Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. Participating studies

Outcome	Participating study	Cases, N	Non-cases (for case-control studies) or participants (for continuous traits studies), N	PubMed ID for cohort description	Website (URL)
Type 2 diabetes – main analysis	InterAct-GWAS[1]*	4,187	4,254	21717116	http://www.inter-act.eu/
	InterAct-CoreExome[1]*	5,121	7,269	21717116	http://www.inter-act.eu/
	UK Biobank[2]	6,627	143,765	22463865	http://www.ukbiobank.ac.uk/
	DIAGRAM[3]	34,840	114,981	22885922	http://diagram-consortium.org/
Type 2 diabetes – exome sequencing analysis	T2D-GENES Consortium, GoT2D Consortium, DIAGRAM Consortium[4]	8,373	8,466	27398621	http://www.type2diabetesgenetics.org/home/portalHome
Coronary artery disease	CARDIoGRAMplusC4D Consortium[5]	60,801	123,504	26343387	http://www.cardiogramplusc4d.org/
LDL cholesterol	Global Lipids Genetics Consortium[6]	-	188,577	24097068	http://csg.sph.umich.edu//abecasis/public/lipids2013/
Fasting plasma glucose	MAGIC Consortium[7,8]	-	133,010	22885924, 22581228	http://www.magicinvestigators.org/
Fasting insulin	MAGIC Consortium[7,8]	-	108,557	22885924, 22581228	http://www.magicinvestigators.org/
Two hour glucose	MAGIC Consortium[7,8]	-	42,854	22885924, 20081857	http://www.magicinvestigators.org/
Body mass index	GIANT Consortium[9]	-	333,495	25673413	https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium
Waist-to-hip ratio	GIANT Consortium[10]	-	224,047	25673412	https://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium

Abbreviations: N, number of participants; LDL, low-density lipoprotein cholesterol.

*In EPIC-Interact, genotyping was performed in two batches using the Illumina 660w quad and Illumina CoreExome genotyping arrays. Therefore, results of the main analysis are presented separately for individuals genotyped with the Illumina 660w quad array (InterAct-GWAS sub-study; 4,187 type 2 diabetes cases and 4,254 non-cases from the subcohort) and for individuals genotyped with the Illumina CoreExome array (InterAct-CoreExome sub-study; 5,121 type 2 diabetes cases and 7,269 non-cases from the subcohort).

eTable 2. Genetic variants included in the main analysis

Gene	Polymorphism	Genomic position	Effect allele	Effect allele frequency, mean (range)	Genotyped or imputed (imputation quality score*), Interact-GWAS	Genotyped or imputed (imputation quality score*), Interact-CoreExome	Genotyped or imputed (imputation quality score*), UK Biobank
NPC1L1	rs2073547	chr7:44582331	A	0.81 (0.81, 0.82)	Imputed (0.995)	Imputed (0.998)	Genotyped
NPC1L1	rs217386	chr7:44600695	A	0.42 (0.41, 0.44)	Imputed (0.991)	Imputed (0.998)	Genotyped
HMGCR	rs12916	chr5:74656539	T	0.58 (0.57, 0.60)	Imputed (0.994)	Genotyped	Genotyped
HMGCR	rs5744707	chr5:74890618	A	0.90 (0.90, 0.91)	Genotyped	Imputed (0.993)	Imputed (0.996)
HMGCR	rs16872526	chr5:74675717	T	0.91 (0.90, 0.92)	Imputed (0.999)	Imputed (0.998)	Imputed (0.997)
PCSK9	rs11591147	chr1:55505647	T	0.02 (0.01, 0.02)	Imputed (0.877)	Genotyped	Genotyped
ABCG5/G8	rs4299376	chr2:44072576	T	0.69 (0.68, 0.70)	Genotyped	Genotyped	Imputed (0.995)
LDLR	rs6511720	chr19:11202306	T	0.11 (0.10, 0.12)	Genotyped	Genotyped	Genotyped

In DIAGRAM, genetic variants were directly genotyped in the Metabochip subset of the DIAGRAM meta-analysis and either directly genotyped or imputed in the genome-wide association subset.[3]
Polymorphism names reported in the table are rsID entries from dbSNP release 147.
Genomic coordinates represent chromosome and physical position of genetic variants according to the Human Reference Genome Build 37.
Effect allele frequency averages and ranges are from EPIC-InterAct,[1] UK Biobank[2] and DIAGRAM.[3]
*imputation quality score reports the correlation between genotyped and imputed genotypes in the reference imputation set, with a value of 1 indicating perfect imputation.

eTable 3. Sensitivity analyses at the *NPC1L1* and *PCSK9* loci

Locus	Model	Reference (PubMed ID)	Polymorphisms	OR of type 2 diabetes (95% CI)	p-value
NPC1L1	Two polymorphisms, adjusted for the *GCK* rs1799884 and rs2041547 lead genetic variants	This study	rs2073547 rs217386	2.16 (1.51 – 3.11)	3 x 10^{-05}
NPC1L1	Five polymorphisms	Ference et al. (25770315)[11]	rs2073547 rs217386 rs7791240 rs2300414 rs10234070	2.20 (1.59 – 3.05)	2 x 10^{-06}
PCSK9	Two polymorphisms	This study	rs11591147 rs471705	1.21 (1.04 – 1.41)	0.01
PCSK9	Nine polymorphisms	This study	rs11591147 rs1998013 rs11206510 rs7523242 rs4927207 rs6662286 rs572512 rs1475701 rs7552841	1.16 (1.03 – 1.31)	0.02

Association with type 2 diabetes of LDL-cholesterol lowering genetic variants at the *NPC1L1* and *PCSK9* loci in sensitivity analyses.
Odds ratios are per a genetically-predicted reduction in LDL cholesterol of 1 mmol/L.
OR, odds ratio; CI, confidence interval.

eTable 4. Correlation between genetic variants

Correlation between genetic variants included in Mendelian randomization models at the *NPC1L1*, *HMGCR* and *PCSK9* loci**.** The correlation between variants was obtained from the SNAP software[12] or from the 1000 Genomes Project browser (URL:http://browser.1000genomes.org/).

Genetic variant 1	Genetic variant 2	Correlation
NPC1L1 locus		
rs2073547	rs10234070	0.294
rs2073547	rs7791240	0.208
rs2073547	rs2300414	0.098
rs2073547	rs217386	0.083
rs217386	rs7791240	0.078
rs217386	rs10234070	0.06
rs217386	rs2300414	0.052
rs7791240	rs2300414	0.363
rs7791240	rs10234070	0.005
rs2300414	rs10234070	0.033
HMGCR locus		
rs12916	rs17238484	0.368
rs12916	rs5744707	0.239
rs12916	rs16872526	0.082
rs5744707	rs17238484	0.036
rs5744707	rs16872526	0.008
rs16872526	rs17238484	0.222
PCSK9 locus		
rs11591147	rs471705	0.028
rs11591147	rs1998013	0.300
rs11591147	rs11206510	0.191
rs11591147	rs7523242	0.066
rs11591147	rs4927207	0.102
rs11591147	rs6662286	0.176
rs11591147	rs572512	0.008
rs11591147	rs1475701	0.028
rs11591147	rs7552841	0.004
rs1998013	rs11206510	0.191
rs1998013	rs7523242	0.066
rs1998013	rs4927207	0.102
rs1998013	rs6662286	0.176
rs1998013	rs572512	0.008
rs1998013	rs1475701	0.028

Genetic variant 1	Genetic variant 2	Correlation
rs1998013	rs7552841	0.004
rs11206510	rs7523242	0.186
rs11206510	rs4927207	0.028
rs11206510	rs6662286	0.017
rs11206510	rs572512	0.200
rs11206510	rs1475701	0.087
rs11206510	rs7552841	0.127
rs7523242	rs4927207	0.048
rs7523242	rs6662286	0.066
rs7523242	rs572512	0.409
rs7523242	rs1475701	0.057
rs7523242	rs7552841	0.068
rs4927207	rs6662286	0.201
rs4927207	rs572512	0.042
rs4927207	rs1475701	0.085
rs4927207	rs7552841	0.232
rs6662286	rs572512	0.163
rs6662286	rs1475701	0.059
rs6662286	rs7552841	0.025
rs572512	rs1475701	0.118
rs572512	rs7552841	0.049
rs1475701	rs7552841	0.102

eTable 5. Burden of rare alleles in exome sequencing studies

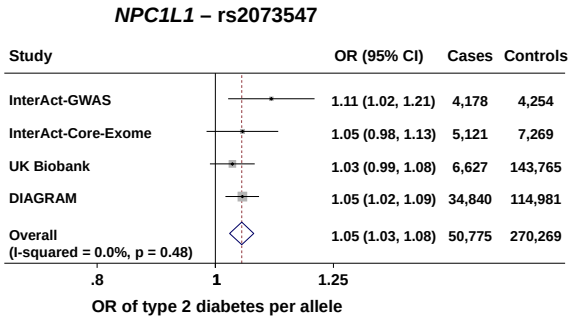
Burden of protein-truncating and missense variants predicted to be "probably deleterious" for protein function in 8,373 type 2 diabetes cases and 8,466 controls from exome sequencing studies.

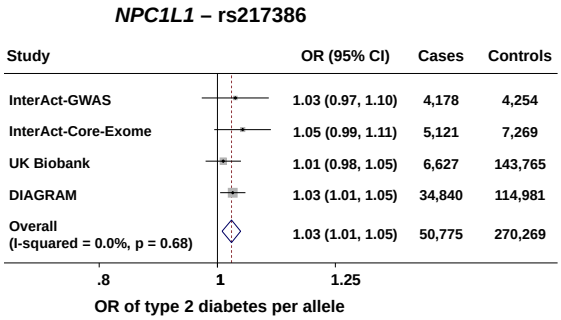
Gene	Class of genetic variants	Carriers with type 2 diabetes	Non-carriers with type 2 diabetes	Carriers among controls	Non-carriers among controls	Odds ratio of type 2 diabetes for carriers (95% CI)	p-value
NPC1L1	Protein truncating	143	8230	129	8337	1.12 (0.88-1.43)	0.34
	Probably deleterious missense	360	8013	294	8172	1.26 (1.07-1.47)	0.005
HMGCR	Protein truncating	0	8373	0	8466	N/A	N/A
	Probably deleterious missense	3	8370	10	8456	0.31 (0.08-1.12)	0.07
PCSK9	Protein truncating	37	8336	33	8433	1.13 (0.71-1.82)	0.61
	Probably deleterious missense	100	8273	85	8381	1.22 (0.91-1.64)	0.18
ABCG5	Protein truncating	5	8368	9	8457	0.59 (0.20-1.75)	0.34
	Probably deleterious missense	54	8319	71	8395	0.77 (0.54-1.10)	0.15
ABCG8	Protein truncating	31	8342	35	8431	0.88 (0.55-1.44)	0.62
	Probably deleterious missense	94	8279	112	8354	0.84 (0.64-1.11)	0.23
LDLR	Protein truncating	2	8371	2	8464	1.02 (0.14-7.26)	0.98
	Probably deleterious missense	53	8320	47	8419	1.15 (0.78-1.70)	0.49

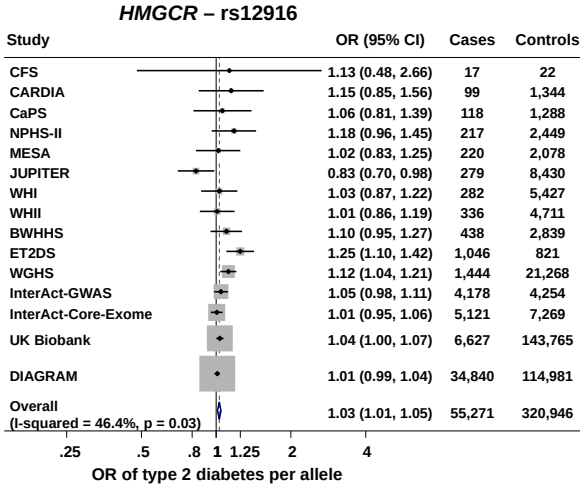
N/A, not available (not calculated); CI, confidence interval.

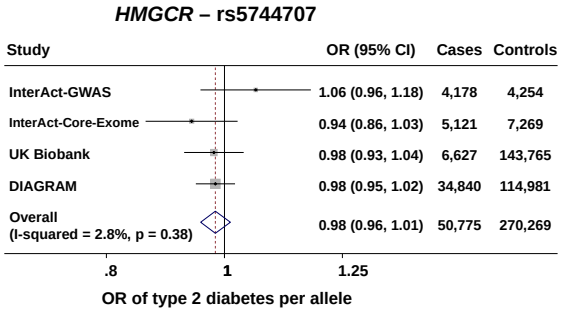
eFigure 1. Meta-analysis results

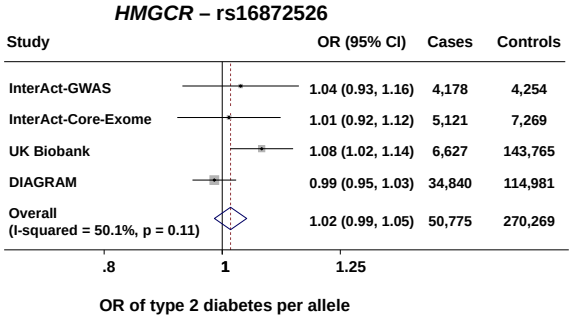
Meta-analysis of the association of LDL-cholesterol lowering polymorphisms with risk of type 2 diabetes in EPIC-InterAct,[1] UK Biobank[2] and DIAGRAM[3]. For rs12916 in *HMGCR*, results of an additional eleven studies reported by Swerdlow and colleagues[13] were included. In EPIC-InterAct, genotyping was performed in two batches using the Illumina 660w quad and Illumina CoreExome genotyping arrays. Therefore, results of the main analysis are presented separately for individuals genotyped with the Illumina 660w quad array (InterAct-GWAS) and for individuals genotyped with the Illumina CoreExome array (InterAct-CoreExome). Squares indicate the odds ratios and error bars their 95% confidence interval. The size of the squares reflects the weight of the study in the inverse-variance weighted meta-analysis. OR indicates the odds ratio; CI, confidence interval.

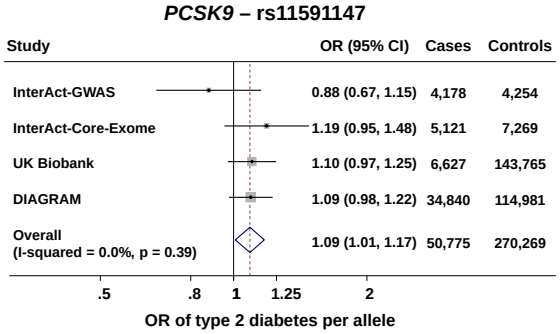


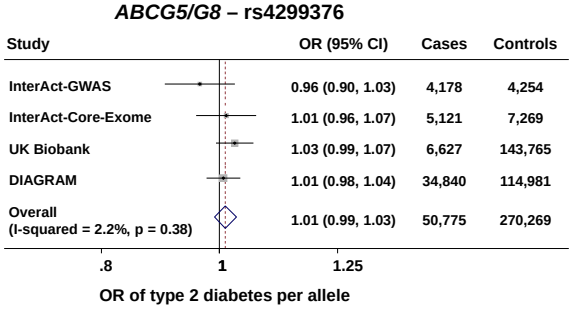


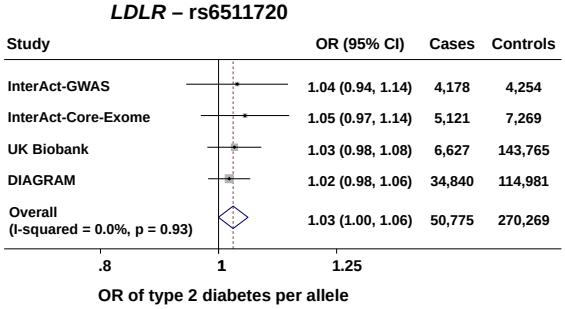






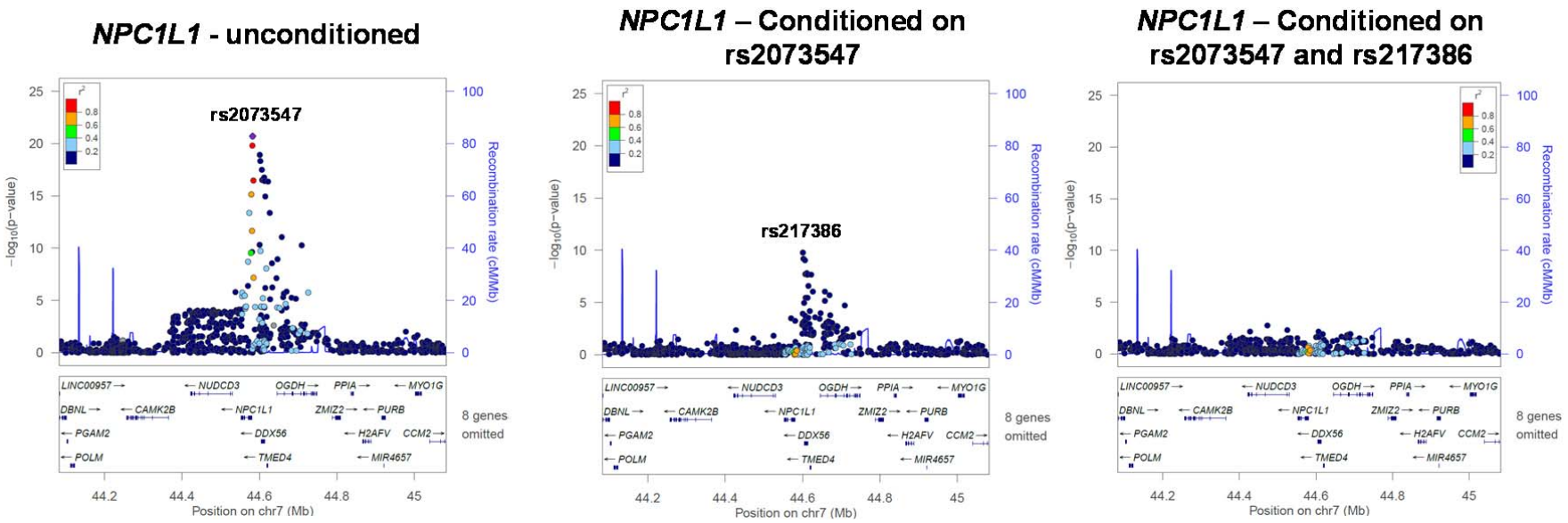






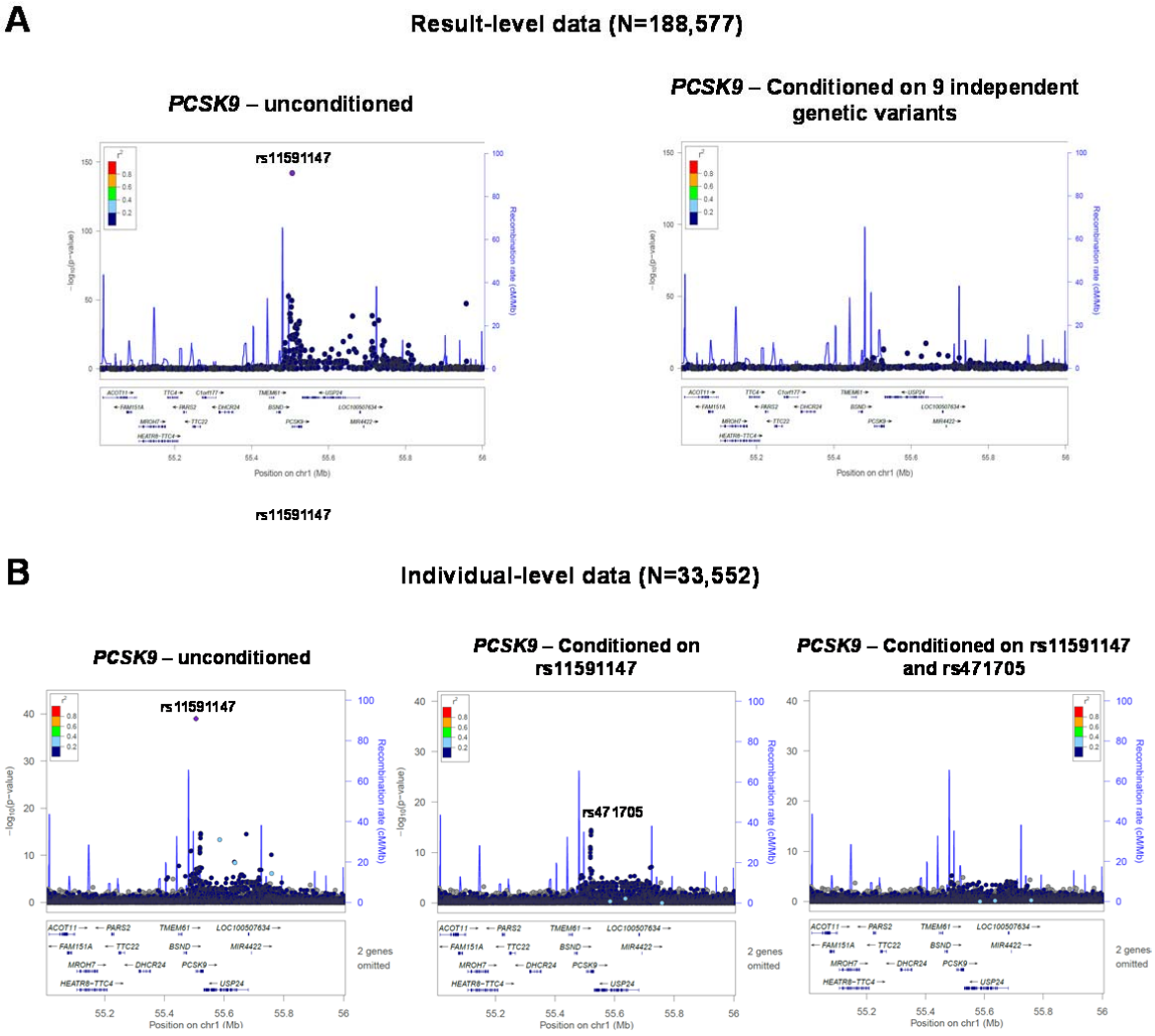
eFigure 2. Conditional analysis at the *NPC1L1* locus

Association with LDL cholesterol at the *NPC1L1* locus in the Global Lipids Genetics Consortium[6] results before conditioning (left), after conditioning on the lead rs2073547 polymorphism (middle) and after conditioning on both the rs2073547 and rs217386 polymorphisms (right) in approximate conditional analyses using the GCTA software.[14] After conditioning on two polymorphisms the signal was attenuated. Genomic coordinates are relative to Human Reference Genome Build 37.



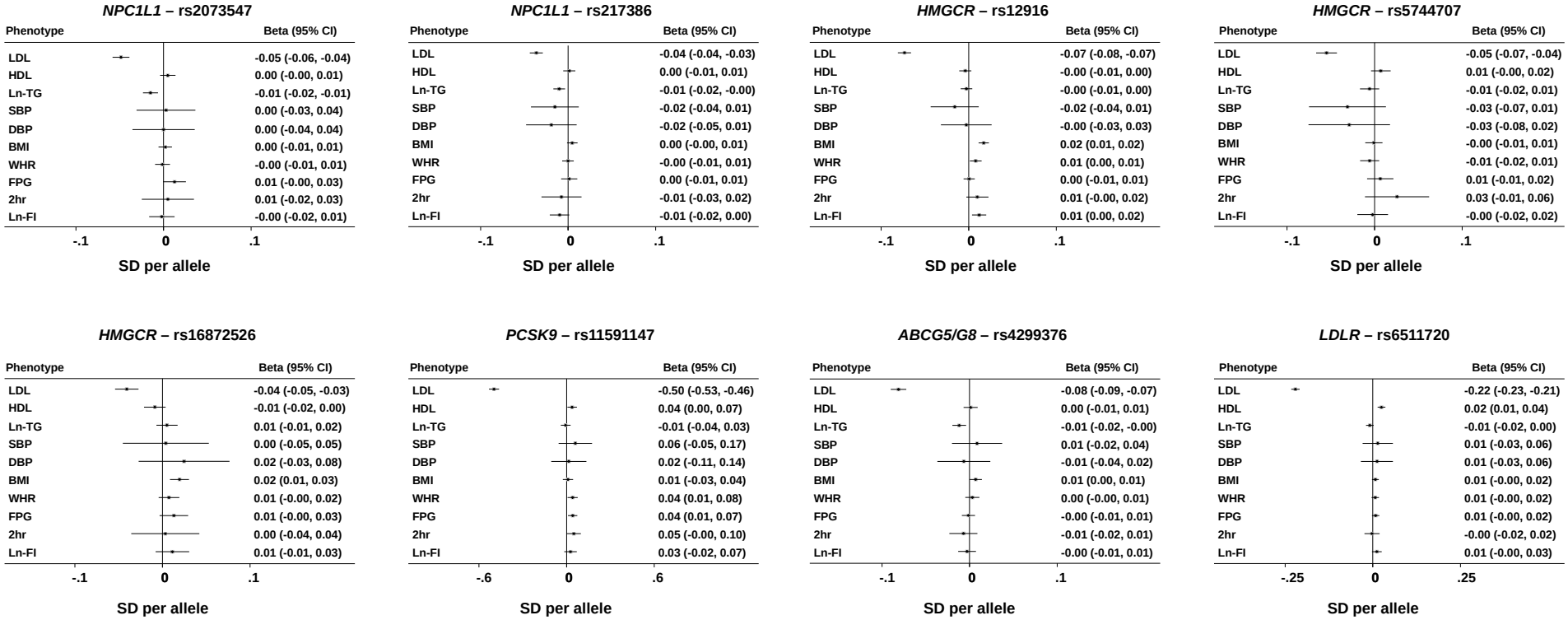
eFigure 3. Conditional analysis at the *PCSK9* locus

Panel A shows associations with LDL cholesterol at the *PCSK9* locus before (left) and after (right) conditioning on rs11591147, rs1998013, rs11206510, rs7523242, rs4927207, rs6662286, rs572512, rs1475701, and rs7552841 in approximate conditional analyses using the GCTA software.[14] Data are from the Global Lipids Genetics Consortium.[6] After conditioning on the nine polymorphisms the signal was attenuated. Panel B shows associations with LDL cholesterol in a smaller sample with available individual level data. There was evidence of two distinct genome-wide significant signals ($p<5 \times 10^{-08}$) represented by rs11591147 and rs471705. The association signal in the region (left graph) was progressively attenuated after conditioning on rs11591147 (middle graph) and, then, after conditioning on both rs11591147 and rs471705 (right graph). Genomic coordinates are relative to Human Reference Genome Build 37.



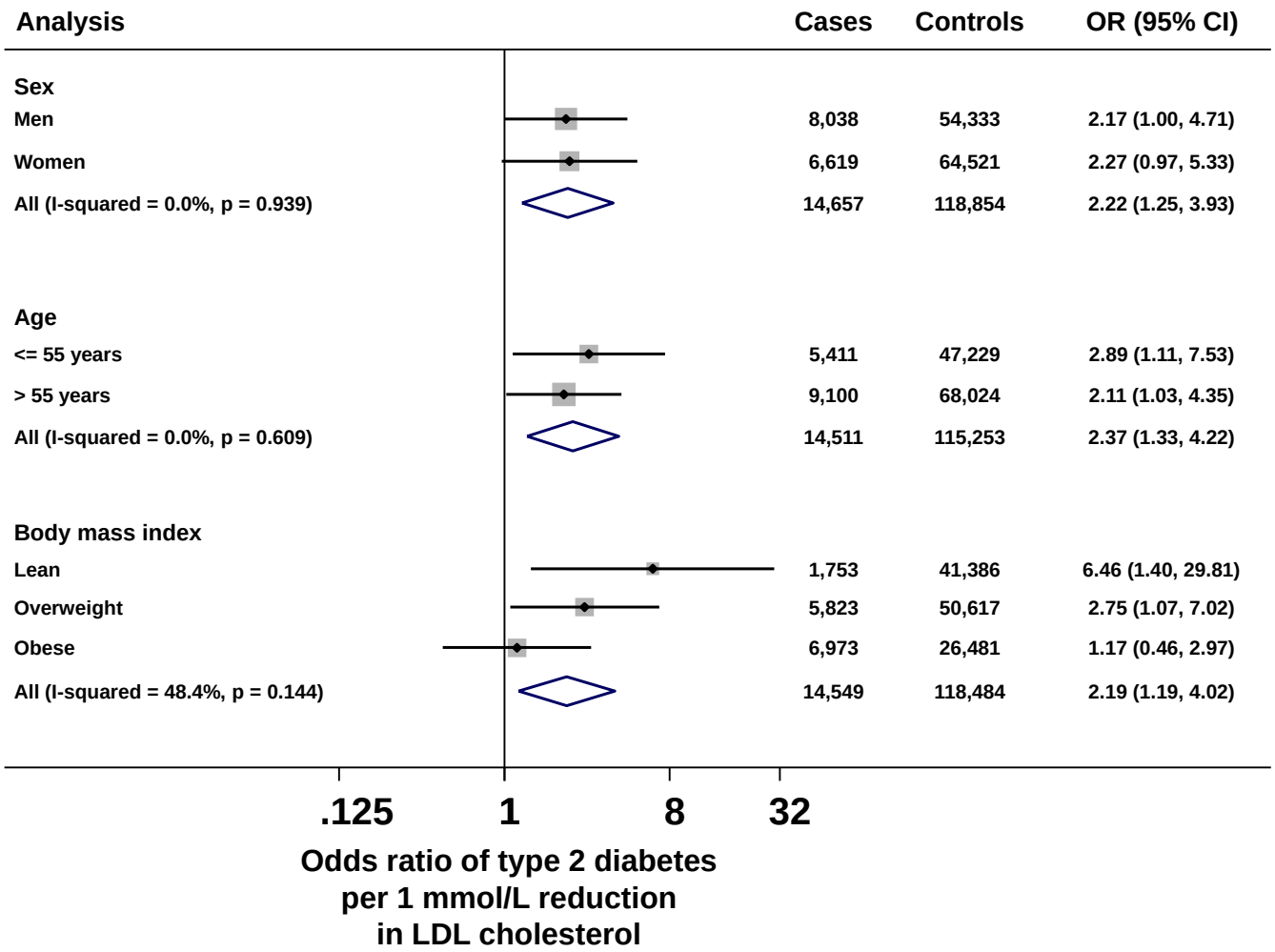
eFigure 4. Associations of LDL-lowering alleles with continuous cardiometabolic traits

Associations are in standardized units per LDL-cholesterol lowering allele. LDL cholesterol (N=173,021), HDL cholesterol (N=187,087), ln-transformed triglycerides (N=177,791) levels data are from the Global Lipids Genetics Consortium.[6] Systolic (N=8,756) and diastolic (N=8,755) blood pressure data are from the EPIC-InterAct[1] subcohort. Body mass index (N=333,495) and waist-to-hip ratio (N=224,047) data are from the GIANT Consortium[9,10]; fasting glucose (N=133,010), two hour glucose (N=42,854) and ln-transformed fasting insulin data (N=108,557) are from the MAGIC Consortium[7,8]. Abbreviations: LDL, low density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; Ln-TG, triglycerides (natural logarithm transformed); SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; 2hr, 2 hour glucose; Ln-FI, fasting insulin (natural logarithm transformed); SD, standard deviation; CI, confidence interval. All genetic variants were strongly associated with LDL cholesterol levels. *NPC1L1* polymorphisms were weakly associated with lower triglyceride levels, consistent with the effect of ezetimibe on triglyceride levels.[15] *HMGCR* polymorphisms were associated with higher BMI levels, consistent with the effect of statins on body weight.[13]



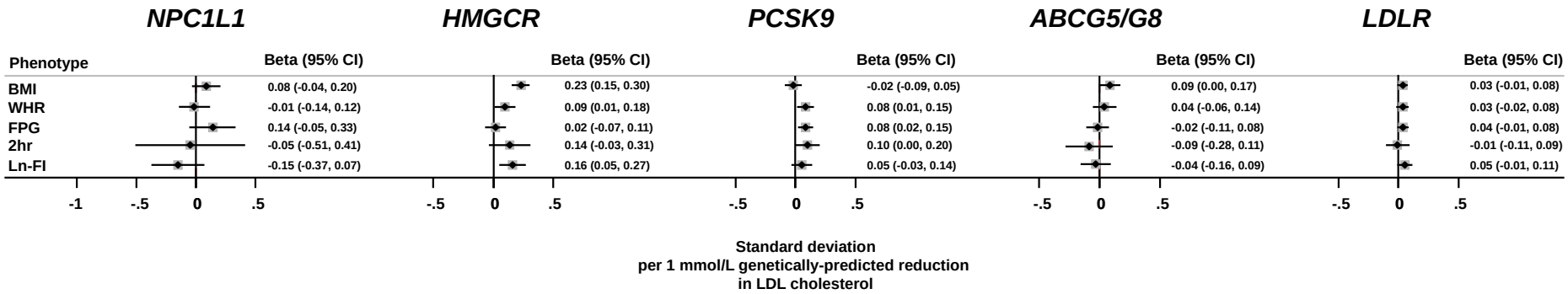
eFigure 5. Stratified associations of *NPC1L1* variants

Combined association of LDL-lowering alleles at *NPC1L1* with risk of type 2 diabetes in strata of sex, age and body mass index. Data are from the EPIC-InterAct[1] and UK Biobank[2] studies. Analyses are scaled to represent the odds ratio of type 2 diabetes for a genetically predicted reduction in LDL cholesterol of 1 mmol/L. Squares indicate the odds ratio and the error bars its 95% confidence interval. The size of the squares indicates the weight of the subgroup analysis in the inverse-variance weighted meta-analysis. OR indicates the odds ratio; CI, confidence interval.



eFigure 6. Associations with continuous cardiometabolic traits

Association of LDL lowering alleles with continuous anthropometric and glycemic traits. Associations are in standardised units per 1 mmol/L reduction in LDL cholesterol. Body mass index (N=333,495) and waist-to-hip ratio (N=224,047) data are from the GIANT Consortium[9,10]; fasting glucose (N=133,010), two hour glucose (N=42,854) and ln-transformed fasting insulin data (N=108,557) are from the MAGIC Consortium[7,8]. Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; 2hr, 2 hour glucose; Ln-FI, fasting insulin (natural logarithm transformed); CI, confidence interval.



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