

Supplementary

Table S1 Association between each SNP related to bipolar disorder

SNP	chr	EA	β	SE	P-value	EAF	LD exclusion	Study
rs7544145	1	T	0.082	0.015	2.68E-08	0.810	NO	31043756
rs73188321	7	T	-0.083	0.013	3.65E-11	0.330	NO	
rs4447398	15	A	0.094	0.016	4.30E-09	0.120	NO	
rs3804640	3	A	0.063	0.011	9.40E-09	0.530	NO	
rs2388334	6	A	-0.062	0.011	1.24E-08	0.520	NO	
rs2302417	3	A	-0.073	0.011	4.60E-11	0.490	NO	
rs12575685	11	A	0.070	0.012	3.84E-09	0.310	NO	
rs12226877	11	A	0.082	0.013	5.71E-10	0.290	NO	
rs9834970	3	T	-0.073	-	5.70E-12	0.510	YES	
rs7122539	11	A	-0.062	-	3.80E-08	0.350	YES	
rs61332983	2	I	-0.073	-	7.90E-10	0.410	YES	
rs59134449	10	I	0.086	-	1.20E-08	0.160	YES	
rs57970360	6	D	0.062	-	3.50E-08	0.440	YES	
rs57195239	2	I	-0.073	-	3.80E-09	0.340	YES	
rs202012857	20	I	-0.074	-	1.10E-08	0.280	YES	
rs201231874	7	D	-0.083	-	6.20E-10	0.250	YES	
rs200550695	5	I	-0.083	-	1.50E-08	0.820	YES	
rs17183814	2	A	-0.128	-	2.00E-09	0.075	YES	
rs139221256	15	I	-0.073	-	2.70E-08	0.280	YES	
rs10035291	5	T	0.068	-	2.70E-08	0.680	YES	
rs11724116	4	T	-0.083	0.015	2.06E-08	0.160	NO	
rs11647445	16	T	-0.073	0.012	2.78E-10	0.650	NO	
rs11557713	18	A	0.067	0.012	2.26E-08	0.290	NO	
rs113779084	7	A	0.073	0.012	9.62E-10	0.300	NO	
rs112114764	17	T	-0.073	0.012	1.35E-09	0.690	NO	
rs111444407	19	T	0.093	0.015	7.20E-10	0.150	NO	
rs10994318	10	C	0.135	0.023	3.10E-09	0.057	NO	
rs10896090	11	A	0.081	0.014	8.48E-09	0.810	NO	
rs10744560	12	T	0.073	0.012	1.92E-10	0.340	NO	
rs10455979	6	C	-0.062	0.011	2.18E-08	0.530	YES	
rs1054442	12	A	0.122	0.018	1.00E-08	0.620	YES	27329760
rs12553324	9	C	0.113	0.021	6.00E-09	0.590	NO	
rs1487441	6	G	0.113	0.016	3.00E-08	0.510	NO	
rs2517959	17	T	0.122	0.018	5.00E-09	0.670	NO	
rs4236274	7	G	0.140	0.022	8.00E-12	0.390	NO	
rs9834970	3	T	0.131	0.020	5.00E-10	0.500	YES	
rs12576775	11	G	0.168	0.028	3.00E-09	0.820	NO	28115744
rs174576	11	A	0.119	0.018	1.00E-10	0.660	NO	
rs28456	11	G	0.166	0.028	6.00E-09	0.690	YES	
rs4332037	7	T	0.154	0.026	2.00E-09	0.810	YES	
rs4926298	19	G	0.124	0.020	6.00E-10	0.650	NO	
rs9834970	3	C	0.109	0.018	2.00E-09	0.500	YES	
rs1012053	13	A	0.464	0.083	2.00E-08	0.840	NO	17486107

SNP: single nucleotide polymorphism, se: standard error, LD: linkage disequilibrium, EA: effect allele, EAF: effect allele frequency.

Table 2 Single SNP result for SNP related to bipolar disorder and risk of breast cancer and subtypes.

exposure	outcome	id.exposure	id.outcome	samplesize	SNP	b	se	p
1	bipolar disorder	Fee588	ieu-a-1126	228951	rs1012053	4.16E-02	1.83E-02	2.32E-02
2	bipolar disorder	Fee588	ieu-a-1126	228951	rs10896090	-2.91E-01	9.79E-02	2.93E-03
3	bipolar disorder	Fee588	ieu-a-1126	228951	rs111444407	4.18E-01	9.29E-02	6.80E-06
4	bipolar disorder	Fee588	ieu-a-1126	228951	rs112114764	4.96E-02	9.51E-02	6.02E-01
5	bipolar disorder	Fee588	ieu-a-1126	228951	rs113779084	3.55E-02	9.28E-02	7.02E-01
6	bipolar disorder	Fee588	ieu-a-1126	228951	rs11557713	-7.94E-02	1.05E-01	4.49E-01
7	bipolar disorder	Fee588	ieu-a-1126	228951	rs11647445	1.07E-01	9.23E-02	2.44E-01
8	bipolar disorder	Fee588	ieu-a-1126	228951	rs11724116	2.01E-01	1.04E-01	5.35E-02
9	bipolar disorder	Fee588	ieu-a-1126	228951	rs12575685	1.56E-02	1.06E-01	8.83E-01
10	bipolar disorder	Fee588	ieu-a-1126	228951	rs4236274	1.60E-01	4.57E-02	4.65E-04
11	bipolar disorder	Fee588	ieu-a-1126	228951	rs4447398	-3.18E-02	9.96E-02	7.50E-01
12	bipolar disorder	Fee588	ieu-a-1126	228951	rs4926298	1.00E-01	5.81E-02	8.50E-02
13	bipolar disorder	Fee588	ieu-a-1126	228951	rs73188321	2.76E-02	8.52E-02	7.46E-01
14	bipolar disorder	Fee588	ieu-a-1126	228951	rs7544145	-3.92E-02	1.03E-01	7.03E-01
15	bipolar disorder	Fee588	ieu-a-1126	228951	All - Inverse variance weighted	5.69E-02	2.50E-02	2.29E-02
16	bipolar disorder	Fee588	ieu-a-1126	228951	All - MR Egger	5.33E-02	4.11E-02	2.19E-01
17	bipolar disorder	Fee588	ieu-a-1127	175475	rs1012053	2.61E-02	2.20E-02	2.36E-01
18	bipolar disorder	Fee588	ieu-a-1127	175475	rs10896090	-2.34E-01	1.17E-01	4.44E-02
19	bipolar disorder	Fee588	ieu-a-1127	175475	rs111444407	4.10E-01	1.10E-01	1.95E-04
20	bipolar disorder	Fee588	ieu-a-1127	175475	rs112114764	2.20E-02	1.13E-01	8.45E-01
21	bipolar disorder	Fee588	ieu-a-1127	175475	rs113779084	1.16E-01	1.11E-01	2.94E-01
22	bipolar disorder	Fee588	ieu-a-1127	175475	rs11557713	-1.80E-01	1.24E-01	1.48E-01
23	bipolar disorder	Fee588	ieu-a-1127	175475	rs11647445	7.58E-02	1.10E-01	4.92E-01
24	bipolar disorder	Fee588	ieu-a-1127	175475	rs11724116	1.26E-01	1.25E-01	3.13E-01
25	bipolar disorder	Fee588	ieu-a-1127	175475	rs12575685	7.10E-03	1.28E-01	9.56E-01
26	bipolar disorder	Fee588	ieu-a-1127	175475	rs4236274	1.17E-01	5.50E-02	3.32E-02
27	bipolar disorder	Fee588	ieu-a-1127	175475	rs4447398	-9.53E-03	1.20E-01	9.37E-01
28	bipolar disorder	Fee588	ieu-a-1127	175475	rs4926298	1.81E-01	6.94E-02	9.20E-03
29	bipolar disorder	Fee588	ieu-a-1127	175475	rs73188321	-2.04E-02	1.02E-01	8.41E-01
30	bipolar disorder	Fee588	ieu-a-1127	175475	rs7544145	9.44E-02	1.24E-01	4.46E-01
31	bipolar disorder	Fee588	ieu-a-1127	175475	All - Inverse variance weighted	4.80E-02	2.51E-02	5.56E-02
32	bipolar disorder	Fee588	ieu-a-1127	175475	All - MR Egger	3.61E-02	4.11E-02	3.97E-01
33	bipolar disorder	Fee588	ieu-a-1128	127442	rs1012053	5.22E-02	3.36E-02	1.21E-01
34	bipolar disorder	Fee588	ieu-a-1128	127442	rs10896090	-4.59E-01	1.76E-01	9.17E-03
35	bipolar disorder	Fee588	ieu-a-1128	127442	rs111444407	5.10E-01	1.67E-01	2.33E-03
36	bipolar disorder	Fee588	ieu-a-1128	127442	rs112114764	8.68E-02	1.72E-01	6.14E-01
37	bipolar disorder	Fee588	ieu-a-1128	127442	rs113779084	-8.05E-02	1.69E-01	6.34E-01
38	bipolar disorder	Fee588	ieu-a-1128	127442	rs11557713	1.20E-02	1.89E-01	9.49E-01
39	bipolar disorder	Fee588	ieu-a-1128	127442	rs11647445	2.76E-01	1.67E-01	9.84E-02
40	bipolar disorder	Fee588	ieu-a-1128	127442	rs11724116	2.18E-01	1.93E-01	2.58E-01
41	bipolar disorder	Fee588	ieu-a-1128	127442	rs12575685	-1.31E-01	1.93E-01	4.99E-01
42	bipolar disorder	Fee588	ieu-a-1128	127442	rs4236274	6.86E-02	8.36E-02	4.12E-01
43	bipolar disorder	Fee588	ieu-a-1128	127442	rs4447398	-7.42E-02	1.81E-01	6.82E-01
44	bipolar disorder	Fee588	ieu-a-1128	127442	rs4926298	-1.15E-01	1.04E-01	2.71E-01
45	bipolar disorder	Fee588	ieu-a-1128	127442	rs73188321	2.40E-02	1.56E-01	8.78E-01
46	bipolar disorder	Fee588	ieu-a-1128	127442	rs7544145	-4.98E-01	1.86E-01	7.56E-03
47	bipolar disorder	Fee588	ieu-a-1128	127442	All - Inverse variance weighted	3.11E-02	4.03E-02	4.41E-01
48	bipolar disorder	Fee588	ieu-a-1128	127442	All - MR Egger	6.46E-02	6.54E-02	3.43E-01

SNP: single nucleotide polymorphism, b: beta, se: standard error, p: p-value.

Table 3 Bi-directional MR analysis on detecting causal effect for breast cancer on bipolar disorder.

id.exposure	outcome	exposure	method	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95	
1	ieu-a-1126	Bipolar disorder	Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	MR Egger	-3.89E-02	1.11E-01	7.27E-01	-2.57E-01	1.79E-01	9.62E-01	7.74E-01	1.20E+00
2	ieu-a-1126	Bipolar disorder	Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	Weighted median	-8.52E-03	6.94E-02	9.02E-01	-1.44E-01	1.27E-01	9.92E-01	8.65E-01	1.14E+00
3	ieu-a-1126	Bipolar disorder	Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	Inverse variance weighted	1.19E-03	4.71E-02	9.80E-01	-9.12E-02	9.35E-02	1.00E+00	9.13E-01	1.10E+00
4	ieu-a-1126	Bipolar disorder	Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	Simple mode	3.81E-03	1.35E-01	9.78E-01	-2.61E-01	2.68E-01	1.00E+00	7.70E-01	1.31E+00
5	ieu-a-1126	Bipolar disorder	Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	Weighted mode	3.81E-03	8.53E-02	9.64E-01	-1.63E-01	1.71E-01	1.00E+00	8.49E-01	1.19E+00
6	ieu-a-1127	Bipolar disorder	ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	MR Egger	-5.10E-02	1.04E-01	6.25E-01	-2.55E-01	1.53E-01	9.50E-01	7.75E-01	1.16E+00
7	ieu-a-1127	Bipolar disorder	ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	Weighted median	-1.17E-02	6.35E-02	8.54E-01	-1.36E-01	1.13E-01	9.88E-01	8.73E-01	1.12E+00
8	ieu-a-1127	Bipolar disorder	ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	Inverse variance weighted	7.97E-03	4.39E-02	8.56E-01	-7.80E-02	9.39E-02	1.01E+00	9.25E-01	1.10E+00
9	ieu-a-1127	Bipolar disorder	ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	Simple mode	-6.33E-02	1.23E-01	6.10E-01	-3.05E-01	1.79E-01	9.39E-01	7.37E-01	1.20E+00
10	ieu-a-1127	Bipolar disorder	ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	Weighted mode	-2.54E-02	7.67E-02	7.41E-01	-1.76E-01	1.25E-01	9.75E-01	8.39E-01	1.13E+00
11	ieu-a-1128	Bipolar disorder	ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	MR Egger	1.01E-04	1.96E-01	1.00E+00	-3.84E-01	3.84E-01	1.00E+00	6.81E-01	1.47E+00
12	ieu-a-1128	Bipolar disorder	ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	Weighted median	-5.27E-02	8.40E-02	5.30E-01	-2.17E-01	1.12E-01	9.49E-01	8.05E-01	1.12E+00
13	ieu-a-1128	Bipolar disorder	ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	Inverse variance weighted	-1.00E-01	6.08E-02	9.90E-02	-2.20E-01	1.89E-02	9.05E-01	8.03E-01	1.02E+00
14	ieu-a-1128	Bipolar disorder	ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	Simple mode	-4.09E-02	1.45E-01	7.81E-01	-3.25E-01	2.43E-01	9.60E-01	7.22E-01	1.28E+00
15	ieu-a-1128	Bipolar disorder	ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	Weighted mode	-5.74E-02	1.29E-01	6.62E-01	-3.11E-01	1.96E-01	9.44E-01	7.33E-01	1.22E+00

Id: identification, b: beta, se: standard error, or: odds ratio, ci: confidence interval, pval: p-value.

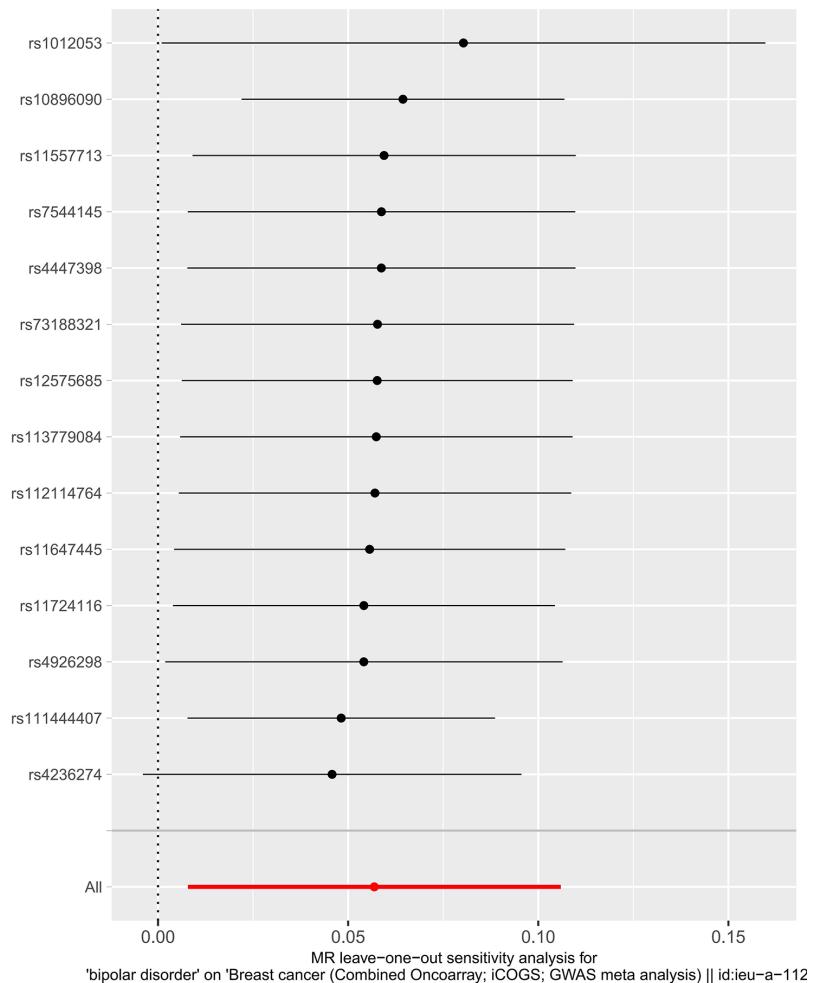


Figure S1 Leave-one-out analysis for genetically predicted bipolar disorder and breast cancer.

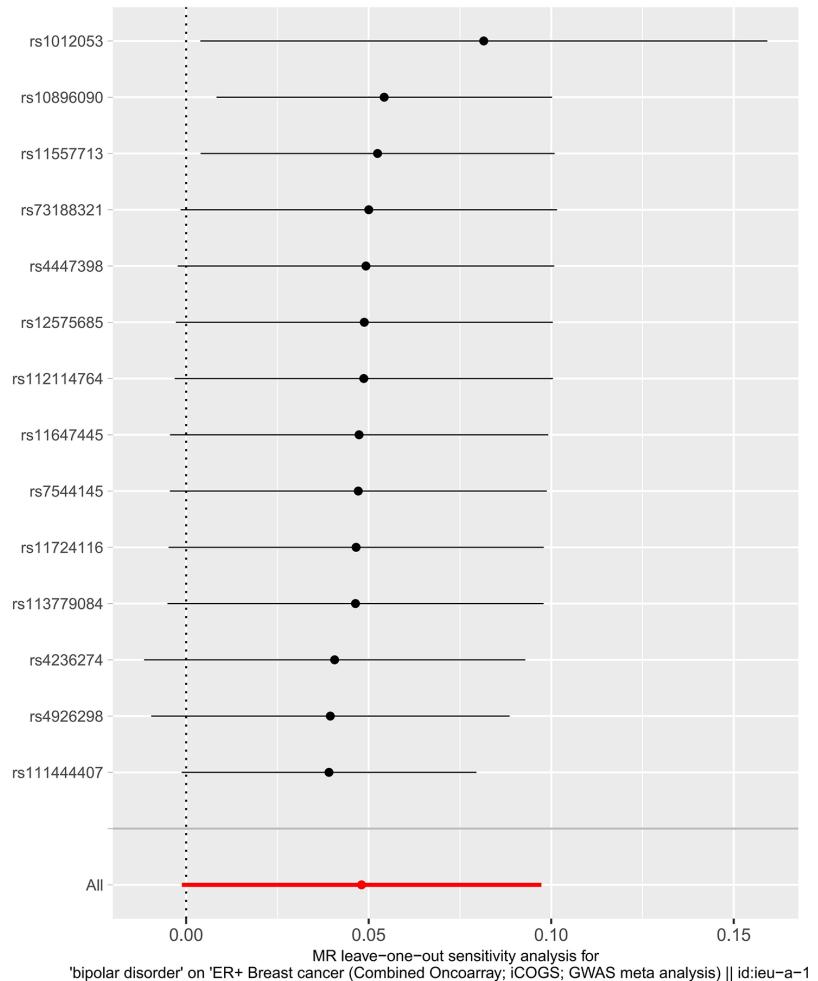


Figure S2 Leave-one-out analysis for genetically predicted bipolar disorder and ER-positive breast cancer.

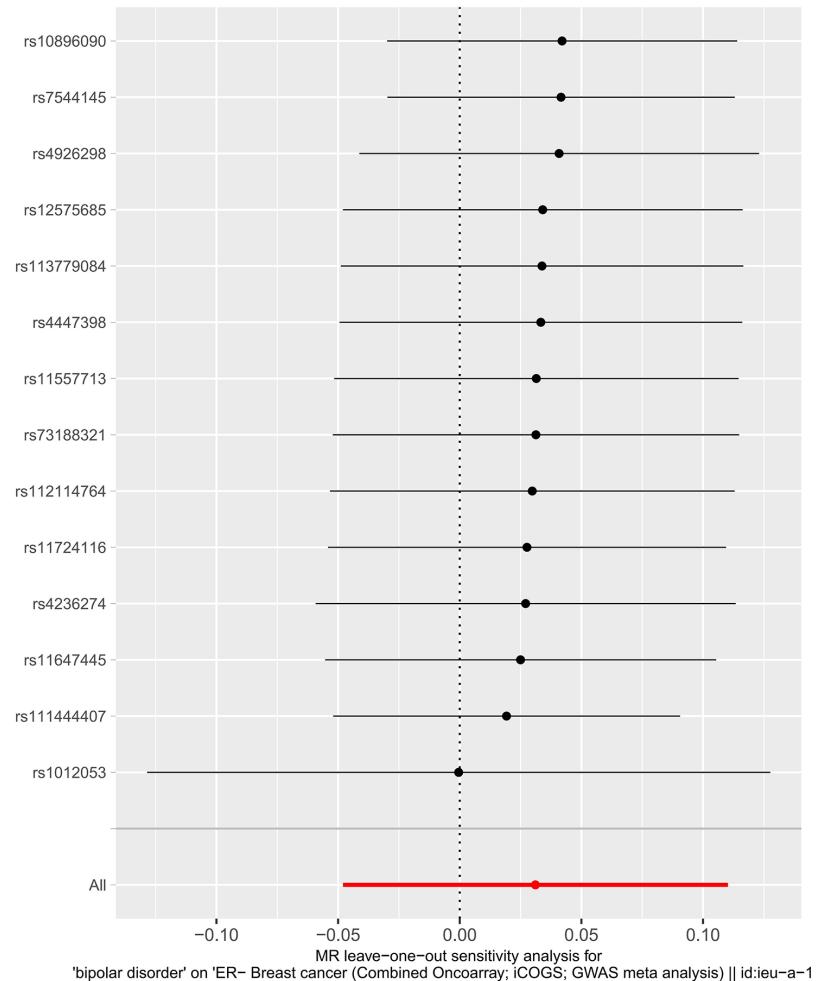


Figure S3 Leave-one-out analysis for genetically predicted bipolar disorder and ER-negative breast cancer.

Table 4 MR-Egger regression analyses on detecting directional pleiotropy.

id.exposure	id.outcome	outcome	exposure	egger intercept	se	pval
1	Fee588	ieu-a-1126 Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	bipolar disorder	6.43E-04	5.78E-03	9.13E-01
2	Fee588	ieu-a-1127 ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	bipolar disorder	2.16E-03	5.76E-03	7.14E-01
3	Fee588	ieu-a-1128 ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	bipolar disorder	-6.03E-03	9.14E-03	5.22E-01

se: standard error, pval: p-value.

Table S5 MR-heterogeneity test on detecting horizontal pleiotropy.

id.exposure	id.outcome	outcome	exposure	method	Q	Q_df	Q_pval
1	Fee588	ieu-a-1126 Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	bipolar disorder	MR Egger	4.00E+01	1.20E+01	7.33E-05
2	Fee588	ieu-a-1126 Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1126	bipolar disorder	Inverse variance weighted	4.00E+01	1.30E+01	1.39E-04
3	Fee588	ieu-a-1127 ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	bipolar disorder	MR Egger	2.78E+01	1.20E+01	5.99E-03
4	Fee588	ieu-a-1127 ER+ Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1127	bipolar disorder	Inverse variance weighted	2.81E+01	1.30E+01	8.80E-03
5	Fee588	ieu-a-1128 ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	bipolar disorder	MR Egger	3.01E+01	1.20E+01	2.69E-03
6	Fee588	ieu-a-1128 ER- Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:ieu-a-1128	bipolar disorder	Inverse variance weighted	3.12E+01	1.30E+01	3.15E-03

df: degrees of freedom, pval: p-value.

Table S6 Association between genetically predicted bipolar disorder and potential confounders and mediators

id.exposure	id.outcome	outcome	exposure	method	n.snp	b	se	pval	or	or_lci95	or_uci95
1	F8Zizd	ieu-a-1283 Alcohol consumption id:ieu-a-1283	bipolar disorder	MR Egger	13	-7.91E-03	9.52E-03	4.24E-01	9.92E-01	9.74E-01	1.01E+00
2	F8Zizd	ieu-a-1283 Alcohol consumption id:ieu-a-1283	bipolar disorder	Weighted median	13	-2.99E-03	6.48E-03	6.44E-01	9.97E-01	9.84E-01	1.01E+00
3	F8Zizd	ieu-a-1283 Alcohol consumption id:ieu-a-1283	bipolar disorder	Inverse variance weighted	13	-6.43E-04	6.17E-03	9.17E-01	9.99E-01	9.87E-01	1.01E+00
6	F8Zizd	ieu-a-90 Obesity class 1 id:ieu-a-90	bipolar disorder	MR Egger	11	5.28E-02	6.43E-02	4.33E-01	1.05E+00	9.29E-01	1.20E+00
7	F8Zizd	ieu-a-90 Obesity class 1 id:ieu-a-90	bipolar disorder	Weighted median	11	-1.06E-03	3.72E-02	9.77E-01	9.99E-01	9.29E-01	1.08E+00
8	F8Zizd	ieu-a-90 Obesity class 1 id:ieu-a-90	bipolar disorder	Inverse variance weighted	11	-1.86E-02	4.45E-02	6.76E-01	9.82E-01	9.00E-01	1.07E+00
11	F8Zizd	ieu-a-91 Obesity class 2 id:ieu-a-91	bipolar disorder	MR Egger	11	1.64E-01	7.33E-02	5.26E-02	1.18E+00	1.02E+00	1.36E+00
12	F8Zizd	ieu-a-91 Obesity class 2 id:ieu-a-91	bipolar disorder	Weighted median	11	7.43E-02	6.54E-02	2.56E-01	1.08E+00	9.48E-01	1.22E+00
13	F8Zizd	ieu-a-91 Obesity class 2 id:ieu-a-91	bipolar disorder	Inverse variance weighted	11	4.36E-03	6.27E-02	9.45E-01	1.00E+00	8.88E-01	1.14E+00
16	F8Zizd	ieu-a-92 Obesity class 3 id:ieu-a-92	bipolar disorder	MR Egger	11	1.80E-02	1.71E-01	9.18E-01	1.02E+00	7.28E-01	1.42E+00
17	F8Zizd	ieu-a-92 Obesity class 3 id:ieu-a-92	bipolar disorder	Weighted median	11	-1.30E-02	1.12E-01	9.07E-01	9.87E-01	7.93E-01	1.23E+00
18	F8Zizd	ieu-a-92 Obesity class 3 id:ieu-a-92	bipolar disorder	Inverse variance weighted	11	-7.18E-02	1.06E-01	4.98E-01	9.31E-01	7.56E-01	1.15E+00
21	F8Zizd	ukb-a-224 Smoking status: Previous id:ukb-a-224	bipolar disorder	MR Egger	14	-9.18E-03	5.62E-03	1.29E-01	9.91E-01	9.80E-01	1.00E+00
22	F8Zizd	ukb-a-224 Smoking status: Previous id:ukb-a-224	bipolar disorder	Weighted median	14	-4.62E-03	3.33E-03	1.66E-01	9.95E-01	9.89E-01	1.00E+00
23	F8Zizd	ukb-a-224 Smoking status: Previous id:ukb-a-224	bipolar disorder	Inverse variance weighted	14	-2.35E-03	3.56E-03	5.09E-01	9.98E-01	9.91E-01	1.01E+00
26	F8Zizd	ukb-a-225 Smoking status: Current id:ukb-a-225	bipolar disorder	MR Egger	14	-2.88E-03	4.42E-03	5.27E-01	9.97E-01	9.89E-01	1.01E+00
27	F8Zizd	ukb-a-225 Smoking status: Current id:ukb-a-225	bipolar disorder	Weighted median	14	-1.32E-03	2.19E-03	5.48E-01	9.99E-01	9.94E-01	1.00E+00
28	F8Zizd	ukb-a-225 Smoking status: Current id:ukb-a-225	bipolar disorder	Inverse variance weighted	14	-3.54E-04	2.62E-03	8.93E-01	1.00E+00	9.95E-01	1.01E+00
31	Xu65Wr	1126 Breast cancer (Combined Oncoarray; iCOGS; GWAS meta analysis) id:1126	Response to lithium treatment in bipolar disorder (NA)	Inverse variance weighted	2	5.30E-03	1.42E-02	7.10E-01	1.01E+00	9.77E-01	1.03E+00

SNP: single nucleotide polymorphism, b: beta, se: standard error, or: odds ratio, p: p-value, id: identification.