Genetically predicted bipolar disorder is causally associated with an increased risk of breast cancer: a two-sample Mendelian randomization analysis

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Background: Epidemiologic findings suggested that bipolar disorder (BD) may be associated with an increased risk of breast cancer. However, there are few studies that comprehensively evaluating their correlation and the causal effect remains unknown. With a two-sample Mendelian randomization (MR) approach, we were able to investigate the causal relationship between genetically predicted BD and breast cancer risk.

Methods: Utilizing 14 BD-related single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) identified by the latest genome-wide association studies (GWASs), we investigated the correlation between genetically predicted BD and breast cancer risk using summary statistics from the Breast Cancer Association Consortium, with a total of 122,977 cases and 105,974 controls. Study-specific estimates were summarized using inverse variance weighted (IVW) method. To further evaluate the pleiotropy, the weighted median and the MR-Egger regression method were implemented. Subgroup analyses according to different immunohistochemical types of breast cancer were also conducted.

Results: MR analyses demonstrated that genetically predicted BD was causally associated with an increased risk of breast cancer (OR =1.059; 95% CI: 1.008–1.112, P=0.0229). When results were examined by immunohistochemical type, no causal effects between genetically predicted BD and estrogen receptor (ER)-positive breast cancer (OR =1.049, 95% CI: 0.999–1.102 P=0.0556) and ER-negative breast cancer (OR =1.032, 95% CI: 0.953–1.116 P=0.4407) were observed. Additionally, the results demonstrated the absence of the horizontal pleiotropy.

Conclusions: Our findings provided evidence for a causal relationship between genetically predicted BD and an increased risk of breast cancer overall. Further studies are warranted to investigate the underlying mechanism.

Keywords: Bipolar disorder (BD); breast cancer; Mendelian randomization (MR)

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Introduction

Breast cancer is the major cause of cancer death and the most common malignancy in women (1). In 2020, the American Cancer Society estimates that approximately 279,100 new breast cancer cases and 42,690 cancer deaths will occur in the United States (2). Mortality from breast cancer in North America and the European Union (EU) has decreased in the past few years, mainly due to early detection and effective systemic therapies (3). However, breast cancer is still considered to be the leading cause of death from cancers in less developed regions and second to lung cancer in more developed countries, possibly because of the lack of early diagnosis and effective treatment (4). Consequently, early identification of potentially modifiable risk factors is of significance for better prevention of breast cancer.

Individuals with serious mental illness (SMI)—defined as a mental illness like schizophrenia or bipolar disorder (BD) which leads to substantial functional impairment, are especially likely to experience significantly reduced life expectancy (5). Much of this difference is correlated with preventable and treatable chronic diseases, like cancer, which ranked as the second leading cause of death of SMI patients (6). Epidemiologic evidence to date regarding mental illness and cancer is growing. In specific, studies investigating the breast cancer incidence among individuals with BD are relatively inconsistent. Due to the nature of conventional observational studies, previous findings are susceptible to reverse causality or potential confounders. For instance, few studies had investigated lifestyle factors in relation to breast cancer risk among people with BD, which possibly contributing to the biased results caused by confounding factors that increase both risk of BD and breast cancer. Consequently, findings are insufficient to draw a definitive conclusion on the causal relationship between BD and breast cancer risk from present studies.

Mendelian randomization (MR) is a novel approach to investigate the causality between an exposure and an outcome using germline genetic variants as instrumental variables (IVs) (7). On the basis of Mendel's second law that genetic variations are randomly distributed at conception, they are generally independent of environmental risk factors, and temporally precede both risk factors and the disease process (8). Consequently, MR offers a means to investigate the causal relationship between an exposure and an outcome in a non-experimental way (9). MR approach is capable to prevent the potential limitations that are common in conventional observational studies, such as reverse causality, confounding, and measurement error when the fundamental principles of MR are not violated (10). In regard to BD, genetic variants have been confirmed to play a crucial role in BD since the heritability of BD was estimated approximately 10.7% (11). Simultaneously, with the published genetic data from the Breast Cancer Association Consortium (BCAC) (122,977 cases and 105,974 controls), the two-sample MR analysis offers a means to evaluate the causality between BD and breast cancer, overall and among specific immunohistochemical type, greatly increasing the scope and statistical power of MR (12). Furthermore, we conducted additional MR analyses to investigate whether genetically predicted BD would be associated with common confounders and mediators of breast cancer risk, like smoking status, use of antipsychotics and so on, based on existing literature (13-16).

Using a two-sample MR method, our study could provide the latest evidence for evaluating a causal relationship between BD and risk of breast cancer.

Methods

Identification of single nucleotide polymorphisms (SNPs) associated with BD

We conducted a literature search to identify and extracted information for SNPs that were associated with BD at the genome-wide significance level ($P<5\times10^{-8}$). We identified 43 SNPs associated with BD from the large-scale and most recent genome-wide association studies (GWASs) publication, including 30 SNPs from Stahl *et al.* (51,710 European ancestry cases and 169,188 European ancestry controls) (17), 6 SNPs from Hou *et al.* (2,137 European ancestry cases and 3,168 European ancestry controls) (18), 6 SNPs from Ikeda *et al.* (2,964 Japanese ancestry and 61,887 Japanese ancestry control) (11) and 1 SNPs from Baum *et al.* (772 European ancestry cases and 876 European ancestry controls) (Table S1) (19). These 43 SNPs explained approximately 10.7% of the variation in BD across individuals. The F-statistic of our study was 27,434.10, which was much larger than the conventional value of 10, indicating the instruments used strongly predicted BD (20). In addition, the number required for 80% power in breast cancer with an odds ratio (OR) of 1.37 was at least 11,908 subjects (21) (*Table 1*). Consequently, it was adequate to conduct a strong genetic instrument based on these 43 SNPs. Of these 43 SNPs, 19 SNPs

Table 1 Power for conventional Mendelian randomization analysis (two-sided α=0.05)

Exposure/genetic instrument	R-squared (of variance in BD phenotype)	Actual n (BCAC)	Proportion of cases (BCAC)	Observational OR	n required for 80% power	Power at actual n
BD/14 SNPs	10.7%	228,951	0.537	1.37	11,908	1.00

BD, bipolar disorder; BCAC, the Breast Cancer Association Consortium; SNP, single nucleotide polymorphism; OR, odds ratio.

Table 2 Characteristics of SNPs selected as instrumental variables for Mendelian randomization analysis

SNP	chr	EA	beta	SE	P value	EAF	LD exclusion	PubMed ID
rs1012053	13	A	0.464	0.083	2.00E−08	0.84	No	17486107
rs4236274	7	G	0.140	0.022	8.00E−12	0.39	No	27329760
rs4926298	19	G	0.124	0.020	6.00E−10	0.65	No	28115744
rs10896090	11	A	0.081	0.014	8.48E−09	0.81	No	
rs111444407	19	T	0.093	0.015	7.20E−10	0.15	No	
rs112114764	17	T	−0.073	0.012	1.35E−09	0.69	No	
rs113779084	7	A	0.073	0.012	9.62E−10	0.30	No	
rs11557713	18	A	0.067	0.012	2.26E−08	0.29	No	31043756
rs11647445	16	T	−0.073	0.012	2.78E−10	0.65	No	
rs11724116	4	T	−0.083	0.015	2.06E−08	0.16	No	
rs12575685	11	A	0.070	0.012	3.84E−09	0.31	No	
rs4447398	15	A	0.094	0.016	4.30E−09	0.12	No	
rs73188321	7	T	−0.083	0.013	3.65E−11	0.33	No	

SNP, single-nucleotide polymorphism; chr, chromosome; SE, standard errors; EAF, effect allele frequency; LD, linkage disequilibrium.

were excluded using linkage disequilibrium (LD) analysis once mutual LD conjugately surpassed the limited value ($R^2 < 0.001$) (Table S1), rs12576775, rs1487441, rs174576, rs2388334, rs28456, rs3804640, rs4332037 and rs9834970 were removed for being palindromic with intermediate allele frequencies, rs7122539 and rs17183814 were removed due to the association with other phenotypes (22,23). Eventually, 14 SNPs were brought into the final IVs set (*Table 2*).

Study participants of breast cancer

Formed in April 2005, the Breast Cancer Association Consortium (BCAC) is a forum of investigators of case-control studies that is conducted with the aim of identifying genes related to the risk of breast cancer. Derived from the European ancestry, genetic data of 122,977 breast cancer cases and 105,974 controls from BCAC (*Table 3*) were used as epidemiological individual-level data. According to the

existence of estrogen receptor (ER) and responsiveness to estrogen of tumor cells growth, subgroup analyses including ER-positive breast cancer (69,501 cases and 105,974 controls) and ER-negative (21,468 cases and 105,974 controls) breast cancer were implemented. We retrieved summary data (the effects of each of the SNPs on the breast cancer; effect sizes and standard errors) from BCAC (http://bcac.ccge.medschl.cam.ac.uk/).

Statistical analysis

To investigate MR estimates of BD for breast cancer, we utilized several MR approaches. First, a random effects inverse variance weighted (IVW) Wald-type estimator was conducted to derive a MR estimate of multiple IVs. Given that the SNP had a cumulative effect on BD, the IVW estimate of the causal effect could be combined with the ratio estimate and standard error of a single SNP using the method of Burgess *et al.* (24). All previous hypotheses were

Table 3 Details of studies included in Mendelian randomization analyses

Trait	First author	Consortium	Number of cases	Number of controls	Sample size	Year
Breast cancer	Michailidou K	BCAC	122,977	105,974	228,951	2017
ER+ breast cancer	Michailidou K	BCAC	69,501	105,974	175,475	2017
ER– breast cancer	Michailidou K	BCAC	21,468	105,974	127,442	2017

ER, estrogen receptor; BCAC, the Breast Cancer Association Consortium.

assumed to be consistent with the previously described genetic variant P (P=1 ... P); which was associated with the mean change in BD (X_p) of the risk factor observed with each other variant allele with standard error (σ_{X_p}) and observed (Y_p) logarithmic change in the outcome of each allele with standard error (σ_{Y_p}). The calculation was as follows:

$$\hat{\beta}_{IVW} = \frac{\sum_{i=1}^{P} X_p Y_p \sigma_{Y_p}^{-2}}{\sum_{i=1}^{P} X_p^2 \sigma_{Y_p}^{-2}}; \ se(\hat{\beta}_{IVW}) = \sqrt{\frac{1}{\sum_{i=1}^{P} X_p^2 \sigma_{Y_p}^{-2}}} \qquad [1]$$

Corresponding OR and 95% confidence intervals (CI) were calculated using $\hat{\beta}_{IVW}$ and $se(\hat{\beta}_{IVW})$.

Three basic assumptions were made in our MR analysis: (I) the SNPs were robustly associated with BD; (II) the SNPs were independent of breast cancer, that was, the SNPs had no pleiotropic effect through pathways other than BD; and (III) the SNPs were independent of factors that confounded the BD-breast cancer relation (25). The first assumption was met since the chosen SNPs were selected at the genome-wide significance threshold of $P<5\times10^{-8}$ and the F-statistics was 27,434.1 (F>100). MR-Egger and weighted median method were performed to test for the second assumption indirectly. For sensitivity analysis, we obtained global pleiotropic effects from the MR-Egger analyses based on the intercept. Leave-one-out analyses were carried out to evaluate whether the estimation of MR was determined or biased by a SNP separately by successively omitting a single SNP. It is worth noting that cancer patients, especially women and young adults, are likely to experience persisting negative mood, like depression and cancer-related fears, which may potentially lead to mental health illness (26). Therefore, to further explore the causal relationship, we performed a bi-directional MR (27) to seek whether breast cancer status would reversely cause BD.

Aiming at verifying the third assumption, we employed additional MR analyses to investigate whether genetic predisposition towards BD could be associated with the potential confounders and mediators underlying the mechanisms from BD to breast cancer. Previous studies have reported that people with BD tend to live an unhealthy lifestyle compared with the general population, like more alcohol consumption and cigarette exposure. Simultaneously, epidemiological studies suggested that alcohol consumption and cigarette exposure are correlated with an increased risk of breast cancer (13,15). Consequently, the unhealthy lifestyles could possibly act as the mediators from BD to breast cancer. In addition, obesity is associated with risk of breast cancer and may increase risk of BD. Hence, obesity is considered to be a potential confounder of the BD-breast cancer relationship (28). Lithium, a major antipsychotics used for the treatment of BD, has been recognized as a potent inhibitor of glycogen synthase kinase-3β (GSK-3β) which plays an important role in the survival, growth, and differentiation of breast cancer cells (29). Hence, use of lithium product could be a potential confounding factor of breast cancer among BD patients. Eventually, conventional MR was applied to investigate whether genetically predicted BD was associated with confounding factors and mediators mentioned above. Genetic summary data on obesity were extracted from Genetic Investigation of ANthropometric Traits (GIANT) (http://giant.princeton.edu/) and data on alcohol assumption were obtained from the UK Biobank (https://www.ukbiobank.ac.uk/). Genetic instruments for use of lithium product were gained from the MRC Integrative Epidemiology Unit (MRC-IEU) (http://www.bristol.ac.uk/integrative-epidemiology/) (*Table 4*). MR analyses were performed in R (version 4.0.0) using the package TwoSampleMR (version 0.5.4) (30).

Power calculation

Based on the approach described by Burgess (31), our sample size of 122,977 breast cancer cases and 105,974 controls had an estimated 100.0% power to investigate the previously estimated causal effect size of BD (OR =1.37) at a significance level of 0.05, assuming the SNPs explain a total of 10.7% variance of BD based on previous studies (11).

Table 4 Details of studies included in confounders and mediators of bipolar disorder

Trait	First author	Consortium	Study participants	Year	Website
Obesity class 1 (BMI: 30–34.9 kg/m^2)	Berndt SI	GIANT	98,697	2013	http://giant.princeton.edu/
Obesity class 2 (BMI: 35–39.9 kg/m^2)	Berndt SI	GIANT	72,546	2013	http://giant.princeton.edu/
Obesity class 3 (BMI: ≥40 kg/m^2)	Berndt SI	GIANT	50,364	2013	http://giant.princeton.edu/
Previous smoker	Neale	Neale Lab	336,024	2017	http://www.nealelab.is/uk-biobank
Current smoker	Neale	Neale Lab	336,024	2017	http://www.nealelab.is/uk-biobank
Alcohol consumption	Clarke	UK Biobank	112,117	2017	http://www.ukbiobank.ac.uk/
Use of lithium product	Ben Elsworth	MRC-IEU	462,933	2018	http://www.bristol.ac.uk/integrative-epidemiology/

BMI, body mass index; GIANT, Genetic Investigation of ANthropometric Traits; MRC-IEU, MRC Integrative Epidemiology Unit.

Results

Causal effect between BD and breast cancer

Using conventional IVW method, genetically predicted BD was causally associated with a 5.9% higher risk of breast cancer (OR =1.059; 95% CI: 1.008–1.112, P=0.0229) (*Figure 1*). As expected, the association was consistent in sensitivity analyses using weighted median (OR =1.043, 95% CI: 1.003–1.086, P=0.0356) and MR-Egger method (OR =1.055, 95% CI: 0.973–1.143, P=0.2187). Similar causal trends in ER-positive breast cancer (OR =1.049, 95% CI: 0.999–1.102, P=0.0556) and ER-negative breast cancer (OR =1.032, 95% CI: 0.953–1.116, P=0.4407) were discovered whereas they were lack of statistical significance (*Table 5*). Meanwhile, as for the causal effect of single SNP analysis, rs1012053, rs111444407 and rs4236274 were observed to causally correlate with an increased risk of breast cancer among BD patients (*Figure 2*, Table S2). Using breast cancer as an exposure phenotype and BD as an outcome, our bi-directional MR result demonstrated an absence of causal relationship between breast cancer and BD (OR =1.001, 95% CI: 0.913–1.098, P=0.9799) (Table S3).

Sensitivity analysis

Leave-one-out sensitivity analyses demonstrated that no single SNP was strongly driving the overall effect of BD on breast cancer (Figures S1-S3). No evidence for the existence of directional pleiotropy in the MR-Egger regression analysis was presented (*Table 6*, Table S4). We found that the P values for the intercept were non statistically significant and the estimates adjusted for pleiotropy

demonstrated null effects (intercept β=0.0006, P=0.9133 for breast cancer; intercept β=0.0022, P=0.9140 for ER-positive breast cancer; intercept β=−0.0060, P=0.5217 for ER-negative breast cancer). Heterogeneity was not observed (*Table 6*, Table S5). To identify whether the association between genetically predicted BD and breast cancer was influenced by potential confounders and mediators, additional MR analyses in conventional IVW method were applied, demonstrating that genetically predicted BD was not causally associated with obesity (OR =0.982, 95% CI: 0.900–1.071, P=0.6756 for obesity class 1; OR =1.004, 95% CI: 0.888–1.136, P=0.9446 for obesity class 2; OR =0.931, 95% CI: 0.756–1.146, P=0.4979 for obesity class 3), alcohol consumption (OR =0.999, 95% CI: 0.987–1.012, P=0.9170), smoking (OR =0.998, 95% CI: 0.991–1.005, P=0.5092 for previous smoker; OR =1.000, 95% CI: 0.995–1.005, P=0.8926 for current smoker) and use of lithium product (OR =1.005, 95% CI: 0.977–1.034, P=0.710) (*Table 7*, Table S6). Consequently, all three assumptions of MR foundations were consistent in our study when combining the sensitivity analyses above, revealing relatively great credibility of the outcome.

Discussion

This two-sample MR analysis provided evidence for causality between genetically predicted BD and an increased risk of breast cancer overall. When results were examined by immunohistochemical type, no causal associations were observed for ER-positive breast cancer nor ER-negative breast cancer risks. Furthermore, to identify the potential confounders and mediators between BD and breast cancer, we observed that genetic predisposition towards BD was

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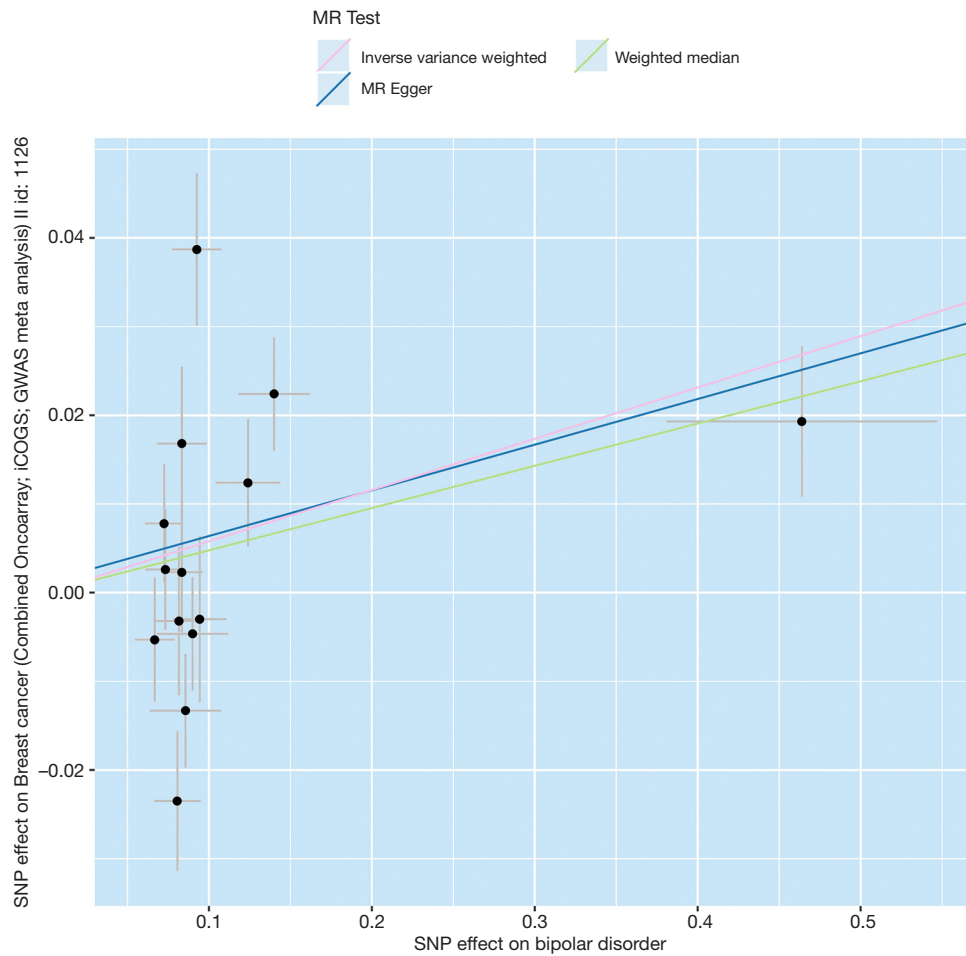
Figure 1 Scatter plot of SNPs associated with bipolar disorder and their risk of breast cancer. A plot relating the SNP effect on bipolar disorder (x-axis, SD units) and SNP effect on breast cancer [y-axis, log(OR)] with 95% confidence intervals. The Mendelian randomization (MR) regression slopes of the lines correspond to the causal estimates using each of the three different methods [inverse variance weighted (IVW), MR-Egger, and weighted median]. The pink line shows causal regression estimates from IVW. The blue line shows causal regression estimates from MR-Egger. The green line shows causal regression estimates from weighted median. SNP, single nucleotide polymorphism; OR, odds ratio.

Table 5 Mendelian randomization estimates of the associations between bipolar disorder and risk of breast cancer overall and immunohistochemical types

Outcome	IVW method		MR-Egger		Weighted median method	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Breast cancer overall	1.059 (1.008, 1.112)	0.0229	1.055 (0.973, 1.143)	0.2187	1.043 (1.003, 1.086)	0.0356
ER-positive breast cancer	1.049 (0.999, 1.102)	0.0556	1.037 (0.957, 1.124)	0.3968	1.036 (0.990, 1.084)	0.1277
ER-negative breast cancer	1.032 (0.953, 1.116)	0.4407	1.066 (0.938, 1.213)	0.3427	1.052 (0.985, 1.124)	0.1318

OR, odds ratio; ER, estrogen receptor; IVW, inverse variance weighted.
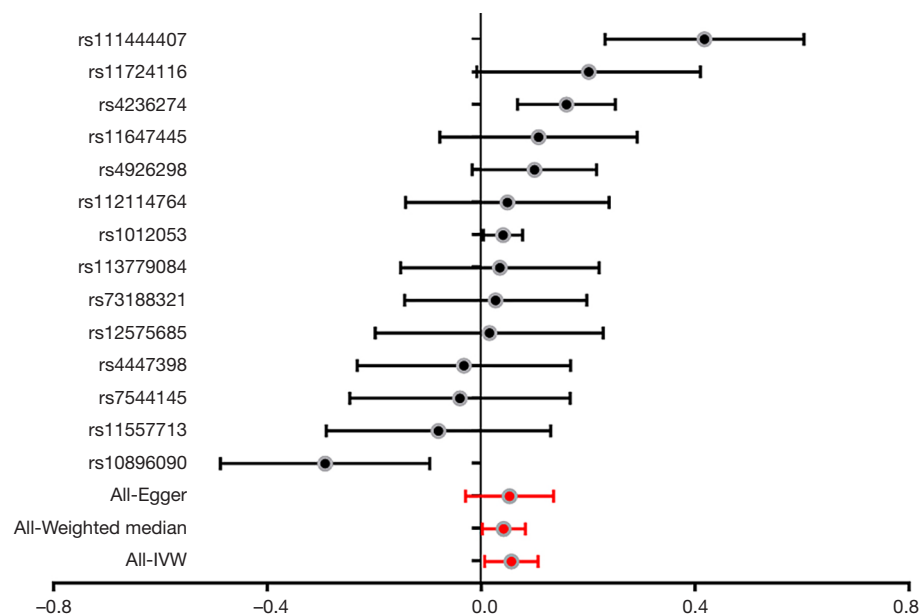
Figure 2 Forest plot of single nucleotide polymorphisms (SNPs) associated with bipolar disorder and their risk of breast cancer. The forest plot shows association of genetic liability to bipolar disorder on breast cancer. Each black point represents the log odds ratio (OR) for breast cancer in bipolar disorder, produced using each of the bipolar disorder SNPs (rs11144407, rs11724116, rs4236274, rs1167445, rs4926298, rs112114764, rs1012053, rs113779084, rs73188321, rs12576775, rs4447398, rs7544145, rs11557713, rs10896090) as separate instruments. Red points show the combined causal estimate using all SNPs together in a single instrument, with three different methods (inverse variance weighted, MR-Egger, and weighted median). Horizontal line segments denote 95% confidence intervals of the estimate.

Table 6 MR-Egger regression and Heterogeneity analysis of the associations between bipolar disorder and breast cancer overall and immunohistochemical types

Outcome	Heterogeneity P		MR-Egger regression	
	MR-Egger	IVW	Intercept	Intercept P
Breast cancer overall	0.0001	0.0001	0.0006	0.9133
ER-positive breast cancer	0.0060	0.0088	0.0022	0.7140
ER-negative breast cancer	0.0027	0.0031	−0.0060	0.5217

ER, estrogen receptor; IVW, inverse variance weighted.

not correlated with established potential risk factors of breast cancer, including obesity, smoking status, alcohol assumption and use of lithium product.

Previously, the outcomes reported by observational studies on the association between BD and breast cancer were inconsistent, with major demonstrating null or suggestive increases in risk. In 2007, Hippisley-Cox *et al.* reported that patients with BD and schizophrenia were not correlated with an increased risk of breast cancer from a nested case-control study after adjusting for obesity,

smoking, use of NSAIDS and antipsychotics (32). Likewise, a nationwide population-based cohort study conducted in China published by Lin *et al.* (33), including 20,567 BD patients, elucidated that no association was observed between BD and breast cancer. In 2013, a cohort study from United Kingdom conducted by Osborn *et al.* examining 106 incident breast cancer events among 20,632 people with SMI (34), denoted a positive association between SMI and breast cancer risk after adjusting for age categories, sex and smoking. Interestingly, the positive association

Table 7 Causal effects between genetically predicted bipolar disorder and potential confounders and mediators

Outcomes	Causal effect (95% CI)	P value
Obesity class 1 (BMI: 30–34.9 kg/m^2)	0.982 (0.900, 1.071)	0.6756
Obesity class 2 (BMI: 35–39.9 kg/m^2)	1.004 (0.888, 1.136)	0.9446
Obesity class 3 (BMI: ≥40 kg/m^2)	0.931 (0.756, 1.146)	0.4979
Previous smoker	0.998 (0.991, 1.005)	0.5092
Current smoker	1.000 (0.995, 1.005)	0.8926
Alcohol consumption	0.999 (0.987, 1.012)	0.9170
Use of lithium product	1.005 (0.977, 1.034)	0.7100

BMI, body mass index.

demonstrated by Osborn *et al.* only limited in obese patients [body mass index (BMI) ≥30 kg/m^2] while null association was presented in overall results. More recently, McGinty *et al.* calculated standardized incidence ratios (SIR) to compare breast cancer incidence among the Maryland Medicaid cohort (3,317 adults with SMI) to the Surveillance Epidemiology and End Results (SEER) population, suggesting breast cancer incidence among participants with schizophrenia or BD was almost twice higher than the SEER population (SIR 1.9, 95% CI: 1.1–3.0) (35).

Nevertheless, in view of the characteristics of previous observational studies, reverse causality and potential confounding factors might bias the results. First, the sample size of breast cancer patients in previous studies was relatively limited, with the largest sample size up to 215, which might lack enough statistical power to precisely evaluate causality between BD and breast cancer risk. Second, several epidemiologic studies (33,34) included people with other mental illnesses such as schizophrenia and depression. Consequently, the results might be biased by a certain type of SMI whereas it remained unclear whether BD was associated with an increased breast cancer risk. Third, only one of the four studies we mentioned above managed to control BMI, and high BMI is considered an important risk factor for breast cancer, which could also increase risk of BD (36). Consequently, high BMI could be a confounder for the BD-breast cancer relation and a BMI-independent BD-breast cancer relation could not be assessed effectively. In addition, use of medication for treatment among BD patients, such as lithium product and lamotrigine (37,38), have long been suggested to be correlated with increased cancer risks whereas none of the present studies managed to fully evaluate or verify the correlation between use of antipsychotics and breast cancer

risk during the follow-up period. Consequently, biased results could possibly occur. More importantly, to date, no prospective large-scale longitudinal cohort studies have been conducted and thus, it is still insufficient to draw a clear conclusion on the causal relationship from BD to breast cancer.

Plausible mechanisms have been proposed that prolactin (PRL) might play a role for the increased breast cancer risk in BD patients. PRL is a polypeptide hormone secreted by the lactotroph cells of the anterior pituitary gland and its secretion is influenced by both central nervous system (CNS) and peripheral processes (39). The prevalent condition correlated with hyperprolactinemia is stress in response to psychology, use of antidepressants, estrogen and so on (40). Previous studies have reported that BD patients were more vulnerable to hyperprolactinemia (41,42). Meanwhile, epidemiologic studies suggested that use of antipsychotic agents among SMI patients are the most common medications that cause hyperprolactinemia (38,43). Further, both *in vivo* and epidemiological data supported a crucial role of the hyperprolactinemia that it associates with an increased risk of breast cancer and the occurrence of metastasis (44,45). Mitogenic effects of estrogen (E2) on breast malignancy growth have been well described, that is, the majority of breast cancer cells are responsive to, or dependent on E2 supply (46). Two recent studies showed that PRL can stimulate Ser118 phosphorylation of ER, the modification of which was demonstrated to potentiate transcriptional activity of the unliganded ER or to stabilize ER allowing maintenance of a response to E2 (47,48). In this regard, the elevated concentration of PRL might potentially attribute to the mechanism from BD to breast cancer.

Considering the consistently long incubation period

between BD and the occurrence of breast cancer, it is neither suitable nor applicable to investigate the causality through RCTs. From this point of view, our MR approach can give evidence from a new type of study design, which is also in support of a positive relationship between BD and breast cancer. Several strengths of our study are as follow. First, as far as we know, it is the largest study to investigate causality between BD and risk of breast cancer using genetic variants. Participants were grouped based on their randomly allocated genotype, and this procedure mimicked a RCT. With large sample sizes (n=228,951) and robustly associated IVs (F-statistics =27,434.1), our MR study with adequate statistical power could offer a relatively precise estimation of causal effect. It is also the first study to investigate whether effects differed between subgroups stratified by immunohistochemical type. Second, since once BD-associated SNPs included in our study were also correlated with confounding factors, an accurate estimation of the causality between BD and breast cancer would not be provided. Thus, we conducted additional MR analyses which indicated that genetically predicted BD was not causally associated with the potential confounders, including obesity, smoking and alcohol consumption, suggesting a relatively independent association between BD and breast cancer. Third, given use of antipsychotics, like lithium product, may increase the incidence of breast cancer among BD patients, we performed additional MR analyses to investigate whether BD-associated SNPs could also be linked to these mediators and the possible potential mechanisms. Our results elucidated that genetically predicted BD was not related to other potential mediators, indicating that the causality between BD and breast cancer was more likely due to the characteristics of breast cancer itself.

Several limitations should also be considered in our study. First, given bipolar I disorder and bipolar II disorder shared distinct characteristics (49), we were unable to examine the association between different BD phenotypes and risk of breast cancer. Consequently, if our included genetic variants did not represent the risk of all subtypes of BD, our obtained effect estimate was difficult to interpret. Second, though we've used the most comprehensive set of genetic variants so far, it merely explained a part of variance of BD across individuals. It is possible that some unknown BD-related SNPs could also play an important role in the development of breast cancer. Third, all three MR assumptions cannot be fully examined in our study

and potential violations against the assumptions may occur. Due to the fact that the second assumption could not be evaluated directly in our study, additional sensitivity analyses were utilized. The results demonstrated no horizontal pleiotropic effects existed in our study, suggesting the second MR assumption was not violated. Nevertheless, it is possible that some of the genetic variants were also associated with confounders of BD and breast cancer in our study and caution is needed in considering the gross effect. Also, despite that genetic factors are estimated to account for about 10.7% of the variation, it is worth noting that BD is mainly determined by social and other environmental factors. Hence, it is inappropriate to deduce that genetic effects are independent of environmental factors.

In conclusion, our present MR study provided relatively strong evidence to suggest that BD plays a causal role in increasing the risk of breast cancer. There is no doubt that cancer prevention is the key to reduce the morbidity and mortality of cancers. Consequently, we should attach great importance to identifying modifiable risk factors correlated with cancers. Afterwards, we can carry out effective interventions to reduce the disease burden worldwide. In 2016, the American Cancer Society had published a review with suggestions at the individual, interpersonal, organizational, community, and policy levels that may improve cancer prevention, screening, and treatment in people with mental illness (50). Nevertheless, in present, both epidemiologic and basic studies concerning the efforts of mental illness on cancer are relatively insufficient. More work is warranted to investigate the potential mechanisms that mediate the association between BD and breast cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

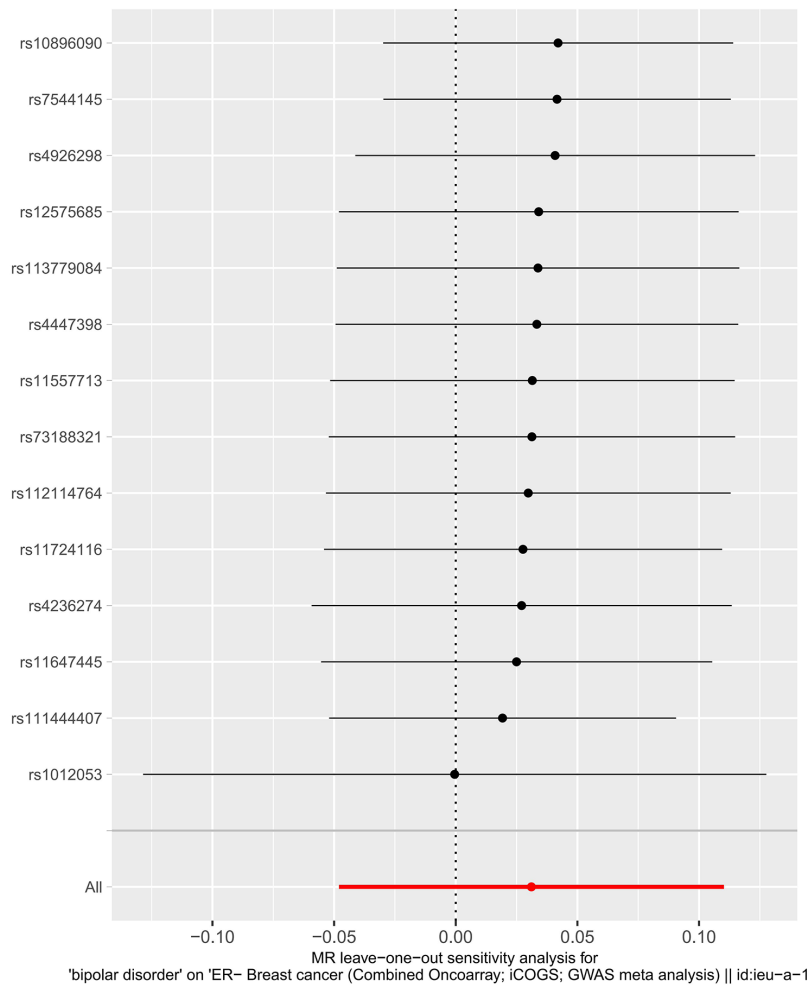Id: identification, b: beta, se: standard error, or: odds ratio, ci: confidence interval, pval: p-value.
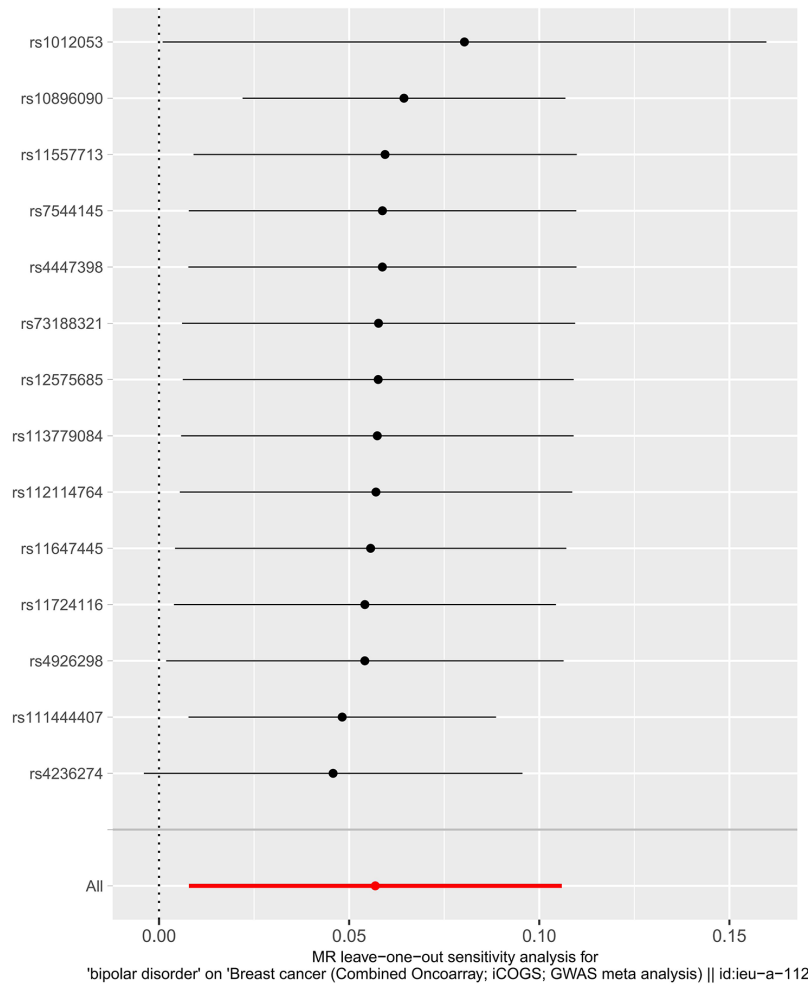
Figure S1 Leave-one-out analysis for genetically predicted bipolar disorder and breast cancer.
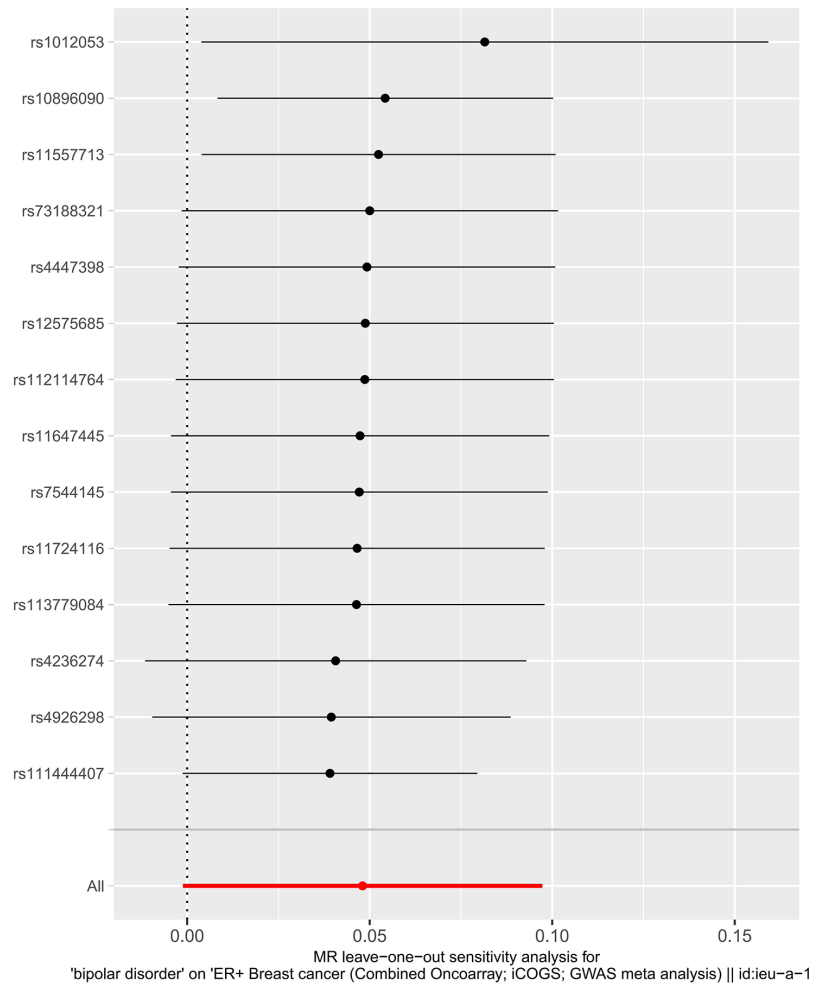
Figure S2 Leave-one-out analysis for genetically predicted bipolar disorder and ER-positive breast cancer.

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	nsnp	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.