Elucidation of causal direction between asthma and obesity: a bi-directional Mendelian randomization study

Supporting Information

CHR	SNP	Genes	Allele	EAF	β (95% CI)	P
1	rs657452	AGBL4	G/A	0.39	0.023 (0.017-0.029)	5.48E-13
1	rs3101336	NEGR1	T/C	0.61	0.033 (0.027-0.039)	2.66E-26
1	rs12566985	FPGT-TNNI3K	A/G	0.45	0.024 (0.018-0.030)	3.28E-15
1	rs12401738	FUBP1,USP33	G/A	0.35	0.021 (0.015-0.027)	1.15E-10
1	rs11165643	PTBP2	C/T	0.58	0.022 (0.016-0.028)	2.07E-12
1	rs17024393	GNAT2,AMPD2	T/C	0.04	0.066 (0.048-0.084)	7.03E-14
1	rs543874	SEC16B	A/G	0.19	0.048 (0.040-0.056)	2.62E-35
1	rs2820292	NAV1	A/C	0.56	0.020 (0.014-0.026)	1.83E-10
2	rs13021737	TMEM18	A/G	0.83	0.060 (0.052-0.068)	1.11E-50
2	rs10182181	ADCY3,POMC, NCOA1	A/G	0.46	0.031 (0.025-0.037)	8.78E-24
2	rs11126666	KCNK3	G/A	0.28	0.021 (0.015-0.027)	1.33E-09
2	rs1016287	LINC01122	C/T	0.29	0.023 (0.017-0.029)	2.25E-11
2	rs11688816	EHBP1	A/G	0.53	0.017 (0.011-0.023)	1.89E-08
2	rs2121279	LRP1B	C/T	0.15	0.025 (0.017-0.033)	2.31E-08
2	rs1528435	UBE2E3	C/T	0.63	0.018 (0.012-0.024)	1.20E-08
2	rs7599312	ERBB4	A/G	0.72	0.022 (0.016-0.028)	1.17E-10
3	rs6804842	RARB	A/G	0.58	0.019 (0.013-0.025)	2.48E-09
3	rs2365389	FHIT	T/C	0.58	0.020 (0.014-0.026)	1.63E-10
3	rs3849570	GBE1	C/A	0.36	0.019 (0.013-0.025)	2.60E-08
3	rs13078960	CADM2	T/G	0.20	0.030 (0.022-0.038)	1.74E-14
3	rs16851483	RASA2	G/T	0.07	0.048 (0.032-0.064)	3.55E-10
3	rs1516725	ETV5	T/C	0.87	0.045 (0.035-0.055)	1.89E-22
4	rs10938397	GNPDA2,GABRG1	A/G	0.43	0.040 (0.034-0.046)	3.21E-38
4	rs17001654	NUP54,SCARB2	C/G	0.15	0.031 (0.021-0.041)	7.76E-09
4	rs13107325	SLC39A8	C/T	0.07	0.048 (0.034-0.062)	1.83E-12
4	rs11727676	HHIP	C/T	0.91	0.036 (0.024-0.048)	2.55E-08
5	rs2112347	POC5,HMGCR, COL4A3BP	G/T	0.63	0.026 (0.020-0.032)	6.19E-17
6	rs205262	C6orf106,SNRPC	A/G	0.27	0.022 (0.014-0.030)	1.75E-10
6	rs2033529	TDRG1,LRFN2	A/G	0.29	0.019 (0.013-0.025)	1.39E-08
6	rs2207139	TFAP2B	A/G	0.18	0.045 (0.037-0.053)	4.13E-29
6	rs9400239	FOXO3,HSS00296402	T/C	0.69	0.019 (0.013-0.025)	1.61E-08
6	rs13191362	PARK2	G/A	0.88	0.028 (0.018-0.038)	7.34E-09
7	rs1167827	HIP1,PMS2L3, PMS2P5,WBSCR16	A/G	0.553	0.020 (0.014-0.026)	6.33E-10
7	rs2245368	PMS2L11	T/C	0.18	0.032 (0.020-0.044)	3.19E-08
8	rs17405819	HNF4G	C/T	0.70	0.022 (0.016-0.028)	2.07E-11
8	rs2033732	RALYL	T/C	0.75	0.019 (0.011-0.027)	4.89E-08
9	rs4740619	C9orf93	C/T	0.54	0.018 (0.012-0.024)	4.56E-09

CHR	SNP	Genes	Allele	EAF	β (95% CI)	P
9	rs10968576	LINGO2	A/G	0.32	0.025 (0.019-0.031)	6.61E-14
9	rs6477694	EPB41L4B,C9orf4	T/C	0.37	0.017 (0.011-0.023)	2.67E-08
9	rs1928295	TLR4	C/T	0.55	0.019 (0.013-0.025)	7.91E-10
9	rs10733682	LMX1B	G/A	0.48	0.017 (0.011-0.023)	1.83E-08
10	rs7899106	GRID1	A/G	0.05	0.040 (0.026-0.054)	2.96E-08
10	rs17094222	HIF1AN	T/C	0.21	0.025 (0.017-0.033)	5.94E-11
10	rs11191560	NT5C2,CYP17A1, SFXN2	T/C	0.09	0.031 (0.021-0.041)	8.45E-09
10	rs7903146	TCF7L2	T/C	0.71	0.023 (0.017-0.029)	1.11E-11
11	rs4256980	TRIM66,TUB	C/G	0.65	0.021 (0.015-0.027)	2.90E-11
11	rs11030104	BDNF	G/A	0.79	0.041 (0.033-0.049)	5.56E-28
11	rs2176598	HSD17B12	C/T	0.25	0.020 (0.012-0.028)	2.97E-08
11	rs3817334	MTCH2,C1QTNF4, SPI1,CELF1	C/T	0.41	0.026 (0.02-0.032)	5.15E-17
11	rs12286929	CADM1	A/G	0.52	0.022 (0.016-0.028)	1.31E-12
12	rs7138803	BCDIN3D,FAIM2	G/A	0.38	0.032 (0.026-0.038)	8.15E-24
12	rs11057405	CLIP1	A/G	0.90	0.031 (0.019-0.043)	2.02E-08
13	rs12429545	OLFM4	G/A	0.13	0.033 (0.023-0.043)	1.09E-12
13	rs9581854*	MTIF3,GTF3A	C/T	0.20	0.030 (0.020-0.040)	2.29E-10
14	rs10132280	STXBP6	A/C	0.68	0.023 (0.017-0.029)	1.14E-11
14	rs12885454	PRKD1	A/C	0.64	0.021 (0.015-0.027)	1.94E-10
14	rs11847697	PRKD1	C/T	0.04	0.049 (0.033-0.065)	3.99E-09
14	rs7141420	NRXN3	C/T	0.53	0.024 (0.018-0.030)	1.23E-14
15	rs3736485	SCG3,DMXL2	G/A	0.45	0.018 (0.012-0.024)	7.41E-09
15	rs16951275	MAP2K5,LBXCOR1	C/T	0.78	0.031 (0.023-0.039)	1.91E-17
16	rs758747	NLRC3	C/T	0.27	0.023 (0.015-0.031)	7.47E-10
16	rs12446632	GPRC5B,IQCK	A/G	0.87	0.040 (0.030-0.050)	1.48E-18
16	rs2650492	SBK1,APOBR	G/A	0.30	0.021 (0.013-0.029)	1.92E-09
16	rs9925964	KAT8,ZNF646, VKORC1,ZNF668, STX1B,FBXL19	G/A	0.62	0.019 (0.013-0.025)	8.11E-10
16	rs1558902	FTO	T/A	0.42	0.082 (0.076-0.088)	7.51E-153
17	rs1000940	RABEP1	A/G	0.32	0.019 (0.013-0.025)	1.28E-08
17	rs12940622	RPTOR	A/G	0.58	0.018 (0.012-0.024)	2.49E-09
18	rs1808579	NPC1,C18orf8	T/C	0.53	0.017 (0.011-0.023)	4.17E-08
18	rs7243357	GRP	G/T	0.81	0.022 (0.014-0.030)	3.86E-08
18	rs6567160	MC4R	T/C	0.24	0.056 (0.048-0.064)	3.93E-53
19	rs17724992	GDF15,PGPEP1	G/A	0.75	0.019 (0.011-0.027)	3.42E-08
19	rs29941	KCTD15	A/G	0.67	0.018 (0.012-0.024)	2.41E-08
19	rs2075650	TOMM40,APOE, APOC1	G/A	0.85	0.026 (0.016-0.036)	1.25E-08
19	rs2287019	QPCTL,GIPR	T/C	0.80	0.036 (0.028-0.044)	4.59E-18
19	rs3810291	ZC3H4	G/A	0.67	0.028 (0.020-0.036)	4.81E-15

Table S1. List of BMI-associated SNPs in European-ancestry. Genes reported are based on biological relevance to obesity, copy number variation, DEPICT analyses, GRAIL results, BMI-association variant in strong LD ($r^2 \geq 0.7$) with a missense variant, nearest to index SNP, association and eQTL data converge to affect gene expression. Allele (reference/effect), effect allele frequency (EAF), marginal effect (β), 95% confidence intervals (95% CI), and significance of marginal effect (P) based on the meta analysis of GWAS data from the European data set [?]. SNP rs9581854* replaces rs12016871 as the latter was deprecated and they are in perfect LD.

CHR	SNP	Genes	Allele	EAF	OR (95% CI)	P
5	rs10455025	SLC25A46,TSLP	A/C	0.34	1.15 (1.12-1.18)	2.00E-25
6	rs2325291	BACH2,GJA10, MAP3K7	G/A	0.33	0.91 (0.89-0.93)	8.60E-13
8	rs12543811	TPD52,ZBTB10	G/A	0.66	0.93 (0.91-0.95)	3.50E-08
9	rs992969	RANBP6,IL33	A/G	0.75	0.85 (0.82-0.88)	1.10E-17
10	rs2589561	GATA3,CELF2	A/G	0.82	0.90 (0.87-0.94)	1.40E-08
15	rs11071558	RORA,NARG2, VPS13C	A/G	0.14	0.89 (0.85-0.92)	1.90E-10
16	rs17806299	CLEC16A,DEXI, SOCS1	G/A	0.20	0.90 (0.88-0.93)	2.10E-10
17	rs17637472	ZNF652,PHB	G/A	0.39	1.08 (1.05-1.11)	3.30E-09

Table S2. List of SNPs associated with asthma among European-ancestry population in TAGC [**?**]. Genes reported are based on where the lead SNP lies that is coding for proteins, Allele (reference/effect allele), effect allele frequency (EAF), odds-ratios (ORs), 95% confidence intervals (95% CI), and significance (*P*) based on the meta analysis of GWAS data using a random effects model.

Causal link	**Method**	**Estimate**	**95% CI**	***P***
BMI → asthma	fixed-effect	1.211	[1.176, 1.247]	6e-38
	random-effect	1.214	[1.169, 1.261]	2e-23
	MR-Egger	1.187	[1.050, 1.342]	0.006
	penalized	1.191	[1.137, 1.248]	2e-13
	MR-PRESSO	1.218	[1.175, 1.263]	3e-25
asthma → BMI	fixed-effect	−0.011	[−0.017, −0.005]	3e-04
	random-effect	−0.013	[−0.024, −0.003]	0.018
	MR-Egger	−0.013	[−0.041, 0.015]	0.369
	penalized	−0.011	[−0.021, −0.001]	0.034
	MR-PRESSO	−0.013	[−0.022, −0.004]	0.004

Table S3. Causal estimates of body mass index z-score on asthma and the reverse direction reported by fixed effect and random effect meta analyses, MR-Egger, penalized weighted median, and MR-PRESSO via one-sample MR.

Causal link	**Method**	**Estimate**	**95% CI**	***P***
BMI → T2D	fixed-effect	2.80	[2.53, 3.09]	5.80e-91
	random-effect	2.50	[1.39, 4.51]	2.24e-03
	MR-Egger	3.66	[1.55, 8.59]	2.97e-03
	(intercept)	0.99	[0.97, 1.01]	4.88e-01
	MR-PRESSO	3.30	[2.89, 3.77]	1.24e-27
BMI → CVD	fixed-effect	1.53	[1.464, 1.60]	8.72e-81
	random-effect	1.60	[1.270, 2.03]	7.38e-05
	MR-Egger	1.28	[0.934, 1.75]	1.25e-01
	(intercept)	1.01	[0.997, 1.01]	2.00e-01
	MR-PRESSO	1.67	[1.556, 1.79]	5.18e-21

Table S4. Causal estimates of body mass index z-score on type-2 diabetes and cardivascular diseases reported by fixed effect and random effect meta analyses, MR-Egger, penalized weighted median, and MR-PRESSO via GIANT–UKB two-sample MR.

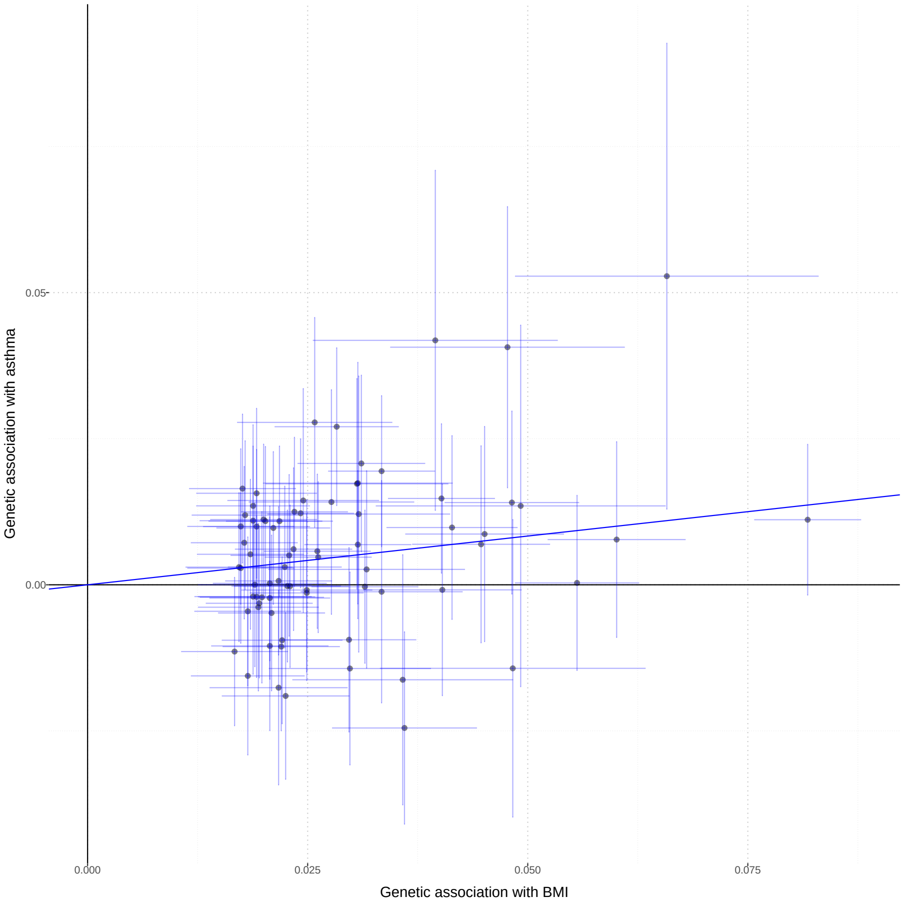

Figure S1. Genetic association with BMI in GIANT versus genetic association with asthma in UKB for 75 BMI-SNPs. Each dot represents a SNP, the horizontal bar indicates the 95% CI for its association with BMI, while the vertical bar does that of asthma.

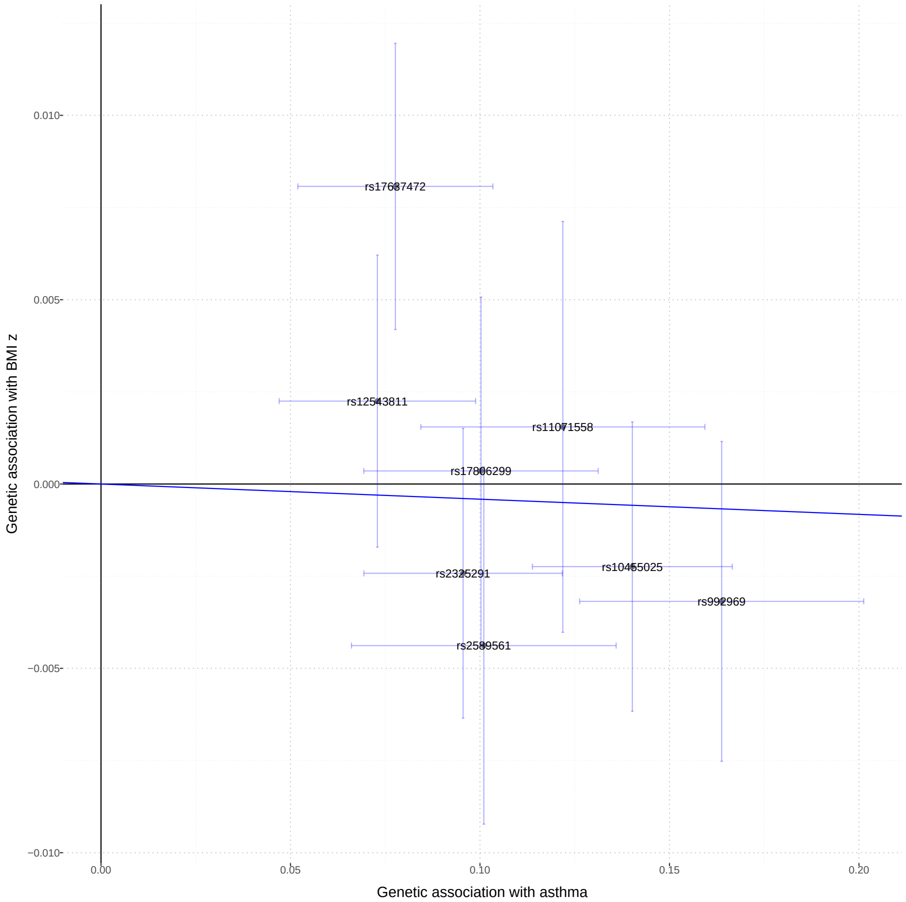

Figure S2. Genetic association with asthma in TAGC versus genetic association with BMI z-scores in UKB. Each dot represents a SNP, the horizontal bar indicates the 95% CI for its association with asthma, while the vertical bar does that of BMI z-score.

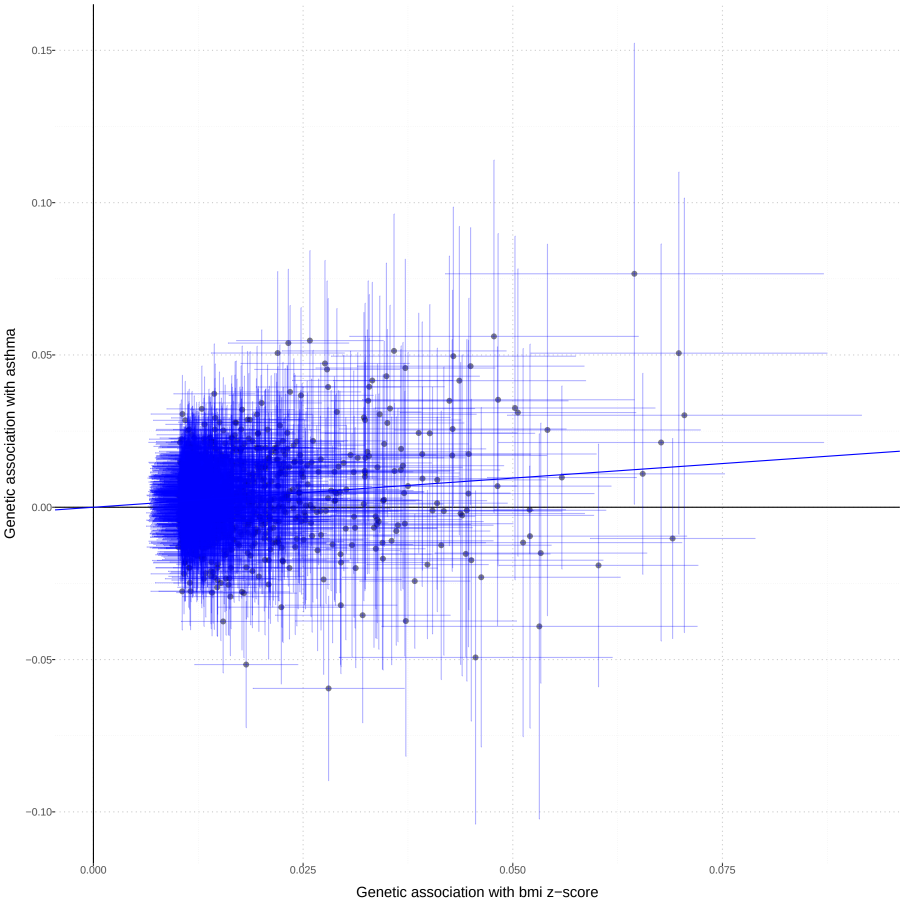

Figure S3. Genetic association with body mass index versus genetic association with asthma in UKB, where the slope indicate fixed effect meta analysis estimate.

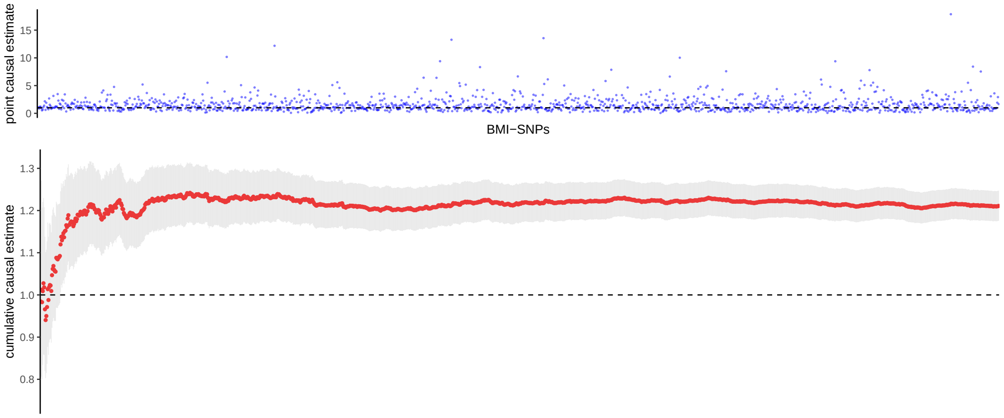

Figure S4. Cumulative effect estimates of BMI on asthma risk in UKB for a total of 1348 independent SNPs are displayed in the bottom panel, where red dots are the point estimates and gray vertical bars suggest the corresponding 95% CIs. Instrumental SNP was added sequentially in the order based on the p-value of its association with BMI z-score. Point estimate of the added SNP is shown on the top panel and colored in blue.

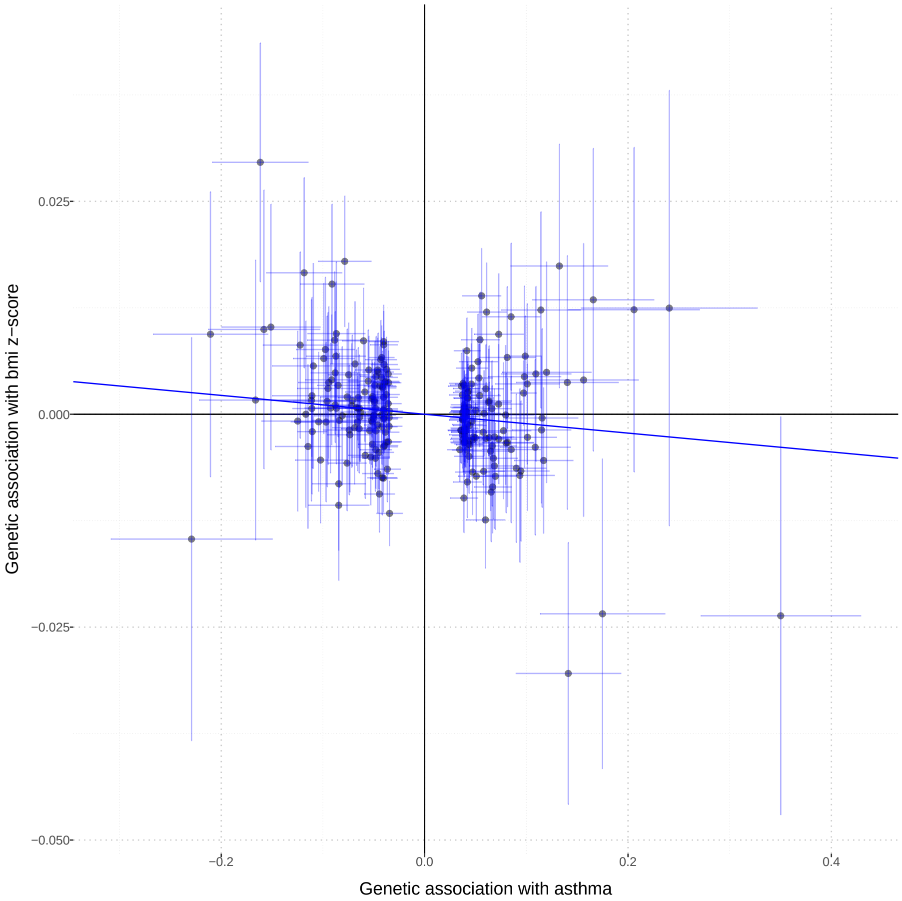

Figure S5. Genetic association with asthma versus genetic association with body mass index in UKB, where the slope indicates fixed effect meta analysis estimate.

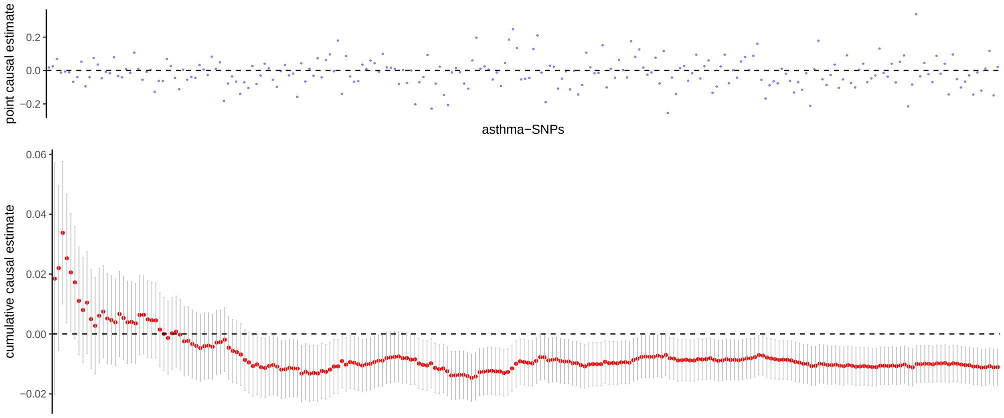

Figure S6. Cumulative effect estimates of asthma on BMI in UKB for a total of 234 independent SNPs are displayed in the bottom panel, where red dots are the point estimates and gray vertical bars suggest the corresponding 95% CIs. Instrumental SNP was added sequentially in the order based on the p-value of its association with asthma. Point estimate of the added SNP is shown on the top panel and colored in blue.