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Supplementary appendix

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HMG-CoA reductase inhibition, type 2 diabetes and body weight: evidence from genetic analysis and randomized trials

Web appendix

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Supplementary methods

Genetic studies - datasets contributing to analysis

Supplementary Table 3 describes the details of studies contributing individual participant-level data (IPD) to the genetic analysis. The participating studies are detailed below.

- Prospective cohort studies

Twenty-five prospective cohort studies (including birth cohorts) contributed genotype and phenotype (either biomarkers, clinical events, or both) data to the genetic analysis. The designs of these studies have been described previously.

From the UCL-LSHTM-Edinburgh-Bristol (UCLEB) Consortium: British Regional Heart Study (BRHS)[1], the British Women's Heart and Health Study (BWHHS)[2], the Caerphilly Prospective Study (CaPS)[3], the Edinburgh Artery Study (EAS)[4], the English Longitudinal Study of Aging (ELSA)[5], the Edinburgh Type 2 Diabetes Study (ET2DS)[6], the Northwick Park Heart Study II (NPHS-II)[7], the Whitehall-II (WHII) study[8], and the MRC National Survey of Health and Development (MRC NSHD, 1946 British Birth Cohort)[9].

From the National Heart, Lung and Blood Institute (NHLBI) Candidate Gene Association Resource (CARe) Consortium: the Atherosclerosis Risk in Communities Study (ARIC)[10], the Coronary Artery Risk Development in Young Adults (CARDIA) Study[11], the Cleveland Family Study (CFS)[12,13], the Cardiovascular Health Study (CHS)[14], the Framingham Heart Study (FHS)[15], and the Multi-Ethnic Study of Atherosclerosis (MESA)[16].

From the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) study[17]: the Czech Republic (HAPIEE-CZ), Lithuania (HAPIEE-LT), Poland (HAPIEE-PL) and Russia (HAPIEE-RU) arms of the study.

Also, the Copenhagen City Heart Study (CCHS)[18], the MRC Ely Cohort[19], the MRC Fenland Cohort[20], the IMPROVE study[21], the Prevention of Renal and Vascular Endstage Disease Study (PREVEND)[22], and the Second Manifestations of Arterial Disease (SMART) Study[23].

- Case-control and case-cohort studies

Three nested case-control studies were included - the InterAct consortium of studies[24], the Utrecht Cardiovascular Pharmacogenetics study (UCP)[25] and the Women's Health Initiative (WHI)[26].

- Intervention trials

Five RCT studies were included - the Aspirin in Asymptomatic Atherosclerosis (AAA) trial[27], the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial[28], the PROSPER trial follow-up study[29], the Thrombosis Prevention Trial follow-up study (TPT)[30], and the Women's Genome Health Study (WHGS)[31]. These trials were treated as prospective cohorts for the purposes of these analyses.

- GWA studies

Two GWA study consortia contributed data.

Data from the Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC) were included in the form of single-SNP lookups[1]. Estimates of the association between the lead *HMGCR* SNPs and fasting insulin were extracted from analysis using the Illumina Metabochip SNP genotyping platform.

An estimate of the association of the lead *HMGCR* SNPs with body weight were accessed from publicly available data from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium[32] at http://csg.sph.umich.edu/locuszoom/ (Accessed 11 August 2011).

From the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium[33], we included the following studies: deCODE[34,35], the Diabetes Gene Discovery Group (DGDG)[36], the Diabetes Genetics Initiative (DGI)[36,37], the European Special Population Network (EUROSPAN)[37–40], the Cooperative Health Research in the Region of Augsburg, Southern Germany Study (KORAgen)[41–43], the Rotterdam Study[44], and the Wellcome Trust Case-Control Consortium (WTCCC)[45].

Genetic studies - Biomarker measurement and definitions

Availability of biomarker data in genetic studies is detailed in **Supplementary Table 4.**

All biomarkers were measured using validated protocols and assays reported previously. Biomarker data used in the present analyses were taken from either the baseline phase of data collection in each study, or the next phase soonest after baseline at which data on the greatest number of biomarkers were available. Where certain biomarker variables were unavailable at the principal survey phase, they were included from closest subsequent phase with data available.

In some studies (BRHS, HAPIEE-Russia, HAPIEE-Lithuania, HAPIEE-Poland, HAPIEE-Czech Republic, CaPS and Whitehall II), LDL-cholesterol (LDL-C) concentration was not measured directly but was derived using the Friedewald formula[46]. In studies where data on total, LDL- and non-HDL-cholesterol were available in units of mg/L, these variables were converted to mmol/L using a multiplication factor of 0.02586.

Genetic studies - T2DM clinical outcome

Definitions of T2D cases differed between studies. Common definitions were therefore set in order to accommodate data from as many studies as possible whilst avoiding reporting or measurement bias. Studies used validated biochemical criteria or physician diagnosis, and others self-report to identify T2D cases (details are given in **Supplementary Table 5)**. We included all T2D cases, although, where possible, unvalidated self-reported cases were excluded.

In the majority of studies, the type of diabetes mellitus (DM) - i.e. type 1, type 2 or others - was not recorded. However, given the relative preponderance of type 2 DM in the general population and the mean age of study participants, we assumed that the overwhelming majority of cases were T2D. In ET2DS, where all participants were diabetic, individuals free from T2D from EAS were used as controls. EAS was selected as the most appropriate source of controls since its participants were recruited from the same area of Scotland as those in ET2DS.

Genetic studies - SNP selection

The aim of the SNP selection process was to identify a minimal set of variants with associations with LDL-C concentration that were both statistically strong and of greatest possible magnitude. Moreover, the highest possible minor allele frequency (MAF) was sought to increase the power of the analysis. To identify suitable SNPs for use as instruments in this analysis, 4,678 individuals in the Whitehall II study (an observational longitudinal study of UK civil servants) were genotyped using the IBC HumanCVD BeadChip (Cardiochip), a gene-centric platform including c. 48,000 SNPs in around 2,100 genes implicated in CVD[47].

Associations of the 38 SNPs included on the array at the *HMGCR* locus with LDL-C concentration were estimated using univariate linear regression models in PLINK [48]. We evaluated suitability of SNPs at the *HMGCR* locus for inclusion based on these parameters: i) p-value $<1x10^{-5}$ for association with LDL-C; ii) linkage disequilibrium (LD) between SNPs assessed using data from the 1000 Genomes Project Pilot 1 (using SNAP pairwise LD tool - www.broadinstitute.org/mpg/snap/); and, iii) a minor allele frequency (MAF) ≥20%. Within the 38 SNPs at the HMGCR locus included on the Cardiochip, we retained only one SNP from groups in strong LD ($r^2>0.85$) (**Supplementary Table 1**). Two SNPs, rs17238484 and rs12916 (between-SNP LD $R^2=0.37$) were selected for analysis in the collaborating studies, with the rs17238484 SNP designated the lead variant. Both rs17238484[49] and rs12916[50] have previously been associated with plasma LDL-C at a genome-wide level of statistical significance. Genotype data in collaborating studies were excluded if the allele call rate was <90% or the Hardy-Weinberg equilibrium (HWE) p-value was $<1x10^{-5}$ (**Supplementary Table 2**).

To confirm the influence of *HMGCR* mRNA transcript levels on LDL, we carried out imputation and eQTL analysis of a liver gene expression dataset and genotypes for 966 human liver samples of unrelated European-Americans[51]. Colocalisation analysis was run using the liver eQTL data together with LDL summary data from a publicly available meta-analysis of LDL in more than 100,000 individuals of European ancestry [50], as previously described (http://arxiv.org/abs/1305.4022).

In studies where the lead *HMGCR* SNPs were not directly genotyped, proxy SNPs were used in the analysis. Proxies were defined on the basis of their LD with each lead SNP, with a threshold of $r^2>0.85$.

Genetic studies - genotyping and genotype data quality control

Genotypes were coded as 0 (GG), 1 (GT), and 2 (TT) and included in regression models as the predictor (independent) variable. Since this coding assumes the T allele to be the effect allele, the sign of regression model beta-coefficients was inverted in order to present the effect of G allele carriage. Existing genotype data were used where available, and new genotyping commissioned where necessary. Details of genotyping platforms and data quality control are shown in **Supplementary Table 2**.

Genetic studies - statistical analysis

- Participant inclusion and relatedness

Only individuals with data available on the lead *HMGCR* SNPs (or their proxies) and at least one phenotype (biomarker or clinical endpoint) were included in the analysis. To avoid bias caused by relatedness, in studies where data on family structure were available, only the eldest member of a group of related individuals was included.

- Associations of *HMGCR* genotype with biomarkers

Mean differences in biomarkers between genotype classes were estimated using the 'metan' command in Stata v11.2 (Stata Corp., College Station, Texas), using an inverse-variance fixed effects meta-analysis model. For $\log_e$ biomarker variables, the summary meta-analysis estimate was exponentiated and subtracted from 1 to yield a proportional difference in geometric means between genotype classes. The Stata 'regress' command (or equivalent in other computer packages) was used to estimate the mean difference in biomarker level associated with carriage of each additional copy of the lead SNP effect allele. Here too, the proportional difference in geometric mean was estimated for $\log_e$-transformed variables the same technique. Within-study estimates of the per-allele SNP association with each biomarker were combined using inverse-variance fixed-effects meta-analysis.

- Subgroup analysis of SNP-biomarker associations

In order to assess potential effect modification or confounding in our estimates of genetic associations with biomarkers, we stratified the analysis according to a number of pre-specified subgroups. These were:

i. Within-study tertiles of non-HDL-C (as a surrogate for LDL-C for data were available in a greater number of studies);
ii. Users and non-users of lipid-lowering drugs;
iii. Normal weight (BMI <25), overweight (BMI ≥25-<30) and obese (BMI ≥30) individuals;
iv. Males and females; and,
v. Individuals with and without prevalent or incident T2D

Biomarker associations were estimated as described above, and heterogeneity between subgroup strata assessed with meta-regression modelling of combined meta-analysis effect estimates (using the 'metareg' command in Stata). These models sought differences between binary subgroup strata, and evidence of linear association in subgroups with ≥3 strata.

- Associations of *HMGCR* genotype with T2D outcome

Where data were available, the association of the lead *HMGCR* SNPs with risk of prevalent and incident T2D was estimated under genotypic and additive models, similarly to the associations with biomarkers. Odds ratios (ORs) for rs17238484 GT vs TT and for GG vs TT genotype, and for rs12916 AA vs AG and AA vs GG were estimated using fixed effects Mantel-Haenszel meta-analysis (Stata 'metan' command). The OR per LDL-lowering allele for each SNP was estimated using logistic regression models within each study (Stata 'logit' command), and within-study estimates were combined using inverse-variance fixed effects meta-analysis in Stata, as above. Meta-analyses were repeated using a random effects model.

Statin treatment trials included

Trials of participants with organ transplants or on dialysis were excluded, as were those with differences in participant follow-up between treatment arms, or which investigated dual lipid-lowering therapy. These meta-analyses included data from 13 intervention trials comparing statin treatment with placebo (ten trials) or standard care (three trials)[52], and from five trials comparing high- to moderate-dose statin treatment[53], respectively. At the time of their publication, data were unavailable from three eligible trials (CARE[54], SPARCL[55] and LIPS[56]). Data on new-onset T2D have subsequently been published for SPARCL[57], and data for LIPS were made available by its industrial sponsor for the present analysis, which now includes 20 trials.

Below are the randomised statin trials included in the present analysis, with references to their respective published reports. The trials are listed in chronological order of publication:

Scandinavian Simvastatin Survival Study (4S)[58]

West of Scotland Coronary Protection Study (WOSCOPS)[59]

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS TexCAPS)[60]

Long-Term Intervention with Pravastatin in Ischaemic Disease Study (LIPID)[61]

GISSI-Prevenzione [62]

Lescol® Intervention Prevention Study (LIPS)[63]

Heart Protection Study (HPS)[64]

Pravastatin in elderly individuals at risk of vascular disease (PROSPER)[65]

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid-lowering Treatment arm (ALLHAT-LLT)[66]

Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA)[67]

Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22)[68]

A to Z Trial[69]

Treating to New Targets Trial (TNT)[70]

Incremental Decrease in End Points Throught Aggressive Lipid Lowering Study (IDEAL)[71]

Stroke Prevention by Aggresive Reduction in Cholesterol Levels Trial (SPARCL)[55]

MEGA Trial[72]

Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[73]

GISSI-Heart Failure Trial (GISSI-HF)[74]

Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)[75]

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)[76]

Statin treatment trials - T2D outcome definition

Diagnostic criteria for T2D varied among the 20 contributing trials, but included one or more of, (i) physician-reported diagnosis of T2D; (ii) commencement of glucose-lowering medication; or, (iii) fasting glucose >7.0mmol/L (on at least one occasion; see **Table 1**); and (iv) T2D defined according to World Health Organisation 1999 criteria. In a subset of trials, T2D was diagnosed by the presence of elevated fasting glucose. In trials where plasma glucose was measured frequently, T2D was diagnosed after two elevated glucose readings, and after one in trials with less frequent testing.

Supplementary results

HMGCR SNP expression and co-localisation analysis

Co-localisation analysis yields a high probability of a shared signal for the eQTL in *HMGCR* and LDL-C lipid biomarkers, suggesting that *HMGCR* gene expression mediates the LDL signal (**Supplementary Figure 2**). Extensive linkage disequilibrium at the eQTL signal, however, limits the power of co-localisation analysis at this locus. The fact that other genes 1Mb around the *HMGCR* gene have a probability of co-localisation less than 3% increases the probability that *HMGCR* is the gene responsible for the LDL signal.

The T allele of rs12916 is associated with lower expression of *HMGCR* in the liver (effect = 0.054, standard error=0.012; $p=1.30x10^{-5}$; MAF = 0.39, imputation $R^2= 0.99$). Out of all the SNPs used in the co-localisation analysis, rs12916 was the SNP with the highest probability of driving the shared association between eQTL and LDL-C (54%, see **Supplementary Figure 1**). Data were unavailable in the dataset for the *HMGCR* rs17238484 SNP or its proxies.

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Supplementary tables and figures

Supplementary Table 1 - SNPs within 55kb of *HMGCR* on the Cardiochip platform and their associations with LDL-C in the Whitehall II study

					Association with LDL-C					
Selected for analysis	SNP	Chr.	Base pair position	No. of participants	LDL-C β-coefficient	95% Confidence interval	Regression model p-value	LDL-C R^2	F-statistic	MAF
✓	rs12916	5	74692295	4,666	0.12	0.08 to 0.17	6.0e-09	7.2e-03	33.96	0.40
	rs10038095	5	74673467	4,667	0.12	0.07 to 0.16	5.8e-08	6.3e-03	29.51	0.38
	rs12654264	5	74684359	4,665	0.12	0.07 to 0.16	8.3e-08	6.1e-03	28.83	0.38
	rs3846662	5	74686840	4,661	0.11	0.07 to 0.15	9.8e-08	6.1e-03	28.51	0.43
✓	rs17238484	5	74684252	4,658	0.12	0.07 to 0.17	1.0e-06	5.1e-03	23.96	0.23
	rs10474434	5	74680437	4,671	0.12	0.07 to 0.17	1.5e-06	4.9e-03	23.17	0.23
	rs3804231	5	74732535	4,672	0.14	0.07 to 0.20	1.5e-05	4.0e-03	18.75	0.13
	rs2303152	5	74677463	4,677	0.07	0.00 to 0.14	.038	9.2e-04	4.31	0.10
	rs17238540	5	74691254	4,673	-0.12	-0.25 to 0.02	.098	5.9e-04	2.74	0.02
	rs3761739	5	74667257	4,672	0.04	-0.02 to 0.10	.152	4.4e-04	2.05	0.15
	rs3761740	5	74667889	4,676	0.04	-0.03 to 0.11	.229	3.1e-04	1.45	0.09
	rs17238372	5	74672629	4,677	0.13	-0.08 to 0.34	.231	3.1e-04	1.44	0.01
	rs17648288	5	74732394	4,674	0.04	-0.03 to 0.11	.258	2.7e-04	1.28	0.09
	rs16872536	5	74714241	4,673	0.04	-0.03 to 0.11	.274	2.6e-04	1.20	0.08
	rs10474435	5	74693036	4,674	0.10	-0.09 to 0.29	.285	2.5e-04	1.15	0.01
	rs16872526	5	74711473	4,664	0.04	-0.03 to 0.11	.29	2.4e-04	1.12	0.08
	rs10038689	5	74718367	4,677	0.10	-0.09 to 0.29	.302	2.3e-04	1.07	0.01
	rs17244848	5	74679426	4,632	0.03	-0.04 to 0.11	.336	2.0e-04	0.92	0.09
	rs17244939	5	74666852	4,671	-0.07	-0.22 to 0.08	.369	1.7e-04	0.81	0.02
	rs4704209	5	74670229	4,670	0.04	-0.05 to 0.13	.42	1.4e-04	0.65	0.06
	rs3889900	5	74741803	4,678	-	-	-	-	-	<0.01
	rs17238477	5	74680879	4,678	-	-	-	-	-	<0.01
	rs17244715	5	74667984	4,678	-	-	-	-	-	<0.01
	rs17238519	5	74689134	4,671	-	-	-	-	-	<0.01
	rs17244946	5	74667566	4,676	-	-	-	-	-	<0.01
	rs17238435	5	74677582	4,678	-	-	-	-	-	<0.01
	rs17244708	5	74667603	4,675	-	-	-	-	-	<0.01
	rs17244890	5	74688485	4,671	-	-	-	-	-	<0.01
	rs17238337	5	74667055	4,675	-	-	-	-	-	<0.01
	rs16872532	5	74713739	4,678	-	-	-	-	-	<0.01
	rs17244722	5	74668837	4,676	-	-	-	-	-	<0.01
	rs17244960	5	74680009	4,676	-	-	-	-	-	<0.01
	rs17244883	5	74688082	4,676	-	-	-	-	-	<0.01
	rs17238449	5	74678164	4,678	-	-	-	-	-	<0.01
	rs17244757	5	74672460	4,676	-	-	-	-	-	<0.01

Selected for analysis	SNP	Chr.	Base pair position	No. of participants	Association with LDL-C: LDL-C β-coefficient	95% Confidence interval	Regression model p-value	LDL-C R^2	F-statistic	MAF
	rs17244729	5	74669229	4,676	-	-	-	-	-	<0.01
	rs17238554	5	74693408	4,674	-	-	-	-	-	<0.01
	rs17238575	5	74680466	4,671	-	-	-	-	-	<0.01

SNPs are ranked on p-value and β-coefficient; β-coefficients are reported on the log scale. For SNPs where β-coefficient is absent, no variation in genotype was observed in the Whitehall II study sample owing to very low minor allele frequency and consequently a regression model could not be fitted.

Abbreviations: Chr – chromosome; R^2 – proportion of variance explained; MAF – minor allele frequency

Supplementary Table 2 – Genotype information for studies contributing individual participant-level data

		rs17238484								rs12916							
Study	Genotyping platform	SNP call rate (%)	Proxy SNP used (LD, r^2)*	GG	GT	TT	MAF (%)	HWE χ^2	HWE p	SNP call rate (%)	Proxy SNP used (LD, r^2)*	TT	TC	CC	MAF (%)	HWE χ^2	HWE p
AAA	KASPAR		-	1,358	792	100	22.0	1.31	0.25	95.9	-	999	943	321	35.0	16.12	6.0×10^{-5}
ARIC	IBC Cardiochip		-	5,635	3,386	565	23.6	3.53	0.06	100.0	-	3,432	4,528	1,628	40.6	4.16	0.04
BRHS	KASPar	98.3	-	2,328	1,325	223	27.4	3.56	0.06	97.3	-	1,620	1,562	657	37.5	66.5	3.5×10^{-16}
BWHHS	IBC Cardiochip		-	2,010	1,245	185	23.5	0.19	0.67	99.9	-	1,218	1,668	557	40.4	0.12	0.72
CaPS	KASPar		-	837	498	70	22.7	0.14	0.71	98.5	-	563	627	216	37.7	3.55	0.06
CARDIA	IBC Cardiochip		-	836	527	80	23.8	0.07	0.80	100.0	-	472	736	235	41.8	3.38	0.07
CCHS	ABI TaqMan	90.5	-	5,532	3,385	488	23.2	1.03	0.31	-	-	-	-	-	-	-	-
CFS	IBC Cardiochip		-	79	48	8	23.7	0.04	0.84	100.0	-	45	58	32	45.2	2.38	0.12
CHS	IBC Cardiochip		-	2,344	1,381	225	23.2	1.31	0.25	100.0	-	1,413	1,911	628	40.1	0.18	0.67
EAS	ABI TaqMan		-	518	287	46	22.3	0.57	0.45	93.9	-	323	402	131	38.8	0.10	0.75
ELSA	KASPar		-	3,352	1,852	277	22.0	1.04	0.31	-	-	-	-	-	-	-	-
Ely	Metabochip		rs3761742 (1.00)	989	544	68	21.2	0.39	0.53	-	-	-	-	-	-	-	-
EPIC-NL	IBC Cardiochip		-	3,009	1,837	251	22.6	1.02	0.31	-	-	-	-	-	-	-	-
ET2DS[1]	KASPar		-	690	311	52	19.71	4.68	0.03	97.8	-	501	390	155	33.5	27.7	0.14
MRC Fenland	Metabochip		rs3761742 (1.00)	1,953	1,061	172	22.1	3.11	0.08	-	-	-	-	-	-	-	-
FHS	IBC Cardiochip		-	807	456	69	22.3	0.19	0.66	100.0	-	491	647	198	39.0	0.41	0.52
HAPIEE-CZ	KASPar		-	3,996	2,384	341	22.8	0.26	0.55	-	-	-	-	-	-	-	-
HAPIEE-LT	KASPar		-	4,049	2,424	407	23.5	3.04	0.08	-	-	-	-	-	-	-	-
HAPIEE-PL	KASPar		-	3,456	1,988	282	22.3	0.03	0.86	-	-	-	-	-	-	-	-
HAPIEE-RU	KASPar		-	4,264	2,423	377	22.5	1.82	0.18	-	-	-	-	-	-	-	-
IMPROVE	Metabochip		-	1,937	1,310	215	25.1	0.11	0.74	100.0	-	1,081	1,748	636	43.6	2.32	0.13
InterAct	Illumina 660W/ Sequenom/ ABI TaqMan	100.0	rs3761742 (1.00)	11,843	6,209	838	20.9	0.45	0.50	100.0	-	3,122	9,138	6,634	40.7	0.07	0.79
JUPITER	Illumina Omni 1M Quad	100.0	-	5,363	2,983	403	21.7	0.21	0.65	100.0	-	3,249	4,157	1,340	39.1	0.03	0.86
MESA	IBC Cardiochip	100.0	-	1,333	829	135	23.9	0.17	0.68	100.0	-	792	1,138	368	40.77	1.47	0.22
MRC NSHD	KASPar	95.8	-	1,432	830	140	23.1	1.82	0.18	100.0	-	1,048	967	387	36.2	39.9	2.7×10^{-10}
NPHS-II	ABI TaqMan		-	1,646	923	131	21.9	0.01	0.91	100.0	-	960	1,286	456	41.1	0.10	0.75
PROSPER	Illumina 660K	>97.5	rs3761742 (1.00)	3,307	1,710	227	20.6	0.10	0.75	-	-	-	-	-	-	-	-
SMART	KASPar	99.4	-	4,915	3,007	449	23.3	0.15	0.70	-	-	-	-	-	-	-	-

TPT	ABI TaqMan		-	2,349	1,403	197	22.8	0.45	0.50	-	-	-	-	-	-	-	-	-
UCP	IBC Cardiochip		-	973	556	102	23.3	3.48	0.06	-	-	-	-	-	-	-	-	-
WGHS	Illumin HumanHap Duo+	100.0	rs1051795 (0.95)	14,559	7,708	1,020	20.9	2.84×10^{-5}	0.99	99.99	-	8,260	11,213	3,818	40.5	0.02	0.90
WHI	IBC Cardiochip		-	3,442	1,779	316	21.8	17.85	2×10^{-5}	100.0	-	2,042	2,692	981	40.7	3.37	0.07
Whitehall II	IBC Cardiochip		-	3,020	1,765	252	22.5	0.08	0.78	99.8	-	1,794	2,421	832	40.5	0.10	0.75

Abbreviations: HWE - Hardy-Weinberg equilibrium; MAF - minor allele frequency; LD – linkage disequilibrium

*Linkage disequilibrium data derived from 1000 Genomes Pilot 1

[1] Minor allele frequency in diabetes cases

Supplementary Table 3 - Collaborating genetic study characteristics

Study name	Study design	Geographical location	Sampling frame	Participants included	Baseline year(s)	% Male	Age (Mean ,SD)	Fasting blood samples?
AAA	RCT	UK	General practice	2,250	1998-2001	28.5	61.9 (6.6)	No
ARIC	Cohort	USA	Community	9,586	1986	53.5	54.3 (5.7)	
BRHS	Cohort	UK	General practice	3,876	1978-1980	100	68.7 (5.5)	
BWHHS	Cohort	UK	General practice	3,440	1999-2001	0	69.3 (5.5)	
CaPS	Cohort	UK	Community	1,405	1984-1988	100	56.7 (4.4)	
CARDIA	Cohort	USA	Community	1,443	1985-1986	53.4	25.6 (3.4)	
CCHS	Cohort	Denmark	Population	9,405	1990-2003	44.2	56 .7 (16)	No
CFS	Cohort	USA	Community (family)	135	1995	41.5	53.9 (14.7)	
CHS	Cohort	USA	Community	3,950	1989	45.0	70.4 (5.3)	Yes
deCODE	Cohort	Iceland	Population, clinic	24,650	-	-	-	-
DGDG	C-C	France	Clinic, population	1,376	-	-	-	-
DGI	C-C	Finland, Sweden	Population	2,097	-	47.7	-	-
EAS	Cohort	UK	General practices	851	1987	50.8	64.3 (5.6)	Yes
ELSA	Cohort	UK	HSE respondents	5,481	1998, 1999, 2001	45.6	61.0 (9.6)	
Ely	Cohort	UK	General practice	1,601	1990-1992	47.0	61.1 (9.2)	
EPIC-NL	Nested C-Ct	Netherlands	Population	5,194	1993-1997	21.9	54.1 (10.1)	No
ET2DS	Cohort	UK	Community (cases)	1,053	2006-2007	50.3	67.9 (4.2)	Yes
EUROSPAN	C-C	Europe	Population	3,978	-	-	-	-
MRC Fenland	Cohort	UK	General practices	3,186	2004 (ongoing)	46.0	46.9 (7.1)	
FHS	Cohort	USA	Community	1,332	1948/1971/2002	52.7	45.7 (10.1)	
FUSION	C-C	Finland	Community	2,335	-	-	-	-
HAPIEE-Czech Republic	Cohort	Czech Republic	Population	6,721	2002-2005	46.6	58.3 (7.1)	
HAPIEE-Lithuania	Cohort	Lithuania	Population	6,880	2006-2008	45.4	61.0 (7.6)	
HAPIEE-Poland	Cohort	Poland	Population	5,726	2002-2005	45.4	57.6 (6.9)	
HAPIEE-Russia	Cohort	Russia	Population	7,064	2002-2005	45.6	58.9 (7.1)	
IMPROVE	Cohort	Europe	Clinic	3,462	2004	48.3	64.2 (5.4)	Yes
InterAct	Cohort	Europe	Population	18,894	1991	49.7	55.6	
JUPITER	RCT	America, Europe, Africa	Clinic	8,749	2003-2005	67.8	66.1	Yes
KORAgen	Nested C-C	Germany	Population	1,871	-	-	-	-
MESA	Cohort	USA	Population	2,297	2000-2002	47.8	62.7 (10.2)	Yes
MRC NSHD	Birth cohort	UK	Birth register	2,402	1946	49.8	53.0 (0.0)	No
NPHS-II	Cohort	UK	General practices	2,700	1989-1994	100	56.6 (3.4)	

PREVEND	Prospective	Netherlands	Population	3,649	1997	51		
PROSPER	RCT	Europe	Clinic	5,804	1997-1999	48.3	75.3 (3.3)	Yes
Rotterdam	Nested C-C	Netherlands	Population	5,939	-	-	-	-
SMART	Cohort	Netherlands	Clinic	8,371	1996-2011	65.1	56.5 (12.4)	Yes
TPT	RCT	UK	General practice	3,949	1984-1989	100	57.4 (6.7)	
UCP	Nested C-C	Netherlands	Clinic	1,631	2007	74.5	62.8 (9.6)	
WGHS	RCT	North America	Professional	23,294	1992-1994	0	54.7	Yes
WHI	Nested C-C	USA	Community	5,537	1994-1998	0	68.1 (6.6)	Yes
Whitehall II	Cohort	UK	Workplace	5,037	1985-1988	73.6	49.2 (6.0)	
WTCCC	C-C	UK	Population	4,862	-	-	-	-

Abbreviations: C-C : case-control; C-Ct: case-cohort; HSE - Health Survey for England
- : Data unavailable

Supplementary Table 4 - Data availability for biomarkers and events in studies contributing to the primary genetic analysis

	Biomarkers										Clinical events (prevalent & incident)
	Total chol.	LDL-C	Non-HDL-C	Weight	BMI	Waist circ.	Hip circ.	Waist:hip ratio	Plasma glucose	Plasma insulin	Diabetes mellitus
AAA	2,242	-	-	-	-	-	-	-	-	-	48
ARIC	9,567	9,412	9,567	9,578	9,578	9,576	9,576	9,575	7,740	9,578	1,184
BRHS	3,855	3,746	3,740	3,867	3,873	3,850	3,859	3,848	3,856	-	294
BWHHS	3,257	3,177	3,253	3,249	3,243	3,233	3,236	3,239	3,252	3,274	439
CaPS	1,338	1,299	-	1,376	1,360	1,354	1,353	1,352	1,339	696	117
CARDIA	1,436	1,436	1,436	1,438	1,437	1,436	1,437	1,436	1,331	1,321	99
CCHS	9,394	9,379	9,388	9,385	9,382	9,364	9,365	9,365	-	-	843
CFS	39	38	39	134	134	45	45	45	39	39	17
CHS	3,941	-	3,936	-	3,938	-	-	-	3,936	-	-
deCODE	-	-	-	-	-	-	-	-	-	-	1,456
DGDG	-	-	-	-	-	-	-	-	-	-	679
DGI	-	-	-	-	-	-	-	-	-	-	1,022
EAS	850	846	846	851	851	-	-	-	849	-	30
ELSA	5,449	5,304	5,447	5,323	5,235	5,362	5,351	5,346	-	-	-
Ely	1,600	1,597	-	1,599	1,598	1,588	1,587	1,586	1,598	1,596	89
EPIC-NL	4,337	4,261	3,060	5,186	5,185	5,181	5,181	5,179	3,455	-	1,110
ET2DS	1,025	-	1,025	1,032	1,032	1,028	1,028	1,028	1,021	-	1,053
EUROSPAN	-	-	-	-	-	-	-	-	-	-	268
MRC Fenland	3,180	3,155	-	3,184	3,184	3,183	3,183	3,182	3,178	3,148	38
FHS	845	844	844	858	316	785	784	783	825	749	161
FUSION	-	-	-	-	-	-	-	-	-	-	1,161
HAPIEE-CZ	6,568	6,301	6,543	6,719	6,716	-	-	6,708	914	-	355
HAPIEE-LT	6,838	6,655	6,720	6,874	6,874	-	-	6,873	6,708	-	389
HAPIEE-PL	5,720	5,647	5,720	5,720	5,716	-	-	5,719	5,713	-	423
HAPIEE-RU	7,062	7,058	7,060	7,064	7,063	-	-	7,061	1,042	-	254
IMPROVE	3,456	3,395	-	3,461	3,461	3,462	3,462	3,462	3,455	-	858
InterAct	-	-	-	-	-	-	-	-	-	-	8,247
JUPITER	-	-	-	8,729	8,723	-	-	-	-	-	279
KORAgen	-	-	-	-	-	-	-	-	-	-	433
MESA	2,292	2,260	2,290	2,297	2,297	2,297	2,297	2,297	2,292	-	220

MRC NSHD	2,236	2,072	2,082	2,382	2,379	2,961	2,388	2,957	-	-	-
NPHS-II	2,680	1,703	1,789	2,698	2,697	-	-	-	-	-	221
PREVEND	3,626	3,496	3,554	3,623	3,622	3,622	3,622	3,622	3,465	3,402	140
PROSPER	5,244	5,242	-	5,243	5,242	-	-	-	5,060	5,032	269
Rotterdam	-	-	-	-	-	-	-	-	-	-	1,178
SMART	7,897	7,448	7,879	7,925	7,924	6,715	6,713	6,716	7,879	4,373	-
TPT	3,912	-	-	3,932	3,932	-	-	-	-	-	-
UCP	-	-	-	1,592	1,487	-	-	-	-	-	-
WGHS	-	-	-	23,043	23,291	-	-	-	-	-	1,444
WHI	2,920	1,472	2,861	-	5,489	-	-	-	-	-	272
Whitehall II	4,739	4,658	4,724	4,752	4,746	4,693	4,692	4,688	4,543	4,245	334
WTCCC	-	-	-	-	-	-	-	-	-	-	1,924
Total	117,545	101,901	84,415	143,114	152,005	69,735	69,159	96,067	73,490	37,453	27,348

Abbreviations: TC - total cholesterol; HDL-C - high density lipoprotein cholesterol; LDL-C - low density lipoprotein cholesterol

Supplementary Table 5 - Clinical outcome definitions

	Diabetes (all aetiology, prevalent & incident)		
	Self report	Medical records	Clinical/lab. measures
AAA	●	●	
ARIC		●	●
BRHS		●	
BWHHS	●	●	
CaPS	●	●	●
CARDIA	●	●	●
CCHS		●	
CFS		●	
CHS		●	●
deCODE	-	-	-
EAS	●		
ELSA	n/a	n/a	n/a
Ely	n/a	n/a	n/a
EPIC-NL	●	●	
ET2DS		●	●
EUROSPAN	-	-	-
MRC Fenland	n/a	n/a	n/a
FHS		●	
FUSION	-	-	-
HAPIEE-CZ	●		
HAPIEE-LT	●		
HAPIEE-PL	●		
HAPIEE-RU	●		
IMPROVE	n/a	n/a	n/a
InterAct	●	●	●
JUPITER		●	●
KORAgen			
MESA	●		●
MRC NSHD	n/a	n/a	n/a
NPHS-II	●	●	
PROSPER		●	●
Rotterdam	-	-	-
SMART	n/a	n/a	n/a
TPT		●	
WGHS	●	●	-
WHI	●		
Whitehall II	●	●	●
WTCCC	-	-	-

Abbreviations: n/a - T2D data not included in analysis; - - T2D definition information unavailable

Supplementary Table 6 – Associations of HMGCR rs17238484 with biomarkers and T2D risk in pre-specified subgroups.

P-values are for meta-regression between subgroup strata.

		Tertiles of non-HDL-C		
Biomarker	Low	Mid	High	
		Estimate (95% CI)		*Meta-regression p-value*
LDL-C (mmol/L)	-0.013 (-0.022 to -0.004)	-0.013 (-0.021 to -0.006)	-0.034 (-0.047 to -0.020)	0.055
Plasma glucose (%)	1.658 (-0.386 to 3.744)	2.364 (0.281 to 4.490)	1.923 (-0.201 to 4.092)	0.855
Plasma insulin (%)	4.628 (1.451 to 7.905)	3.761 (0.625 to 6.995)	2.884 (-0.089 to 5.946)	0.445
BMI (kg/m^2)	0.035 (0.018 to 0.052)	0.035 (0.018 to 0.052)	0.029 (0.012 to 0.045)	0.596
Body weight (kg)	0.032 (0.013 to 0.050)	0.042 (0.024 to 0.060)	0.020 (0.002 to 0.037)	0.354

		Lipid-lowering drug use	
Biomarker	Users	Non-users	
	Estimate (95% CI)		*Meta-regression p-value*
LDL-C (mmol/L)	-0.044 (-0.072 to -0.016)	-0.075 (-0.088 to -0.062)	0.122
Plasma glucose (%)	1.531 (-1.460 to 4.613)	0.773 (-0.909 to 2.483)	0.671
Plasma insulin (%)	5.265 (0.562 to 10.189)	2.987 (0.424 to 5.615)	0.423
BMI (kg/m^2)	0.039 (0.013 to 0.065)	0.025 (0.013 to 0.038)	0.349
Body weight (kg)	0.035 (0.008 to 0.062)	0.023 (0.010 to 0.036)	0.448
T2D (odds ratio)	0.981 (0.890 to 1.082)	1.038 (0.985 to 1.094)	0.316

		BMI classes		
Biomarker	Normal (<25)	Overweight (25-30)	Obese (>30)	
		Estimate (95% CI)		*Meta-regression p-value*
LDL-C (mmol/L)	-0.073 (-0.090 to -0.056)	-0.059 (-0.076 to -0.043)	-0.070 (-0.092 to -0.048)	0.247
Plasma glucose (%)	1.631 (0.033 to 3.254)	0.199 (-1.565 to 1.994)	1.126 (-1.935 to 4.282)	0.249
Plasma insulin (%)	2.558 (0.136 to 5.039)	-0.130 (-2.622 to 2.426)	2.488 (-1.422 to 6.552)	0.150
BMI (kg/m^2)	-	-	-	-
Body weight (kg)	0.007 (-0.003 to 0.017)	0.011 (0.002 to 0.021)	0.007 (-0.012 to 0.026)	0.538

		Sex	
Biomarker	Male	Female	
	Estimate (95% CI)		*Meta-regression p-value*
LDL-C (mmol/L)	-0.065 (-0.079 to -0.051)	-0.061 (-0.076 to -0.046)	0.909
Plasma glucose (%)	0.881 (-0.823 to 2.613)	2.097 (0.326 to 3.900)	0.346
Plasma insulin (%)	2.054 (-0.495 to 4.668)	2.868 (0.350 to 5.450)	0.665
BMI (kg/m^2)	0.019 (0.007 to 0.031)	0.032 (0.017 to 0.046)	0.197
Body weight (kg)	0.022 (0.009 to 0.034)	0.026 (0.012 to 0.039)	0.650

		T2D cases/controls	
Biomarker	Cases	Controls	
	Estimate (95% CI)		*Meta-regression p-value*
LDL-C (mmol/L)	-0.051 (-0.085 to -0.016)	-0.065 (-0.077 to -0.053)	0.570
Plasma glucose (%)	-2.704 (-7.494 to 2.335)	0.698 (-0.306 to 1.712)	0.199
Plasma insulin (%)	0.245 (-6.159 to 7.086)	1.945 (0.012 to 3.915)	0.637
BMI (kg/m^2)	0.022 (-0.011 to 0.055)	0.024 (0.013 to 0.035)	0.906
Body weight (kg)	-0.003 (-0.035 to 0.030)	0.024 (0.012 to 0.035)	0.136

Supplementary Table 7 – Associations of *HMGCR* rs12916 with plasma lipids, T2D-related biomarkers and T2D risk – fixed effects meta-analysis

		rs12916			Heterogeneity	
Biomarker	**Total n (studies)**	**Per-allele effect**	**95% CI**	**Effect p-value**	**I^2**	**Heterogeneity p-value**
Total cholesterol (mmol/L)	40,712 (15)	-0.077	-0.091 to -0.062	4.74×10^{-25}	27.5	0.15
LDL-C (mmol/L)	32,674 (13)	-0.083	-0.098 to -0.068	4.40×10^{-28}	33.3	0.12
Non-HDL-C (mmol/L)	39,591 (15)	-0.074	-0.089 to -0.059	9.50×10^{-22}	28.2	0.15
Plasma insulin (%)	19,918 (7)	0.659	-0.631 to 1.967	0.318	44.4	010
Plasma glucose (%)	30,641 (12)	0.125	-0.135 to 0.387	0.35	0.0	0.54
Body weight (kg)	65,871 (15)	0.203	0.043 to 0.362	0.01	0.0	0.84
BMI (kg/m^2)	75,140 (17)	0.083	0.031 to 0.135	1.62×10^{-3}	0.0	0.90
Height (m)	39,771, (14)	0.0001	-0.001 to 0.001	0.77	0	0.67
Waist circumference (cm)	30,313 (11)	0.303	0.102 to 0.504	0.003	0	0.55
Hip circumference (cm)	30,313 (11)	0.193	0.050 to 0.337	8.07×10^{-3}	28.6	0.17
Outcome	**No. of cases/controls (studies)**	**Per-allele odds ratio**	**95% CI**	**Effect p-value**	**I^2**	**Heterogeneity p-value**
T2D	14,976/73,574 (16)	1.06	1.03 to 1.09	9.58×10^{-5}	36.7	0.07

Supplementary Table 8 - Associations of rs17238484 and rs12916 with T2D-related biomarkers and T2D risk - random effects meta-analyses

rs17238484	Biomarker	No. of individuals (studies)	Per-allele beta coefficient	95% confidence interval	Effect p-value
	LDL-C (mmol/L)	101,919 (26)	-0.065	-0.077 to -0.052	6.20×10^{-25}
	Total cholesterol (mmol/L)	117,545 (30)	-0.067	-0.079 to -0.055	4.60×10^{-30}
	Non-HDL-C (mmol/L)	103,375 (27)	-0.067	-0.081 to -0.053	1.20×10^{-21}
	Body weight (kg)	143,113 (30)	0.301	0.175 to 0.428	3.20×10^{-6}
	BMI (kg/m^2)	152,004 (32)	0.105	0.066 to 0.145	1.80×10^{-7}
	Height (m)	77,291 (23)	0.001	-0.000 to 0.002	0.23
	Waist circumference (cm)	69,163 (19)	0.315	0.158 to 0.472	8.30×10^{-5}
	Hip circumference (cm)	69,159 (19)	0.211	0.101 to 0.321	1.70×10^{-4}
	Plasma glucose (%)	73,490 (23)	0.230	0.020 to 0.441	0.03
	Plasma insulin (%)	37,453 (12)	0.016	0.005 to 0.027	3.60×10^{-3}
	Outcome	**No. of cases/controls (studies)**	**Odds ratio**	**95% confidence interval**	**p-value**
	T2DM	26,236/164,021 (35)	1.02	1.00 to 1.04	0.10

rs12916	Biomarker	No. of individuals (studies)	Per-allele beta coefficient	95% confidence interval	Effect p-value
	LDL-C (mmol/L)	32,674 (13)	-0.081	-0.101 to -0.062	5.50×10^{-16}
	Total cholesterol (mmol/L)	40,712 (15)	-0.075	-0.093 to -0.057	7.20×10^{-16}
	Non-HDL-C (mmol/L)	39,591 (15)	-0.072	-0.091 to -0.053	8.10×10^{-14}
	Body weight (kg)	65,871 (15)	0.203	0.043 to 0.362	0.01
	BMI (kg/m^2)	75,140 (17)	0.083	0.031 to 0.135	1.60×10^{-3}
	Waist circumference (cm)	39,771 (14)	0.000	-0.001 to 0.001	0.77
	Hip circumference (cm)	30,313 (11)	0.303	0.102 to 0.504	3.10×10^{-3}
	Plasma glucose (%)	30,313 (11)	0.195	0.008 to 0.382	0.04
	Plasma insulin (%)	30,641 (12)	0.130	-0.140 to 0.391	0.35
	Height (m)	19,918 (7)	0.004	-0.016 to 0.023	0.72
	Outcome	**No. of cases/controls (studies)**	**Odds ratio**	**95% confidence interval**	**p-value**
	T2DM	14,976/73,574 (16)	1.07	1.02 to 1.12	1.10×10^{-3}

Supplementary Table 9 – Effect of statin therapy on body weight and new-onset T2D risk– fixed effects meta-analysis

Trials	Weight change (kg)	95 % CI
Placebo- or standard care- controlled	0.33	0.26 to 0.41
Intensive vs moderate dose	-0.08	-0.16 to 0.01
All trials combined	0.16	0.11 to 0.22

Trials	T2D Odds Ratio	95 % CI
Placebo- or standard care- controlled	1.12	1.05 to 1.19
Intensive vs moderate dose	1.12	1.04 to 1.22
All trials combined	1.12	1.07 to 1.17

Supplementary Table 10 – Associations of *HMGCR* rs17238484 and rs12916 with T2D risk in 35 studies contributing to this analysis, and in combination with data from GWA study data from the DIAGRAM consortium

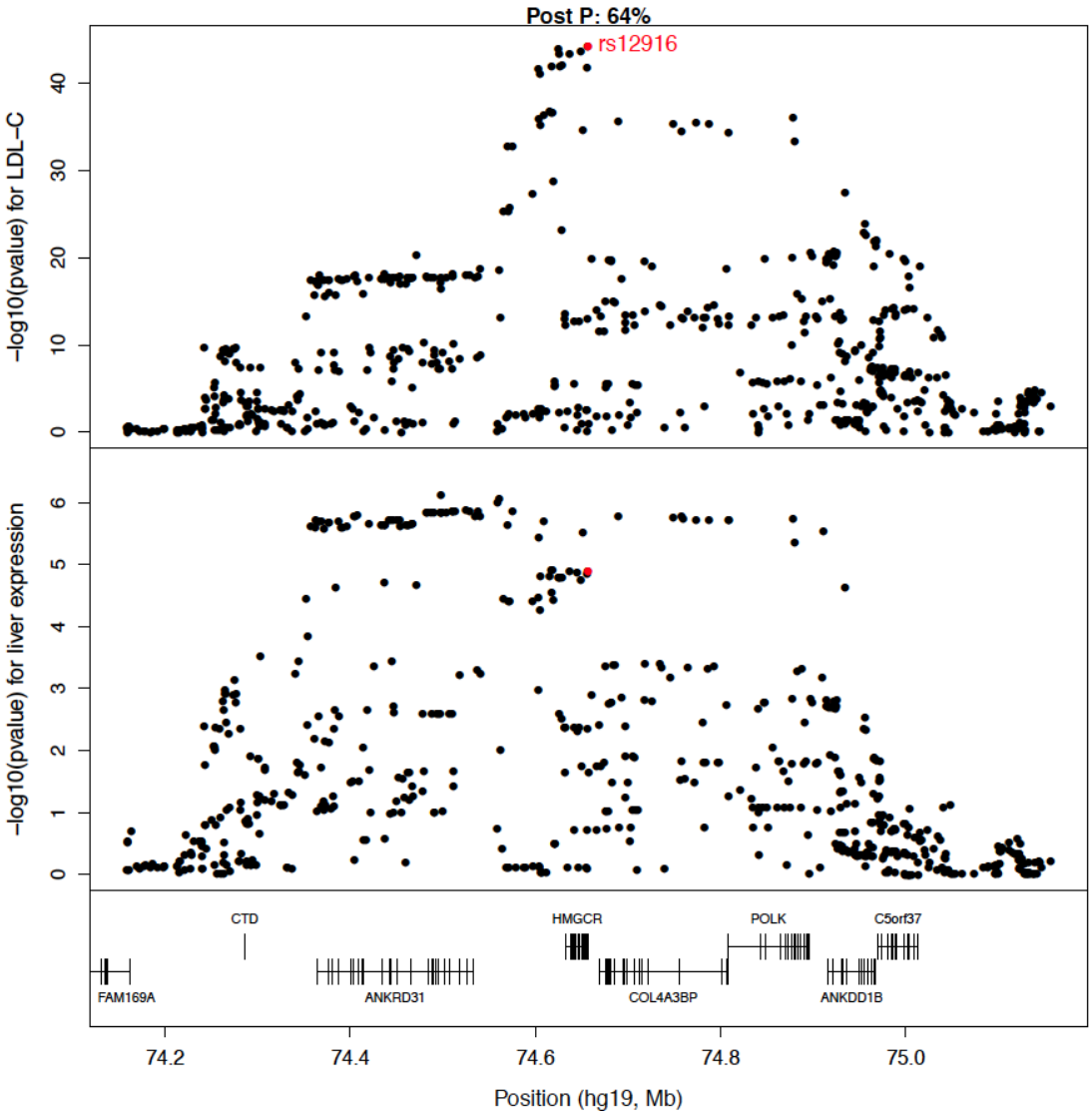
	rs17238484-G *OR (95% CI)*	*Cases/controls or total n (studies)*	**rs12916-T** *OR (95% CI)*	*Cases/controls or total n (studies)*
Risk of T2D: original studies	1.02 (1.00 to 1.05)	26,236/164,021 (35)	1.06 (1.03 to 1.09)	14,976/73,574 (16)
Risk of T2D: Morris GWAS+Metabochip analysis	1.03 (0.99 to 1.06)	51,943 (19)*	1.01 (0.99 to 1.04)	76,774 (19)*
Risk of T2D: original studies + unique Morris data	1.03 (1.01 to 1.06)	181,111 (38)*	1.02 (1.00 to 1.04)	151,329 (38)*

Estimates shown are derived from i) 35 observational population studies contributing to the current analysis; ii) Morris et al. GWAS+Metabochip studies consortium; iii) meta-analysis of original studies and studies contributing to the current analysis combined with the remaining studies unique to the Morris et al. *consortium.*

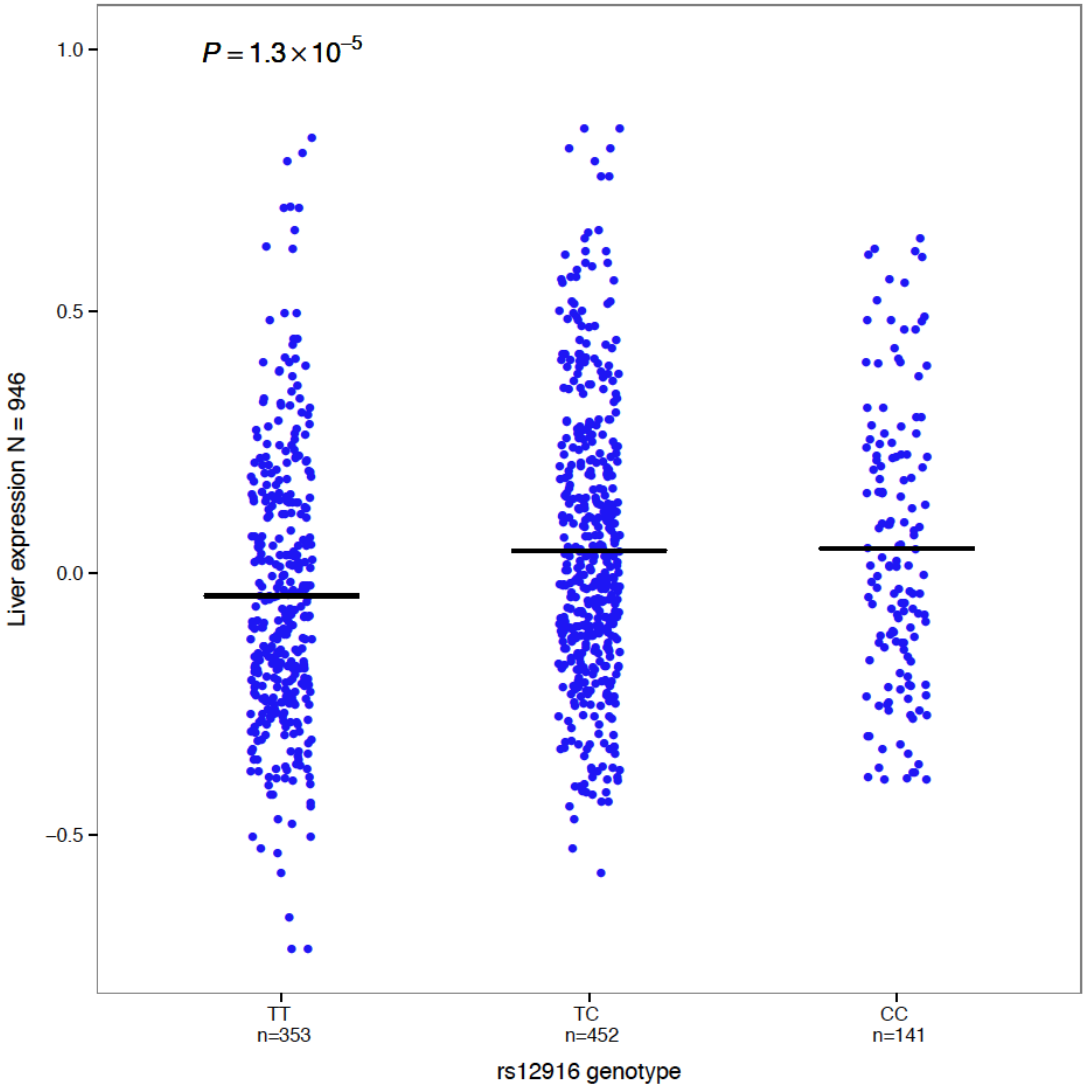
Effective sample size as reported by the DIAGRAM consortium at [*http://diagram-consortium.org/downloads.htm*](http://diagram-consortium.org/downloads.htm)
**Numbers of cases and controls unavailable from Morris* et al*. data*

Supplementary Figure 1 - Associations of SNPs at the *HMGCR* locus with LDL-C concentration and liver gene expression

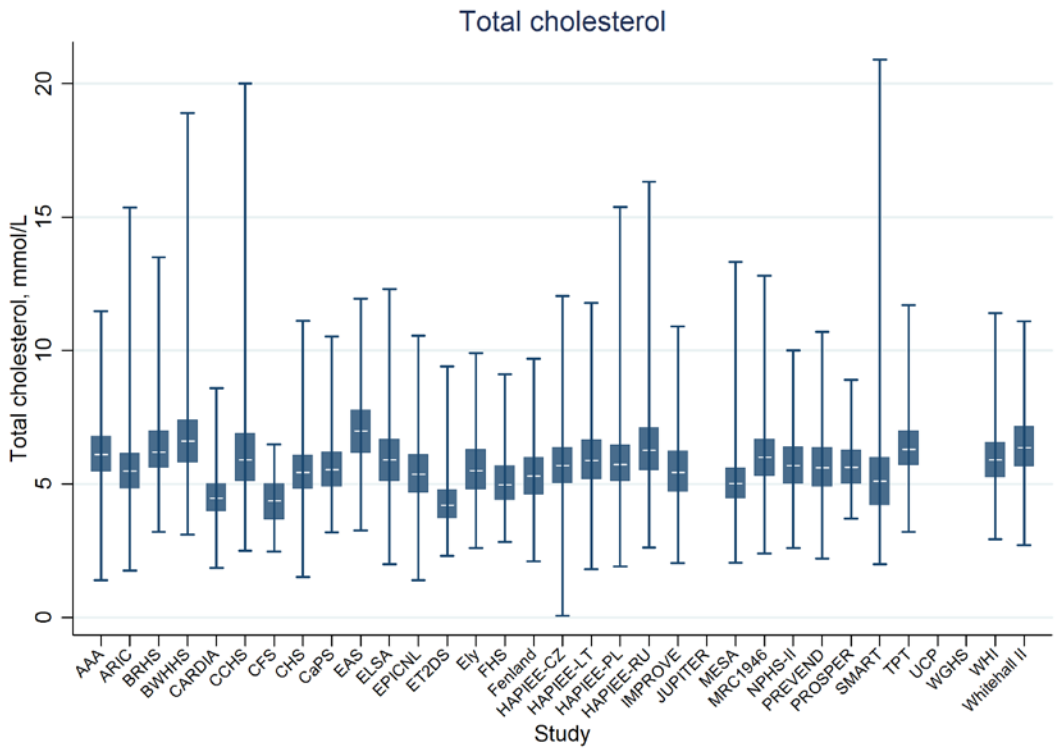
The x-axis shows the physical position on chromosome 5 (Mb). Each dot represents one variant (SNP or indel - imputed or directly typed). Upper panel graph y-axis uses p-values from a published meta-analysis of LDL-C levels in >100,000 individuals[50]. Lower panel y-axis shows the -$\log_{10}$p-value for association with *HMGCR* gene expression in liver. The posterior probability ("Post P") that LDL-C co-localises with *HMGCR* liver expression is shown on top of the graph. There is a high probability that *HMGCR* expression is mediating the LDL-C signal.

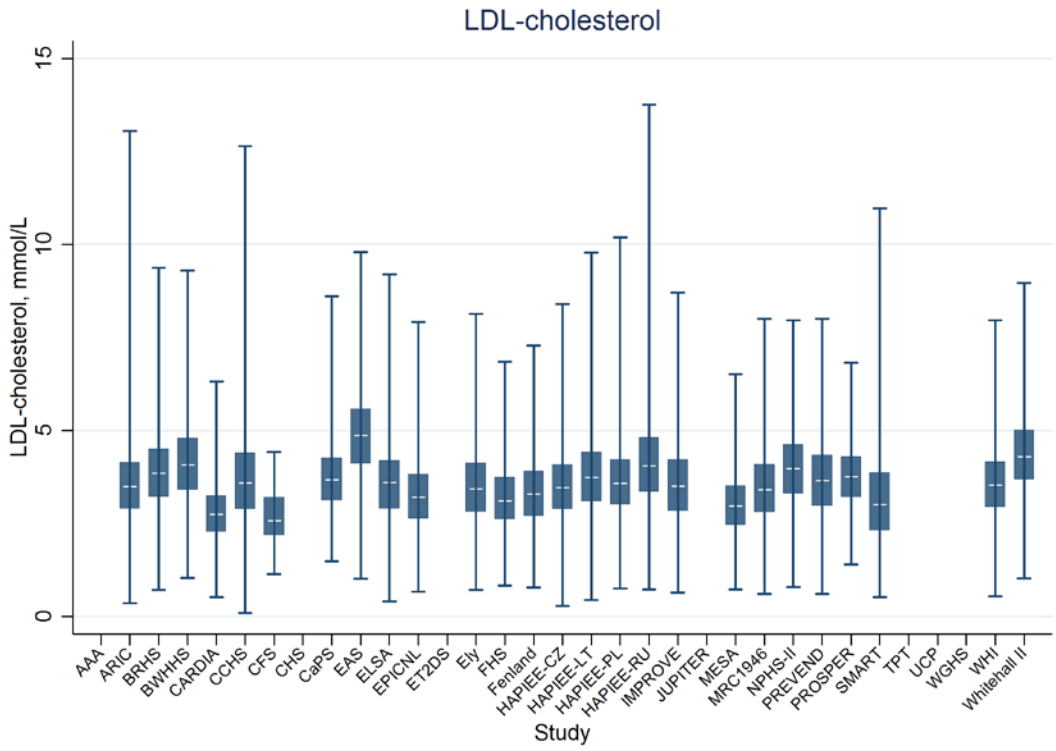


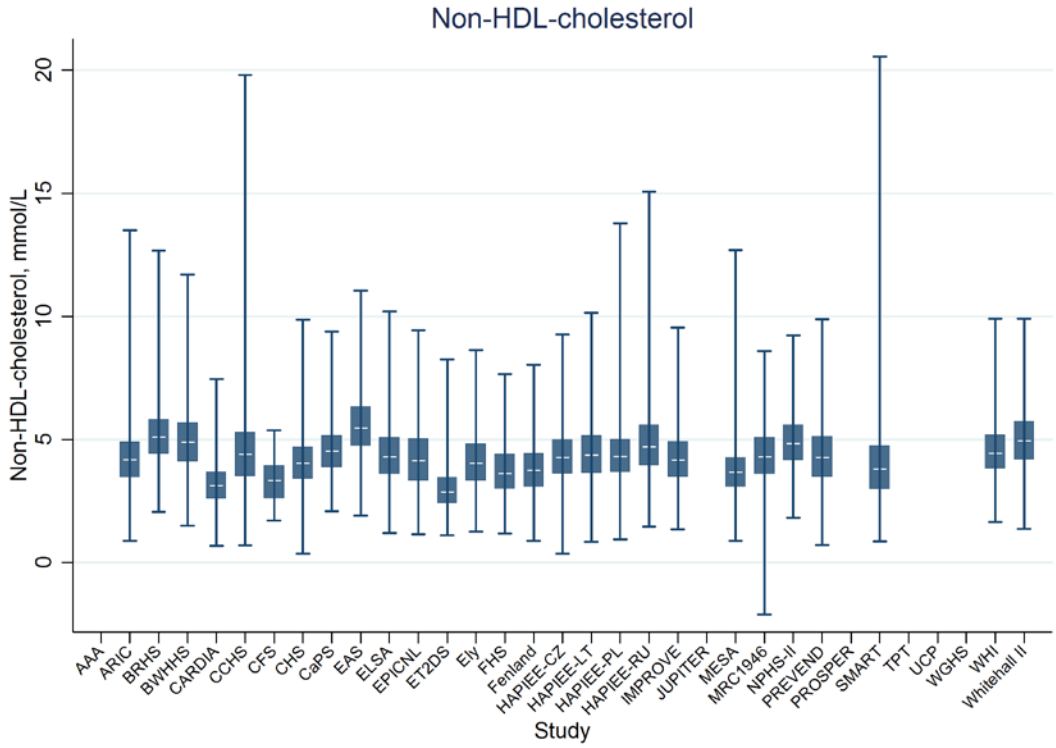
Supplementary Figure 2 - Effect of HMGCR rs12916 genotype on liver expression of HMGCR
946 individuals had expression measurements and genotypes that were directly typed or imputed (uncertain genotypes were removed). The allele T of the SNP rs12916 is associated with a decreased effect of HMGCR expression in liver (1-d.f. $p=1.3x10^{-5}$).

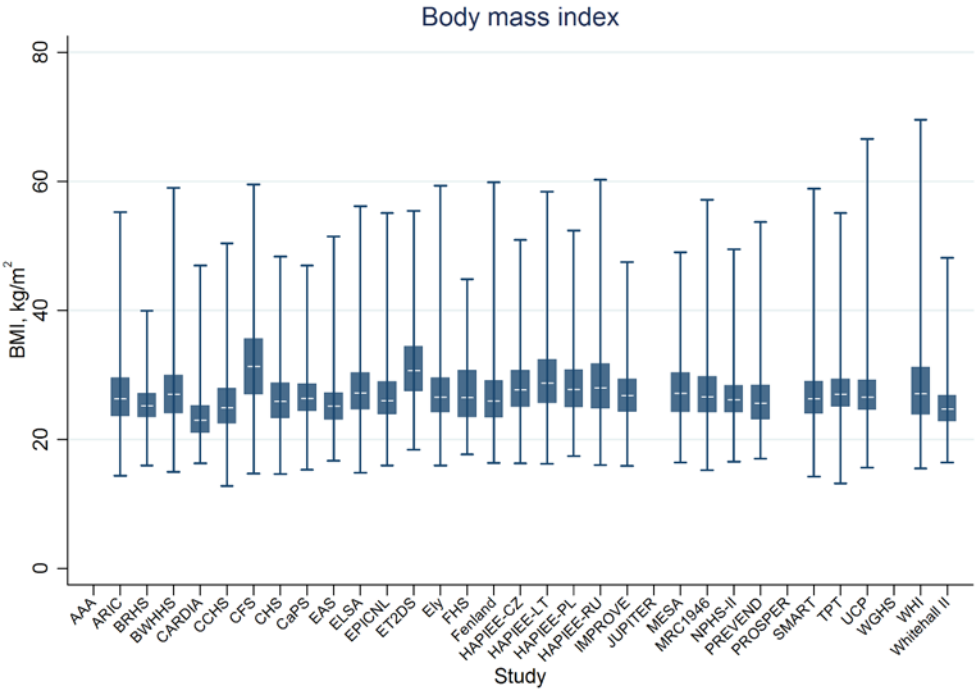


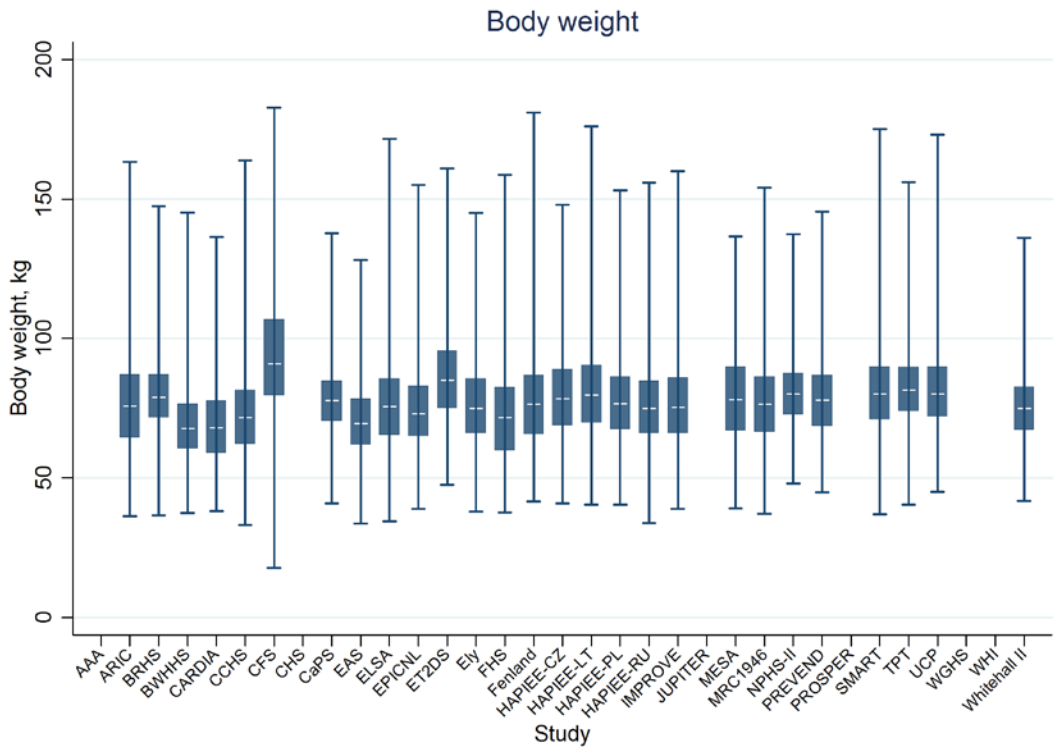
Supplementary Figure 3 - Genetic analysis biomarker data - box and whisker plots

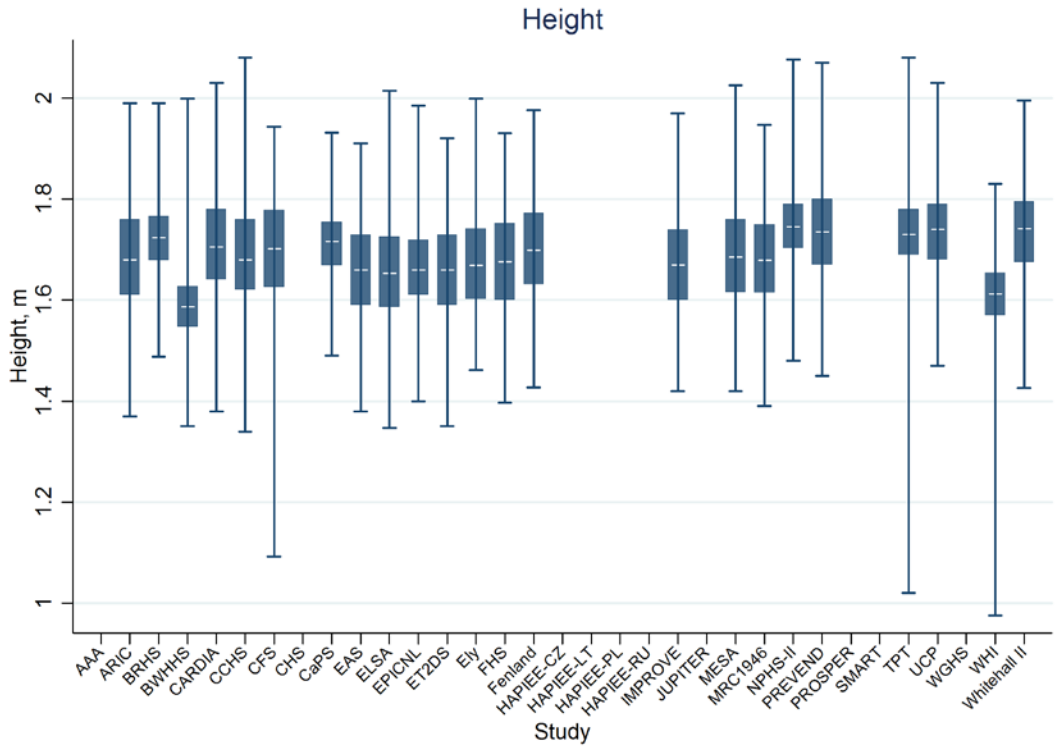


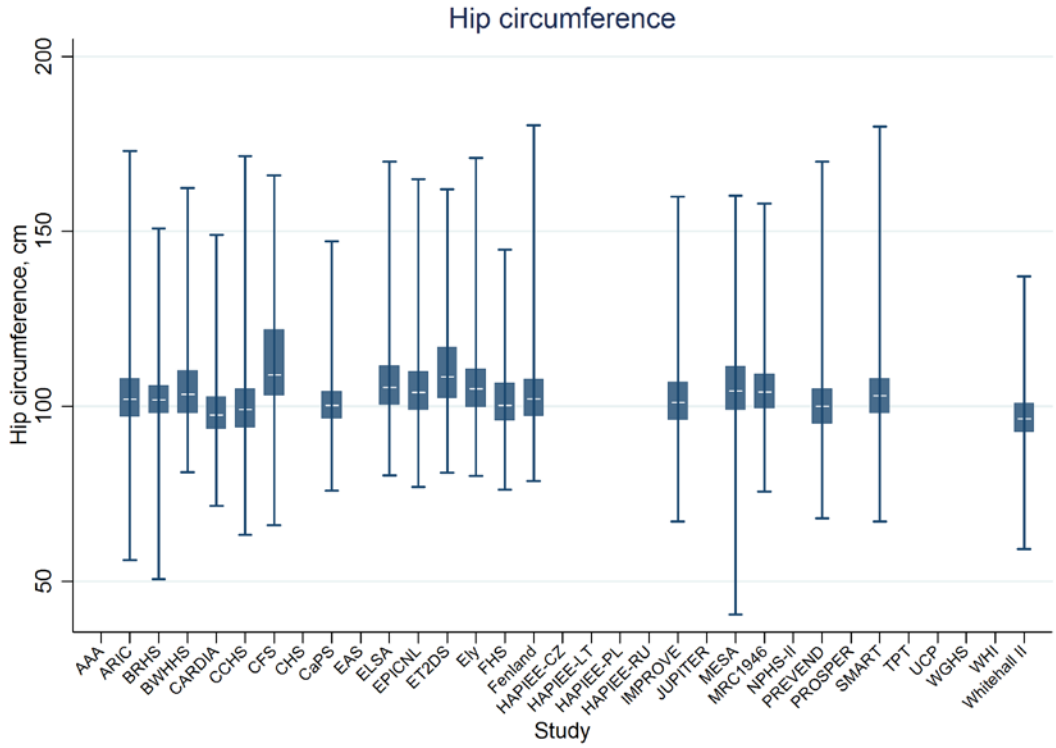


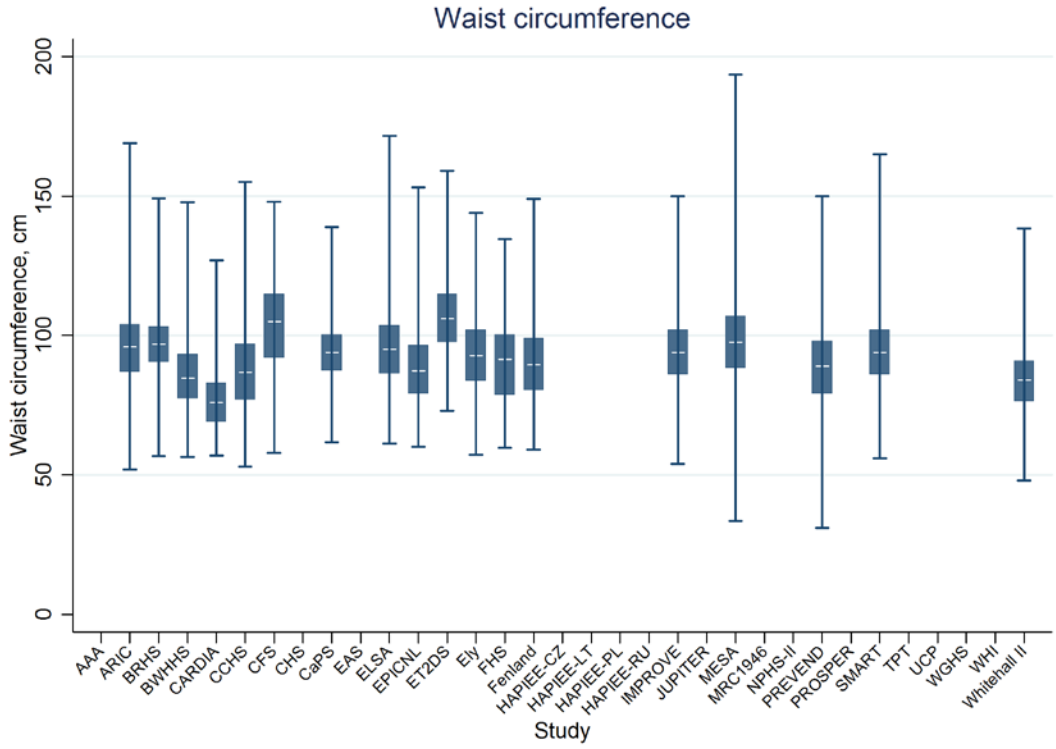

Non-HDL-cholesterol
Non-HDL-cholesterol, mmol/L
0
5
10
15
20
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study

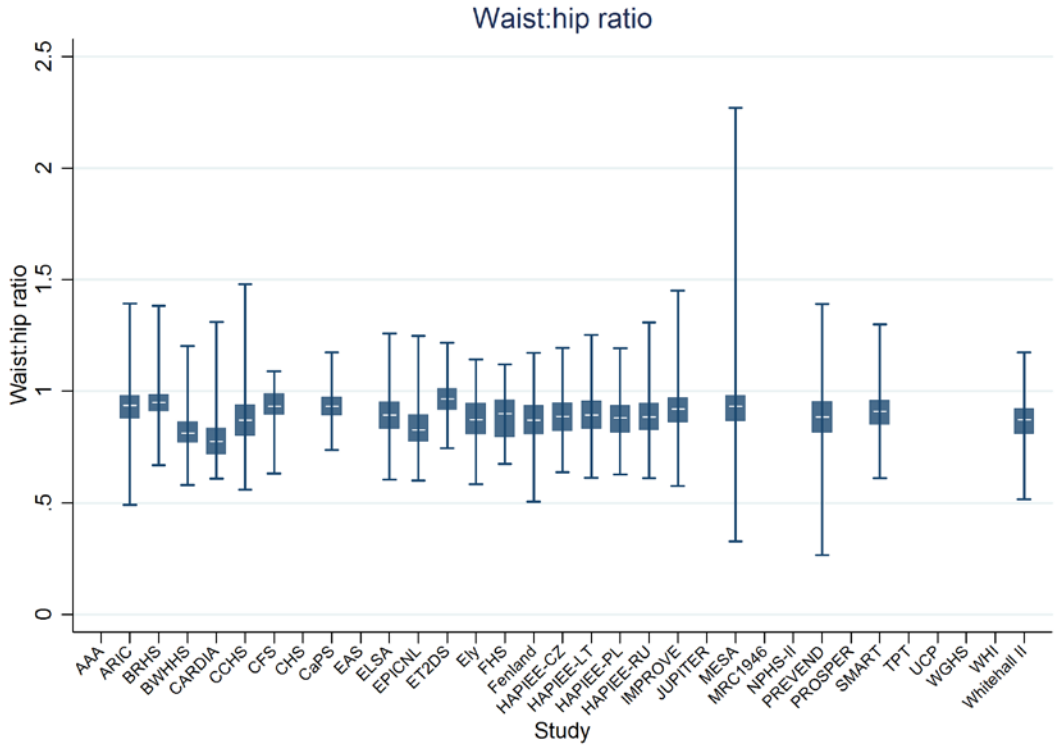

Body mass index
BMI, kg/m^2
0
20
40
60
80
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study

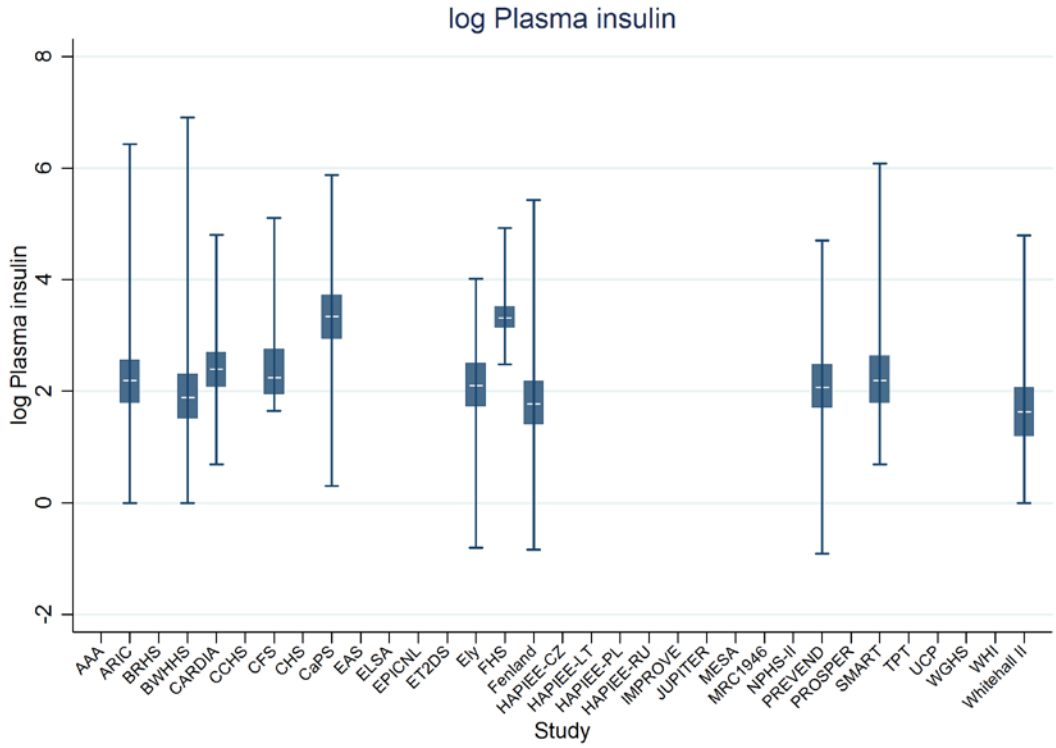

Body weight
Body weight, kg
0
50
100
150
200
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study

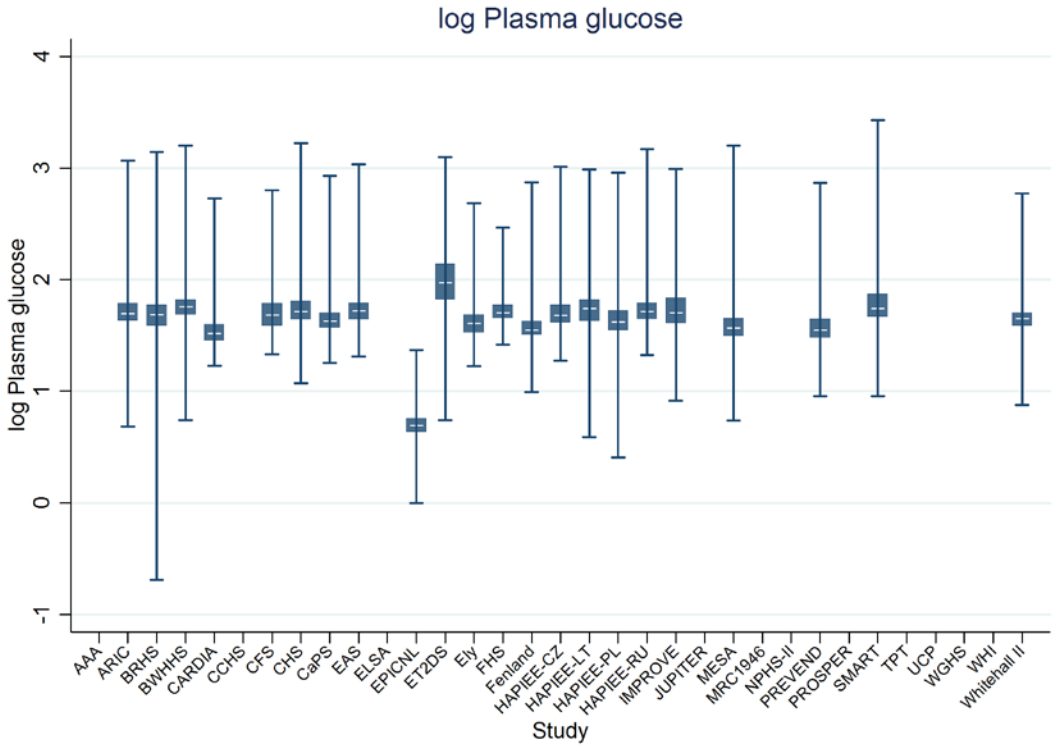

Height
Height, m
1
1.2
1.4
1.6
1.8
2
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study


Hip circumference
Hip circumference, cm
50
100
150
200
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study


Waist circumference
Waist circumference, cm
0
50
100
150
200
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study

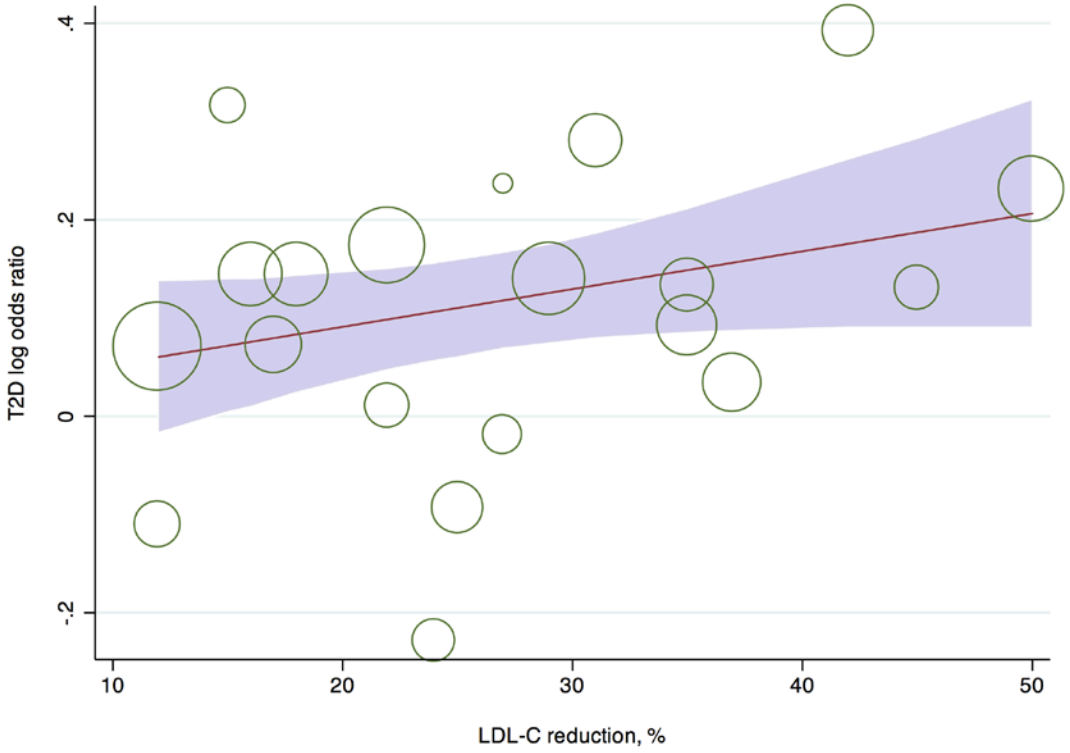

Waist:hip ratio
Waist:hip ratio
0
.5
1
1.5
2
2.5
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study


log Plasma insulin
log Plasma insulin
-2
0
2
4
6
8
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study


log Plasma glucose
log Plasma glucose
-1
0
1
2
3
4
AAA
ARIC
BRHS
BWHHS
CARDIA
CCHS
CFS
CHS
CaPS
EAS
ELSA
EPICNL
ET2DS
Ely
FHS
Fenland
HAPIEE-CZ
HAPIEE-LT
HAPIEE-PL
HAPIEE-RU
IMPROVE
JUPITER
MESA
MRC1946
NPHS-II
PREVEND
PROSPER
SMART
TPT
UCP
WGHS
WHI
Whitehall II
Study

Supplementary Figure 4 – Meta-regression model of the relationship between new-onset diabetes and percentage LDL-C reduction in statin trials at 1 year

20 trials, meta-regression p=0.10. Shaded area represents 95% confidence interval. The size of markers is determined by the standard error of the within-trial estimate of T2D odds ratio.



Supplementary Figure 5 –Meta-regression model of the relationship between change in weight and relative change in LDL-C in statin trials at 1 year

15 trials, meta-regression p=0.58. Shaded area represents 95% confidence interval. The size of markers is determined by the standard error of within-trial estimates of weight change.