Online-Only Supplement

Supplementary Table 1. Definition of outcomes in phenome wide association study in UK Biobank.

Outcome	Definition (UK Biobank unless otherwise specified)
Coronary artery disease	(1) Myocardial infarction (MI), coronary artery bypass grafting, or coronary artery angioplasty documented in medical history at time of enrollment by a trained nurse or (2) Hospitalization for ICD-10 code for acute myocardial infarction (I21.0, I21.1, I21.2, I21.4, I21.9) or (3) Hospitalization for OPCS-4 coded procedure: coronary artery bypass grafting (K40.1-40.4, K41.1-41.4, K45.1-45.5) or (4) Hospitalization for OPCS-4 coded procedure: coronary angioplasty ± stenting (K49.1-49.2, K49.8-49.9, K50.2, K75.1-75.4, K75.8-75.9)
Atrial fibrillation/flutter	History of atrial fibrillation or flutter during verbal interview with trained nurse or hospitalization for or death due to ICD code I48
Heart failure	History of heart failure during verbal interview with trained nurse or hospitalization for or death due to ICD code I11.0, I13.0, I13.2, I125.5, I42, I50
Stroke	History of stroke, adjudicated by UK Biobank centrally as report of stroke during verbal interview with trained nurse or hospitalization for or death due to ICD code I60-64 *(http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=462)*
Peripheral vascular disease	History of peripheral vascular disease or intermittent claudication during verbal interview with trained nurse or hospitalization for or death due to ICD code I70, I73.8 or I73.9
Venous thromboembolism	History of venous thromboembolism, deep vein thrombosis or pulmonary embolism during verbal interview with trained nurse or hospitalization for death due to I26, I80.1, I80.2, I81, or I82.0
Aortic stenosis	History of aortic stenosis during verbal interview with trained nurse or hospitalization for ICD code I06.0, I06.2 I35.0 or I35.2
Inflammatory bowel disease	History of inflammatory bowel disease, Crohn's disease or ulcerative colitis during verbal interview with trained nurse or hospitalization for or death due to ICD code K50 or K51
Gastric reflux	History of gastric reflux during verbal interview with trained nurse or hospitalization for or death due to ICD code K21
Gallstone	History of gallstones during verbal interview with trained nurse or hospitalization for or death due to ICD code K56.3 or K80
Hyperthyroidisim	History of hyperthyroidism during verbal interview with trained nurse or hospitalization for or death due to ICD code E05
Hypothyroidism	History of hypothyroidism during verbal interview with trained nurse or hospitalization for or death due to ICD code E03
Gout	History of gout during verbal interview with trained nurse or hospitalization for or death due to ICD code M10
Enlarged prostate	History of enlarged prostate during verbal interview with trained nurse or hospitalization for or death due to ICD code N40
Uterine fibroids	History of uterine fibroids during verbal interview with trained nurse or hospitalization for or death due to ICD code D25
Migraine	History of migraine during verbal interview with trained nurse or hospitalization for or death due to ICD code G43
Depression	History of depression during verbal interview with trained nurse or hospitalization for or death due to ICD code F32
Anxiety	History of anxiety/panic attacks during verbal interview with trained nurse or hospitalization for or death due to ICD code F41

Osteoporosis	History of osteoporosis during verbal interview with trained nurse or hospitalization for or death due to ICD code M80 or M81
Osteoarthritis	History of osteoarthritis during verbal interview with trained nurse or hospitalization for or death due to ICD code M15-19
Sciatica	History of sciatica during verbal interview with trained nurse or hospitalization for or death due to ICD code M54.3
Prolapsed disc	History of prolapsed disc/slipped disc during verbal interview with trained nurse or hospitalization for or death due to ICD code M50.2 or M51.2
Asthma	History of asthma during verbal interview with trained nurse or hospitalization for or death due to ICD code J45 or J46
COPD/Emphysema	History of chronic obstructive airways disease, emphysema/chronic bronchitis or emphysema during verbal interview with trained nurse or hospitalization for or death due to ICD code J41-44
Pneumonia	History of pneumonia during verbal interview with trained nurse or hospitalization for or death due to ICD code J12-18
Hayfever	History of hayfever during verbal interview with trained nurse or hospitalization for or death due to ICD code J30
Lung cancer	History of breast cancer during verbal interview with trained nurse or hospitalization for or death due to ICD code C34
Colorectal cancer	History of large bowel cancer/colorectal cancer, colon cancer/sigmoid cancer or rectal cancer during verbal interview with trained nurse or hospitalization for or death due to ICD code C18
Skin cancer	History of skin cancer, malignant melanoma, non-melanoma skin cnacer, basal cell carcinoma or squamous cell carcinoma during verbal interview with trained nurse or hospitalization for or death due to ICD code C43-44
Prostate cancer	History of prostate cancer during verbal interview with trained nurse or hospitalization for or death due to ICD code C61
Cervical cancer	History of cervical cancer or cin cells at the cervix during verbal interview with trained nurse or hospitalization for or death due to ICD code C53

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD, international classification of disease

Supplementary Table 2. Low frequency variants at novel loci associated with WHRadjBMI at genome wide significance in UK Biobank.

Variant	CHR	BP	EA	MAF	Gene	Consequence	Beta	SE	P-value
rs141845046	1	154987704	T	0.0207	ZBTB7B	Pro190Ser	-0.056	0.008	9.95E-13
rs72704117	1	155175089	T	0.02193	THBS3	Arg102Gln	-0.052	0.008	7.82E-12
rs52826764	2	20205541	T	0.02913	MATN3	Glu252Lys	-0.039	0.007	2.93E-09
rs56188432	2	158406865	G	0.002185	ACVR1C	Ile195Thr	-0.147	0.024	1.00E-09
rs55920843	2	158412701	G	0.01135	ACVR1C	Asn150His	-0.088	0.010	3.40E-17
rs144397126	3	129207191	C	0.01439	IFT122	Glu699Ala	0.066	0.009	1.76E-12
rs11722554	4	5016883	A	0.03724	CYTL1	Arg136Cys	-0.034	0.006	5.60E-09
rs140201358	11	823586	G	0.01324	PNPLA2	Asn252Lys	0.087	0.010	3.21E-19
rs62621409	11	36458997	G	0.04136	PRR5L	Thr113Ala	0.031	0.006	1.86E-08
rs145878042	12	48143315	G	0.01035	RAPGEF3	Leu258Pro	-0.077	0.011	1.72E-12
rs75173589	12	124333367	A	0.01387	DNAH10	Val1896Met	-0.059	0.009	5.90E-10
rs151177426	14	21463013	T	2.36E-05	METTL17	Arg277Cys	-1.369	0.235	5.65E-09
rs61747585	14	52508842	A	0.04157	NID2	Glu602Asp	0.031	0.006	3.60E-08
rs62070804	17	27889643	T	0.01768	ABHD15	Arg448Gln	0.046	0.008	3.50E-08
rs141385558	17	27893545	T	0.002571	ABHD15	Gly147Asp	0.148	0.022	1.66E-11
rs62621197	19	8670147	T	0.03098	ADAMTS10	Arg62Gln	-0.039	0.006	1.21E-09

CHR, chromosome; BP, base pair; EA, effect allele; MAF, minor allele frequency. Variants within the MHC locus are reported in online data table 1.

Supplementary Table 3. Common variants at novel loci associated with WHRadjBMI at genome wide significance in UK Biobank.

Variant	CHR	BP	EA	MAF	Gene	Consequence	Beta	SE	P-value
rs3753841	1	103379918	G	0.3985	COL11A1	Pro1284Leu	-0.017	0.002	5.07E-13
rs1129942	1	172437592	G	0.221	C1orf105	Ser127Asn	0.021	0.003	1.72E-14
rs3851294	1	205130413	A	0.0895	DSTYK	Cys641Arg	-0.024	0.004	1.19E-09
rs3732083	2	207041053	C	0.4344	GPR1	Ile307Val	0.013	0.002	1.10E-08
rs1250259	2	216300482	T	0.2608	FN1	Gln15Leu	0.016	0.003	1.06E-10
rs9711321	2	239697444	T	0.4902	AC144525.1	Splice Acceptor	-0.014	0.002	6.78E-10
rs2276853	3	47282303	G	0.4058	KIF9	Arg638Trp	-0.015	0.002	9.51E-11
rs3087866	3	49054692	T	0.2233	DALRD3	Gln132Arg	-0.021	0.003	4.04E-15
rs2625973	3	129284818	C	0.2826	PLXND1	Leu1412Val	-0.020	0.002	1.07E-15
rs34884217	4	944210	C	0.1064	TMEM175	Splice Acceptor	-0.021	0.004	6.59E-09
rs34311866	4	951947	C	0.1753	TMEM175	Met393Thr	0.021	0.003	9.03E-13
rs13107325	4	103188709	T	0.07169	SLC39A8	Ala391Thr	-0.033	0.004	2.07E-14
rs4532349	5	77473165	G	0.2281	AP3B1	Synonymous	0.015	0.003	1.85E-08
rs34813	5	102433409	A	0.3098	GIN1	Thr239Met	-0.016	0.002	9.80E-11
rs9388768	6	130374102	C	0.3388	L3MBTL3	Thr183Asn	-0.017	0.002	1.05E-12
rs3124784	6	160952838	A	0.2779	LPA	Arg2016Cys	0.014	0.002	6.77E-09
rs2301680	7	93116299	T	0.4991	CALCR	Ser17Pro	0.014	0.002	1.13E-09
rs4072134	8	11872395	G	0.4653	RP11-481A20.11	Val55Ala	0.016	0.002	2.04E-12
rs10902221	11	802379	G	0.4993	PIDD	Gln331Arg	0.016	0.002	3.29E-13
rs5215	11	17408630	T	0.3521	KCNJ11	Val337Ile	0.016	0.002	2.68E-11
rs34312154	11	47470345	C	0.1071	RAPSN	Arg58Cys	0.021	0.004	3.24E-09
rs3741378	11	65408937	A	0.1394	SIPA1	Ser182Phe	-0.023	0.003	1.24E-12
rs10891314	11	111916647	T	0.3599	DLAT	Asp451Asn	-0.023	0.002	4.48E-23

rs12146709	12	30888001	A	0.2464	CAPRIN2	Lys237Arg	-0.015	0.003	6.21E-09
rs2277339	12	57146069	C	0.1067	PRIM1	Asp5Ala	0.024	0.004	4.55E-11
rs3764002	12	108618630	G	0.26	WSCD2	Thr266Ile	-0.017	0.003	5.37E-11
rs11057353	12	124265687	T	0.3898	DNAH10	Ser167Pro	0.019	0.002	3.22E-17
rs11057401	12	124427306	T	0.3092	CCDC92	Ser70Cys	-0.036	0.002	1.78E-50
rs36127550	12	133780309	A	0.177	ZNF268	Leu679Phe	-0.018	0.003	5.45E-10
rs1051858	14	58831142	T	0.3488	ARID4A	Thr779Ala	0.013	0.002	1.23E-08
rs3959569	15	42115747	G	0.3272	MAPKBP1	Arg1117Pro	0.016	0.002	2.97E-11
rs1715919	15	56756285	C	0.1023	MNS1	Gln55Pro	0.022	0.004	1.31E-09
rs3747579	16	4445327	G	0.2959	CORO7	Arg193Gln	0.019	0.002	3.30E-14
rs12923138	16	67233266	C	0.4259	ELMO3	Lys66Gln	-0.012	0.002	4.85E-08
rs8052655	16	67409180	C	0.05493	LRRC36	Gly241Ser	-0.031	0.005	1.64E-09
rs10445337	17	44067400	A	0.2174	MAPT	Ser447Pro	0.018	0.003	6.74E-11
rs9907379	17	59489893	C	0.2144	C17orf82	Leu186Pro	0.015	0.003	1.30E-08
rs3744448	17	59533868	T	0.1472	TBX4	Gly6Ala	0.020	0.003	1.45E-10
rs61742072	17	76433899	C	0.1744	DNAH17	His3947Tyr	-0.018	0.003	1.56E-09
rs429358	19	45411941	A	0.1541	APOE	Cys130Arg	-0.030	0.003	2.97E-22
rs1042917	21	47545768	C	0.4856	COL6A2	Arg680His	-0.013	0.002	1.41E-09
rs4823086	22	30688659	A	0.1224	TBC1D10A	Arg441His	0.019	0.003	3.88E-08
rs1053593	22	35660875	T	0.3628	HMGXB4	Gly165Val	0.014	0.002	6.88E-09

CHR, chromosome; BP, base pair; EA, effect allele; MAF, minor allele frequency. Variants within the MHC locus are reported in online data table 1.

Supplementary Table 4. Replication of novel variants associated with WHRadjBMI in the GIANT consortium.

					UK Biobank			GIANT			
Variant	CHR	BP	EA	Gene	Beta	SE	P-value	Beta	SE	P-value	P-heterogeneity
rs11722554	4	5016883	A	CYTL1	-0.034	0.006	5.60E-09	-0.030	0.015	0.044	0.8
rs3753841	1	103379918	G	COL11A1	-0.017	0.002	5.07E-13	0.001	0.004	0.91	0.00059
rs1129942	1	172437592	G	C1orf105	0.021	0.003	1.72E-14	0.023	0.004	1.80E-07	0.63
rs3851294	1	205130413	A	DSTYK	-0.024	0.004	1.19E-09	-0.026	0.007	0.00024	0.77
rs3732083	2	207041053	C	GPR1	0.013	0.002	1.10E-08	0.007	0.004	0.091	0.23
rs1250259	2	216300482	T	FN1	0.016	0.003	1.06E-10	0.017	0.005	0.00078	0.92
rs9711321	2	239697444	T	AC144525.1	-0.014	0.002	6.78E-10	0.003	0.004	0.51	0.00068
rs2276853	3	47282303	G	KIF9	-0.015	0.002	9.51E-11	-0.010	0.004	0.019	0.34
rs3087866	3	49054692	T	DALRD3	-0.021	0.003	4.04E-15	-0.019	0.005	0.00011	0.72
rs2625973	3	129284818	C	PLXND1	-0.020	0.002	1.07E-15	-0.012	0.005	0.0092	0.15
rs13107325	4	103188709	T	SLC39A8	-0.033	0.004	2.07E-14	-0.026	0.008	0.00066	0.42
rs4532349	5	77473165	G	AP3B1	0.015	0.003	1.85E-08	0.007	0.004	0.074	0.12
rs34813	5	102433409	A	GIN1	-0.016	0.002	9.80E-11	-0.010	0.005	0.062	0.28
rs9388768	6	130374102	C	L3MBTL3	-0.017	0.002	1.05E-12	-0.017	0.005	0.00023	0.98
rs2301680	7	93116299	A	CALCR	0.014	0.002	1.13E-09	0.012	0.004	0.005	0.75
rs10902221	11	802379	T	PIDD	0.016	0.002	3.29E-13	0.005	0.005	0.26	0.04
rs5215	11	17408630	C	KCNJ11	0.016	0.002	2.68E-11	0.007	0.004	0.04	0.045
rs3741378	11	65408937	T	SIPA1	-0.023	0.003	1.24E-12	-0.016	0.005	0.001	0.24
rs10891314	11	111916647	A	DLAT	-0.023	0.002	4.48E-23	-0.018	0.005	0.00033	0.36
rs12146709	12	30888001	C	CAPRIN2	-0.015	0.003	6.21E-09	-0.016	0.005	0.001	0.85
rs2277339	12	57146069	G	PRIM1	0.024	0.004	4.55E-11	0.018	0.008	0.014	0.5
rs3764002	12	108618630	T	WSCD2	-0.017	0.003	5.37E-11	-0.018	0.004	7.40E-06	0.78
rs11057353	12	124265687	T	DNAH10	0.019	0.002	3.22E-17	0.017	0.004	1.50E-06	0.6

rs11057401	12	124427306	A	CCDC92	-0.036	0.002	1.78E-50	-0.028	0.005	2.80E-10	0.13
rs1051858	14	58831142	G	ARID4A	0.013	0.002	1.23E-08	0.006	0.004	0.15	0.16
rs1715919	15	56756285	G	MNS1	0.022	0.004	1.31E-09	0.025	0.007	0.00041	0.73
rs3747579	16	4445327	C	CORO7	0.019	0.002	3.30E-14	0.018	0.004	8.20E-07	0.87
rs12923138	16	67233266	C	ELMO3	-0.012	0.002	4.85E-08	-0.005	0.005	0.3	0.22
rs8052655	16	67409180	A	LRRC36	-0.031	0.005	1.64E-09	-0.044	0.011	3.80E-05	0.28
rs10445337	17	44067400	C	MAPT	0.018	0.003	6.74E-11	0.013	0.004	0.0033	0.37
rs3744448	17	59533868	C	TBX4	0.020	0.003	1.45E-10	0.011	0.006	0.073	0.19
rs1042917	21	47545768	A	COL6A2	-0.013	0.002	1.41E-09	-0.011	0.005	0.017	0.62
rs4823086	22	30688659	T	TBC1D10A	0.019	0.003	3.88E-08	0.008	0.007	0.28	0.18
rs1053593	22	35660875	G	HMGXB4	0.014	0.002	6.88E-09	0.014	0.004	5.10E-05	0.91

CHR, chromosome; BP, base pair; EA, effect allele.

Supplementary Table 5. Replication of association of *ACVR1C* variants with WHRadjBMI in the GIANT consortium, Atherosclerosis Risk in Communities study and Framingham Heart Study.

Variant	**UK Biobank**	**Replication Source**	**Replication**	**Test for Heterogeneity**
rs7594480	Beta -0.019, $p=1.6*10^{-5}$	GIANT (n=224156)	Beta -0.019, p=0.002	p=0.99
rs72927479	Beta -0.035, $p=2.6*10^{-12}$	ARIC+FHS (n=13704)	Beta -0.03, p=0.48	p=0.78
rs55920843	Beta -0.09, $p=3.4*10^{-17}$	ARIC+FHS (n=13704)	Beta -0.06, p=0.39	p=0.66
rs56188432	Beta -0.15, $p=1.0*10^{-9}$	ARIC+FHS (n=13704)	Beta -0.28, p=0.08	p=0.41
Gene score meta-analysis (GIANT+ARIC+FHS)			Beta -0.07, p=0.0005	p=0.79
Gene score meta-analysis (ARIC+FHS)			Beta -0.07, p=0.06	p=0.69

Supplementary Table 6. Rare predicted damaging variants in MIGEN.

CHR:POS_REF/ALT	Consequence	Amino Acid Change	Cases With Variant	Controls with Variant
2:158390466_T/C	Missense	Ile482Met	1	2
2:158390483_G/A	Missense	Arg477Cys	0	1
2:158390507_C/T	Missense	Gly469Arg	0	1
2:158390522_A/T	Missense	Cys464Ser	0	1
2:158390552_G/A	Missense	Leu454Phe	0	1
2:158395119_C/T	Missense	Arg441Gln	0	1
2:158395120_G/A	Stop Gained	Arg441Ter	1	0
2:158395148_C/T	Missense	Met431Ile	1	0
2:158395150_T/C	Missense	Met431Val	0	1
2:158397620_G/A	Missense	Arg403Trp	0	3
2:158397673_G/A	Missense	Ser385Phe	0	1
2:158400983_A/C	Missense	Leu306Arg	0	1
2:158401013_G/T	Missense	Ala296Glu	0	1
2:158401014_C/T	Missense	Ala296Thr	0	1
2:158401074_C/A	Missense	Gly276Cys	0	1
2:158401099_C/G	Missense	Trp267Cys	0	1
2:158401119_C/T	Missense	Gly261Arg	0	1
2:158406764_C/T	Missense	Glu229Lys	0	1
2:158406778_A/T	Missense	Phe224Tyr	0	1
2:158406804_A/C	Missense	Cys215Trp	0	1
2:158406807_C/T	Stop Gained	Trp214Ter	0	1
2:158406865_A/G	Missense	Ile195Thr	1	21
2:158406883_C/T	Missense	Arg189Lys	0	2
2:158443708_G/A	Missense	Leu99Phe	0	1
2:158443738_T/G	Missense	Thr89Pro	1	0
2:158443752_G/A	Missense	Thr84Ile	0	1
Total			5	47

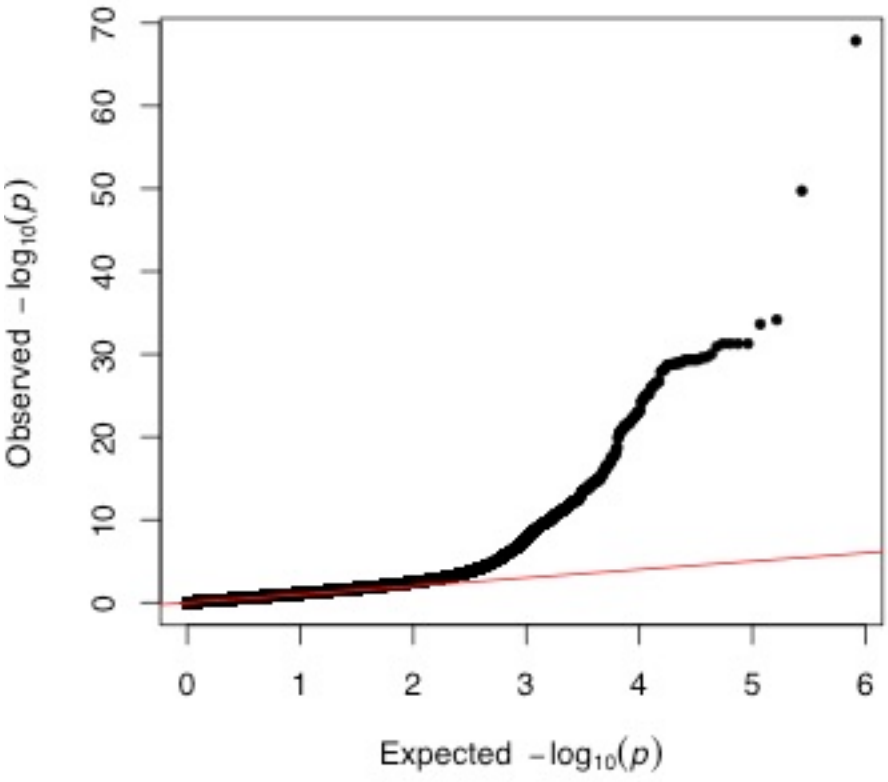
Supplementary Table 7. Rare predicted damaging variants in ARIC.

CHR:POS_REF/ALT	Consequence	Amino Acid Change	Cases With Variant	Controls with Variant
2:158397620_G/A	Missense	Arg403Trp	0	3
2:158406865_A/G	Missense	Ile195Thr	0	13
Total			0	16

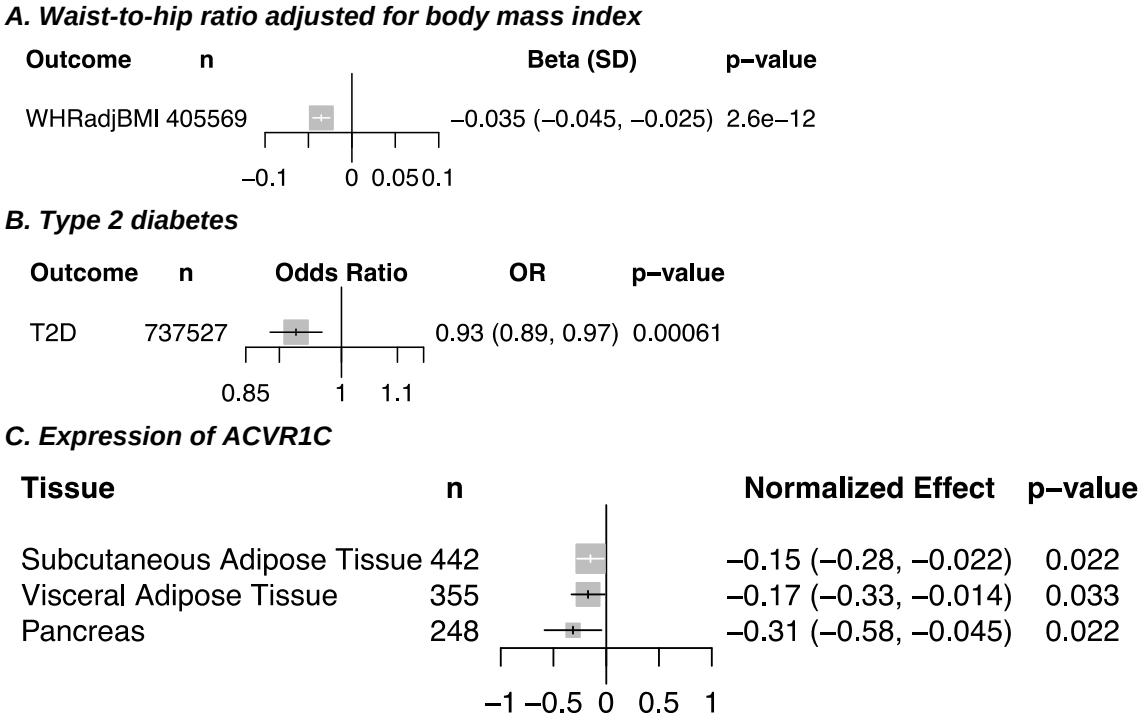
Supplementary Table 8. Rare predicted damaging variants in T2D Genes.

CHR:POS_REF/ALT	Consequence	Amino Acid Change	Individuals With Variant
2:158397652_T/C	Missense	Tyr392Cys	1
2:158399291_C/G	Missense	Gly343Arg	1
2:158399353_C/T	Missense	Arg322Gln	1
2:158399372_T/C	Missense	Lys316Gly	1
2:158400962_G/C	Missense	Thr313Arg	1
2:158400987_G/A	Missense	His305Tyr	1
2:158406865_A/G	Missense	Ile195Thr	13*
2:158401112_C/T	Stop Gained	Trp263Ter	1
2:158406872_T/C	Missense	Arg193Gly	1
2:158406883_C/T	Missense	Arg189Lys	3
2:158412605_C/G	Missense	Gly182Arg	1
2:158412659_C/G	Missense	Gly164Arg	9
2:158443926_A/C	Missense	Leu26Arg	2
2:158443747_A/T	Missense	Cys86Ser	1
2:158485113_A/G	Missense	Leu15Pro	1
Total			37

Note: *One individual with I195T also carries an additional damaging variant, hence 37 individuals carried damaging variants in total. The Genetic Association Interactive Tool does not provide information on individual variants by case-control status, hence this supplementary table does not report variant case-control status as supplementary tables 2 and 3 do.



Supp. Figure 1. Quantile-quantile plot of p-values from waist-to-hip ratio adjusted for body mass index GWAS.



Supp. Figure 2. Association of the minor allele (G) of rs72927479 with abdominal obesity, type 2 diabetes and *ACVR1C* expression in the Genotype-Tissue Expression dataset.