Supplemental Material

Data S1.

Supplemental Methods

Definition of depression
1. UK biobank[10]
1) The broad definition of depression was used in the UK Biobank. Measured in a variety of ways:
  a. *Have you ever seen a general practitioner for nerves, anxiety, tension or depression?*
  b. *Have you ever seen a psychiatrist for nerves, anxiety, tension or depression?*
2) Does not include the participants who were identified with bipolar disorder, schizophrenia, or personality disorder using self-declared data as well as prescriptions for antipsychotic medications.

2. 23andMe_307k[11]
1) The data were derived from the genome-wide association study results of the discovery 23andMe.
2) Depression was defined based on responses to web-based surveys, with individuals that self-reported as having received a clinical diagnosis or treatment for depression classified as cases.

3. PGC_139k[12]
1) PGC_139k cohort was obtained from the meta-analysis of major depressive disorder utilizing European-ancestry PGC cohorts with the 23andMe_307k and the previous UK Biobank cohorts removed.
2) Depression was defined based on structured diagnostic interviews, or electronic medical records，with individuals that self-reported as having received a clinical diagnosis or treatment for depression.

Table S1. Descriptive information of the studies and datasets included in the analyses

GWAS	Phenotype	Participants	Ancestry	Use in this MR study	Adjustments*
Howard et al, 2019[9]	Depression	246,363 cases 561,190 controls	Multi-ancestry	Exposure	Age, sex, genotype platform
CARDIoGRAMplusC4D[13]	CAD/MI	60,801 cases 123,504 controls	Multi-ancestry (77% European)	Primary outcome	age, sex
Aragam et al, 2018[14]	HF	6,504 cases 387,652 controls	European	Secondary outcome	age, sex, genotyping platform array
AF HRC[15]	AF	65,446 cases 522,744 controls	Multi-ancestry (91% European)	Secondary outcome	age, sex
MEGASTROKE[16]	Any ischemic stroke and subtypes (LAS, SVS, CES)	34,217 cases 404,630 controls	European	Secondary outcome	age, sex
GIANT[27]	BMI	322,154 individuals	European	Confounder in multivariable MR	age, age squared
GLGC[28]	LDL-C, HDL-C, TGL	188,578 individuals	European	Confounder in multivariable MR	age, sex
UK Biobank[29] (Neale lab analysis)	SBP, DBP, hypertension	317,754 individuals	European	Confounder in multivariable MR	sex
DIAGRAM[26]	T2D	34,840 cases 114,981 controls	European Pakistani	Mediator in mediation analysis	age, sex
GSCAN[25]	Smoking, alcohol use	1,232,091 individuals	European	Mediator in mediation analysis	age, sex, interaction between age and sex

*All GWAS studies have further adjusted for principal components.

GWAS names: AF HRC, Atrial Fibrillation Haplotype Reference Consortium; CARDIoGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics; DIAGRAM, DIAbetes Genetics Replication and Meta-analysis; GIANT, Genetic Investigation of Anthropometric Traits; GLGC, global lipids genetics consortium; GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use.

Phenotypes: AF, atrial fibrillation; BMI, body mass index；CAD, coronary artery disease; CES, cardioembolic stroke; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LAS, large artery stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; SVS, small vessel stroke; T2D, type 2 diabetes; TGL, triglycerides.

Table S2. Characteristics of the genetic variants associated with depression

SNP	Effect allele	Non-effect allele	Effect allele frequency	Chromosome	Position	Gene	Beta*	Standard Error	P-value
rs301799	T	C	0.5694	1	8489302	RERE	-0.025	0.0035	1.356E-12
rs1002656	T	C	0.7033	1	37192741	RP4-614N24.1	-0.0266	0.0038	3.739E-12
rs1466887	T	C	0.5511	1	37709328	RP5-1180C18.1	-0.0199	0.0036	4.118E-08
rs11579246	A	G	0.9067	1	50559162	ELAVL4	0.0381	0.0061	5.706E-10
rs1890946	T	C	0.4671	1	52342427	NRDC	-0.0235	0.0035	2.68E-11
rs10789214	T	C	0.5661	1	67146817	SGIP1	0.0193	0.0035	4.442E-08
rs2568958	A	G	0.6156	1	72765116	RPL31P12	0.0373	0.0036	8.473E-25
rs10890020	A	G	0.5156	1	73668836	RN7SKP19	-0.0277	0.0035	4.028E-15
rs113188507	A	G	0.2838	1	80809636	AL606519.1	0.0221	0.0039	1.871E-08
rs10913112	T	C	0.3767	1	175913828	RFWD2	-0.0264	0.0036	3.4E-13
rs72710803	A	C	0.9121	1	177428018	RP1-35C21.2	-0.041	0.0062	5.289E-11
rs169235	A	G	0.753	1	181740924	CACNA1E	-0.0229	0.0041	2.976E-08
rs17641524	T	C	0.2091	1	197704717	DENND1B	-0.032	0.0043	1.522E-13
rs12052908	A	T	0.5325	2	22503044	N.A.	-0.022	0.0035	4.436E-10
rs1568452	T	C	0.3851	2	58012833	ACTG1P22	0.0248	0.0036	8.118E-12
rs7585722	T	C	0.8458	2	86819128	RNF103-CHMP3	-0.0269	0.0048	2.675E-08
rs1226412	T	C	0.7917	2	157111313	LINC01876	0.0256	0.0043	3.459E-09
rs62188629	A	G	0.3136	2	208044470	AC007879.1	0.0236	0.0038	7.127E-10
rs4346585	T	C	0.696	3	44736493	RP11-944L7.4	-0.0236	0.0038	7.127E-10
rs13084037	A	G	0.774	3	49214066	KLHDC8B	-0.0245	0.0042	7.084E-09
rs7624336	T	G	0.2087	3	53244151	AC097015.1	0.0238	0.0043	3.957E-08
rs141954845	A	G	0.388	3	61192911	FHIT	0.0229	0.0037	8.145E-10
rs6783233	T	C	0.2833	3	117509984	RP11-384F7.2	0.0218	0.0039	2.903E-08

rs1095626	T	C	0.5799	3	157977962	RSRC1	-0.0264	0.0035	7.131E-14
rs7685686	A	G	0.5753	4	3207142	HTT	0.0202	0.0036	2.571E-08
rs34937911	T	C	0.8838	4	42110353	BEND4	0.0304	0.0055	4.13E-08
rs45510091	A	G	0.9472	4	123186393	KIAA1109	0.0448	0.008	1.826E-08
rs35553410	T	C	0.7462	4	131237381	RP11-404I7.1	-0.0244	0.004	1.417E-09
rs7659414	A	C	0.5782	4	177350956	RN7SKP13	-0.0201	0.0035	1.204E-08
rs60157091	T	C	0.515	5	61509655	AC010376.1	0.02	0.0035	1.421E-08
rs3099439	T	C	0.5288	5	87545318	TMEM161B	-0.0276	0.0035	5.049E-15
rs10061069	C	G	0.2212	5	93071630	POU5F2	-0.0275	0.0042	8.152E-11
rs30266	A	G	0.3296	5	103972357	RP11-6N13.1	0.0308	0.0037	1.445E-16
rs11135349	A	C	0.4713	5	164523472	CTC-340A15.2	-0.0295	0.0035	6.042E-17
rs200949	A	G	0.8744	6	27835435	HIST1H1B	0.048	0.0053	2.525E-19
rs9363467	T	C	0.6035	6	66565703	RNU7-66P	0.0237	0.0036	6.437E-11
rs7758630	A	T	0.4051	6	101387304	RP3-359N14.1	-0.0225	0.0036	5.56E-10
rs1933802	C	G	0.4536	6	105365891	LIN28B-AS1	-0.0223	0.0035	2.567E-10
rs2876520	C	G	0.5271	6	142996618	AL356739.1	-0.023	0.0036	2.294E-10
rs725616	T	C	0.3644	6	147950422	SAMD5	0.0204	0.0036	1.871E-08
rs2029865	A	T	0.4534	6	165121844	XX-C2158C12.1	-0.0201	0.0035	1.204E-08
rs3823624	T	C	0.8067	7	2110346	MAD1L1	0.0272	0.0045	1.992E-09
rs2043539	A	G	0.4177	7	12253880	TMEM106B	0.0273	0.0035	9.893E-15
rs2247523	C	G	0.5319	7	82454404	PCLO	-0.0207	0.0035	4.377E-09
rs16887442	T	C	0.4347	7	82936909	AC079799.2	0.0203	0.0035	8.621E-09
rs58104186	A	G	0.4689	7	109099919	AC073071.1	0.0237	0.0035	1.819E-11
rs7807677	T	C	0.5505	7	117502574	CTTNBP2	0.0237	0.0035	1.819E-11
rs7837935	T	G	0.1522	8	65562019	CYP7B1	-0.0292	0.0049	3.343E-09
rs67436663	C	G	0.2402	8	71347626	RP11-333A23.1	-0.0259	0.0042	9.374E-10

rs1354115	A	C	0.6243	9	2983774	CARM1P1	0.021	0.0036	7.084E-09
rs1982277	T	C	0.7594	9	11513019	RP11-32D4.1	0.0279	0.0041	1.447E-11
rs263645	A	T	0.5438	9	17016503	RP11-132E11.2	0.0221	0.0035	3.699E-10
rs3793577	A	G	0.4665	9	23737627	ELAVL2	-0.0229	0.0035	8.411E-11
rs59283172	A	G	0.1069	9	25232978	RN7SKP120	-0.0329	0.0057	1.016E-08
rs34653192	C	G	0.3196	9	31124452	RP11-572H4.1	-0.0229	0.0038	2.225E-09
rs7030813	T	C	0.3736	9	36999369	PAX5	0.0253	0.0036	3.074E-12
rs10817969	T	G	0.7173	9	119731045	ASTN2	0.0261	0.0039	3.108E-11
rs913930	A	G	0.6433	9	120484009	TLR4	-0.0208	0.0037	2.421E-08
rs2670139	T	C	0.7609	9	126634255	DENND1A	-0.0266	0.0041	1.207E-10
rs997934	T	C	0.3795	10	1795194	ADARB2	0.0198	0.0036	4.812E-08
rs1021363	A	G	0.3547	10	106610839	SORCS3	0.0303	0.0037	4.406E-16
rs1448938	A	G	0.4171	11	30892824	DCDC1	0.0214	0.0035	1.297E-09
rs2509805	T	C	0.3209	11	57650796	RP11-734C14.2	0.022	0.0038	9.17E-09
rs198457	T	C	0.1925	11	61471678	DAGLA	-0.0292	0.0046	2.986E-10
rs58621819	A	T	0.7903	11	65314830	LTBP3	-0.0245	0.0043	1.565E-08
rs7117514	A	G	0.5417	11	70544937	SHANK2	-0.0204	0.0035	7.286E-09
rs7932640	T	C	0.4417	11	88744425	GRM5	0.0281	0.0035	1.62E-15
rs61902811	A	G	0.3682	11	113370758	DRD2	-0.0257	0.0036	1.395E-12
rs2187490	T	G	0.9106	11	118713180	Y_RNA	-0.0338	0.0061	3.824E-08
rs57344483	A	G	0.9259	11	127022560	CTD-2234N14.2	-0.038	0.0068	1.818E-08
rs78337797	T	G	0.8781	12	23987925	SOX5	0.0306	0.0055	3.365E-08
rs56314503	T	G	0.7487	12	84465022	SNORA3	-0.0254	0.004	2.945E-10
rs10774600	T	C	0.1656	12	110741356	ATP2A2	-0.0267	0.0048	3.387E-08
rs3213572	A	G	0.4745	12	121205078	SPPL3	0.0217	0.0035	7.612E-10
rs1409379	T	C	0.7641	13	31907741	B3GLCT	0.0249	0.0041	1.671E-09

rs1343605	A	C	0.384	13	53647048	OLFM4	0.0313	0.0036	6.229E-18
rs9592461	A	G	0.4874	13	66941792	PCDH9	0.0216	0.0035	9.1E-10
rs9545360	A	C	0.1807	13	80826373	SPRY2	-0.0271	0.0046	5.021E-09
rs4772087	T	C	0.3732	13	99115041	STK24	0.0227	0.0036	3.911E-10
rs61990288	A	G	0.5083	14	42074726	LRFN5	-0.026	0.0035	1.681E-13
rs1956373	T	G	0.7436	14	60141822	RTN1	-0.0226	0.004	2.059E-08
rs1152578	T	C	0.4357	14	64697037	ESR2	-0.0218	0.0035	6.363E-10
rs1045430	T	G	0.4792	14	75130235	AREL1	-0.0253	0.0035	7.308E-13
rs10149470	A	G	0.4869	14	104017953	BAG5	-0.0267	0.0035	3.718E-14
rs8037355	T	C	0.5556	15	37643831	RP11-720L8.1	-0.0233	0.0035	3.936E-11
rs34488670	T	C	0.7887	15	47684936	SEMA6D	-0.0252	0.0043	6.033E-09
rs7193263	A	G	0.6679	16	6315880	RBFOX1	-0.0239	0.0038	4.331E-10
rs7198928	T	C	0.6159	16	7666402	rs7198928	0.0239	0.0036	4.447E-11
rs7200826	T	C	0.2551	16	13066833	SHISA9	0.028	0.004	3.739E-12
rs56887639	A	G	0.7264	16	13755530	U95743.1	-0.0278	0.0039	1.506E-12
rs12923444	A	C	0.5625	16	21639710	METTL9	-0.0214	0.0035	1.297E-09
rs75581564	A	G	0.1165	17	27363750	PIPOX	0.0301	0.0054	3.172E-08
rs12967855	A	G	0.3295	18	35138245	CELF4	0.0265	0.0037	1.18E-12
rs7227069	A	G	0.4326	18	50731802	DCC	0.0238	0.0035	1.497E-11
rs62091461	T	C	0.2274	18	52488672	RAB27B	-0.0254	0.0042	1.954E-09
rs12966052	C	G	0.1805	18	52751639	LINC01929	-0.0314	0.0046	1.252E-11
rs12967143	C	G	0.6984	18	53099012	TCF4	-0.0312	0.0038	3.699E-16
rs7241572	A	G	0.201	18	77580712	RP11-154H12.3	0.028	0.0044	2.698E-10
rs33431	T	C	0.6144	19	30939989	ZNF536	0.0198	0.0036	4.812E-08
rs143186028	T	G	0.1778	20	39997404	EMILIN3	0.0277	0.0046	2.288E-09
rs12624433	A	G	0.2584	20	44680853	SLC12A5	0.0233	0.004	7.441E-09

| rs5995992 | T | C | 0.7155 | 22 | 41487218 | rs5995992 | -0.0266 | 0.0039 | 1.3E-11 |

*The beta coefficients represent the 1-unit change in the probability of getting depression for each additional effect allele.

Table S3. Mendelian randomization associations of genetically predicted cardiovascular diseases with depression.

Outcome	Risk factors	SNP	IVW OR (95% CI)	*p*	MR-PRESSO OR (95%CI)	*p*
Depression	Coronary artery disease	39	1.01 (1.00-1.03)	0.14	1.01 (0.99-1.03)*	0.20
	Myocardial infarction	23	1.01 (0.99-1.03)	0.50	NA†	NA
	Heart failure	5	1.01 (0.97-1.05)	0.79	1.04 (0.97-1.12)‡	0.35
	Atrial fibrillation	90	1.00 (0.99-1.02)	0.71	1.00 (0.99-1.02)§	0.62
	Any Ischemic Stroke	9	1.02 (0.96-1.07)	0.54	NA†	NA
	Large artery stroke	3	1.01 (0.97-1.05)	0.73	NA†	NA
	Small vessel stroke	0	/	/	/	/
	Cardioembolic stroke	3	1.02 (0.99-1.05)	0.32	NA†	NA

CI, confidence interval; OR, odds ratio; IVW, the inverse-variance weighted method; MR-PRESSO, MR-Pleiotropy Residual Sum and Outlier; NA, not available; SNP, single nucleotide polymorphism.

*MR-PRESSO IV outliers detected: rs11191416 and rs663129.

†No outlier detected.

‡MR-PRESSO IV outliers detected: rs2234962.

§ MR-PRESSO IV outliers detected: rs2738413, rs62011291, rs72926475, and rs7978685.

Figure S1. Diagram for the mediation analysis of the mediation effect of depression on coronary artery disease and myocardial infarction via type 2 diabetes mellitus, smoking or alcohol use.
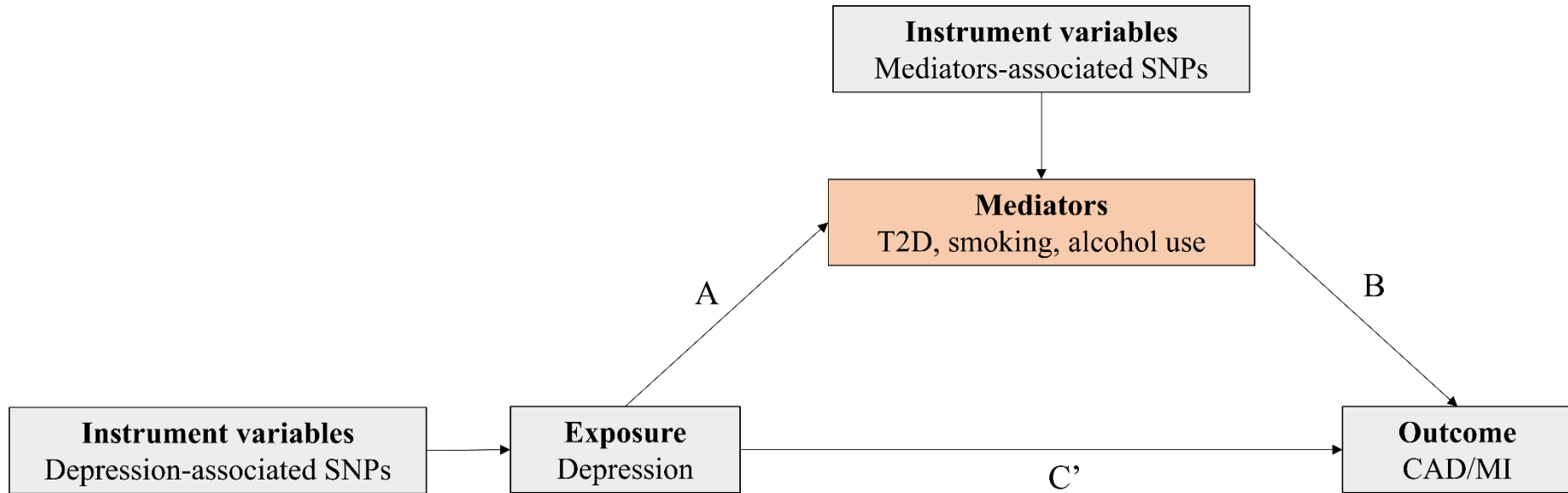
A, the effect of the depression on the mediator. B, the effect of the mediator on the outcome after adjusting for depression. C', the effect of depression on the outcome acting through the mediator. The mediation effect (C') is calculated by multiplying A times B. The standard error of mediation effect is calculated as

$$S_{C'} = C' \sqrt{(\frac{S_A}{A})^2 + (\frac{S_B}{B})^2}$$

with $S_{C'}$, S_A, S_B the standard errors of C', A, B, respectively. The corresponding 95% confidence intervals are implemented as

$$95\% \text{ confidence intervals} = e^{C'-1.96S_{C'}} \text{ to } e^{C'+1.96S_{C'}}$$

CAD, coronary artery disease; MI, myocardial infarction; SNPs, Single nucleotide polymorphisms; T2D, type 2 diabetes mellitus.

Figure S2. Scatter plots of SNP potential effects regarding the associations of genetically determined depression with (A) coronary artery disease and (B) myocardial infarction, with the slope of line corresponding to estimated MR effect derived from inverse-variance-weighted MR analyses.
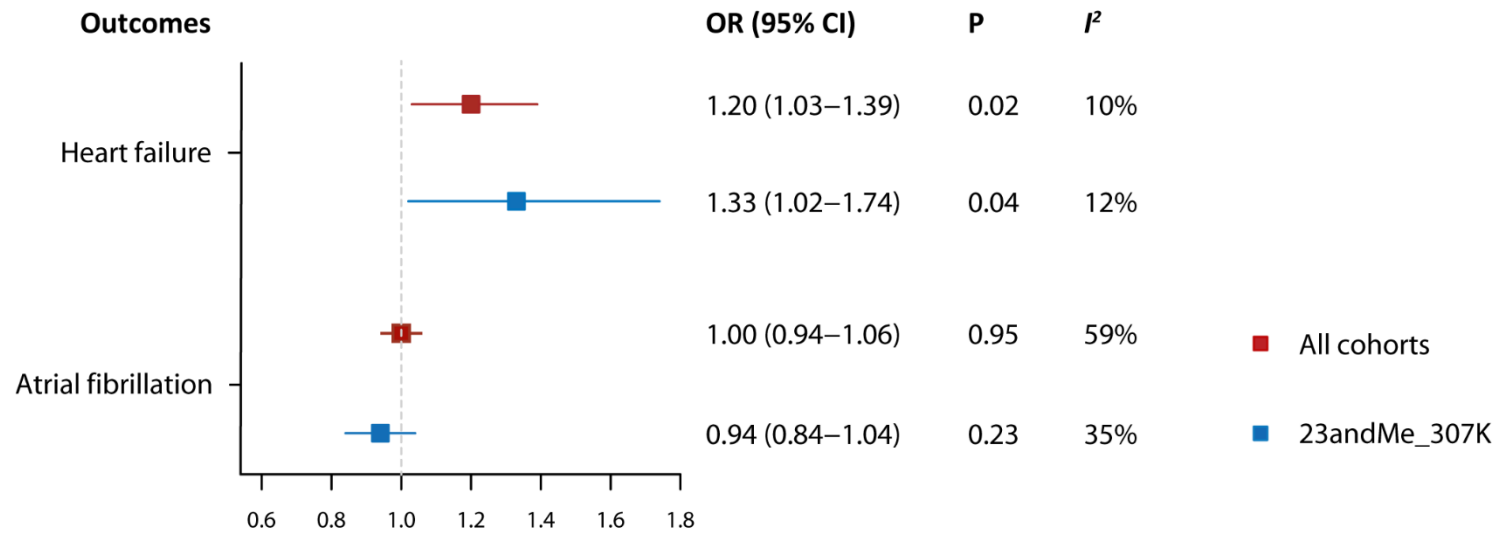
A
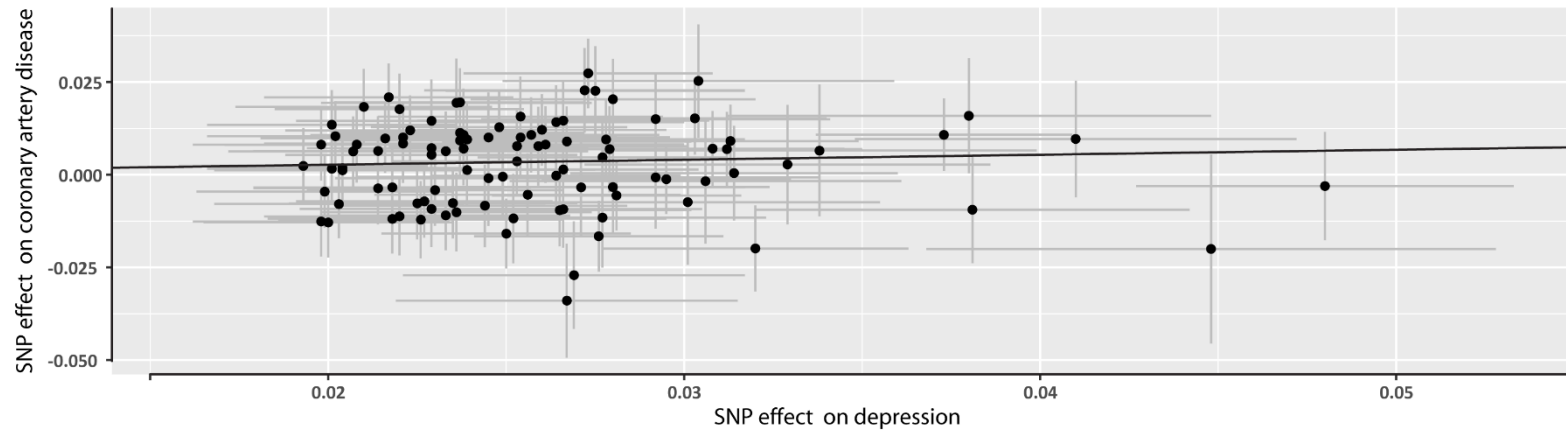
B
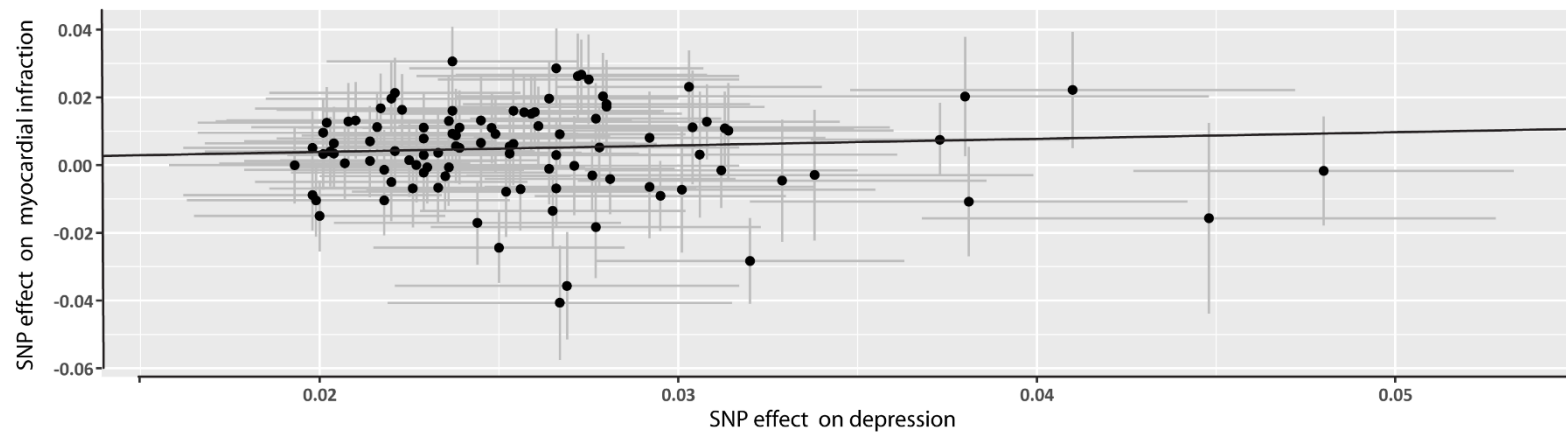
Figure S3. Mendelian randomization association of genetically predicted depression with heart failure and atrial fibrillation.

Odds ratios are scaled to per genetically predicted 2.72-fold (1 log-odds unit) increase in the liability to depression.

CI, confidence interval; OR, odds ratio