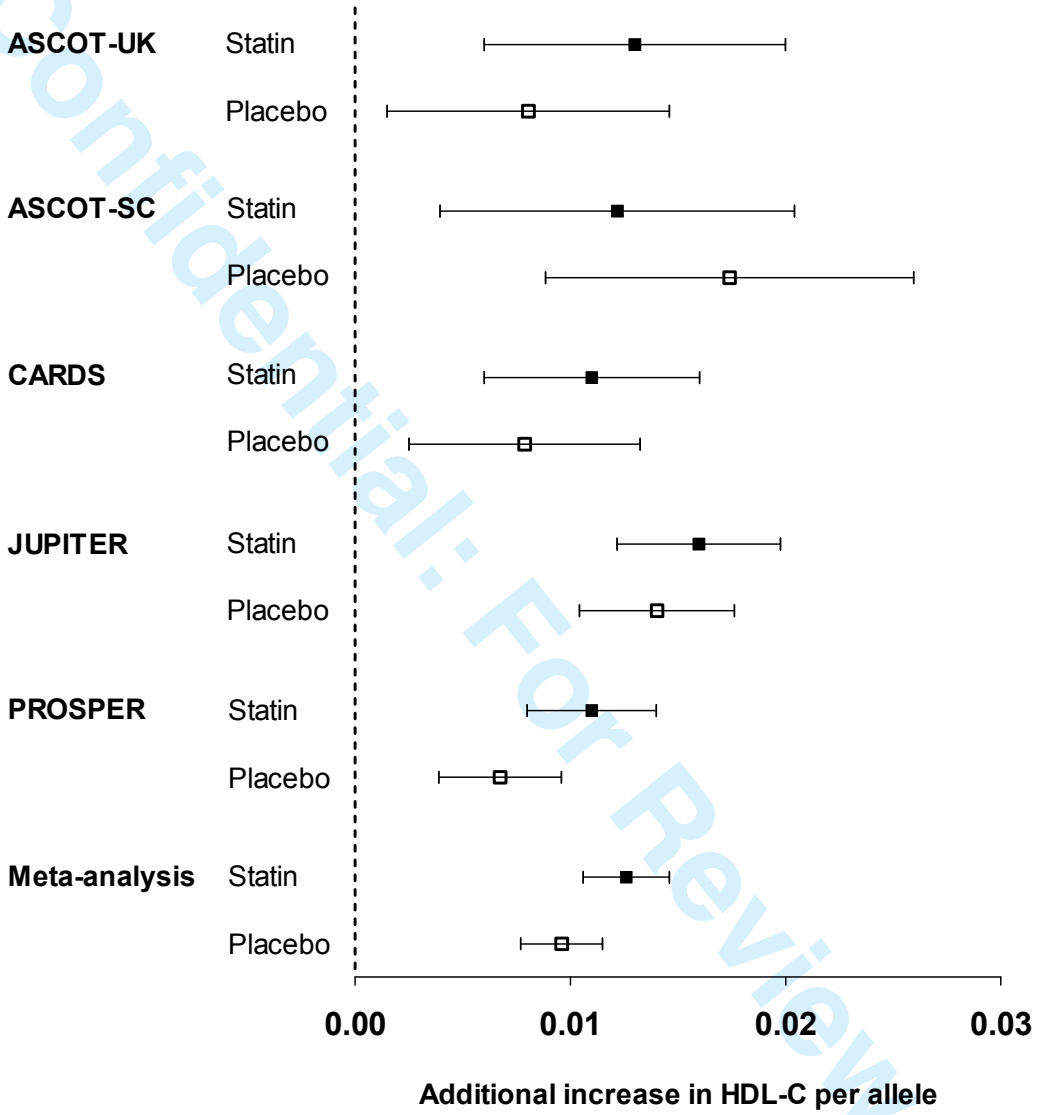
GLGC denotes Global Lipids Genetics Consortium; GIST, Genomic Investigation of Statin Therapy. Effect sizes are per allele in *s.d. and †statin-induced fractional HDL-c response.

Supplementary figures

Supplementary Figure 1: Quantile-quantile plots of the expected versus observed -logP values for all studies participating in the first stage meta-analysis.



Supplementary Figure 2: HDL-C change during follow-up for the CETP SNP rs247616 in statin and placebo users.



Supplementary Note 1. Participating Randomized controlled trials in Phase 1

Anglo-Scandinavian cardiac Outcomes Trial (ASCOT)

Of 19,342 hypertensive patients (40–79 years of age with at least three other cardiovascular risk factors) who were randomized to one of two antihypertensive regimens in ASCOT, 10,305 with non-fasting TC concentrations of 6.5 mmol/l or less (measured at the non-fasting screening visit) had been randomly assigned additional atorvastatin 10 mg or placebo. These patients formed the lipid-lowering arm (LLA) of the study. For this genome-wide study only a proportion of United Kingdom, Irish, Sweden, Norway, Finland and Denmark consented to participate. For GWAS data, the available samples were genotyped separately, first for the UK and Irish GWAS (ASCOT-UK), and subsequently for the Scandinavian GWAS (ASCOT-SC). Within GIST analyses, ASCOT-UK was used within the discovery stage and ASCOT-SC within the replication. In both the GWAS resources there were two subpopulations from ASCOT included. The first subpopulation used the RCT data (ASCOT-RCT) and included individuals randomized to 10 mg atorvastatin in whom pre-treatment HDL-C was measured at the (fasting) randomization visit and on-treatment HDL-C was calculated as the simple average of measures at the (fasting) visits 6 months and 12 months post-randomization. Following the end of the randomization phase, there was an observational period. The second subpopulation used this observational data (ASCOT-OBS) and included all individuals not originally randomized to 10 mg atorvastatin (i.e., those randomized to placebo and those not eligible for the LLA) who were subsequently prescribed atorvastatin 10 mg during follow-up. For these individuals, pre-treatment HDL- C was defined as the measurement on the last visit before or equal to date of starting atorvastatin, and on-treatment HDL- C was defined as the measurement taken from the first visit after date of starting atorvastatin.

Collaborative Atorvastatin Diabetes Study (CARDS)

Methods in CARDS have been described previously [2, 3]. In brief, 2838 patients with Type 2 diabetes and no previous CVD were randomized to receive either placebo or atorvastatin 10mg once daily and followed for a median of 3.7 years. Allocation was double blinded. Mean serum LDL- C concentration during baseline visits prior to randomization had to be = 4.14mmol/L (160 mg/dl) and serum triglycerides = 6.78mmol/L (600mg/dl). After randomization, total cholesterol, HDL-C, and triglycerides were measured at one, two, and three months and 6 monthly thereafter. Patients attended after an overnight fast. Serum HDL-cholesterol was measured after precipitation of apolipoprotein B-containing lipoproteins with heparin manganese with prior removal of very-low-density lipoproteins (VLDL) by ultracentrifugation in samples from patients whose serum triglycerides exceeded 4.00 mmol/ l [3]. Once ultracentrifugation was used, it was employed for all subsequent HDL measurements in that patient. Serum HDL-cholesterol was calibrated against the Center for Disease Control registered laboratory in RIQAS (Pacific Biometrics Ltd, Seattle, WA, USA) using the regression equation from 86 comparisons between 1999 and 2003. The genotyping methods in CARDS have been described in details elsewhere [4].

Cholesterol and Atherosclerosis Pharmacogenetics (CAP)[1]

The trial involved 944 healthy volunteers, 609 of whom were Caucasian [5]. Participants were aged 30 and above, who received open label 40 mg simvastatin daily for 6 weeks. They were recruited from two clinical sites located in Los Angeles and San Francisco, California, respectively. Screening criteria included serum total cholesterol levels of 4.14-10.36 mmol/L (160-400 mg/dL). Lipids, including HDL-C, were measured twice prior to treatment (at screening and after a two-week run-in period) and twice on treatment (4 and 6 weeks), and the averages were used for each time point. Human subject approvals were obtained at all participating institutions and all participants signed statements of informed consent. In total, 591 subjects with both lipids and DNA data were available for analysis. Discovery genotyping was performed for half of the subjects using beadchip technology (HumanHap300 BeadChip , Illumina Inc. San Diego CA) for whole-genome genotyping of 314,621 tagSNP markers derived from the International HapMap Project. Genome-wide genotyping was performed on the remaining half of the samples using the Illumina HumanCNV610-Quad beadchip containing 620,901 tagSNPs. SNPs with MAF < 1% and proper information <0.30 (obtained by SNPTEST) were excluded from analysis. Imputation was performed using BIMBAM v0.99 with reference to HapMap CEU using release 23, build 36.

PRavastatin INflammation CRP Evaluation study (PRINCE)

Participants were Caucasians, aged 21 and older, who received 40 mg daily pravastatin for 12 weeks [6]. They were enrolled from 1143 sites representing 49 states and the District of Columbia, with no single site enrolling more than 4 individuals. Recruitment criteria included either an LDL-C concentration ≥3.5 mmol/L (>135 mg/dL) or a history of myocardial infarction, stroke, or coronary revascularization regardless of baseline LDL-C. Lipid measurements, including HDL-C, were obtained once prior to treatment and once following 12 weeks of treatment. Human subjects approvals were obtained at all participating institutions and all participants signed statements of informed consent. In total, 1348 participants had DNA available for whole genome-wide association analysis. Genotyping and imputation were performed using the same platforms and procedures as for CAP i.e., half of the samples with each of the Illumina platforms).

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

All data come from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). A detailed description of the study has been published elsewhere [7, 8]. PROSPER was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major vascular events in elderly. Between December 1997 and May 1999, we screened and enrolled subjects in Scotland (Glasgow), Ireland (Cork), and the Netherlands (Leiden). Men and women aged 70-82 years were recruited if they had pre-existing vascular disease or increased risk of such disease because of smoking, hypertension, or diabetes. A total number of 5,804 subjects were randomly assigned to pravastatin or placebo. A large number of prospective tests were performed including Biobank tests and cognitive function measurements.
A whole genome wide screening has been performed in the sequential PHASE project with the use of

[1] CAP was designed as a pharmacogenetics study and therefore not a randomized placebo-controlled trial

the Illumina 660K beadchip [9]. Of 5,763 subjects DNA was available for genotyping. Genotyping was performed with the Illumina 660K beadchip, after QC (call rate <95%) 5,244 subjects and 557,192 SNPs were left for analysis. These SNPs were imputed to 2.5 million SNPs based on the HAPMAP built 36 with MACH imputation software.

Plasma lipids and lipoproteins were measured twice during the screening phase, i.e. at the beginning and end of the single-blind, placebo "run-in" phase according to the standardized Lipid Research Clinics protocol. Baseline HDL-C levels were taken as the average of these 2 determinations prior to randomization to statin treatment. During follow-up, plasma lipids and lipoproteins were measured after 3, 6, 12, 24, and 36 months. Total cholesterol (TC), HDL cholesterol, and triglycerides were assessed after an overnight fast, LDL-C was calculated by the Friedewald formula, as previously described [7].

Treating to New Targets (TNT)

The design of the TNT trial has been described in details elsewhere [10]. In brief, 10 001 patients with stable coronary heart disease (CHD) and LDL-C levels <130 mg/dL (3.4 mmol/L) were randomly assigned to receive either 10 or 80 mg of atorvastatin per day and were followed up for a median of 4.9 years. Mean HDL-C levels during treatment were 47 mg/dL (1.22 mmol/L) for the 10- and 80-mg groups. At screening, LDL-C, HDL-C, triglycerides (TG), and total cholesterol were measured in all subjects in a fasting state. In addition, blood pressure and body mass index as well as other standard blood chemistries were measured. All laboratory tests were performed at a central laboratory (Medical Research Laboratories, Highland Heights, Ky) certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control Part III Program. These were repeated 4 weeks later, at randomization, 3 and 6 months post randomization, and annually thereafter.

After approval by the institutional review committee, informed consent for genetic analysis was sought on entry into the trial and 5966 DNA samples were obtained from consenting individuals. A subset was chosen for whole-genome analysis based on the cardiovascular events during the course of the trial and those individuals were matched 3:1 with controls based on age, gender, treatment arm, smoking, diabetes, hypertension, baseline lipid values, baseline glucose levels, and screening LDL-C. The Perlegen 322K array genotyping array was used to perform genome-wide genotyping. Samples and SNPs will call rate equal or under 98% were removed prior to the analyses. IMPUTE 2 (v. 2.1.0) and GTOOL (v.0.6.6) were used to impute additional SNPs which were analyzed for their association with LDL response with PLINK (v.1.07)

Supplementary Note 2. Participating observational studies in phase 1

Age, Gene/Environment Susceptibility-Reykjavik (AGES) study

The Reykjavik Study cohort originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967. A total of 19,381 attended, resulting in 71% recruitment rate. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5,764 survivors of the original cohort who had participated before in the Reykjavik Study [11]. Serum lipid levels were measured at baseline (AGES:2002-2006), and at a follow-up five years later (AGESII:2007-2001). Individuals were recruited in the same order. Of the 5,764 participants, 3,664 participants were randomly selected for the GWAS. Genotyping was undertaken using the HumanCNV370-Duo (Illumina) at the Laboratory of Neurogenetics, Intramural Research Program, at the National Institute of Aging, Bethesda, Maryland.

Atherosclerosis Risk in Communities (ARIC) study

The ARIC study is an ongoing population-based cohort of 15,792 predominantly Caucasian and African-American males and females aged 45-64 years at baseline and selected using probability sampling from four United States communities (Forsyth County NC, Jackson MS, suburban Minneapolis MN, and Washington County MD) [12]. Participants were recruited in 1987-1989 to examine cardiovascular and pulmonary disease, patterns of medical care, and disease variation over time. Standardized physical examinations and interviewer-administered questionnaires were conducted at baseline (1987-1989), three triennial follow-up examinations (1990-1998), and a fifth exam (2011-2013). Eligible participants for this effort were from the NC, MN, and MD field centers, as only Caucasian participants were examined in this analysis and the MS center only recruited African American participants.

Twelve-hour fasting total cholesterol and HDL were measured as previously described at baseline and during the three triennial exams; [13, 14] data from the fifth exam did not contribute to this analysis. To evaluate the effect of lipid lowering therapy, we selected the first exam at which the participant reported using statins. We then used the HDL measure from that examination and the previous examination (approximately three years earlier) to calculate the logarithm of HDL before statin treatment minus the logarithm of HDL after beginning statin treatment. Participants who reported using statins at the baseline visit were excluded, as we did not have a pre-treatment HDL measure to evaluate.

The Affymetrix 6.0 genotype array was used to genotype n=669,450 SNPs that passed quality control (sample call rate ≥ 0.95; SNP call rate ≥ 0.90; SNP MAF filter ≥ 0.01, HWE p-value filter ≥ 10^{-5}). SNPs were imputed based on the HAPMAP build 36 with MACH v1.16 and analyses were performed using ProbABEL.

BioVU

BioVU is the nation's largest collection of DNA samples linked to a comprehensive, de-identified electronic medical record (EMR) [15, 16]. BioVU began in 2007 and accrues DNA samples via an opt-out model (the design and ethical principles of which have been described previously [15] primarily from outpatient visits. On September 3, 2013, the biobank contains 151,605 adults linked to de-identified mirror images of individual comprehensive EMRs. This database is scrubbed of all Health Insurance Portability Accountability Act (HIPAA) identifiers; e.g., if the name "John Smith" appears in the

original record, its corresponding record in the synthetic derivative is permanently replaced with a tag [NAME AAA, BBB] to maintain the semantic integrity of the text.
Per BioVU policy, all projects utilizing BioVU samples are required to redeposit their genotyping results into the BioVU databases for reuse by other investigators. Of note, 16,701 individuals have genome-wide SNP data available on September 3, 2013, and were among the available population used for this study.
Plasma lipid data is extracted from linked de-identified EMRs. Before Treatment HDL-C is defined as median HDL-C within an 18 month window before first ever statin mentioned in the EMRs. After Treatment HDL-C is defined as median HDL-C within an 18 month window after first ever statin mentioned in the EMRs, with right censoring within the 18 month window at the first drug or dose changes.
Statin exposures were derived from electronic prescribing tools and use of the MedEx natural language processing tool, which extracts medication references from narrative text [17]. When using MedEx, we apply heuristic rules to identify patients truly receiving medications and filter out adverse events, medication discussions, and other non-prescription events.

Cardiovascular Health Study (CHS)

The CHS is a population-based cohort study of risk factors for CHD and stroke in adults ≥65 years conducted across four field centers [18]. The original predominantly Caucasian cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, in 1992-1993, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. DNA was extracted from blood samples drawn on all participants at their baseline examination. In 2007-2008, genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV BeadChip system on 3980 CHS participants who were free of CVD at baseline, consented to genetic testing, and had DNA available for genotyping. Because the other cohorts were predominantly white, the African American participants were excluded from this analysis. Thus, for this analysis, the study sample is limited to European ancestry participants who used statins during follow up with available genotype data as well as on- and off-treatment lipid measures.
In CHS, the following exclusions were applied to identify a final set of 306,655 autosomal SNPs: call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap. Imputation was performed using BIMBAM v0.99 with reference to HapMap CEU using release 22, build 36 using one round of imputations and the default expectation-maximization warm-ups and runs.
Plasma lipids and lipoproteins were measured several times during follow-up; HDL-C measurements are available from baseline (year 2), year 5, and year 18. Subjects came to the clinic after an overnight fast, and blood was obtained on their arrival at the clinic. Samples were shipped weekly, on dry ice, to the CHS Central Blood Laboratory at the University of Vermont, where all analyses were performed. Plasma total cholesterol and triglyceride (TG) were measured by enzymatic methods on an Olympus Demand System (Olympus Corp., Lake Success, N.Y.). HDL-C was measured by an enzymatic method after precipitation of apo-lipoprotein B-containing lipoproteins with dextran sulfate/magnesium sulfate. LDL-C was calculated according to the Friedewald equation for individuals whose serum TG was <4.51mmol/l [19].

Framingham Heart Study (FHS)

The methods for recruitment and clinical covariate collection have been described previously for the original Framingham Heart Study cohort (5,209 participants ascertained systematically from two-thirds of the households in the town of Framingham, MA, beginning in 1948)[20], the Framingham Heart Study Offspring cohort (5,124 children of the original cohort, and spouses of those children, beginning in 1972)[21], and the Third Generation cohort (4,095 children of the Offspring cohort, beginning in 2002)[22]. The current study was conducted in 1266 participants recruited in the Offspring Cohort from Exam 4 (1987-1991) through Exam 8 (2005-2008) and 266 participants in the Third Generation from Exam 1 (2002-2005) and Exam 2 (2008-2011). HDL-C was collected at each exam using standard protocols. To evaluate the effect of lipid lowering therapy, we selected the first exam at which a person reported using lipid lowering medication. It is assumed that most of the therapy during this time was statin, but we did not have specific data on which medications were used except for Exams 8 in the Offspring and 1 and 2 for the Third Generation. Then we used the HDL-C measure from that examination and the previous exam (approximately 3-4 years before) to calculate the logarithm of HDL-C before lipid lowering treatment minus the logarithm of HDL-C after the beginning use of lipid lowering treatment. This trait was analysed in mixed effects linear regression models (accounting for familial relationships) for all genetic variants in the CEU sample of the Phase 2 HapMap Release 22. We adjusted for sex, age, time between the HDL-C measurements and Principal Component 7 to control for population substructure.
Genotyping was conducted for the SNP Health Association Resource (SHARe) project (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v20.p8) using the Affymetrix 500K mapping array (250K Nsp and 250K Sty arrays) and the Affymetrix 50K supplemental gene focused array on a total of 9,274 individuals from all three cohorts. BRLMM was used to call these data. To evaluate population substratification, we conducted principal component analyses using EIGENSTRAT [23] on the genotypes from 882 unrelated participants. We estimated the first 10 principal components and applied the loadings of these components to all genotyped participants. Finally, we evaluated whether any of these principal components were associated with the difference in the logarithms of HDL before and after lipid lowering initiation. Only Principle Component 7 was associated with HDL-C and was thus included in the regression model. Genotyping resulted in 503,551 SNPs with successful call rate >95% and HWE P>1.0x10-6 in 8,481 individuals with call rate >97%. Imputation of 2,543,887 autosomal SNPs in HapMap release 22, CEU sample was conducted using the algorithm implemented in MACH (version 1.0.15). From a total of 534,982 genotyped autosomal SNPs in Framingham, 378,163 SNPs were used in imputation after filtering out 15,586 SNPs (HWE $P<1.0x10^{-6}$), 64,511 SNPs (missingness >0.03), 45,361 SNPs (mishap $P<1.0x10^{-9}$), 4,857 SNPs (>100 Mendel errors), 67,269 SNPs (frequency <0.01), 2 SNPs (due to strand issues upon merging data with HapMap), and a further 13,394 SNPs that were not present on HapMap. We used 200 biologically unrelated participants to estimate the parameters of the imputation model and subsequently applied the estimated parameters to obtain imputed SNPs for all 8,481 participants. The Framingham Heart Study, including genetic association studies of Framingham phenotypes, was approved by the institutional review boards of Boston University and the National Institutes of Health. All participants provided written informed consent.

Health Aging and Body Composition (Health ABC) Study

Health ABC is a NIA-sponsored ongoing cohort study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age. Health ABC enrolled well-functioning, community-dwelling black (n=1281) and white (n=1794) men and women aged 70-79 years between April 1997 and June 1998. Participants were recruited from a random sample of white and all black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. The key components of Health ABC include a baseline exam, annual follow-up clinical exams, and phone contacts every 6 months to identify major health events and document functional status between clinic visits. HDL cholesterol was measured from plasma stabilized with EDTA in the entire cohort using the VITROS CHOL slide (Ortho-Clinical Diagnostics, Inc.). GWAS data are available from 1663 white participants. Genomic DNA was extracted from buffy coat collected using PUREGENE® DNA Purification Kit during the baseline exam. Genotyping was performed by the Center for Inherited Disease Research (CIDR) using the Illumina Human1M-Duo BeadChip system. Samples were excluded from the dataset for the reasons of sample failure, genotypic sex mismatch, and first-degree relative of an included individual based on genotype data. Genotyping was successful for 1,151,215 SNPs in 1663 unrelated. Imputation was done for the autosomes using the MACH software version 1.0.16. SNPs with minor allele frequency ≥ 1%, call rate ≥97% and HWE p≥10-6 were used for imputation. HapMap II phased haplotypes were used as reference panels. For EAs, genotypes were available on 914,263 high quality SNPs for imputation based on the HapMap CEPH reference panel (release 22, build 36). A total of 2,543,887 SNPs in EAs are available for analysis.

Heart and Vascular Health (HVH) Study

HVH is a case-control study set in Group Health (GH), a large integrated health care system in Washington State, and is comprised of incident myocardial infarction (MI) and stroke cases with a shared common control group. All participants were GH members and aged 30-79 years. MI and stroke cases were identified from hospital discharge diagnosis codes and were validated by medical record review. Controls were a random sample of GH members frequency matched to MI cases on age (within decade), sex, treated hypertension, and calendar year of identification. The index date for controls was a computer-generated random date within the calendar year for which they had been selected. For MI cases, the index date was the date of admission for the first acute MI. Participants were excluded if they were recent enrollees at GHC, had a history of prior MI or stroke, or if the incident event was a complication of a procedure or surgery. Methods for the study have been described previously. [24-26]

Eligibility and risk factor information were collected by trained medical record abstractors from a review of the GH medical record using only data available prior to the index date and through a telephone interview. Medication use was ascertained using computerized GH pharmacy records. A venous blood sample was collected from all consenting subjects, and DNA was extracted from white blood cells using standard procedures.

Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai using the Illumina 370CNV BeadChip system. Genotypes were called using the Illumina BeadStudio software. Samples were excluded from analysis for sex mismatch or call rate < 95%. The following exclusions were applied to identify a final set of 301,321 autosomal SNPs: call rate < 97%, HWE P < 10-5, > 2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios), heterozygote frequency = 0, SNP not found in HapMap, inconsistencies across genotyping

batches. Imputation was performed using BIMBAM with reference to HapMap CEU using release 22, build 36 using one round of imputations and the default expectation-maximization warm-ups and runs.
Plasma lipids and lipoproteins were measured over the course of general care at Group Health and were obtained from the outpatient medical record and/or Group Health laboratory database.

Multi-Ethnic Study of Atherosclerosis (MESA)

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants were white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent [27]. Participants were recruited from six field centers across the United States and followed-up three times with an average time period of follow-up of 2 years between each visit. Data from four visits (exam1 to exam4) was used for the analysis. Subjects on statin treatment at the time point of follow-up visit and off treatment at the previous visit were qualified for inclusion. Phenotype (lipids measures before and after statin treatment) and genotype data were available for 360 Caucasian subjects. The tenets of the Declaration of Helsinki were followed and institutional review board approval was granted at all MESA sites. Written informed consent was obtained from each participant.
Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0. IMPUTE version 2.1.0 was used to perform imputation for the MESA Caucasian participants (chromosomes 1-22) using HapMap Phase I and II - CEU as the reference panel (release #24 - NCBI Build 36 (dbSNP b126)). SNPs with MAF less than 0.02 or HWE p value less than 0.001 were removed from the analysis.

Rotterdam study

The Rotterdam Study is a prospective population-based cohort study of chronic diseases in the elderly population. From 1990 to 1993, 7983 inhabitants of the suburb Ommoord in Rotterdam, the Netherlands, aged 55 years or older, entered the Rotterdam Study (RS-I), and have been continuously followed since then. Medication prescription data were obtained from all seven fully computerized pharmacies in the Ommoord suburb. These pharmacies dispense the prescriptions of more than 99% of all participants. Information on all filled prescriptions from January 1st 1991 until June 1st 2008 was available and included information on the product name of the drug, the Anatomical Therapeutical Chemical code, the amount dispensed, the prescribed dosage regimen and the date of dispensing. Furthermore, in 2000, an extended cohort was enrolled, the Rotterdam Study II (RS-II). 3011 inhabitants entered the study and have been continuously followed since then. Detailed information on design, objectives and methods of this study have been described before [28, 29]. The Rotterdam Study has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants gave informed consent to participate in the study and to obtain information from treating physicians and pharmacy records,

separately.

Lipid measurements were obtained from all participants at each visit. Fasting total cholesterol, HDL-cholesterol and triglyceride levels were determined using enzymatic procedures (Hitachi Analyzer, Roche Diagnostics).

At baseline examination of the Rotterdam Study, blood was taken from which genomic DNA was extracted, using the salting-out method [30]. Microarray genotyping was performed in both Rotterdam Study cohorts, using the Infinium II HumanHap550K Genotyping BeadChip version 3 (Illumina Inc., San Diego, CA, USA). Genotyping procedures were followed according to the manufacturer's protocols. Microarray genotyping procedures in the Rotterdam Study have been previously described [31].

Supplementary Note 3. Participating studies in Phase II

Genetics of Diabetes Autdit and Research Tayside Study (GoDARTS)

The GODARTS cohort was ascertained from the Diabetes Audit and Research Tayside Study (DARTS) and has been described before [32]. Each individual in Go-DARTS has multiple measures of clinical parameters recorded over a period of time during the course of their clinical management. These clinical parameters were BMI, total cholesterol, high-density lipoprotein cholesterol (HDL-C). For the purpose of this study we included the baseline HDL-C as the HDL-c at first study visit and follow-up HDL as HDL the highest HDL-c attained during the follow-up period. The Go-Darts data were genotyped on affymetrix (N=3094) and illumina platform (n=3039).

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) population

The study population was derived from JUPITER, an international, randomized, placebo-controlled trial of rosuvastatin (20mg/day) in the primary prevention of cardiovascular disease conducted among apparently healthy men and women with LDL-C < 130 mg/dL and hsCRP ≥ 2 mg/L [33]. Individuals with diabetes or triglyceride concentration >500mg/dL were also excluded. Approximately 71.2% of JUPITER participants had European ancestry among whom 71.4% provided DNA and consent for genetic analysis. The present analysis includes only individuals with genotype information who had verified European ancestry (see below) and who were deemed compliant with the study protocol as judged by on the basis of pill counts and reported absence of non-trial statin use, i.e. information that was independent of LDL-C reduction. After applying these restrictions, 3417 statin- and 3388 placebo-allocated participants remained for analysis with HDL-C measures at baseline and follow-up.

Per study protocol, all JUPITER participants had standard lipid measurements made in a core laboratory facility prior to randomization and again after one year of placebo or rosuvastatin treatment. HDL-C was after heparin-manganese precipitation of apolipoprotein B-containing particles.

Genotyping in the JUPITER population was performed using the Omni 1M Quad platform (Illumina, San Diego) as described previously [34]. In the final data used for analysis, samples were retained if >98% of the SNPs had successfully genotype, while SNPs were retained if genotyping was successful in >90% of the samples. Of JUPITER participants with self-reported European ancestry over 99% had successful genotyping and verification of their ancestry using multi-dimensional scaling procedures in PLINK [35] applied to 1,067 ancestry informative SNPs from HapMap3. Among JUPITER participants with verified European ancestry, rs7412, which distinguishes the APOE E2 from E3/E4 genotypes deviated from Hardy-Weinberg equilibrium, likely due to the ascertainment criteria related to LDL-C levels in JUPITER. This SNP was included in the final data only after manual inspection of genotyping clusters. Sub-European ancestral stratification was estimated using the principal component approach in EIGENSTRAT [23]. Genotypes for SNPs in the 1000 genomes pilot data (release 2010-03) were imputed with MaCH v. 1.0.16 [36].

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