Breast cancer risks following antipsychotic use in women with bipolar disorder versus schizophrenia: a territory-wide nested case-control study spanning two decades

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DATA AVAILABILITY

Data will not be available for others as the data custodians have not given permission.

AUTHOR CONTRIBUTIONS

Rachel Chu, Esther Chan and Francisco Lai contributed to the conception of the work. All authors designed the study. Rachel Chu and Yue Wei contributed to the acquisition and analysis of the data, and all authors interpreted the data. Rachel Chu drafted the manuscript. All of the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Rachel Chu and Yue Wei are co-first authors and Esther Chan and Francisco Lai share the senior authorship.

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ABSTRACT

Accrued epidemiologic data largely support an association of antipsychotic use with breast cancer in women with schizophrenia. No studies have specifically investigated such risks in women with bipolar disorder. This study aims to examine the association between antipsychotics and breast cancer in women with bipolar disorder and compare it against schizophrenia. We conducted a nested case-control study using a territory-wide public healthcare database in Hong Kong examining women aged ≥18 years with bipolar disorder or schizophrenia. Using incidence density sampling, women with a breast cancer diagnosis were matched by up to 10 control participants. In total, 672 case participants (109 with bipolar disorder) and 6,450 control participants (931 with bipolar disorder) were included. Results show a significant association of first-generation antipsychotics with breast cancer in both women with schizophrenia [adjusted odds ratio (aOR) 1.49, 95% confidence interval (CI) 1.17-1.90] or bipolar disorder (aOR 1.80, 95% CI 1.11-2.93). Second-generation antipsychotics was associated with breast cancer only in women with bipolar disorder (aOR 2.49, 95% CI 1.29-4.79), with no significant association found in women with schizophrenia (aOR 1.10, 95% CI 0.88-1.36). In conclusion, further research on breast cancer risks is warranted for women with bipolar disorder on antipsychotics.

HIGHLIGHTS

- A territory-wide public healthcare database was used to conduct a nested case-control study on breast cancer risks
- Increased risk followed typical antipsychotic use in both women with schizophrenia and bipolar disorder
- Increased risk following atypical antipsychotic use was observed only in women with bipolar disorder
- More research is needed to evaluate risks and benefits associated with antipsychotics in women with bipolar disorder

KEYWORDS

Cancer epidemiology; Chinese; drug safety; multimorbidity; prolactin; psychotic disorders

INTRODUCTION

Existing research has suggested an association of antipsychotic use with breast cancer, particularly in individuals with schizophrenia (Leung et al., 2022; Pottegård et al., 2018; Taipale et al., 2021). We recently conducted a meta-analysis and reported a moderate association with over 30%-elevated risk (Leung et al., 2022), consistent with an independently conducted subsequent meta-analysis on the same question (Gao et al., 2022). This association is plausibly mediated by increased prolactin levels induced by certain antipsychotic agents (Pottegård et al., 2018; Rahman et al., 2022). However, the potential differences of such a risk between schizophrenia and bipolar disorder remain to be further investigated.

Although schizophrenia and bipolar disorder share genetic similarities (Prata et al., 2019), under microarray analysis, these two conditions were expressed by unique genome signatures, with eight putative biomarkers for discrimination demonstrating genetic differences (Tsuang et al., 2005). In particular, marked differences in inflammatory gene expression have been observed. As chronic inflammatory responses are conducive to cell mutation and cancer development (Drexhage et al., 2010), the risk of breast cancer in association with antipsychotic use between women living with these two conditions may also differ (Launders et al., 2022). Of note, the recommended initial and maximum prescription dosage for schizophrenia and bipolar disorders are different due to the pathological and symptomatologic differences. Specifically, the prescription dosage for bipolar disorder depends on the state of mood, with specific recommended dosages for mania and depression respectively (National Health Service, 2021).

To the best of our knowledge, no studies have examined the association specifically in women with bipolar disorder. In this study, we aim to examine the association of antipsychotic use with breast cancer in women with bipolar disorder and compare it against those living with schizophrenia.

METHODS

Study design and data source

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We conducted a territory-wide case-control study using a longitudinal electronic health record system established for the purpose of clinical management by the Hospital Authority (HA). The HA is the statutory body managing all public hospital services in Hong Kong SAR, China. It is the sole provider of public inpatient services and a major provider of outpatient services in the city. Data from the HA electronic health records since 1993 are de-identified and transferred daily to the Clinical Data Analysis and Reporting System, a data tabulation platform that has been used for numerous pharmacovigilance studies (Lai et al., 2022; Wan et al., 2022; Wong et al., 2016). Demographics, clinical diagnoses records, medication dispensing records, and diagnosis settings (in/out-patient) of individuals who have ever used the HA healthcare services are included in the database.

Ethics approval

All clinical data were anonymized such that informed consent was waived as a requirement for ethics approval. This study was approved by the Institutional Review Board of the [*Masked Institution Names*].

Underlying cohort for nested case-control study

All women first diagnosed with schizophrenia [International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM): 295.0 - 295.9] or bipolar disorder (ICD-9-CM: 296.1, 296.4 - 296.8) between January 1, 1999, and December 31, 2018 (both dates inclusive) by licensed psychiatrists in public healthcare facilities, were examined for inclusion. Those who had missing information on date of birth or sex, with a history of breast cancer, or aged under 18 (as of index date) were excluded. We also excluded those diagnosed with both schizophrenia and bipolar disorder within the study period to avoid misclassification. The underlying cohort was identified upon schizophrenia or bipolar disorder diagnosis and followed up until the first breast cancer diagnosis, all-cause mortality, or the end of data availability, whichever was the earliest.

Case and control participant selection

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Stratified by schizophrenia and bipolar disorder, participants of the underlying cohort first diagnosed with breast cancer were identified as cases. Up to ten control participants in the cohort who had not developed breast cancer and were alive were matched with each case participant by birth year and healthcare setting (inpatient versus outpatient) using incidence density sampling with replacement. The breast cancer diagnosis date was considered as the index date of the corresponding matched set of case and control participants. Exposure and covariates were all ascertained using the records before the index date.

Outcomes

The primary outcome of interest in this study was breast cancer diagnosis (ICD-9-CM: 174.0 – 174.9). In a sensitivity analysis, subtypes of this outcome, indicative of the location of the tumor were also investigated as secondary outcomes. **Table S1** shows the specific subtypes and corresponding ICD-9-CM codes.

Exposure

Antipsychotic use was categorized into first- and second-generation antipsychotics (FGAs and SGAs) and dichotomized as two binary indicators. Exposure was defined as the use of antipsychotics (FGA or SGA) for more than one year, based on dispensing records. Generic names were used to identify the specific medications of interest. **Table S2** shows the generic names adopted and the categorization of FGAs and SGAs (Lao et al., 2017).

Statistical analysis

Multivariable conditional logistic regression was used to examine the association of antipsychotics with breast cancer. Adjusted odds ratios (aOR) of breast cancer associated with the use of FGAs or SGAs, compared with non-users (non-use or less than one year of use) were estimated, stratified by schizophrenia and bipolar disorder. In a combined analysis of both schizophrenia and bipolar disorder groups, the interactions between FGA and bipolar disorder (schizophrenia as referent) as well as between

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SGA and bipolar disorder (schizophrenia as referent) were tested to detect the potential differences of the association of FGA or SGA with breast cancer between the women with the two different psychiatric conditions.

Covariates for multivariable adjustment included the time since the first psychiatric diagnosis (schizophrenia or bipolar disorder) as a continuous variable, clinical history of circulatory system diseases (excluding hypertension), hypertension, obesity, overweight (not entered into the model eventually as no records of this diagnosis in participants were identified), diabetes, suicide/ self-inflicted injury, asthma, alcohol abuse (unspecified), and chronic pulmonary diseases (excluding asthma), as well as the previous use (prior to index date) of calcium channel blocker, loop diuretics, statin, opioid, selective serotonin reuptake inhibitor, serotonin modulators, serotonin–norepinephrine reuptake inhibitor, tricyclic antidepressant, tetracyclic antidepressants, hypnotics, anxiolytic, benzodiazepines, and non-steroidal anti-inflammatory drugs as separate binary indicators. The corresponding generic names of the medications are tabulated at **Table S3. Table S4** shows the ICD-9-CM codes used to identify the clinical history covariates.

Three sensitivity analyses were performed. First, the main analysis was repeated eight times with each of the breast cancer subtypes (different locations of the tumor) excluded to examine the robustness of the findings across subtypes. Second, to examine a potential dose-response relationship, the use of FGAs and SGAs were further categorized into non-use, one to four years of use, and five or more years of use to observe the change in the strength of associations with the varying duration of use. Third, to assess potential impacts from cancers other than breast cancer, we repeated the main analysis but case patients who had a history of any other cancer (ICD-9-CM: 140-239) were excluded together with their matched control participants. Control participants with a cancer history were also removed.

Regarding missing data, we excluded patient records with no documented date of birth, sex, and other essential factors for analysis, as shown in **Figure 1**. Similar with other studies using electronic health

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records, the absence of diagnosis or prescription records was treated as the absence of such a disease and medication use. Python (3.8.10) was used for the analysis with library *statsmodels* adopted for the implementation of multivariable conditional logistic regression. The main analysis was conducted by [*Author Initials Masked*] and independently cross-checked by [*Author Initials Masked*] to ensure accuracy.

RESULTS

During the observation period, there were 14,913 with bipolar disorder and 68,708 patients diagnosed with schizophrenia. After applying the pre-specified exclusion criteria, we identified 672 case participants diagnosed with breast cancer (563 for schizophrenia; 109 for bipolar disorder. A total of 6,450 control participants (5,519 for schizophrenia; 931 for bipolar disorder) were matched with the case participants for analyses. **Figure 1** illustrates the patient identification of this study.

Patient characteristics

Women with schizophrenia were older than those with bipolar disorder (case: 57.92 versus 52.94; control: 57.94 versus 52. 18) and the time (years) since psychiatric diagnosis was also longer (case: 8.56 versus 7.33; control: 8.42 versus 7.77). No marked difference was observed between case and control participants in the clinical or medication history in women with either condition, with standardized mean difference all less than 0.1. In general, there was a higher proportion of antipsychotic use in case participants than in control participants for both psychiatric conditions, although the difference in SGAs use between cases and controls in women with schizophrenia is small with a standardized mean difference of 0.014 (**Table 1**).

Multivariable conditional logistic regression

The results of multivariable conditional logistic regression analyses indicated a significant positive association between FGA and breast cancer in both women with schizophrenia [aOR 1.49, 95%

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confidence interval (CI) 1.17 - 1.90] and women with bipolar disorder (aOR 1.80, 95% CI 1.11 - 2.93). There was an approximate 1.5-fold increase in the odds of breast cancer associated with SGA in women with bipolar disorder (aOR 2.49, 95% CI 1.29 - 4.79) compared with non-use (**Table 2**), while no significant association of SGA with breast cancer was observed in women with schizophrenia (aOR 1.10, 95% CI 0.88 - 1.36). The interaction between SGA use and bipolar disorder was statistically significant in a combined model including women with the two conditions ($p = 0.006$), suggesting a greater association between SGA use and breast cancer in women with bipolar disorder than in women with schizophrenia. Such an interaction was observed for FGAs as well ($p = 0.018$).

Table 3 shows the results of a sensitivity analysis further investigating longer durations of antipsychotic use and the risk of breast cancer. In women with schizophrenia, only five years or longer of FGA use was associated with increased odds of breast cancer versus non-use group (aOR 1.74, 95% CI 1.33 - 2.28). In women with bipolar disorder, one to four years of both FGA (aOR 1.90, 95% CI 1.16 - 3.10) and SGA (aOR 2.27, 95% CI 1.15 - 4.49) use were associated with an increased odds of breast cancer. The aOR for SGA use over five years or more did not reach statistical significance ($p > 0.05$). In a combined model including women with the two conditions, the interaction between various durations of antipsychotic use (either FGA or SGA) and bipolar disorder was non-significant ($p > 0.05$), suggesting no evidence of a different association between different durations of antipsychotic use and breast cancer in women with bipolar disorder compared with women with schizophrenia.

Another sensitivity analysis, as shown in **Table S5**, examined specific locations of breast cancer, each of which was excluded in replications of the main analysis. The interaction between SGA use and bipolar disorder (schizophrenia as referent) were still significant ($p < 0.05$) except when 174.4 or 174.9 were excluded from the analysis, respectively. However, the direction and effect size of the aOR multiplier generated from the interaction analysis was largely consistent with the main analysis.

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Table S6 shows the results of a sensitivity analysis with participants with a history of other cancers excluded. Results are largely in line with the main analysis.

Table S7 shows the proportion of women who had breast cancer (case participants) using different specific antipsychotic agents stratified by schizophrenia and bipolar disorder. It is shown that for both women with schizophrenia and women with bipolar disorder, the most widely used FGAs were haloperidol and trifluoperazine, which are known to be hyperprolactinemia-inducing antipsychotics (Bostwick et al., 2009). Likewise, the most widely used SGA was risperidone which has a similar property.

DISCUSSION

Our data supports an association of the use of FGAs with breast cancer in both women with bipolar disorder and women with schizophrenia. The use of SGAs was found to be associated with an approximate 1.5-fold increase in the odds of breast cancer only in women with bipolar disorder, but not in women with schizophrenia. This difference in the association of SGA with breast cancer between the two conditions was largely robust across different locations of the tumor.

Our results for women with schizophrenia are highly consistent with previous studies. In a Finnish case-control study (Taipale et al., 2021), it was shown that the odds of breast cancer increased by 56% with more than five years of antipsychotic use compared with non-use in women with schizophrenia. A more recent cohort study of over 0.5 million women in the United States showed that antipsychotics with prolactin-inducing properties were associated with a similar extent of increase in breast cancer incidence (Rahman et al., 2022). Our recent meta-analysis of observational data with two million participants also supported a moderate association, 30%-increased risk, of overall antipsychotic use with breast cancer in more broadly defined populations (Leung et al., 2022). This current study, however, reports novel epidemiologic data specific to the population of women with bipolar disorder to better inform clinical management and prompt further studies.

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There may be different pathways between antipsychotic use and breast cancer which explain the association of SGAs with breast cancer only in women with bipolar disorder. First, apart from hyperprolactinemia induced by SGAs such as risperidone, previous research has reported increased metabolic side effects specifically from SGAs (Hsu et al., 2012; Nasrallah, 2008), which may also be risk factors for breast cancer (Tsuang et al., 2005). In a previous matched comparison between patients with schizophrenia and bipolar disorder (Bly et al., 2014), significantly higher cholesterol levels and hip/ waist ratio was found in patients with bipolar disorder. It is possible that metabolic abnormalities following SGAs use are more pronounced in women with bipolar disorder than in women with schizophrenia so that SGAs was only associated with breast cancer in women with bipolar disorder. Second, the specific agents used for the two different conditions may also be a reason for the observed association. According to some current guidelines, certain antipsychotics with a low prolactin profile, such as aripiprazole, are only recommended for individuals with schizophrenia (National Health Service, 2021). Likewise, in our sample, SGAs with lesser change in serum prolactin levels are less commonly used in bipolar than in schizophrenia (Fountoulakis and Vieta, 2009). (**Table S7**)

Moreover, the initial dosage and daily maximum dosage of some antipsychotics varied between treatments for schizophrenia and bipolar disorder. For instance, the initial dosage of quetiapine for individuals with schizophrenia is half of that for individuals with bipolar disorder, with a 50-mg difference in the daily maximum dose recommended (National Health Service, 2021). Apart from the initial dosage, one of the key hallmarks of bipolar disorder is the cycling between mania and depression. The National Health Service in the United Kingdom has published prescribing guidelines for antipsychotic medications in the treatment of recurrent episodes of mania and depression in bipolar disorder. Quetiapine provides an example of how dosing recommendations can vary depending on the indication for use. The recommended initial dosages for quetiapine differ depending on the indication for use. In the treatment of schizophrenia, the usual initial dosage is 25 mg twice daily, with a gradual increase up to 150 mg on the fourth day. For the treatment of mania associated with bipolar disorder, the

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usual initial dosage is 50 mg twice daily, with a subsequent increase of 50 mg per day up to the fourth day. In the treatment of depression associated with bipolar disorder, the usual initial dosage is 50 mg once daily, with a subsequent increase of 50-100 mg per day up to a 300 mg per day (National Health Service, 2021). Such differences in the dosage may affect the cumulative exposure of antipsychotics and thus the risk of breast cancer. Third, there are differences in the two conditions' genetic underpinnings, although they share similarities (McGuffin et al., 2004). Research has shown that genetic determinants of inflammatory responses were different between the conditions (Drexhage et al., 2010), and pathomechanisms determining the risk of breast cancer thus may also differ. Fourth, antipsychotic medication is typically used for acute treatment in bipolar disorders whereas for schizophrenia it is indicated for both acute and maintenance treatment. For bipolar disorders, most patients will have mood stabilizers as a maintenance treatment to prevent relapse. Therefore, a longer period of use of antipsychotics in bipolar disorders signifies a disease of different severity. Furthermore, more SGA has an indication of mood stabilization effect for maintenance treatment but not the FGA.

With the increasingly prevalent use of antipsychotics, the safety of these medications for schizophrenia and bipolar disorder patients warrants deliberate real-world pharmacovigilance efforts. Existing evidence has suggested extrapyramidal and long-term side effects including diabetes, weight gain, stroke, and myocardial infarction (Douglas and Smeeth, 2008; Lai et al., 2020; Smith et al., 2008). In the view of the observed association between antipsychotics and breast cancer among women with schizophrenia and bipolar disorder, the safety profile of antipsychotics as well as the patients' clinical history should be more comprehensively considered before prescription. Specifically, antipsychotics with a high prolactin-elevating propensity should be cautioned for women, especially SGAs for women with bipolar disorder. Patient counselling, careful comprehensive consideration of side effects, and regular monitoring of prolactin levels are recommended.

There are two key strengths to this study. First, this study is one of the first to report epidemiologic data on breast cancer risks associated with antipsychotics separately for schizophrenia and bipolar disorder.

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Second, the territory-wide database used in the study is representative of the Hong Kong population as the public healthcare services provided by the Hospital Authority cover more than 83% of the residential population of the city at a negligible out-of-pocket cost (Census and Statistics Department of the Hong Kong SAR, 2018). Previous research has shown that the vast majority of the inpatient services and nearly one-third of outpatient services in Hong Kong are provided by the Hospital Authority (Leung et al., 2007). Despite these strengths, there are limitations. First, we investigated users of public healthcare facilities only, and patients diagnosed with schizophrenia or bipolar disorder in private sectors were not included. Also, women with bipolar disorder or schizophrenia may be, in an early stage of diagnosis, coded as non-organic psychosis or acute and transient psychotic disorders and thus not included. That might slightly reduce the representativeness of our results (Chang et al., 2009). Second, the sample size for bipolar disorder was modest and thus the estimate of the aOR was not highly precise. Further research with a larger sample size is needed to substantiate the findings. Third, we did not consider the dosage of antipsychotics but focused on the categorization of FGAs and SGAs, as well as the duration of use. Future studies should consider the cumulative dosage of antipsychotics which may likely also affect the risk of breast cancer. Fourth, we did not investigate the potential effects of the use of multiple agents simultaneously or the patterns of combined antipsychotic agents. The interactions between various agents may warrant further investigation. Fifth, the Hong Kong population is predominantly ethnic Chinese and the generalizability of the findings should be tested in other populations. Sixth, the sample size of women with bipolar disorder is relatively small. Specific agents could not be separately investigated. Future studies should further explore the association of specific agents with breast cancer. Seventh, there are covariates that were not considered in the multivariable adjustment such as current and history of tobacco use and nulliparity. Also, there may be under-diagnosis of relevant conditions, albeit not primary condition of concern in the current episode, such as overweight in the database. Further research should consider including those factors for a more comprehensive investigation. Last, ascertainment bias in cancer diagnosis in people with psychiatric disorders such as schizophrenia may also be one of the factors

affecting the results. Various degrees of disease severity or different diagnoses may be indicative of differing degrees of ascertainment bias.

CONCLUSION

In this territory-wide nested case-control study, we identified a significantly increased risk of breast cancer in women with bipolar disorder, with an evident risk following the use of SGAs specific to this population, but not in women with schizophrenia. Additional research is required to assess the comparative risks and benefits of specific antipsychotic medications in women living with bipolar disorder.

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Figure 1. Sample selection procedures.

Table 1. Clinical characteristics of case and control participants by psychiatric disorder, i.e., schizophrenia versus bipolar disorder

	Bipolar disorder			Schizophrenia		
	Case	Control	SMD	Case	Control	SMD
n	109	931		563	5519	
Mean age (standard deviation)	52.94 (11.55)	52.18 (10.87)	-	57.92 (11.68)	57.94 (11.60)	-
Time since psychiatric diagnosis (years, standard deviation)	7.33 (5.08)	7.77 (5.04)	0.087	8.56 (5.08)	8.42 (4.91)	0.028
Medication history, n (%)						
Calcium channel blocker	15 (13.8)	112 (12)	0.017	138 (24.5)	1366 (24.8)	-0.002
Loop diuretics	7 (6.4)	39 (4.2)	0.022	40 (7.1)	521 (9.4)	-0.023
Statin	12 (11.0)	52 (5.6)	0.054	76 (13.5)	635 (11.5)	0.02
Opioid	11 (10.1)	63 (6.8)	0.033	163 (29)	861 (15.6)	0.134
Selective serotonin reuptake inhibitor	34 (31.2)	295 (31.7)	-0.005	129 (22.9)	1048 (19)	0.039
Serotonin modulators	0 (0.0)	1 (0.1)	-0.001	0 (0)	0 (0)	0
Serotonin–norepinephrine reuptake inhibitor	5 (4.6)	71 (7.6)	-0.03	17 (3)	123 (2.2)	0.008
Tricyclic antidepressant	19 (17.4)	160 (17.2)	0.002	69 (12.3)	662 (12)	0.003
Tetracyclic antidepressants	7 (6.4)	125 (13.4)	-0.07	42 (7.5)	338 (6.1)	0.013
Hypnotics	55 (50.5)	452 (48.5)	0.019	293 (52)	2811 (50.9)	0.011
Anxiolytic	56 (51.4)	490 (52.6)	-0.013	311 (55.2)	2850 (51.6)	0.036
Benzodiazepines	24 (22.0)	228 (24.5)	-0.025	94 (16.7)	775 (14)	0.027
Non-steroidal anti-inflammatory drug	52 (47.7)	407 (43.7)	0.04	297 (52.8)	2512 (45.5)	0.072
Clinical history (%)						
Hypertension	14 (12.8)	98 (10.5)	0.023	66 (11.7)	699 (12.7)	-0.01
Other circulatory system diseases	16 (14.7)	87 (9.3)	0.076	51 (9.1)	574 (10.4)	-0.023
Obesity	3 (2.8)	16 (1.7)	0.011	1 (0.2)	34 (0.6)	-0.004
Overweight	0 (0)	0 (0)	0	0 (0)	0 (0)	0
Diabetes	19 (17.4)	99 (10.6)	0.068	62 (11)	625 (11.3)	-0.003
Suicide/self-inflicted injury	0 (0)	13 (1.4)	-0.014	4 (0.7)	41 (0.7)	0
Asthma	2 (1.8)	21 (2.3)	-0.005	1 (0.2)	111 (2)	-0.018
Alcohol abuse, unspecified	1 (0.9)	8 (0.9)	0	0 (0)	17 (0.3)	-0.003
Chronic pulmonary diseases	3 (2.8)	23 (2.5)	0.003	7 (1.2)	124 (2.2)	-0.01
Antipsychotic use						
Non-user (none or less than one year of use)	49 (45.0)	544 (58.4)	-0.135	79 (14)	961 (17.4)	-0.034
First-generation antipsychotics	48 (44.0)	332 (35.7)	0.084	430 (76.4)	3870 (70.1)	0.063
Second-generation antipsychotics	17 (15.6)	85 (9.1)	0.065	195 (34.6)	1834 (33.2)	0.014

SMD = standardized mean difference

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Table 2. Adjusted odds ratios (aOR) of breast cancer by antipsychotic use status and psychiatric disorder (schizophrenia versus bipolar disorder)

Antipsychotic use status	Control participants (n=6450), n (%)	Case Patients (n=672), n (%)	Crude OR (95% confidence interval)	aOR (95% confidence interval)
Schizophrenia	n=5519	n=563		
Non-user	961 (17.4)	79 (14.0)	Ref	Ref
First-generation antipsychotics	3870 (70.1)	430 (76.4)	1.56 (1.24 - 1.96)	1.49 (1.17 - 1.90)
Second-generation antipsychotics	1834 (33.2)	195 (34.6)	1.15 (0.95 - 1.41)	1.10 (0.88 - 1.36)
Bipolar disorder	n=931	n=109		
Non-user	544 (58.4)	49 (45.0)	Ref	Ref
First-generation antipsychotics	332 (35.7)	48 (44.0)	1.58 (1.03 - 2.42)	1.80 (1.11 - 2.93)
Second-generation antipsychotics	85 (9.1)	17 (15.6)	2.13 (1.18 - 3.82)	2.49 (1.29 - 4.79)

Significant interaction between bipolar disorder and second-generation antipsychotics ($p = 0.006$) and between bipolar disorder and first-generation antipsychotics ($p = 0.018$)

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Table 3. Adjusted odds ratios (aOR) of breast cancer by antipsychotic use duration and status as well as psychiatric disorder (schizophrenia versus bipolar disorder)

Antipsychotic use status	Control participants (n=6450), n (%)	Case Patients (n=672), n (%)	Crude OR (95% confidence interval)	aOR (95% confidence interval)
Schizophrenia	n=5519	n=563		
First-generation antipsychotics				
Non-user	1649 (29.9)	133 (23.6)	Ref	Ref
One to four years	1478 (26.8)	145 (25.8)	1.29 (0.98 - 1.70)	1.20 (0.96 - 1.68)
Five years or more	2392 (43.3)	285 (50.6)	1.80 (1.40 - 2.31)	1.74 (1.33 - 2.28)
Second-generation antipsychotics				
Non-user	3685 (66.8)	368 (65.4)	Ref	Ref
One to four years	914 (16.6)	93 (16.5)	1.13 (0.88 - 1.45)	1.11 (0.86 - 1.44)
Five years or more	920 (16.7)	102 (18.1)	1.32 (1.02 - 1.71)	1.22 (0.92 - 1.62)
Bipolar disorder	n=931	n=109		
First-generation antipsychotics				
Non-user	599 (64.3)	61 (56.0)	Ref	Ref
One to four years	310 (33.3)	47 (43.1)	1.66 (1.08 - 2.55)	1.90 (1.16 - 3.10)
Five years or more	22 (2.4)	1 (0.9)	0.44 (0.06 - 3.49)	0.33 (0.04 - 2.97)
Second-generation antipsychotics				
Non-user	846 (90.9)	92 (84.4)	Ref	Ref
One to four years	80 (8.6)	15 (13.8)	1.97 (1.07 - 3.63)	2.27 (1.15 - 4.49)
Five years or more	5 (0.5)	2 (1.8)	4.79 (0.83 - 27.61)	5.95 (0.86 - 41.26)

Non-significant interactions between both durations of first-generation antipsychotic use and bipolar disorder (five years or more: $p = 0.324$) and between both durations of second-generation antipsychotic use and bipolar disorder (five years or more: $p = 0.071$)