

## Supplementary Online Content

Lyall DM, Celis-Morales C, Ward J, et al. Association of body mass index with cardiometabolic disease in the UK Biobank: a mendelian randomization study. *JAMA Cardiol*. Published online July 5, 2017. doi:10.1001/jamacardio.2016.5804

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

**eTable 1.** List of BMI-associated SNPs in Europeans as reported by Locke et al.\*

SNP	Chr.	Base-pair position	Gene	Effect allele	Other allele	Effect allele freq.	$\beta$ coefficient per effect allele (BMI, SD units)
rs1558902	16	52,361,075	<i>FTO</i>	A	T	0.42	0.082
rs6567160	18	55,980,115	<i>MC4R</i>	C	T	0.24	0.056
rs13021737	2	622,348	<i>TMEM18</i>	G	A	0.83	0.060
rs10938397	4	44,877,284	<i>GNPDA2</i>	G	A	0.43	0.040
rs543874	1	176,156,103	<i>SEC16B</i>	G	A	0.19	0.048
rs2207139	6	50,953,449	<i>TFAP2B</i>	G	A	0.18	0.045
rs11030104	11	27,641,093	<i>BDNF</i>	A	G	0.79	0.041
rs3101336	1	72,523,773	<i>NEGR1</i>	C	T	0.61	0.033
rs7138803	12	48,533,735	<i>BCDIN3D</i>	A	G	0.38	0.032
rs10182181	2	25,003,800	<i>ADCY3</i>	G	A	0.46	0.031
rs3888190	16	28,796,987	<i>ATP2A1</i>	A	C	0.40	0.031
rs1516725	3	187,306,698	<i>ETV5</i>	C	T	0.87	0.045
rs12446632	16	19,842,890	<i>GPRC5B</i>	G	A	0.87	0.040
rs2287019	19	50,894,012	<i>QPCTL</i>	C	T	0.80	0.036
rs16951275	15	65,864,222	<i>MAP2K5</i>	T	C	0.78	0.031
rs3817334	11	47,607,569	<i>MTCH2</i>	T	C	0.41	0.026
rs2112347	5	75,050,998	<i>POC5</i>	T	G	0.63	0.026
rs12566985	1	74,774,781	<i>FPGT</i>	G	A	0.45	0.024
rs3810291	19	52,260,843	<i>ZC3H4</i>	A	G	0.67	0.028
rs7141420	14	78,969,207	<i>NRXN3</i>	T	C	0.53	0.024
rs13078960	3	85,890,280	<i>CADM2</i>	G	T	0.20	0.030
rs10968576	9	28,404,339	<i>LINGO2</i>	G	A	0.32	0.025
rs17024393	1	109,956,211	<i>GNAT2</i>	C	T	0.04	0.066
rs12429545	13	53,000,207	<i>OLFM4</i>	A	G	0.13	0.033
rs13107325	4	103,407,732	<i>SLC39A8</i>	T	C	0.07	0.048
rs11165643	1	96,696,685	<i>PTBP2</i>	T	C	0.58	0.022
rs17405819	8	76,969,139	<i>HNF4G</i>	T	C	0.70	0.022

SNP	Chr.	Base-pair position	Gene	Effect allele	Other allele	Effect allele freq.	$\beta$ coefficient per effect allele (BMI, SD units)
rs1016287	2	59,159,129	<i>LINC01122</i>	T	C	0.29	0.023
rs4256980	11	8,630,515	<i>TRIM66</i>	G	C	0.65	0.021
rs12401738	1	78,219,349	<i>FUBP1</i>	A	G	0.35	0.021
rs205262	6	34,671,142	<i>C6orf106</i>	G	A	0.27	0.022
rs12016871**	13	26,915,782	<i>MTIF3</i>	T	C	0.20	0.030
rs12940622	17	76,230,166	<i>RPTOR</i>	G	A	0.57	0.018
rs11847697	14	29,584,863	<i>PRKD1</i>	T	C	0.04	0.049
rs2075650	19	50,087,459	<i>TOMM40</i>	A	G	0.85	0.026
rs2121279	2	142,759,755	<i>LRP1B</i>	T	C	0.15	0.025
rs29941	19	39,001,372	<i>KCTD15</i>	G	A	0.67	0.018
rs6091540	20	50,521,269	<i>ZFP64</i>	C	T	0.72	0.019
rs7715256	5	153,518,086	<i>GALNT10</i>	G	T	0.42	0.016
rs2176040	2	226,801,046	<i>LOC646736</i>	A	G	0.37	0.014
rs657452	1	49,362,434	<i>AGBL4</i>	A	G	0.39	0.023
rs12286929	11	114,527,614	<i>CADM1</i>	G	A	0.52	0.022
rs7903146	10	114,748,339	<i>TCF7L2</i>	C	T	0.71	0.023
rs10132280	14	24,998,019	<i>STXBP6</i>	C	A	0.68	0.023
rs17094222	10	102,385,430	<i>HIF1AN</i>	C	T	0.21	0.025
rs7599312	2	213,121,476	<i>ERBB4</i>	G	A	0.72	0.022
rs2365389	3	61,211,502	<i>FHIT</i>	C	T	0.58	0.020
rs2820292	1	200,050,910	<i>NAV1</i>	C	A	0.56	0.020
rs12885454	14	28,806,589	<i>PRKD1</i>	C	A	0.64	0.021
rs16851483	3	142,758,126	<i>RASA2</i>	T	G	0.07	0.048
rs1167827	7	75,001,105	<i>HIP1</i>	G	A	0.55	0.020
rs758747	16	3,567,359	<i>NLRC3</i>	T	C	0.27	0.023
rs1928295	9	119,418,304	<i>TLR4</i>	T	C	0.55	0.019
rs9925964†	16	31,037,396	<i>KAT8</i>	A	G	0.62	0.019
rs11126666	2	26,782,315	<i>KCNK3</i>	A	G	0.28	0.021
rs2650492	16	28,240,912	<i>SBK1</i>	A	G	0.30	0.021
rs6804842	3	25,081,441	<i>RARB</i>	G	A	0.57	0.019
rs4740619	9	15,624,326	<i>C9orf93</i>	T	C	0.54	0.018

SNP	Chr.	Base-pair position	Gene	Effect allele	Other allele	Effect allele freq.	$\beta$ coefficient per effect allele (BMI, SD units)
rs13191362	6	162,953,340	<i>PARK2</i>	A	G	0.88	0.028
rs3736485	15	49,535,902	<i>DMXL2</i>	A	G	0.45	0.018
rs17001654†	4	77,348,592	<i>SCARB2</i>	G	C	0.15	0.031
rs11191560	10	104,859,028	<i>NT5C2</i>	C	T	0.09	0.031
rs1528435	2	181,259,207	<i>UBE2E3</i>	T	C	0.63	0.018
rs1000940	17	5,223,976	<i>RABEP1</i>	G	A	0.32	0.019
rs2033529**	6	40,456,631	<i>TDRG1</i>	G	A	0.29	0.019
rs11583200	1	50,332,407	<i>ELAVL4</i>	C	T	0.40	0.018
rs9400239	6	109,084,356	<i>FOXO3</i>	C	T	0.69	0.019
rs10733682	9	128,500,735	<i>LMX1B</i>	A	G	0.48	0.017
rs11688816	2	62,906,552	<i>EHBP1</i>	G	A	0.52	0.017
rs11057405	12	121,347,850	<i>CLIP1</i>	G	A	0.90	0.031
rs11727676	4	145,878,514	<i>HHIP</i>	T	C	0.91	0.036
rs3849570	3	81,874,802	<i>GBE1</i>	A	C	0.36	0.019
rs6477694	9	110,972,163	<i>EPB41L4B</i>	C	T	0.37	0.017
rs7899106	10	87,400,884	<i>GRID1</i>	G	A	0.05	0.040
rs2176598	11	43,820,854	<i>HSD17B12</i>	T	C	0.25	0.020
rs2245368	7	76,446,079	<i>DTX2P1 (PMS2L11)</i>	C	T	0.18	0.032
rs17724992	19	18,315,825	<i>PGPEP1</i>	A	G	0.75	0.019
rs7243357	18	55,034,299	<i>GRP</i>	T	G	0.81	0.022
rs1808579	18	19,358,886	<i>C18orf8</i>	C	T	0.53	0.017
rs2033732	8	85,242,264	<i>RALYL</i>	C	T	0.75	0.019
rs1441264	13	78,478,920	<i>MIR548A2</i>	A	G	0.61	0.018
rs2080454	16	47,620,091	<i>CBLN1</i>	C	A	0.41	0.017
rs7164727	15	70,881,044	<i>LOC100287559</i>	T	C	0.69	0.018
rs17203016	2	207,963,763	<i>CREB1</i>	G	A	0.20	0.021
rs977747	1	47,457,264	<i>TAL1</i>	T	G	0.39	0.017
rs9914578	17	1,951,886	<i>SMG6</i>	G	C	0.21	0.020
rs9374842	6	120,227,364	<i>LOC285762</i>	T	C	0.75	0.019
rs16907751	8	81,538,012	<i>ZBTB10</i>	C	T	0.92	0.035
rs9540493	13	65,103,705	<i>MIR548X2</i>	A	G	0.46	0.017

SNP	Chr.	Base-pair position	Gene	Effect allele	Other allele	Effect allele freq.	$\beta$ coefficient per effect allele (BMI, SD units)
rs7239883	18	38,401,669	<i>LOC284260</i>	G	A	0.39	0.016
rs13201877	6	137,717,234	<i>IFNGR1</i>	G	A	0.14	0.023
rs2836754	21	39,213,610	<i>ETS2</i>	C	T	0.61	0.016
rs492400	2	219,057,996	<i>USP37</i>	C	T	0.42	0.016
rs9641123	7	93,035,668	<i>CALCR</i>	C	G	0.43	0.019
rs1460676	2	164,275,935	<i>FIGN</i>	C	T	0.17	0.020
rs4787491	16	29,922,838	<i>INO80E</i>	G	A	0.51	0.016
rs6465468	7	95,007,450	<i>ASB4</i>	T	G	0.30	0.017

\* Data originate from Supplementary table 9 (European ancestry; sex-combined) from Locke AE, Kahali B, Berndt SI, et al; LifeLines Cohort Study; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518(7538):197-206.

† Excluded due to failing Hardy-Weinberg test. \*\*Not genotyped in UK Biobank sample.

eTable 2. Intercorrelations Among PGR Score, BMI, and Potential Confounders

	PGR score		BMI	
	Pearson <i>r</i>	P-value	Pearson <i>r</i>	P-value
Total N = 119 859 (case N; % of total)				
Townsend score	0.007	0.019	0.086	<0.001
Age	-0.001	0.659	0.040	<0.001
Male sex	0.004	0.128	0.082	<0.001
Smoking	0.016	<0.001	0.040	<0.001
Alcohol intake	0.026	<0.001	0.124	<0.001

eTable 3. Constant Terms From MR-Egger Regression Analyses

	Partially adjusted model 95% CI				Fully adjusted model 95% CI			
	Intercept <i>b</i>	lower	upper	P-value	Intercept <i>b</i>	lower	upper	P-value
Total N = 119 859 (case N; % of total)								
Stroke (1,958; 2%)	0.006	-0.008	0.019	0.418	0.005	-0.009	0.020	0.462
CHD (5,760; 5%)	0.001	-0.002	0.021	0.102	0.011	-0.001	0.023	0.072
Hypertension (32,874; 27%)	0.004	-0.003	0.010	0.287	0.004	-0.003	0.010	0.248
T2D (6,290; 5%)	0.000	-0.018	0.018	0.987	0.001	-0.017	0.019	0.950
Systolic BP*	0.043	-0.016	0.102	0.154	0.043	-0.016	0.103	0.150
Diastolic BP*	0.029	-0.003	0.061	0.071	0.030	-0.002	0.061	0.069
Pulse rate*	0.011	-0.028	0.050	0.572	0.015	-0.024	0.053	0.450

Confidence intervals; CHD = coronary heart disease; T2D = type 2 diabetes. Partially adjusted model adjusted for age and sex, plus ten genetic principal components, assessment centre and batch effects. Fully adjusted model additionally adjusted for smoking history, alcohol intake and Townsend scores. \*Additionally corrected for use of anti-hypertensive medication. Constants are from log-beta equations.

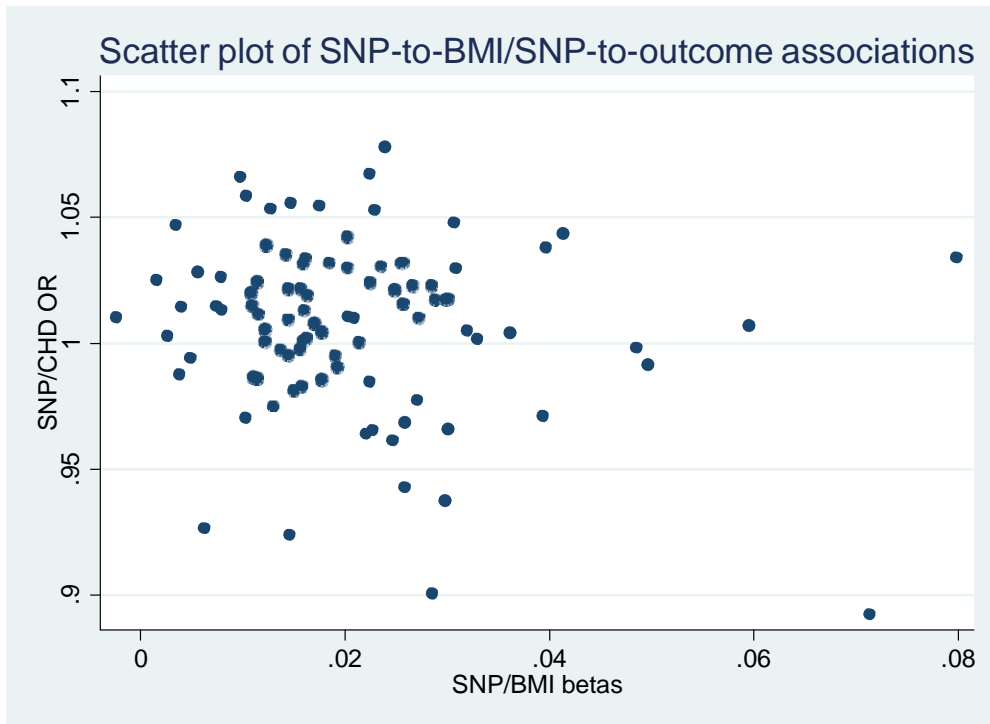
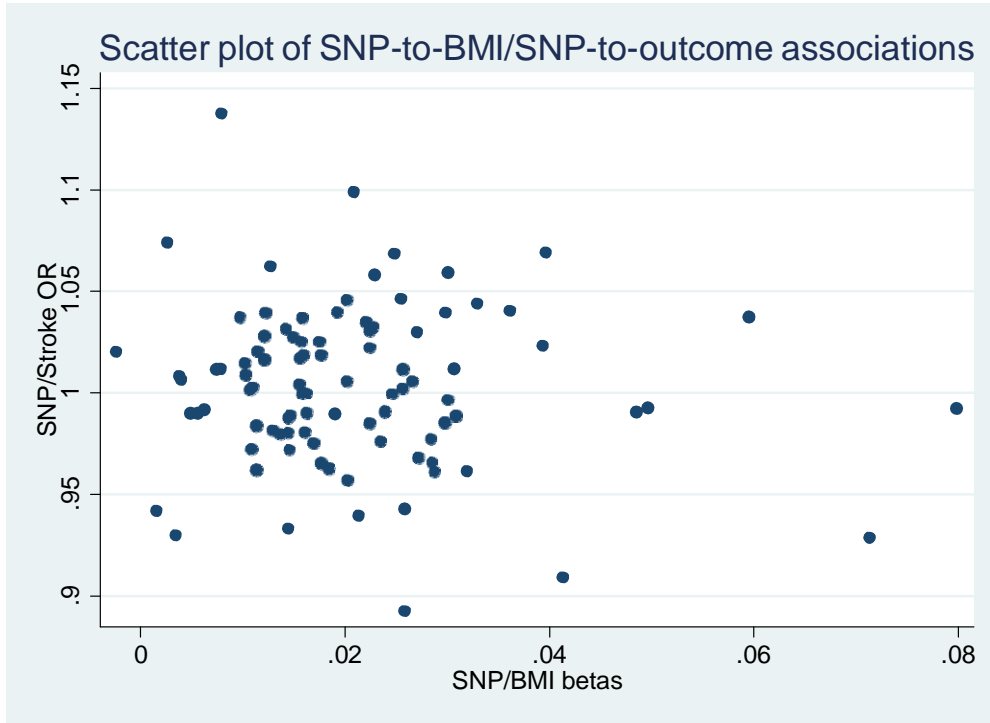
**Table 4.** Causal Estimates Derived From MR-Egger Analysis for a One Standard Deviation Increase in BMI, and Cardiometabolic Traits

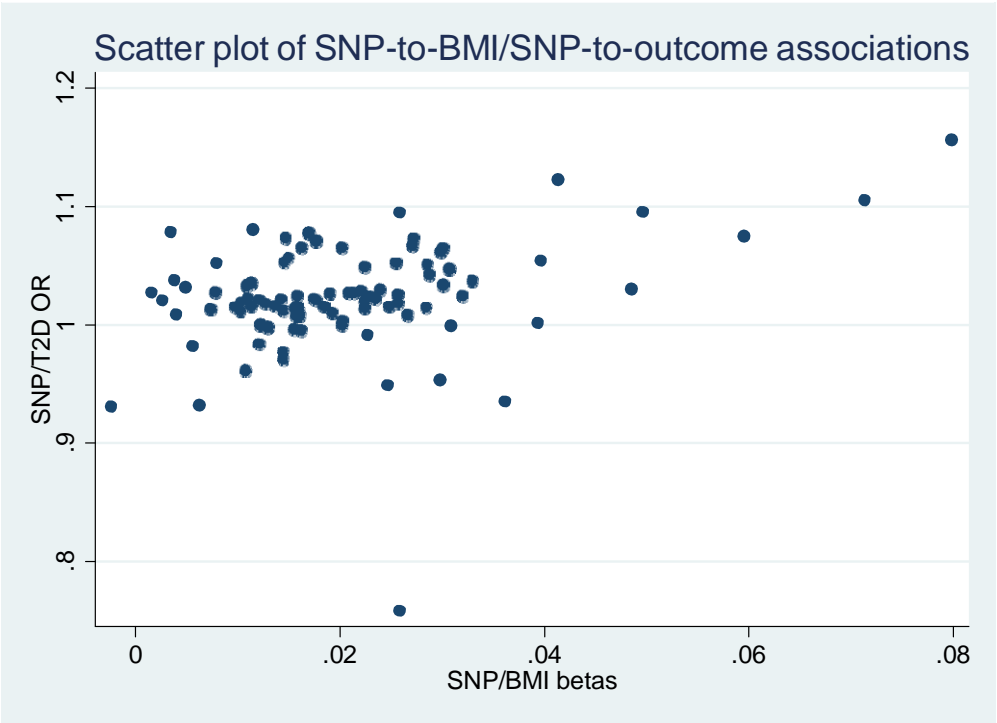
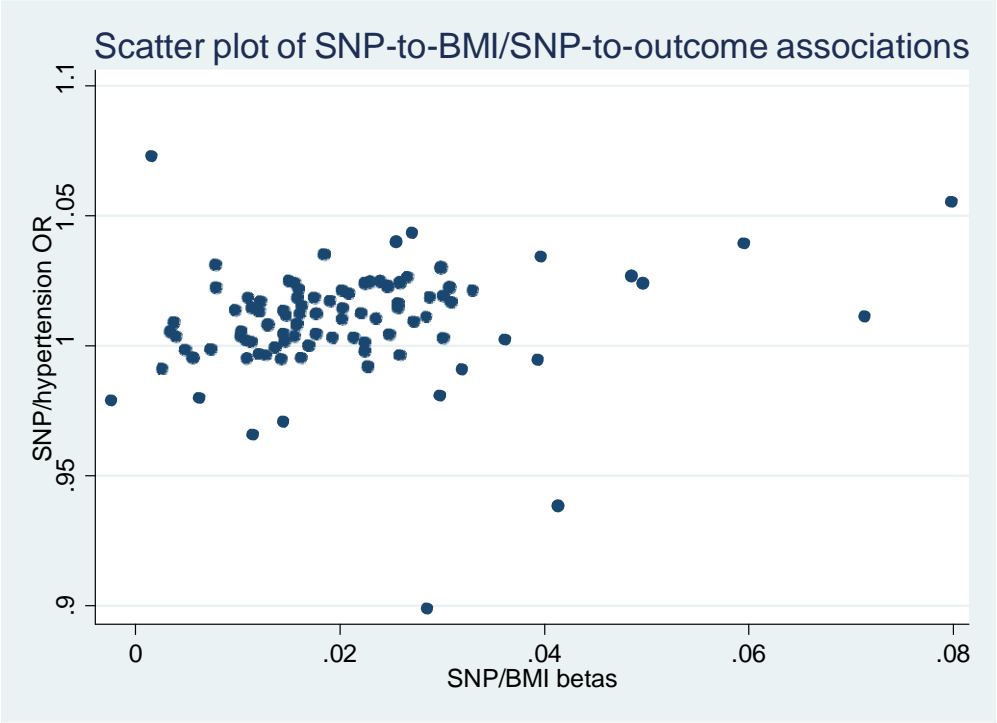
	Partially adjusted model 95% CI				Fully adjusted model 95% CI			
	OR	lower	upper	P-value	OR	lower	upper	P-value
Stroke (1,958; 2%)	0.915	0.484	1.73	0.767	0.840	0.418	1.626	0.582
CHD (5,760; 5%)	1.054	0.723	1.636	0.833	0.922	0.633	1.490	0.760
Hypertension (32,874; 27%)	1.449	1.189	1.918	0.010	1.413	1.157	1.894	0.020
T2D (6,290; 5%)	2.860	1.871	4.661	0.007	2.621	1.183	5.807	0.018
	<i>b</i>	lower	upper	P-value	<i>b</i>	lower	upper	P-value
Systolic BP*	-0.088	-1.673	2.048	0.945	0.151	-1.463	2.319	0.910
Diastolic BP*	0.181	-0.078	1.237	0.794	0.342	-0.667	1.400	0.631
Pulse rate*	-0.415	-1.755	0.552	0.620	-0.806	-2.192	0.260	0.350

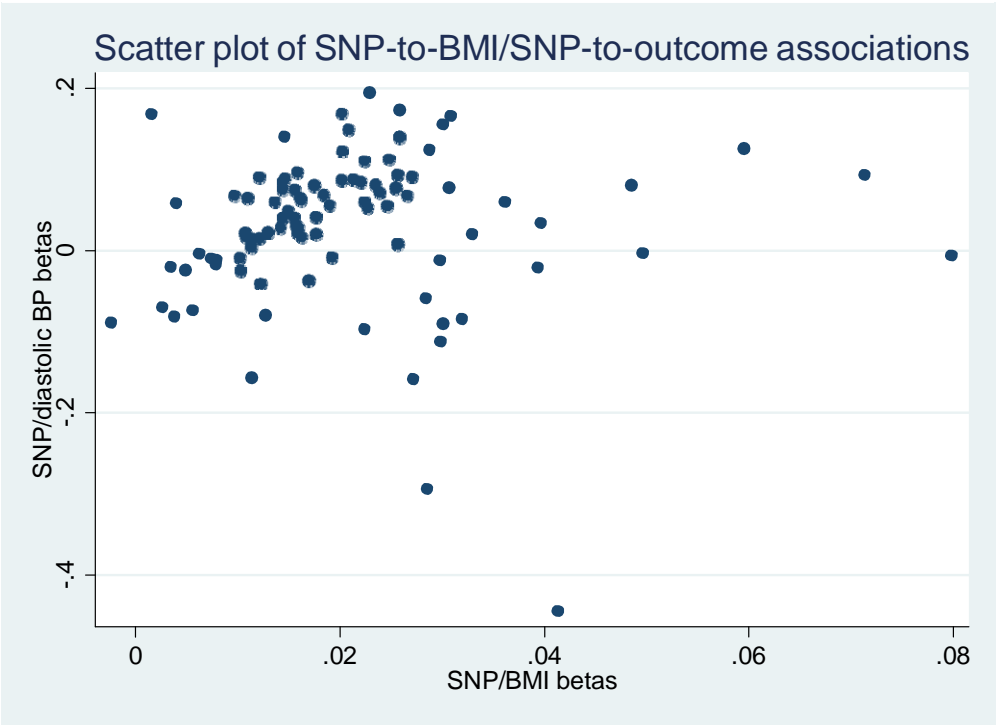
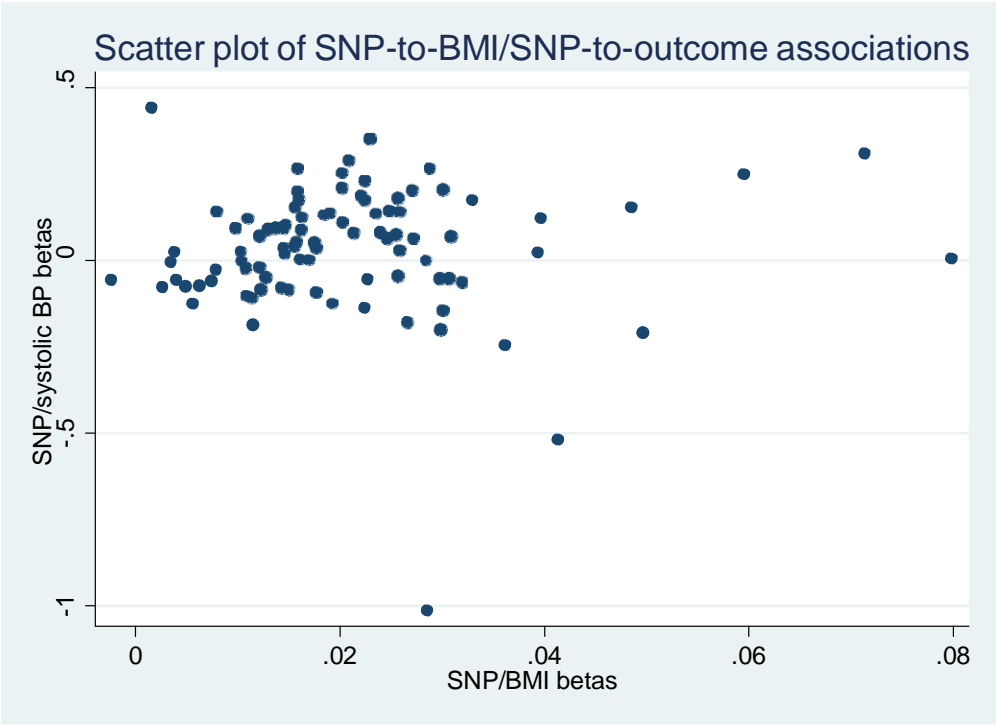
OR = odds ratios, 95% CI = confidence intervals; CHD = coronary heart disease; T2D = type 2 diabetes. Partially adjusted model adjusted for age and sex, plus ten genetic principal components, assessment centre and batch effects. Fully adjusted model additionally adjusted for smoking history, alcohol intake and Townsend scores. \*Additionally corrected for use of anti-hypertensive medication.

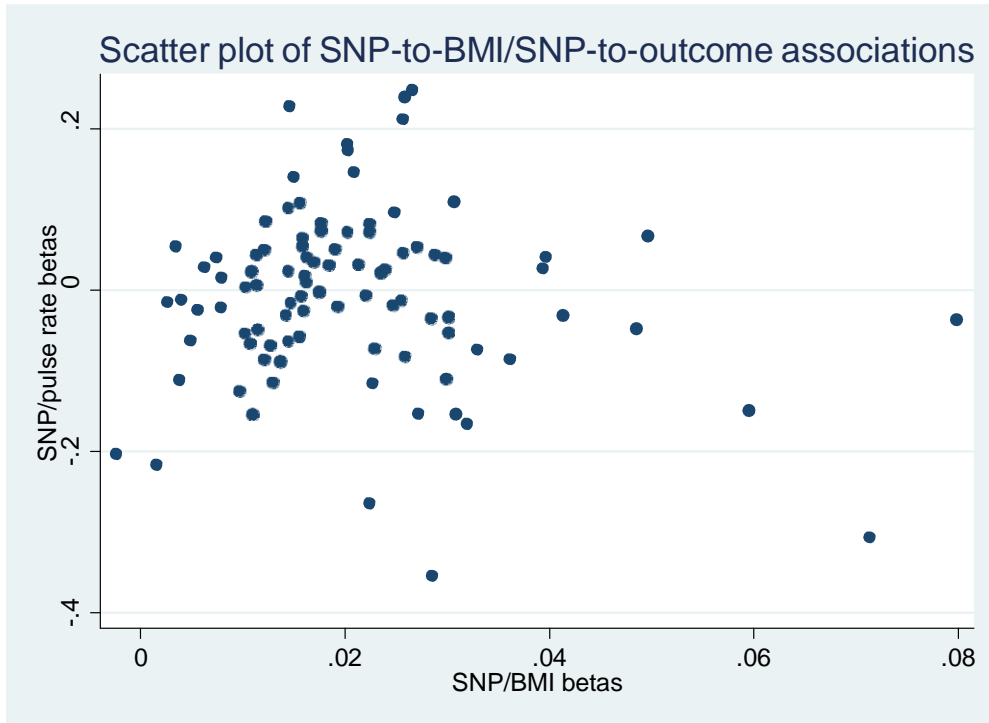


eFigure. Scatter Plots of Genetic Associations With the Outcome (e.g.CHD) Against Genetic Associations With BMI









**Notes:** Possible pleiotropy for each of the 93 SNPs can be assessed visually by a scatterplot, where each point should be roughly compatible with a linear relationship of genetic associations with the outcome (OR for binary traits, standardized betas for continuous) vs. genetic associations with the risk factor.<sup>28</sup> Absence of an outlier is supportive of homogeneity of causal estimates from different genetic variants