Maintenance pharmacotherapy strategy for relapse prevention in patients with severe mental illness

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ABSTRACT

Maintenance pharmacotherapy strategy for relapse prevention in patients with severe mental illness

Background: Schizophrenia and bipolar disorder are serious mental illnesses that cause significant disability. Psychotropic medications, such as antipsychotics and mood stabilizers, are commonly used in the treatment of these conditions. The association between the type and formulation of these medications and relapse risk has been extensively studied in randomized controlled trials and large observational studies. However, evidence on the optimal maintenance dose of these medications is limited. This thesis aimed to investigate the association between maintenance dose and relapse risk in patients with schizophrenia and bipolar disorder, providing real-world evidence to support clinical practice.

Methods: Two studies were conducted: (1) a validation study of case definitions and relapse identification, and (2) an analysis of the association between maintenance dose and relapse risk. For the first study, data from the Severance Clinical Research Analysis Portal (SCRAP) spanning November 1, 2005, to December 31, 2023, were used. Patients identified based on specified algorithms were confirmed as true cases through medical chart reviews. Positive predictive values (PPVs) were calculated for each algorithm to evaluate validity. For the second study, data from the National Health Information Database (NHID), provided by the National Health Insurance Service of Korea, were utilized. Patients with incident schizophrenia or incident bipolar disorder who were hospitalized for the first time (index admission) between January 1, 2002, and December 31, 2022, were identified. Five groups were constructed based on disease and therapeutic medications: schizophrenia-antipsychotic, bipolar disorder-mood stabilizer, bipolar disorder-lithium, bipolar disorder-valproate, and bipolar disorder-antipsychotic. Each group consisted of patients with specific diseases who used target medications during the index admission. Maintenance dose episodes were constructed based on prescription data from the NHID. Doses of different medications were summed using the defined daily dose (DDD). In addition to the crude maintenance dose (actual dose, DDDs/day), a relative maintenance dose (%)—calculated by dividing the crude maintenance

dose by the dose during the index admission—was used in the analyses. Patients were followed from discharge after their first hospitalization (the index date) until relapse, discontinuation of therapeutic medication for ≥1 year, death, or December 31, 2022, whichever came first. Extended Cox regression with time-varying exposure was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between time-varying maintenance dose and relapse risk. Time-lag and sensitivity analyses were conducted.

Results: In the validation study using SCRAP, the case definition algorithms for schizophrenia demonstrated considerable validity, with PPVs ranging from 80.5% to 86.5%. For the case definition of bipolar disorder, the algorithm based only on hospitalization records showed a PPV of 84.1%. The relapse identification algorithms for schizophrenia and bipolar disorder based on rehospitalization showed a PPV of 88.0% and 72.0%, respectively. In the schizophrenia-antipsychotic group from the NHID, there was a significant association between low antipsychotic dose and relapse risk (<0.5 vs. 0.75–1.25 DDDs/day, HR = 1.31 [95% CI: 1.25–1.37]; 50% vs. 75–125%, HR = 1.31 [95% CI: 1.25–1.36]). In the bipolar disorder-mood stabilizer group, low maintenance doses of mood stabilizers were associated with a higher risk of relapse (<0.5 vs. 0.75–1.25 DDDs/day, HR = 1.26 [95% CI: 1.12–1.42]; 50% vs. 75–125%, HR = 1.38 [95% CI: 1.25–1.52]). This association was particularly evident in the valproate subgroup but not in the lithium subgroup. In the bipolar disorder-antipsychotic group, there was a marginal association between low antipsychotic doses and relapse risk (<0.5 vs. 0.75–1.25 DDDs/day, HR = 1.23 [95% CI: 1.12–1.35]; 50% vs. 75–125%, HR = 1.16 [95% CI: 1.06–1.27]). The lowest effective doses for antipsychotics and mood stabilizers were derived from restricted cubic spline analyses. Sufficient use (≥75%) of mood stabilizers weakened the association between low antipsychotic dose and relapse risk, and vice versa.

Conclusion: In patients with schizophrenia and bipolar disorder, lower maintenance doses of therapeutic medications were associated with a higher risk of relapse. These findings may help physicians consider the quantitative risk of relapse when reducing a patient's medication dose. Further studies on relapse risk prediction models are needed.

Key words: schizophrenia; bipolar disorder; relapse; pharmacoepidemiology

1. INTRODUCTION

Schizophrenia and bipolar disorder are severe mental illness that significantly hinder one's life. In the Global Burden of Disease Study 2019, schizophrenia and bipolar disorder accounted for 12.1% and 6.8%, respectively, of the total disability-adjusted life-years for mental disorders, despite their relatively low prevalence.[1] Schizophrenia is characterized by psychotic symptoms such as hallucination and delusion. Patients with schizophrenia experience deterioration in various areas of functioning, including progressive impairment in social, cognitive, and self-care abilities. After each relapse, they experience a substantial decline in functioning and usually fail to return to the baseline functioning.[2] Patients with bipolar disorder experience manic episodes or major depressive episodes, and these mood episodes can cause marked impairment in social or occupational functioning.[3] As mood episodes recur, patients with bipolar disorder often face shorter intervals between relapses and are at risk of experiencing functional decline.[4,5] Therefore, even if the symptoms of patients with schizophrenia or bipolar disorder are stabilized, they require maintenance treatment to prevent relapse. Since about half, or as many as 80%, of patients with schizophrenia and bipolar disorder experience relapse within several years after the onset,[6-10] effective maintenance treatment strategies is important to improve long-term outcomes in the majority of patients.

Pharmacotherapy is the primary treatment for preventing relapse in patients with schizophrenia and bipolar disorder.[2] Antipsychotic medications are mainly used for treating schizophrenia, while both antipsychotics and mood stabilizers are used for treating bipolar disorder. The effectiveness of different types and formulations of these medications have been widely studied in large epidemiological cohorts.[11-14] A study analyzing patients with schizophrenia from nationwide databases in Sweden found that the use of clozapine and long-acting injectable (LAI) antipsychotics was associated with a lower risk of rehospitalization.[14] In patients with bipolar disorder from the same database, the use of lithium and LAI antipsychotics showed superiority compared to other mood stabilizers and antipsychotics in preventing rehospitalization.[13] However, evidence on the appropriate dosing of these medications is scarce. Multiple pharmacological treatment guidelines recommend using the lowest effective dose during the maintenance phase, considering the side effects associated with higher doses of psychotropic medications.[15,16] To find the lowest effective dose, physicians often adjust doses up or down to observe whether symptoms or side effects improve.

During this trial-and-error process, some patients may experience irreversible consequences, such as relapse. Real-world evidence on the risk of relapse associated with different doses of psychotropic medications can help physicians more accurately estimate the lowest effective dose. For instance, this may help quantitatively predict the increased risk of relapse due to dose reduction and identify a safe zone where the risk of relapse does not increase.

The National Health Information Database (NHID) is a nationwide health information database of the National Health Insurance Service of Korea.[17] The NHID covers almost the entire Korean population and contains information on diagnostic claims and prescribed medications for both inpatient and outpatient care. Notably, the prescription data include medication type, dosage form, dose, and prescribed duration, making the NHID suitable for analyzing frequently changing maintenance doses of psychotropic medications. However, case definition for schizophrenia and bipolar disorder and identification of relapse in the NHID relies solely on claims data, and these procedures have not yet been validated. Notably, the diagnostic instability of psychiatric disorders underscores the need for validation of diagnostic codes in claims data.[18-20] To validate these diagnostic claims, true cases should be confirmed, typically based on medical chart review.[21,22] The Severance Clinical Research Analysis Portal (SCRAP) allows researchers to extract electronic medical records and various data on diagnoses and prescriptions from Severance Hospital. Using SCRAP, various operational definitions based on claim records can be validated against diagnoses obtained through medical chart review.

This thesis aimed to: (1) validate case definition and relapse identification algorithms for schizophrenia and bipolar disorder in the NHID using the SCRAP database, (2) study the association between the maintenance dose of antipsychotics and the risk of relapse in patients with schizophrenia, and (3) study the association between the maintenance dose of mood stabilizers and antipsychotics and the risk of relapse in patients with bipolar disorder.

2. MATERIALS AND METHODS

2.1. Data source and study population

2.1.1. Validation studies using SCRAP

SCRAP is an ongoing clinical data warehouse of Yonsei University Health System, including Severance Hospital, Gangnam Severance Hospital, and Yongin Severance Hospital, since 2005. SCRAP contains various electronic medical records, including diagnoses, medication prescriptions, procedures, and the results of laboratory, imaging, and pathology tests, as well as medical charts. The data from Severance Hospital were analyzed in this thesis.

From SCRAP, 4,974 and 4,653 patients with main diagnostic codes for schizophrenia (F20, F25) and bipolar disorder (F30, F31), respectively, were identified between November 1, 2005, and December 31, 2023. For the validation of case definition algorithms, 200 patients with schizophrenia and 200 patients with bipolar disorder were randomly sampled. For the validation of relapse identification algorithms among patients who were hospitalized, 960 patients with schizophrenia and 870 patients with bipolar disorder who were hospitalized with primary diagnostic codes for schizophrenia and bipolar disorder, respectively, were identified. Among them, 100 patients with schizophrenia and 100 patients with bipolar disorder were randomly sampled. Additionally, among patients who were hospitalized, patients who were re-hospitalized (relapse) were identified to obtain robust positive predictive value for the relapse identification algorithms. Thus, 213 patients with schizophrenia and 197 patients with bipolar disorder who were re-hospitalized with primary diagnostic codes for psychotic disorders (F2.x) and mood disorders (F3.x), respectively, were identified. Among them, 50 patients with schizophrenia and 50 patients with bipolar disorder were randomly sampled.

2.1.2. Studies using the NHID

The NHID contains sociodemographic information about insurance qualifications, diagnosis records based on International Classification of Disease-Tenth Edition (ICD-10) coding, information on prescribed medications, and mortality data.[17] The NHID can be assessed in the form of

customized data. Accordingly, customized data consisting of individuals who had at least one main diagnosis of schizophrenia (ICD-10, F20, F25) or bipolar disorder (F30, F31) between January 1, 2002, and December 31, 2022, were analyzed (NHIS-2024-1-252).

Patients aged ≥19 years with incident schizophrenia or incident bipolar disorder who were firstly hospitalized with main diagnostic codes for between 2002 and 2022 were identified from the NHID. Incident cases were defined as: (1) no use of main therapeutic medications (antipsychotics for schizophrenia; mood stabilizers and antipsychotics for bipolar disorder) for 1 year prior to the first diagnosis, and (2) age under 60 years at the time of the first diagnosis.[13] This procedure for prior medication use aimed to exclude prevalent cases who were receiving treatment without diagnostic codes. For the schizophrenia group, the non-use of antipsychotics was confirmed during the 1-year period prior to the first diagnosis of psychotic disorders (F2.x), because the first diagnosis of schizophrenia can be made late after an initiation of treatment with antipsychotics, as it requires a minimum six-month disease duration.[3] The first hospitalization was designated as the index admission. To account for the continuation of the episode, readmission within 30 days of discharge from the index admission were considered an extension of the index admission.

There were three exclusion processes. First, among incident cases of schizophrenia who were firstly hospitalized, patients who had been diagnosed with dementia (F00–F03, G30) before the index admission were excluded. Among incident cases of bipolar disorder who were firstly hospitalized, patients who had been diagnosed with dementia or schizophrenia before the index admission were excluded. Second, patients who used an average dose of main therapeutic medications of <0.1 defined daily doses (DDDs)/day or >10 DDDs/day during the index admission were excluded. Third, patients who had a follow-up time of ≤90 days were excluded.

As described above, study populations vary depending on the target disease and medication. For example, the flowcharts for patient selection in the schizophrenia-antipsychotic group and the bipolar disorder-mood stabilizer group are demonstrated in Figure 1 and Figure 2, respectively.

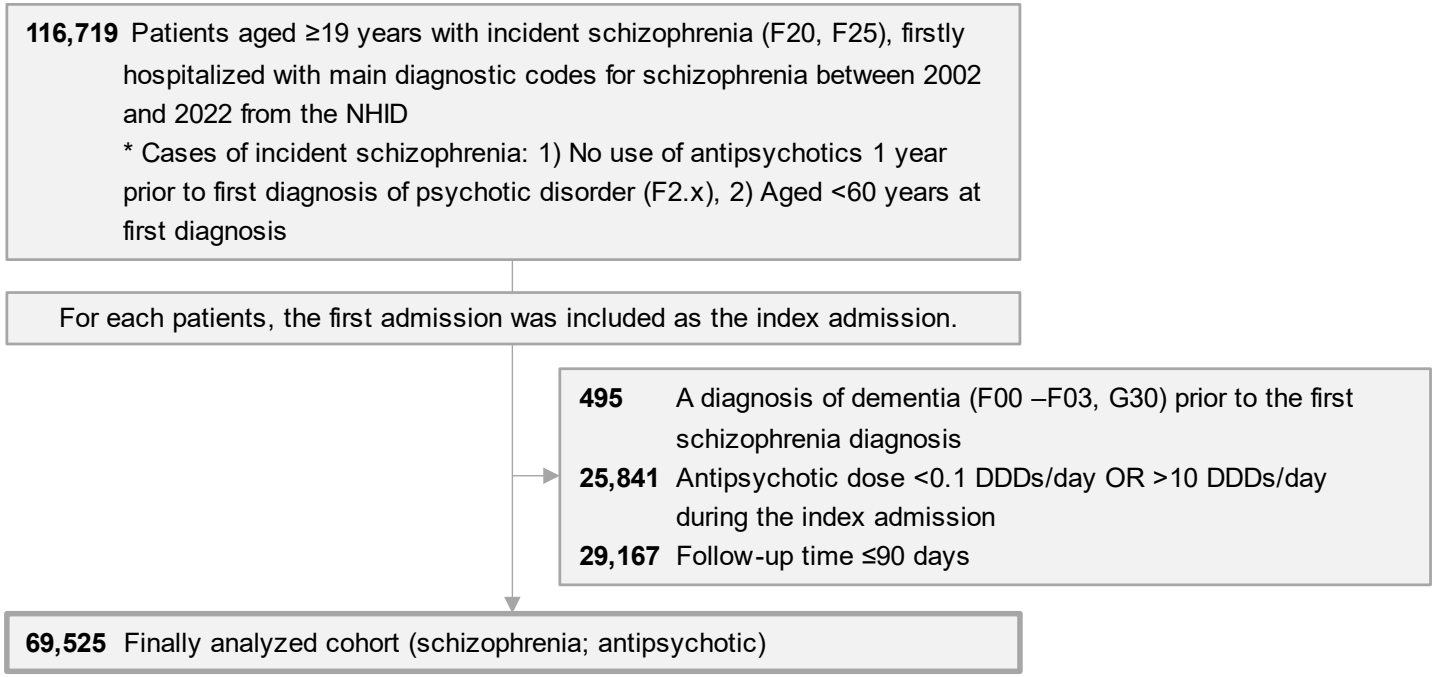

Figure 1. Flowchart of the schizophrenia-antipsychotics group from the NHID. DDD, defined daily dose.

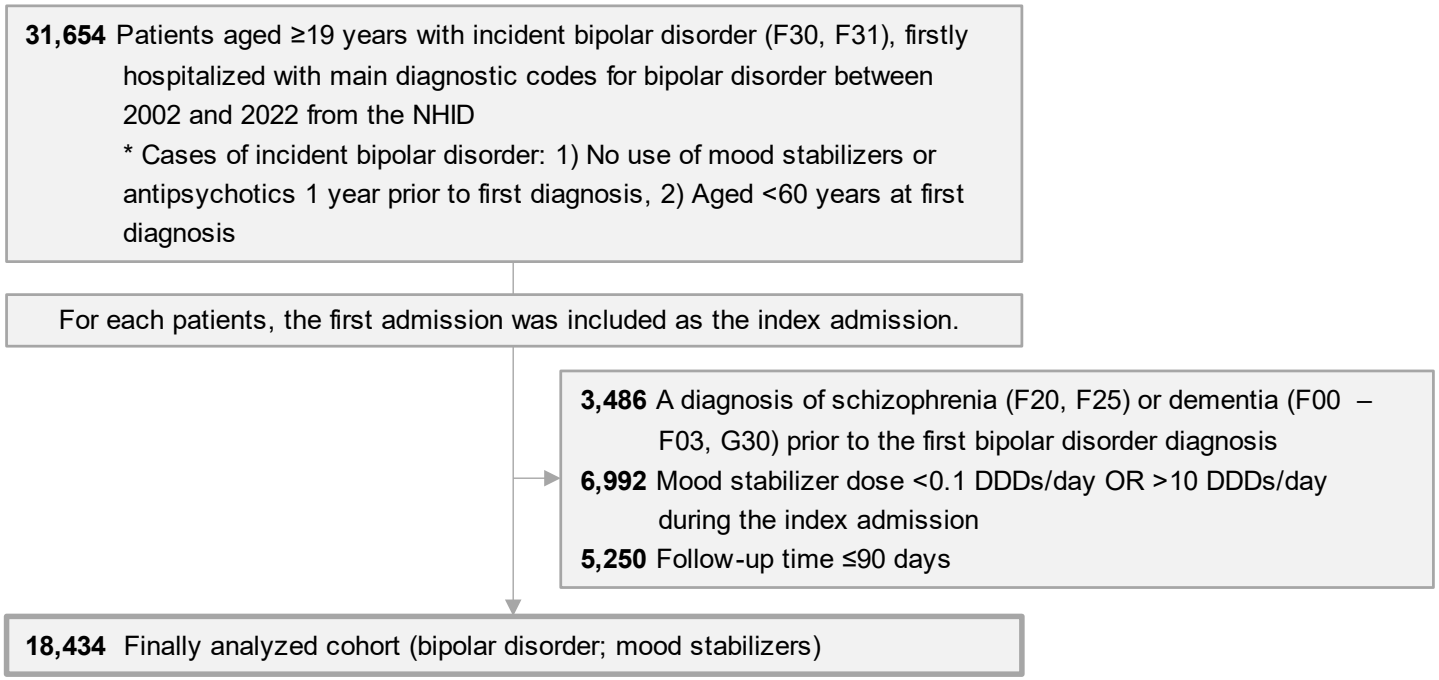

Figure 2. Flowchart of the bipolar disorder-mood stabilizers group from the NHID. DDD, defined daily dose.

2.1.3. Ethical considerations

All procedures contributing to this thesis comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The study protocol was approved by the Institutional Review Board of Yonsei University (YUIRB-4-2023-1345). Informed consent was waived due to the observational study design using de-identified data.

2.2. Measurements and variables

2.2.1. Validation studies using SCRAP

2.2.1.1. Case definition algorithms

The selected study populations from SCRAP inherently presented a case definition algorithm for having main diagnostic codes, regardless of inpatient or outpatient care. Using records with main diagnostic codes (schizophrenia: F20, F25; bipolar disorder: F30, F31), those corresponding to the following algorithms were identified: (1) hospitalization only, (2) hospitalization OR ≥2 outpatient visit, and (3) hospitalization OR ≥3 outpatient visit. Additionally, these procedures were repeated using records with both main diagnostic codes and prescriptions for main therapeutic medications (schizophrenia: antipsychotics; bipolar disorder: mood stabilizers and antipsychotics). Accordingly, eight case definition algorithms per disease were defined.

2.2.1.2. Relapse identification algorithms

For schizophrenia and bipolar disorder, rehospitalizations for psychotic disorders (F2.x) and mood disorders (F3.x), respectively, were validated for relapse identification. Relapses without rehospitalization were identified using medical chart review.

2.2.1.3. Medical chart review

All medical charts of the selected study populations between November 1, 2005, and December 31, 2023, were reviewed by the licensed psychiatrist. The reviewed medical charts included admission records, inpatient progress notes, discharge records, outpatient first/re-visit records, emergency room records, and consultation records. The true cases and relapses of schizophrenia and bipolar disorder were identified based on Diagnostic and Statistical Manual of Mental Disorders,

Fifth Edition, Text Revision.[3]

2.2.2. Association between maintenance dose and relapse risk from the NHID

2.2.2.1. Maintenance doses of antipsychotics and mood stabilizers

In the schizophrenia group, maintenance dose episodes for antipsychotics were constructed. In the bipolar disorder groups, maintenance dose episodes for mood stabilizers (including lithium and valproate) and antipsychotics were constructed. The doses of different medications in each category were summed based on DDDs.[23] A list of included medications and the DDD index is shown in Table 1. Maintenance dose episodes were constructed for the period between the discharge date from the index admission and the end of follow-up (either relapse or censored). A single dose episode starts on the prescription date and is maintained for the prescribed duration. If a new prescription occurred before the end of the previous dose episode, the previous episode was discontinued and updated to the new dose. If a new prescription occurred within 30 days after the previous episode ended, the previous episode was considered extended until the start of the new episode (30-day grace period). If there was a gap of more than 30 days after the previous episode ended, an episode of non-use was inserted. Adjacent episodes of the same dose were lumped.

The maintenance dose was calculated and used as the exposure in two ways: a crude maintenance dose and a relative maintenance dose. The crude maintenance dose (DDDs/day) referred to the actual dose prescribed. The relative maintenance dose (%) was defined as the proportion of the crude maintenance dose divided by the average dose during the index admission. Using the relative dose as the exposure helps interpret the degree of dose reduction more intuitively and minimizes indication bias, where more severe patients might use higher doses of medications and be more likely to experience relapse. Additionally, using the relative dose may be particularly appropriate for mood stabilizers. The pharmacological effects of lithium and valproate, the most widely used mood stabilizers, vary greatly depending on the patient's pharmacokinetic factors and metabolic enzyme activities.[24-26] Therefore, plasma concentrations of these medications serve as a gauge for determining the actual effective dose. Assuming that patients received sufficient acute treatment during their index admissions and achieved similar plasma concentrations of mood stabilizers, the relative maintenance dose may better reflect their individual dose levels.

Table 1. List of included psychotropic medications and defined daily dose index

Medication	mg per 1 defined daily dose
Antipsychotics	
Haloperidol	8 (PO, IV/IM), 3.3 (depot)
Levomepromazine	300
Chlorpromazine	300
Perphenazine	30
Pimozide	4
Risperidone	5 (PO), 2.7 (depot)
Paliperidone	6 (PO), 2.5 (depot)
Olanzapine	10
Quetiapine	400
Clozapine	300
Aripiprazole	15 (PO), 13.3 (depot)
Ziprasidone	80
Sulpiride	800
Amisulpride	400
Zotepin	200
Blonanserin	20[1]
Mood stabilizers	
Lithium	1773
Valproate (Divalproex)	1500
Topiramate	300
Lamotrigine	300
Carbamazepine	1000
Oxcarbazepine	1000

[1]Calculated based on blonanserin dose equivalent to 5mg risperidone (Ref: Yang J, Bahk W-M, Cho H-S, Jeon Y-W, Jon D-I, Jung H-Y, et al. Efficacy and tolerability of Blonanserin in the patients with schizophrenia: a randomized, double-blind, risperidone-compared trial. Clinical neuropharmacology 2010;33:169-75.)

2.2.2.2. Relapse and follow-up

The relapse of patients with schizophrenia was identified by admission for psychosis, defined as a hospitalization ≥2 days with a main diagnostic code of F20–29. This outcome has been commonly used in large epidemiological studies using claim data.[12,27] The relapse of patients with bipolar disorder was captured with admission for mood disorders, defined as a hospitalization ≥2 days with

a main diagnostic code of F30–39. This definition aimed to account for both manic and depressive episodes.

From the discharge date of the index admission, patients were followed-up until the relapse, discontinuation of the target medication ≥1 year, death, or December 31, 2022, whichever came first. Censoring those who discontinued their medications was intended to diminish the influence of treatment termination and focus on the on-treatment dose of medication. Graphical demonstrations of the study design for the schizophrenia-antipsychotic group and the bipolar disorder-mood stabilizer group were shown in Figure 3 and Figure 4, respectively.

2.2.2.3. Covariates

Information on sex and age at the index admission was obtained from insurance qualification data. Household income was determined based on medical insurance premiums at the time of the index admission. Individuals with medical aid, who are socioeconomically disadvantaged and do not pay insurance premiums, were categorized separately. A history of substance use disorders (F1.x), anxiety disorders (F40, F41), obsessive-compulsive disorders (F42), personality disorders (F6.x), and psychiatric developmental disorders (F70–89) was defined as a diagnosis before the index admission (Appendix 1). Additionally, for the schizophrenia group, a history of mood disorders (F3.x) was also included as a covariate. Disease duration was defined as the time gap between the first diagnosis and the index admission. The duration of the index admission was categorized as follows: <7 days, 7–90 days, and ≥90 days. The year of the index admission was also included as a covariate. The average dose of the target medication during the index admission was calculated by dividing the summed dose during the index admission by the duration of the index admission.

For the schizophrenia group, polytherapy with antipsychotics was included as a time-varying covariate. For the bipolar disorder group, doses of medications other than the target medication, as well as polytherapy with the target medication, were included as time-varying covariates.

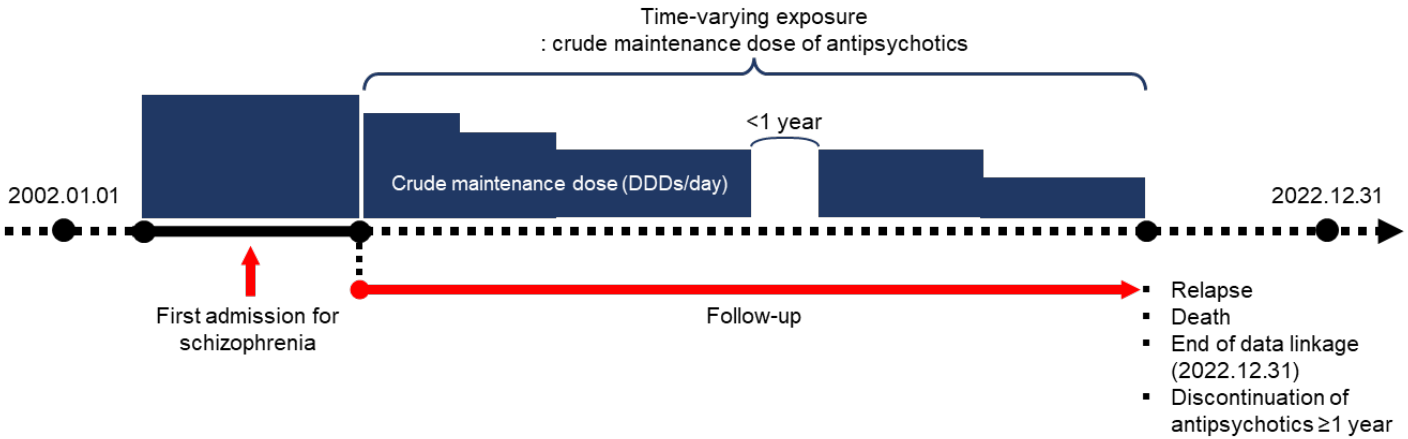

Figure 3. Study design for the schizophrenia-antipsychotic group from the NHID. Using the crude maintenance dose as the exposure was illustrated. DDD, defined daily dose.

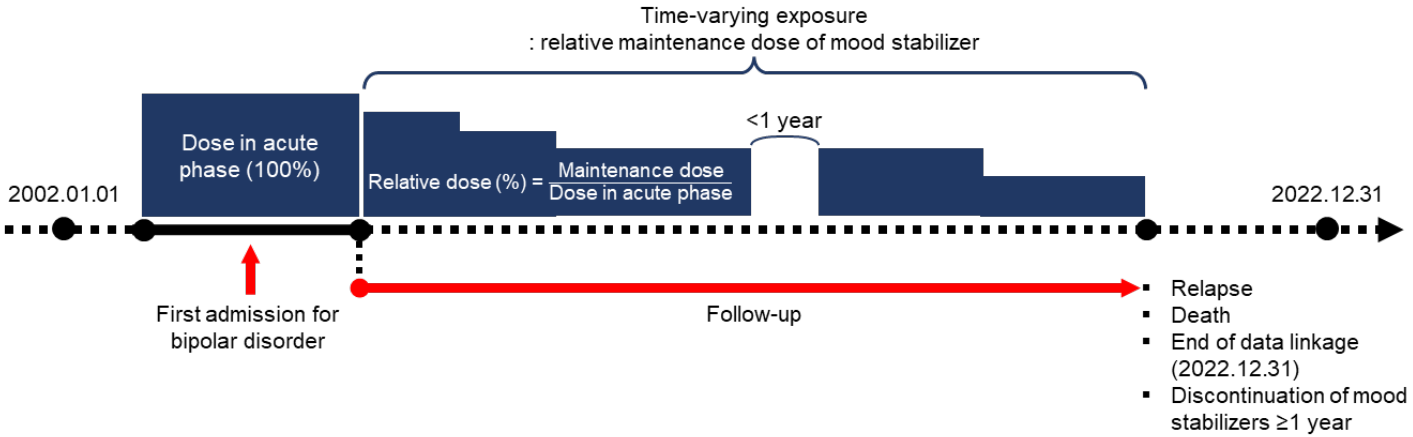

Figure 4. Study design for the bipolar disorder-mood stabilizer group from the NHID. Using the relative maintenance dose as the exposure was illustrated.

2.3. Statistical analyses

The general characteristics of individuals were presented as N (%) for categorical variables and mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables.

2.3.1. Validation of diagnostic codes

To validate case definition algorithms and relapse identification algorithms, the positive predictive value (PPV) for each algorithm was obtained. It was calculated as proportion of true cases from the chart review among individuals who were identified by each algorithm. The sensitivity of relapse identification algorithms was calculated as proportion of true rehospitalization relapses among patients who experienced relapse. Analyses were performed using R software V.4.4.0 (R Foundation for Statistical Computing).

2.3.2. Association between maintenance dose and relapse risk

An individual dose trajectory during the follow-up period was modeled based on the average dose in each 90-day interval. In each interval, doses of patients at risk were aggregated using the median and IQR. The incidence rates of relapse were calculated as the number of relapses per 1,000 person-years during follow-up. To compare relapse risk across different maintenance doses, extended Cox regression with time-varying exposure was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).[27,28] For categorical analyses of the crude maintenance dose, dose episodes were categorized as follows: (1) no use, (2) <0.5 DDDs/day, (3) 0.5–0.75 DDDs/day, (4) 0.75–1.25 DDDs/day (reference), and (5) ≥1.25 DDDs/day. For categorical analyses of the relative maintenance dose, dose episodes were categorized as follows: (1) no use, (2) <50%, (3) 50–75%, (4) 75–125%, and (5) ≥125%. To visualize the association, maintenance doses were modeled using a restricted cubic spline term with a reference crude dose of 1 DDDs/day and a relative dose of 100%, with four knots at the 5th, 35th, 65th, and 95th percentiles. Models were adjusted for sex, age at the index admission, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission, index year (time-invariant covariates), polytherapy, and crude doses of other therapeutic medications (time-varying covariates). Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R software V.4.0.3 (R Foundation for Statistical

Computing).

2.3.2.1. Time-lag analyses

To consider for the delayed effect of maintenance dose on relapse risk, analyses with time-lag period of 14, 30, 60, 90 days were conducted. In the primary analyses, the association with the dose just before relapse was estimated. However, for instance, if a specific dose worsens the patient's symptoms, the time to admission may be delayed while a physician adjusts the medication doses in an outpatient setting. Time-lag analyses can examine these delayed effects and complement the primary analysis.

2.3.2.2. Sensitivity analyses

Four sensitivity analyses were conducted. First, subgroup analyses stratified by sex, age, index year, and average dose during the index admission (only for the mood stabilizer group) were conducted. Second, analyses were repeated with different grace periods (14 and 60 days) of dose episodes. Third, sensitivity analyses with different censoring conditions based on medication discontinuation (no censoring, discontinuation ≥2 years, and discontinuation ≥30 days) were conducted. Fourth, the follow-up period was restricted to 1, 3, and 5 years.

2.3.2.3. Secondary analyses

To examine the interactions between mood stabilizer and antipsychotic doses in patients with bipolar disorder, stratified analyses were conducted based on the dose of the other medication. Among patients with bipolar disorder who used both mood stabilizers and antipsychotics during the index admission, the association between the maintenance dose of antipsychotics and relapse risk was estimated in two mutually exclusive groups: those with a median relative maintenance dose of mood stabilizers <75% and those with ≥75%. Similarly, the association between the maintenance dose of mood stabilizers and relapse risk was estimated in two mutually exclusive groups: median relative maintenance dose of antipsychotics <75% and ≥75%. The median relative maintenance dose during the follow-up period was calculated using a follow-up time-weighted median.

3. RESULTS

3.1. Validation studies

3.1.1. Validation of case definition algorithms

From SCRAP, 4,974 patients with a main diagnostic code of schizophrenia and 4.653 patients with a main diagnostic code of bipolar disorder were identified between November 1, 2005, and December 31, 2023. Among them, 200 patients of the schizophrenia validation set and 200 patients of the bipolar disorder validation set were randomly sampled (Table 2).

Table 2. Characteristics of validation sets for case definitions

Variable	Schizophrenia		Bipolar disorder	
	Entire population (N=4,974)	Random validation set (N=200)	Entire population (N=4,653)	Random validation set (N=200)
Women, No. (%)	2,773 (55.7)	117 (58.5)	2,777 (59.7)	133 (66.5)
Age at the first diagnosis, Mean (SD)	36.1 (13.4)	36.4 (14.1)	36.6 (17.1)	36.0 (17.0)
Year at the first diagnosis, No. (%)				
2005–2008	1,664 (33.5)	81 (40.5)	674 (14.5)	33 (16.5)
2009–2011	640 (12.9)	26 (13.0)	545 (11.7)	25 (12.5)
2012–2014	862 (17.3)	21 (10.5)	730 (15.7)	29 (14.5)
2015–2017	653 (13.1)	25 (12.5)	737 (15.8)	30 (15.0)
2018–2020	715 (14.4)	28 (14.0)	1,269 (27.3)	56 (28.0)
2021–2023	439 (8.8)	19 (9.5)	699 (15.0)	27 (13.5)

In the schizophrenia validation set, all algorithms showed a PPV of >80%. The PPV for the algorithm based on any records with main diagnostic codes was 80.5%, while the PPV for the algorithm based on hospitalization or ≥3 outpatient visits was 86.2%. In the bipolar disorder validation set, the PPV for the algorithm based on any records with main diagnostic codes was 68.5%. The PPV increased as the algorithm became more stringent, with the PPV for the algorithm based

on hospitalization-only reaching 84.1%. For both schizophrenia and bipolar disorder algorithms, adding prescription information did not remarkably improve the PPV. Additionally, the number of patients identified by the algorithms based on hospitalization-only was relatively low compared to other algorithms. Detailed results of validation study were shown in Table 3.

Table 3. Validation of case definition algorithms

Algorithm	N	True case	PPV (%)
Schizophrenia			
Main diagnostic codes			
Any records	200	161	80.5
Hospitalization OR ≥2 outpatient visits	154	131	85.1
Hospitalization OR ≥3 outpatient visits	145	125	86.2
Hospitalization only	39	33	84.6
Diagnosis + antipsychotic prescription			
Any records	162	137	84.6
Hospitalization OR ≥2 outpatient visits	140	121	86.4
Hospitalization OR ≥3 outpatient visits	138	119	86.2
Hospitalization only	37	32	86.5
Bipolar disorder			
Main diagnostic codes			
Any records	200	137	68.5
Hospitalization OR ≥2 outpatient visits	158	113	71.5
Hospitalization OR ≥3 outpatient visits	141	102	72.3
Hospitalization only	44	37	84.1
Diagnosis + prescription of antipsychotics or mood stabilizers			
Any records	167	118	70.7
Hospitalization OR ≥2 outpatient visits	136	98	72.1
Hospitalization OR ≥3 outpatient visits	127	92	72.4
Hospitalization only	44	37	84.1

PPV, positive predictive value.

Descriptions of false cases in the case definition algorithms were presented in Table 4. In the algorithms for schizophrenia, mood disorders accounted for 20.5% and 50.0% of false cases in the algorithm based on any records and the hospitalization-only algorithm, respectively. Psychotic

disorders other than schizophrenia (schizophreniform disorder and psychotic disorder NOS) represented a substantial proportion of false cases (any records: 23.1%; hospitalization only: 33.3%). In the algorithms for bipolar disorder, depressive disorders accounted for 34.9% (any records) and 42.9% (hospitalization only) of false cases. Personality disorders accounted for 11.1% (any records) and 42.9% (hospitalization only) of false cases in the bipolar disorder algorithms.

3.1.2. Validation of relapse identification algorithms

3.1.2.1 Validation among patients who were hospitalized

From SCRAP, 960 patients who were hospitalized for schizophrenia (F20, F25) and 870 patients who were hospitalized for bipolar disorder (F30, F31) were identified between November 1, 2005, and December 31, 2023. Among them, 100 patients of the schizophrenia validation set, and 100 patients of the bipolar validation set were randomly sampled (Table 5).

Among 100 patients with schizophrenia and bipolar disorder, 43 and 23 patients experienced a relapse after their admission, respectively. The sensitivity of rehospitalization for relapse identification was 62.8% and 52.2% in the schizophrenia set and the bipolar disorder set, respectively. The PPV of rehospitalization for relapse identification was 84.4% and 70.6% in the schizophrenia set and the bipolar disorder set, respectively (Table 6).

3.1.2.2 Validation among patients who were hospitalized and re-hospitalized

From SCRAP, 213 patients who were hospitalized for schizophrenia (F20, F25) and re-hospitalized for psychotic disorders (F2.x) and 197 patients who were hospitalized for bipolar disorder (F30, F31) and re-hospitalized for mood disorders (F3.x) were identified between November 1, 2005, and December 31, 2023. Among them, 50 patients of the schizophrenia validation set, and 50 patients of the bipolar disorder validation set were randomly sampled (Table 7).

Results for the validation of relapse identification algorithms and descriptions of false cases were shown in Table 8 and Table 9, respectively. The relapse identification algorithm for schizophrenia showed a PPV of 88.0%. Half of the false cases were rehospitalizations for treating physical symptoms. The relapse identification algorithm for bipolar disorder showed a PPV of 72.0%. The false cases in this algorithm were mainly due to wrong diagnosis, with the majority being personality disorders (50.0%).

Table 4. Description of false cases in case definition algorithms

Diagnosis of false cases	N (%)	Proportion among false cases (%)
Schizophrenia		
Any records with main diagnostic codes (N=200)		
True cases	161 (80.5)	-
Schizophreniform disorder	4 (2.0)	10.3
Psychotic disorder NOS	5 (2.5)	12.8
Mood disorders	8 (4.0)	20.5
Organic mental disorders	4 (2.0)	10.3
Psychiatric developmental disorders	3 (1.5)	7.7
Others (alcohol use disorder, delirium)	2 (1.0)	5.1
Unspecified	13 (6.5)	33.3
Hospitalization only with main diagnostic codes (N=39)		
True case	33 (84.6)	-
Schizophreniform disorder	2 (5.1)	33.3
Mood disorders	3 (7.7)	50.0
Unspecified	1 (2.6)	16.7
Bipolar disorder		
Any records with main diagnostic codes (N=200)		
True cases	137 (68.5)	-
Psychotic disorders	6 (3.0)	9.5
Depressive disorders	22 (11.0)	34.9
Anxiety disorders	4 (2.0)	6.3
Obsessive compulsive disorders	3 (1.5)	4.8
Personality disorders	7 (3.5)	11.1
Organic mental disorders	5 (2.5)	7.9
Psychiatric developmental disorders	4 (2.0)	6.3
Others (alcohol use disorder, PTSD)	2 (1.0)	3.2
Unspecified	10 (5.0)	15.9
Hospitalization only with main diagnostic codes (N=44)		
True cases	37 (84.1)	-
Psychotic disorders	1 (2.3)	14.3
Depressive disorders	3 (6.8)	42.9
Personality disorders	3 (6.8)	42.9

NOS, not otherwise specified; PTSD, posttraumatic stress disorder

Table 5. Characteristics of relapse identification validation sets among patients who were hospitalized

Variable	Schizophrenia		Bipolar disorder	
	Entire population (N=960)	Random validation set (N=100)	Entire population (N=870)	Random validation set (N=100)
Women, No. (%)	129 (60.6)	35 (70.0)	562 (64.6)	61 (61.0)
Age at the first hospitalization, Median (IQR)	31 (23–42)	30 (24–43)	30 (22–47)	32 (22–47)
Year at the first hospitalization, No. (%)				
2005–2008	223 (23.0)	17 (17.0)	24 (12.2)	12 (12.0)
2009–2011	99 (10.3)	10 (10.0)	20 (10.2)	10 (10.0)
2012–2014	121 (11.3)	13 (13.0)	28 (14.2)	9 (9.0)
2015–2017	274 (28.5)	32 (32.0)	61 (31.0)	28 (28.0)
2018–2020	139 (14.5)	18 (18.0)	42 (21.3)	27 (27.0)
2021–2023	104 (10.8)	10 (10.0)	22 (11.2)	14 (14.0)

IQR, interquartile range

Table 6. Validation of relapse identification algorithm among patients who were hospitalized

Algorithm	Relapse	Rehospitalization	Relapse among rehospitalization	Sensitivity (%)	PPV (%)
Schizophrenia (N=100)					
Rehospitalization for psychotic disorders	43	32	27	62.8	84.3
Bipolar disorder (N=100)					
Rehospitalization for mood disorders	23	17	12	52.2	70.6

PPV, positive predictive value.

Table 7. Characteristics of relapse identification validation sets among patients who were hospitalized and re-hospitalized

Variable	Schizophrenia		Bipolar disorder	
	Entire population (N=213)	Random validation set (N=50)	Entire population (N=197)	Random validation set (N=50)
Women, No. (%)	129 (60.6)	35 (70.0)	134 (68.0)	35 (70.0)
Age at the first hospitalization, Median (IQR)	34 (24–43)	34 (24–41)	28 (21–43)	31 (21–45)
Year at the first hospitalization, No. (%)				
2005–2008	49 (23.0)	14 (28.0)	24 (12.2)	5 (10.0)
2009–2011	22 (10.3)	3 (6.0)	20 (10.2)	4 (8.0)
2012–2014	24 (11.3)	3 (6.0)	28 (14.2)	8 (16.0)
2015–2017	74 (34.7)	18 (36.0)	61 (31.0)	16 (36.0)
2018–2020	34 (16.0)	10 (20.0)	42 (21.3)	13 (26.0)
2021–2023	10 (4.7)	2 (4.0)	22 (11.2)	4 (8.0)
Time to rehospitalization, year, Median (IQR)	1.5 (0.6–3.0)	0.9 (0.5–3.0)	1.2 (0.4–2.5)	1.7 (0.5–2.9)

IQR, interquartile range

Table 8. Validation of relapse identification algorithms among patients who were hospitalized and re-hospitalized

Algorithm	N	True case	PPV (%)
Schizophrenia			
Rehospitalization for psychotic disorders	50	44	88.0
Bipolar disorder			
Rehospitalization for mood disorders	50	36	72.0

PPV, positive predictive value.

Table 9. Description of false cases in relapse identification algorithms

Diagnosis of false cases	N (%)	Proportion among false cases (%)
Schizophrenia-rehospitalization for psychotic disorders (N=50)		
True cases	44 (88.0)	-
Wrong diagnosis		
Psychotic disorder NOS	1 (2.0)	16.7
Bipolar disorder	1 (2.0)	16.7
Not relapse		
For physical symptoms	3 (6.0)	50.0
For initiation of clozapine	1 (2.0)	16.7
Bipolar disorder-rehospitalization for mood disorders (N=50)		
True case	36 (72.0)	-
Wrong diagnosis		
Anxiety disorders	1 (2.0)	7.1
Personality disorders	7 (14.0)	50.0
Not relapse		
For other psychiatric symptoms	2 (4.0)	14.3
For physical symptoms	2 (4.0)	14.3
For military medical examination	2 (4.0)	14.3

NOS, not otherwise specified

3.2. Maintenance dose and relapse risk in patients with schizophrenia

The schizophrenia-antipsychotic group included 69,525 patients with incident schizophrenia. Among them, 52.0% were women, and the median age was 39 years (IQR: 30–49). The median antipsychotic dose during the index admission was 1.2 DDDs/day (IQR: 0.8–1.8). Baseline characteristics of the schizophrenia-antipsychotic group are shown in Table 10. During the follow-up period (median [IQR]: 2.1 [0.8–5.5] years; range: 0.2–20.0 years), 46.1% (32,052/69,525) of patients experienced a relapse. The crude and relative maintenance dose of antipsychotics remained consistent at approximately 1 DDD/day and 80%, respectively, throughout the follow-up period (Figure 5). The trajectories of antipsychotic doses stratified according to relapse were shown in

Appendix 2. Spaghetti plots of crude and relative antipsychotic dose of 100 randomly sampled patients with schizophrenia were shown in Appendix 3.

Table 10. Characteristics of the schizophrenia group

Variable	Schizophrenia-antipsychotic group (N=69,525)
Women, No. (%)	36,137 (52.0)
Age at the index admission, years, Median [IQR]	39 [30–49]
Household income, No. (%)	
Medical aid	15,459 (22.3)
Q1 (lowest)	14,977 (21.6)
Q2	12,711 (18.3)
Q3	12,605 (18.2)
Q4 (highest)	13,573 (19.6)
Mood disorders, No. (%)	35,522 (51.1)
SUD, No. (%)	5,142 (7.4)
Anxiety disorders, No. (%)	27,634 (39.7)
OCD, No. (%)	2,022 (2.9)
Personality disorders, No. (%)	3,131 (4.5)
Psychiatric developmental disorders, No. (%)	5,478 (7.9)
Duration of schizophrenia, years, No. (%)	
0 (first diagnosis=admission)	35,946 (51.7)
<1	11,079 (15.9)
≥1	22,500 (32.4)
Year of the index admission	
≤2006	15,792 (22.7)
2007–2010	16,621 (23.9)
2011–2015	15,438 (22.2)
≥2016	21,674 (31.2)
Average antipsychotic dose during the index admission, DDDs/day, Median [IQR]	1.2 [0.8–1.8]
Duration of the index admission, days, No. (%)	
<7 days	2,708 (3.9)
7–90 days	43,568 (62.7)
≥90 days	23,249 (33.4)
Relapse, No. (%)	32,052 (46.1)

SUD, substance use disorder; OCD, obsessive-compulsive disorder; DDD, defined daily dose.

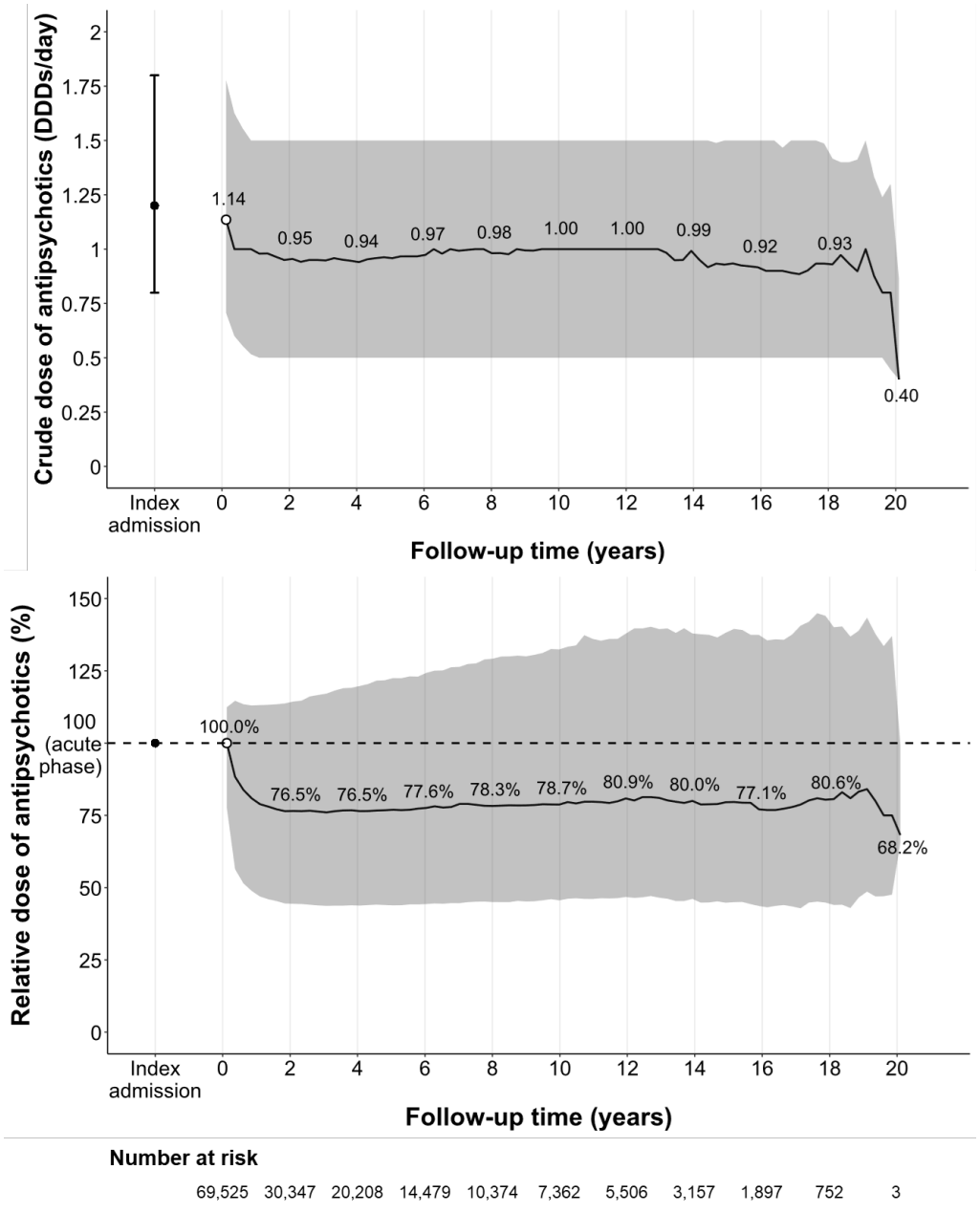

Figure 5. Antipsychotic dose during follow-up in patients with schizophrenia. The median values (represented by solid lines) and the interquartile ranges (indicated by shaded areas) of antipsychotic dose in each 90-day interval were presented.

Figure 6 demonstrated the association between crude maintenance dose of antipsychotics and relapse risk in patients with schizophrenia. Incidence rates of relapse were 271.6, 100.7, 84.1, 82.2, and 103.0 per 1,000 person-years in the crude dose categories of no use, <0.5 DDDs/day, 0.5–0.75 DDDs/day, 0.75–1.25 DDDs/day, and ≥1.25 DDDs/day, respectively. Using the dose episode of 0.75–1.25 DDDs/day as the reference, adjusted HRs were 3.37 (95% CI: 3.24–3.50), 1.31 (1.25–1.37), 1.08 (1.03–1.13), and 1.11 (1.07–1.15) in the dose categories of no use, <0.5 DDDs/day, 0.5–0.75 DDDs/day, and ≥1.25 DDDs/day, respectively. The restricted cubic spline analysis showed J-shaped association with lowest relapse risk at crude dose of 0.75–1 DDDs/day. With crude dose below 0.75 DDDs/day, the relapse risk inversely increased as the dose decreased. In time-lag and sensitivity analyses, the associations were generally similar to those from the primary analysis (Appendix 4).

Figure 7 showed the association between relative maintenance dose of antipsychotics and relapse risk in patients with schizophrenia. Incidence rates of relapse were 271.6, 94.4, 81.8, 96.9, and 111.1 per 1,000 person-years in the relative dose categories of no use, <50%, 50–75%, 75–125%, and ≥125%, respectively. Using the dose episode of 75–125% as the reference, adjusted HRs were 3.51 (95% CI: 3.38–3.64), 1.31 (1.25–1.36), 1.02 (0.97–1.06), and 1.33 (1.28–1.38) in the dose categories of no use, <50%, 50–75%, and ≥125%, respectively. The restricted cubic spline analysis showed U-shaped association with lowest relapse risk at relative dose of 75–100%. When the relative dose was below 75%, the relapse risk rose progressively as the dose declined. In time-lag and sensitivity analyses, the associations were generally similar to those from the primary analysis (Appendix 5).

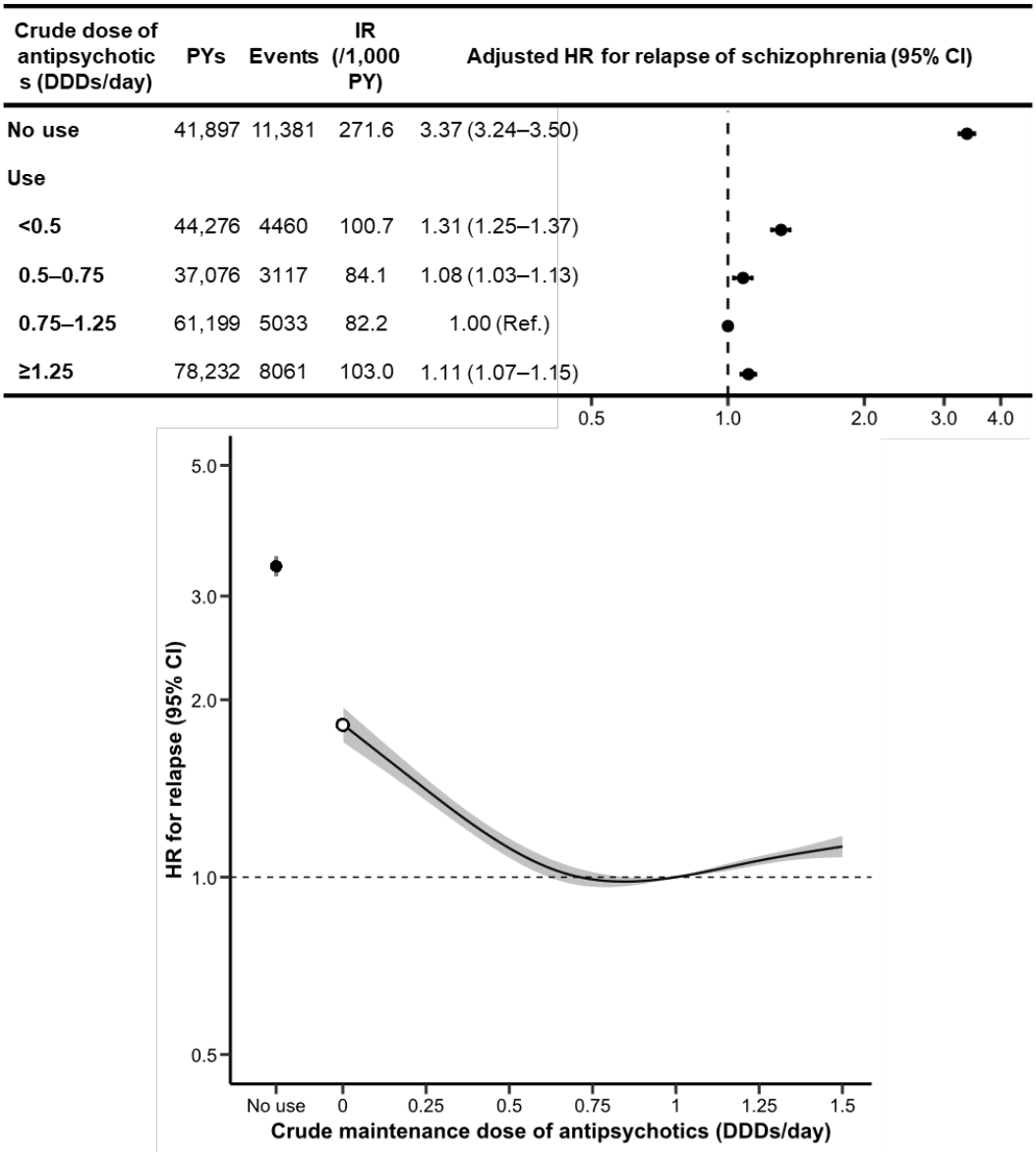

Figure 6. The association between crude maintenance dose of antipsychotics and risk of relapse in patients with schizophrenia. The model was adjusted for sex, age, household income, mood disorders, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission index year, average dose of antipsychotics during the index admission, and polytherapy. DDD, defined daily dose; PY, person-year; IR, incidence rate; HR, hazard ratio.

Relative dose of antipsychotics (%)	PYs	Events	IR (/1,000 PY)	Adjusted HR for relapse of schizophrenia (95% CI)
No use	41,897	11,381	271.6	3.51 (3.38–3.64)
Use				
<50	55,814	5,553	94.4	1.31 (1.25–1.36)
50–75	40,950	3,350	81.8	1.02 (0.97–1.06)
75–125	69,363	6,029	96.9	1.00 (Ref.)
≥125	51,656	5,739	111.1	1.33 (1.28–1.38)

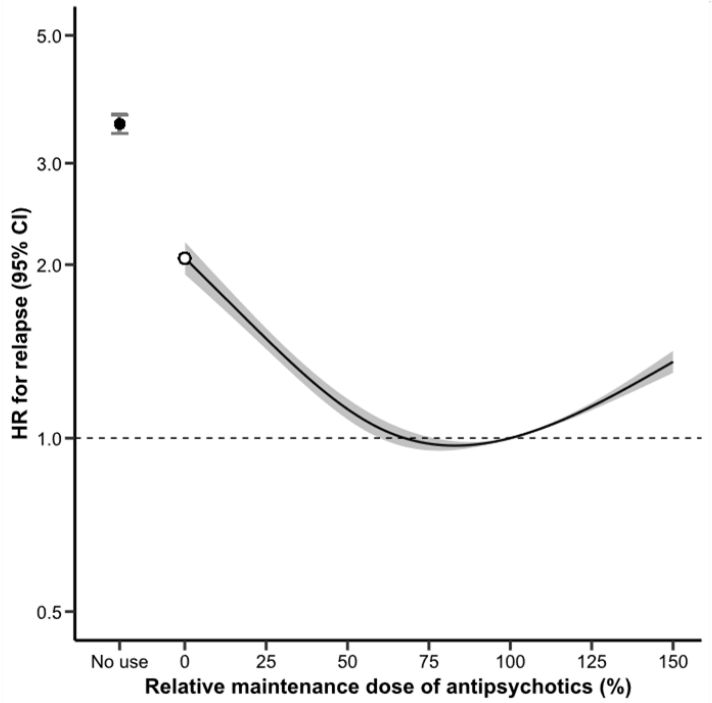

Figure 7. The association between relative maintenance dose of antipsychotics and risk of relapse in patients with schizophrenia. The model was adjusted for sex, age, household income, mood disorders, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission index year, average dose of antipsychotics during the index admission, and polytherapy. DDD, defined daily dose; PY, person-year; IR, incidence rate; HR, hazard ratio.

3.3. Maintenance dose and relapse risk in patients with bipolar disorder

Notably, four groups of patients with incident bipolar disorder were constructed: mood stabilizer group, lithium sub-group, valproate sub-group, and antipsychotic group. Baseline characteristics of these groups are presented in Table 11.

3.3.1. Mood stabilizer group

The bipolar disorder-mood stabilizer group included 18,434 patients with incident bipolar disorder. Among them, 53.6% were women, and the median age was 36 years (IQR: 27–47). The median mood stabilizer dose during the index admission was 0.5 DDDs/day (IQR: 0.4–0.7). During the follow-up period (median [IQR]: 1.8 [0.8–4.5] years; range: 0.2–20.0 years), 34.4% (6,340/18,434) of patients experienced a relapse. The crude and relative maintenance dose of mood stabilizers maintained at 0.5 DDDs/day and 80–90%, respectively, during the follow-up (Figure 8). The trajectories of mood stabilizer doses stratified according to relapse were shown in Appendix 6. Spaghetti plots of crude and relative mood stabilizer dose of 100 randomly sampled patients with bipolar disorder were shown in Appendix 7.

Figure 9 presented the association between crude maintenance dose of mood stabilizers and relapse risk in patients with bipolar disorder. Incidence rates of relapse were 124.3, 98.7, 92.9, 87.6, and 119.6 per 1,000 person-years in the crude dose categories of no use, <0.5 DDDs/day, 0.5–0.75 DDDs/day, 0.75–1.25 DDDs/day, and ≥1.25 DDDs/day, respectively. Using the dose episode of 0.75–1.25 DDDs/day as the reference, adjusted HRs were 2.86 (95% CI: 2.53–3.23), 1.26 (1.12–1.42), 1.12 (1.00–1.25), and 1.26 (1.04–1.54) in the dose categories of no use, <0.5 DDDs/day, 0.5–0.75 DDDs/day, and ≥1.25 DDDs/day, respectively. The restricted cubic spline analysis showed an increasing risk of relapse at crude doses below 0.5 DDDs/day. The risk of relapse did not appear to differ at crude doses of mood stabilizers above 0.5 DDDs/day. The associations in time-lag and sensitivity analyses were generally consistent with the primary analysis (Appendix 8).

Table 11. Characteristics of the bipolar disorder group

Variable	Bipolar disorder group			
	Mood stabilizer group			Antipsychotic group (N=19,276)
	Entire mood stabilizer group (N=18,434)	Subgroup		
		Lithium subgroup (N=8,363)	Valproate subgroup (N=11,765)	
Women, No. (%)	9,886 (53.6)	4,390 (52.5)	6,134 (52.1)	10,619 (55.1)
Age, years, Median [IQR]	36 [27–47]	36 [27–46]	36 [27–47]	36 [27–47]
Household income, No. (%)				
Medical aid	1,265 (6.9)	552 (6.6)	819 (7.0)	1,308 (6.8)
Q1 (lowest)	3,794 (20.7)	1,771 (21.3)	2,414 (20.6)	4,056 (21.1)
Q2	3,919 (21.4)	1,802 (21.7)	2,503 (21.4)	4,122 (21.5)
Q3	4,113 (22.4)	1,892 (22.8)	2,624 (22.4)	4,336 (22.6)
Q4 (highest)	5,261 (28.7)	2,299 (27.6)	3,360 (28.7)	5,373 (28.0)
SUD, No. (%)	2,163 (11.7)	870 (10.4)	1,490 (12.7)	2,265 (11.8)
Anxiety disorders, No. (%)	8,753 (47.5)	3,478 (41.6)	6,015 (51.1)	9,257 (48.0)
OCD, No. (%)	444 (2.4)	170 (2.0)	301 (2.6)	475 (2.5)
Personality disorders, No. (%)	1,145 (6.2)	386 (4.6)	828 (7.0)	1,198 (6.2)
Developmental disorders, No. (%)	1,098 (6.0)	400 (4.8)	806 (6.9)	1,168 (6.1)
Disease duration, years, No. (%)				
0 (first diagnosis=admission)	10,244 (55.6)	4,470 (53.4)	6,690 (56.9)	11,016 (57.1)
<1	3,763 (20.4)	1,765 (21.1)	2,334 (19.8)	3,787 (19.6)
≥1	4,427 (24.0)	2,128 (25.4)	2,741 (23.3)	4,473 (23.2)
Year of the index admission				
≤2006	3,768 (20.4)	2,391 (28.6)	1,765 (15.0)	3,638 (18.9)
2007–2010	4,118 (22.3)	2,041 (24.4)	2,488 (21.1)	4,320 (22.4)
2011–2015	4,073 (22.1)	1,658 (19.8)	2,784 (23.7)	4,358 (22.6)
≥2016	6,475 (35.1)	2,273 (27.2)	4,728 (40.2)	6,960 (36.1)
Index dose of mood stabilizers, DDDs/day, Median [IQR]	0.5 [0.4–0.7]	0.4 [0.3–0.5] (lithium)	0.5 [0.3–0.6] (valproate)	0.5 [0.3–0.7]
Index dose of antipsychotics, DDDs/day, Median [IQR]	0.9 [0.5–1.5]	0.9 [0.5–1.5]	1.0 [0.5–1.6]	1.0 [0.5–1.6]
Duration of the index admission, days, No. (%)				
<7 days	1,068 (5.8)	383 (4.6)	704 (6.0)	1,222 (6.3)
7–90 days	15,055 (81.7)	6,891 (82.4)	9,435 (80.2)	15,601 (80.9)
≥90 days	2,311 (12.5)	1,089 (13.0)	1,626 (13.8)	2,453 (12.7)
Relapse, No. (%)	6,340 (34.4)	3,323 (39.7)	3,636 (30.9)	6,268 (32.5)

SUD, substance use disorder; OCD, obsessive-compulsive disorder; DDD, defined daily dose.

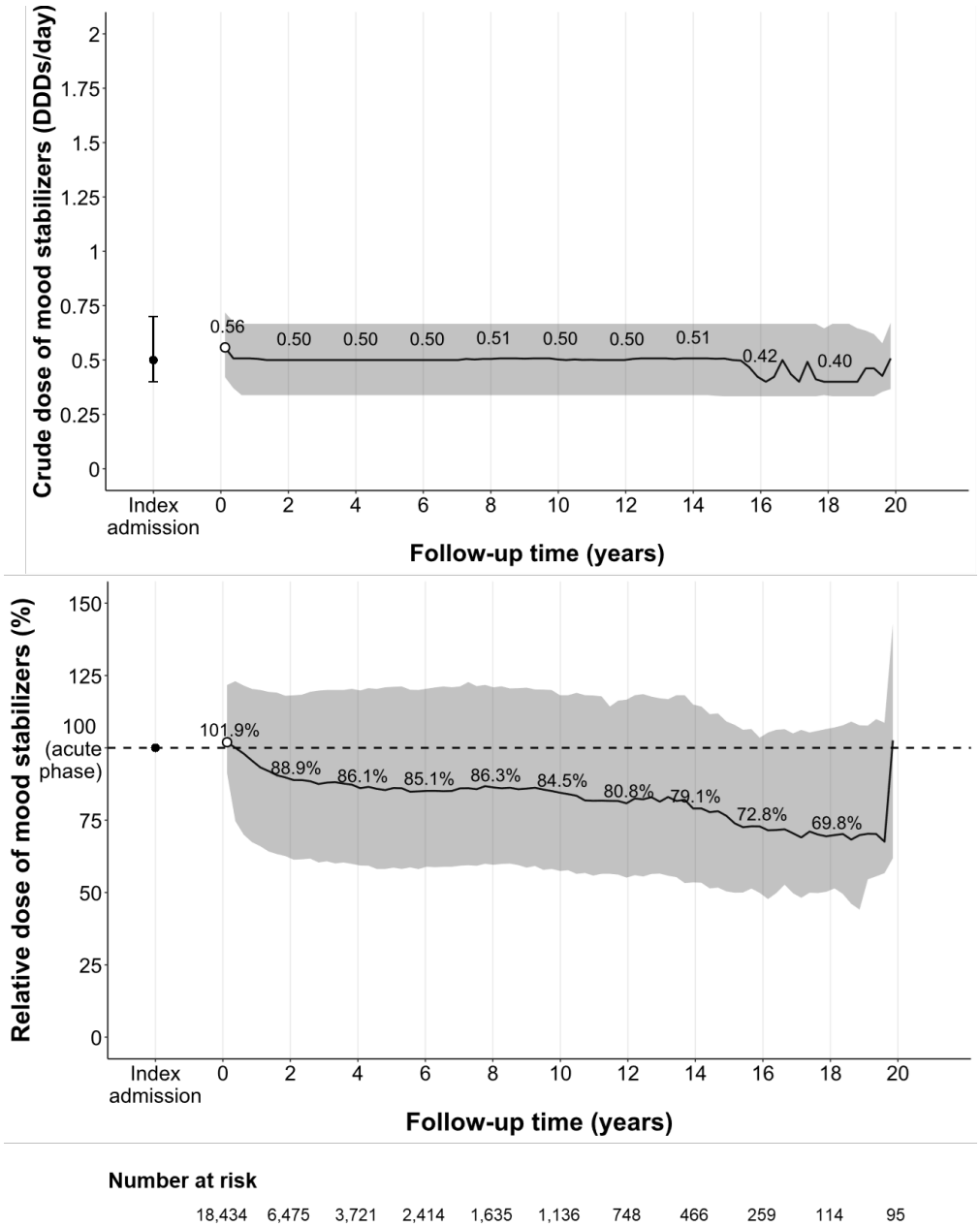

Figure 8. Dose of mood stabilizer during follow-up in the bipolar disorder-mood stabilizer group. The median values (represented by solid lines) and the interquartile ranges (indicated by shaded areas) of relative mood stabilizer dose in each 90-day interval were presented.

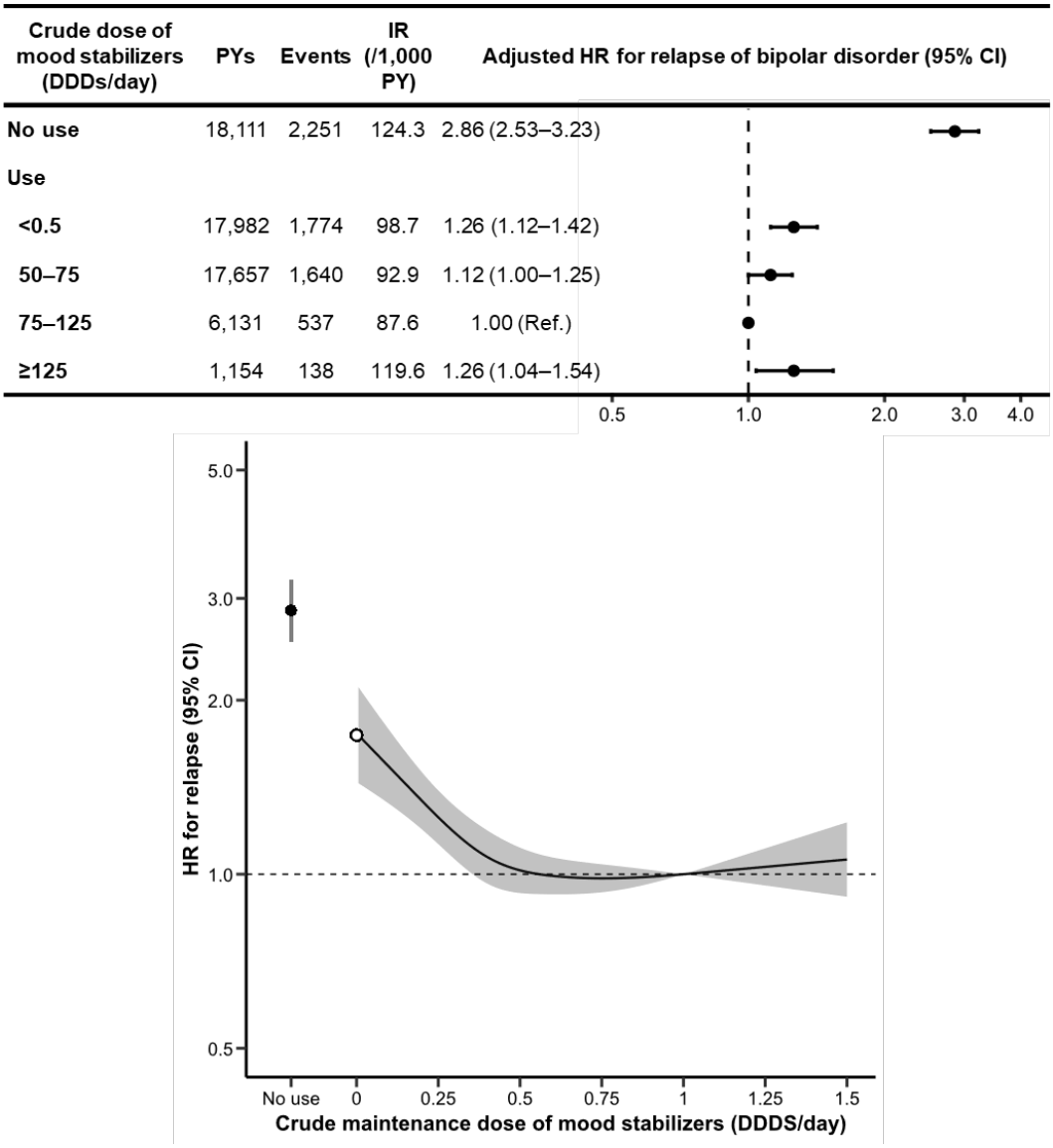

Figure 9. The association between crude maintenance dose of mood stabilizers and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission, index year, average dose of mood stabilizers during the index admission, polytherapy, and crude maintenance dose of antipsychotics. PY, person-year; IR, incidence rate; HR, hazard ratio.

Figure 10 demonstrated the association between relative maintenance dose of mood stabilizers and relapse risk in patients with bipolar disorder. Incidence rates of relapse were 124.3, 113.0, 100.9, 88.0, and 92.7 per 1,000 person-years in the relative dose categories of no use, <50%, 50–75%, 75–125%, and ≥125%, respectively. Using the dose episode of 75–125% as the reference, adjusted HRs were 2.69 (95% CI: 2.49–2.90), 1.38 (1.25–1.52), 1.16 (1.07–1.27), and 1.05 (0.96–1.15) in the dose categories of no use, <50%, 50–75%, and ≥125%, respectively. The restricted cubic spline analysis showed an inversely increasing risk of relapse at lower relative dose below 100%. The association in the primary analysis was generally replicated in time-lag and sensitivity analyses (Appendix 9). Notably, the subgroup analysis stratified mood stabilizer dose during the index admission showed the similar HRs at low relative maintenance dose ((<50% v. 75–125%; index mood stabilizer dose <0.5 DDDs/day, HR=1.41 [95% CI: 1.17–1.71]; index mood stabilizer dose ≥0.5 DDDs/day, 1.36 [1.21–1.53]).

3.3.1.1. Lithium sub-group

The bipolar disorder-lithium sub-group included 8,363 patients with incident bipolar disorder. During the follow-up period (median [IQR]: 1.7 [0.8–4.3] years; range: 0.2–20.0 years), 39.7% (3,323/8,363) of patients experienced a relapse. Incidence rates of relapse were 125.4, 111.9, 119.8, 108.5, and 111.3 per 1,000 person-years in the relative dose categories of no use, <50%, 50–75%, 75–125%, and ≥125%, respectively. Using the dose episode of 75–125% as the reference, adjusted HRs were 2.84 (95% CI: 2.56–3.16), 1.12 (0.94–1.33), 1.12 (0.99–1.28), and 1.02 (0.89–1.16) in the dose categories of no use, <50%, 50–75%, and ≥125%, respectively. In restricted cubic spline analyses for both crude and relative dose, relapse risk did not change remarkably depending on the maintenance dose of lithium (Figure 11 and Figure 12).

Relative dose of mood stabilizers (%)	PYs	Events	IR (/1,000 PY)	Adjusted HR for relapse of bipolar disorder (95% CI)
No use	18111	2251	124.3	2.69 (2.49–2.90)
Use				
<50	6116	691	113.0	1.38 (1.25–1.52)
50–75	8790	887	100.9	1.16 (1.07–1.27)
75–125	18241	1605	88.0	1.00 (Ref.)
≥125	9776	906	92.7	1.05 (0.96–1.15)

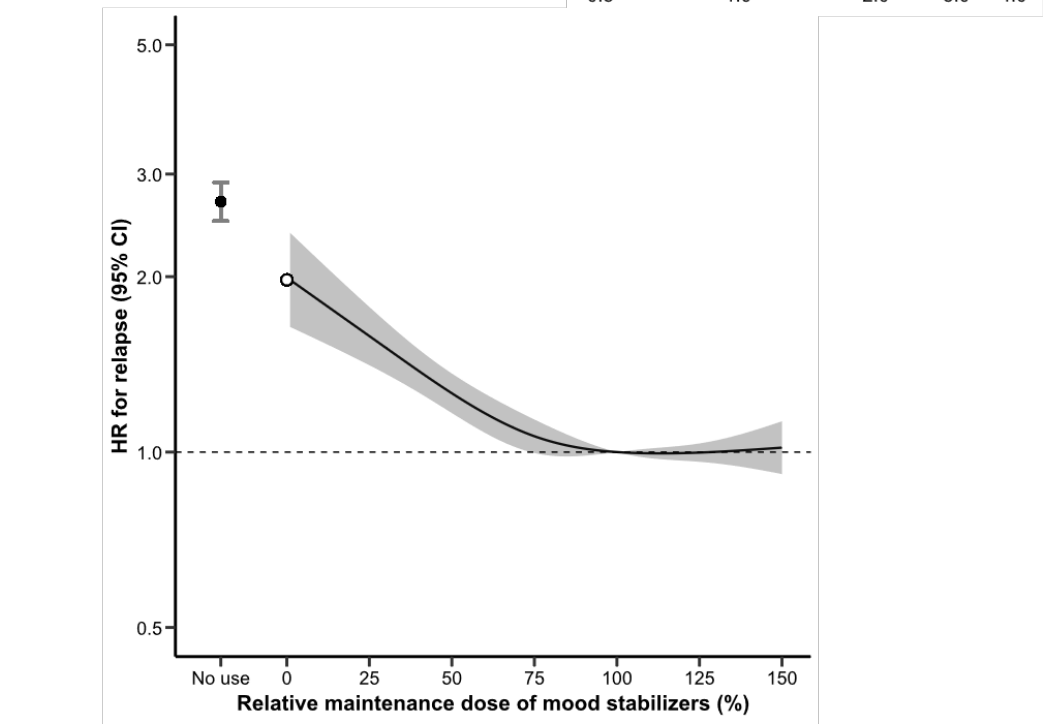

Figure 10. The association between relative maintenance dose of mood stabilizers and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission, index year, average dose of mood stabilizers during the index admission, polytherapy, and crude maintenance dose of antipsychotics. PY, person-year; IR, incidence rate; HR, hazard ratio.

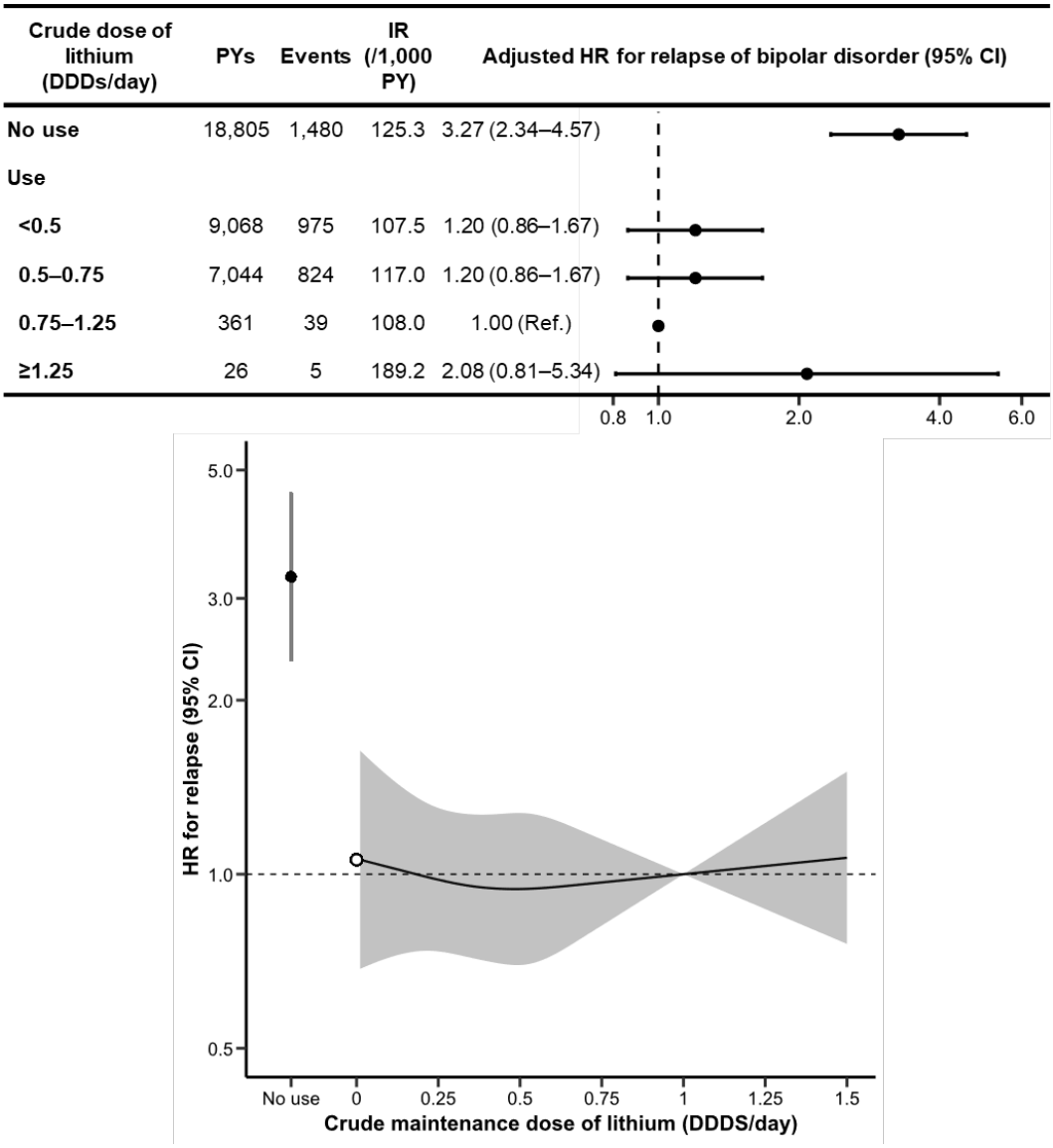

Figure 11. The association between crude maintenance dose of lithium and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, index year, average dose of lithium during the index admission, crude maintenance dose of antipsychotics, crude maintenance dose of mood stabilizers except lithium. PY, person-year; IR, incidence rate.

Relative dose of lithium (%)	PYs	Events	IR (/1,000 PY)	Adjusted HR for relapse of bipolar disorder (95% CI)
No use	11805	1480	125.4	2.84 (2.56–3.16)
Use				
<50	1590	178	111.9	1.12 (0.94–1.33)
50–75	3348	401	119.8	1.12 (0.99–1.28)
75–125	7993	867	108.5	1.00 (Ref.)
≥125	3568	397	111.3	1.02 (0.89–1.16)

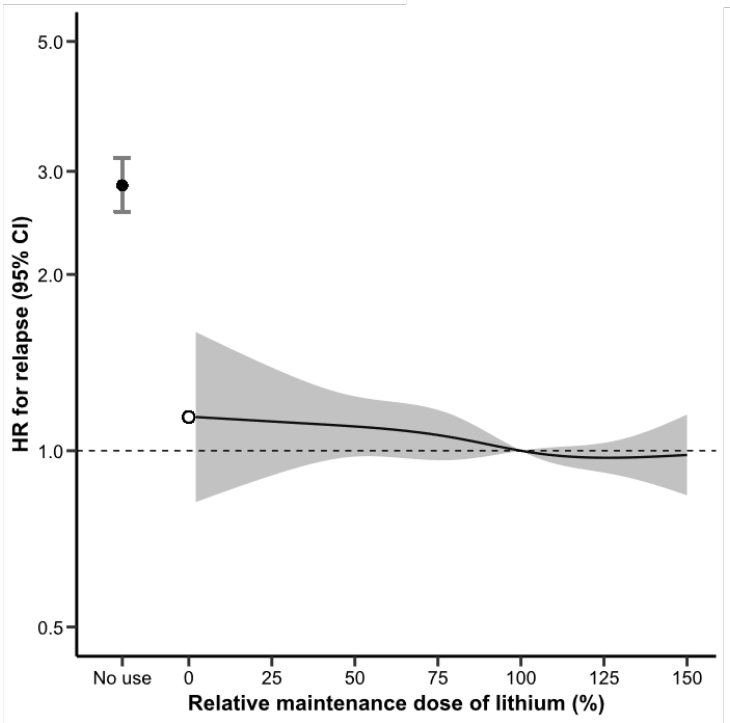

Figure 12. The association between relative maintenance dose of lithium and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, index year, average dose of lithium during the index admission, crude maintenance dose of antipsychotics, crude maintenance dose of mood stabilizers except lithium. PY, person-year; IR, incidence rate.

3.3.1.2. Valproate sub-group

The bipolar disorder-valproate sub-group included 11,765 patients with incident bipolar disorder. During the follow-up period (median [IQR]: 1.7 [0.7–4.2] years; range: 0.2–20.0 years), 30.9% (3,636/11,765) of patients experienced a relapse. Incidence rates of relapse were 117.7, 99.0, 90.6, 80.3, and 91.6 per 1,000 person-years in the relative dose categories of no use, <50%, 50–75%, 75–125%, and ≥125%, respectively. Using the dose episode of 75–125% as the reference, adjusted HRs were 3.72 (95% CI: 3.36–4.12), 1.36 (1.17–1.59), 1.18 (1.04–1.35), and 1.18 (1.04–1.33) in the dose categories of no use, <50%, 50–75%, and ≥125%, respectively. The restricted cubic spline analysis for crude dose showed that inversely increasing pattern of relapse risk at crude dose below 0.5 DDDs/day (Figure 13). Relative dose of valproate showed a J-shape association with relapse risk, with the lowest risk at a relative dose of 100–125% (Figure 14).

3.3.2. Antipsychotic group

The bipolar disorder-antipsychotic group included 19,276 patients with incident bipolar disorder. Among them, 55.1% were women, and the median age was 36 years (IQR: 27–47). The median antipsychotic dose during the index admission was 1.0 DDDs/day (IQR: 0.5–1.6). During the follow-up period (median [IQR]: 1.7 [0.8–4.2] years; range: 0.2–20.0 years), 32.5% (6,268/19,276) of patients experienced a relapse. During the first year of follow-up, antipsychotic doses decreased abruptly and were maintained at approximately 50–75% throughout the remainder of the follow-up period (Figure 15). The trajectories of antipsychotic doses stratified according to relapse were shown in Appendix 10. Spaghetti plots of crude and relative antipsychotic dose of 100 randomly sampled patients with bipolar disorder were shown in Appendix 11.

Crude dose of valproate (DDDs/day)	PYs	Events	IR (/1,000 PY)	Adjusted HR for relapse of bipolar disorder (95% CI)
No use	15,494	1,824	117.7	3.80 (3.22–4.49)
Use				
<0.5	9,249	841	90.9	1.23 (1.04–1.46)
0.5–0.75	9,033	767	84.9	1.08 (0.91–1.28)
0.75–1.25	2,342	191	81.6	1.00 (Ref.)
≥1.25	164	13	79.4	0.93 (0.52–1.67)

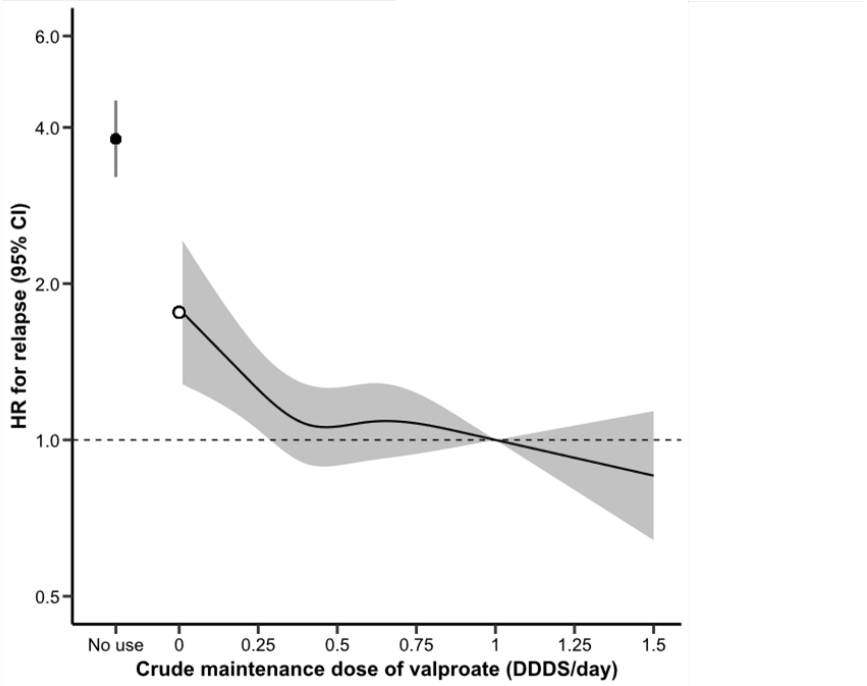

Figure 13. The association between crude maintenance dose of valproate and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, index year, average dose of valproate during the index admission, crude maintenance dose of antipsychotics, crude maintenance dose of mood stabilizers except valproate. PY, person-year; IR, incidence rate.

Relative dose of valproate (%)	PYs	Events	IR (/1,000 PY)	Adjusted HR for relapse of bipolar disorder (95% CI)
No use	15494	1824	117.7	3.72 (3.36–4.12)
Use				
<50	2464	244	99.0	1.36 (1.17–1.59)
50–75	4192	380	90.6	1.18 (1.04–1.35)
75–125	9406	755	80.3	1.00 (Ref.)
≥125	4724	433	91.6	1.18 (1.04–1.33)

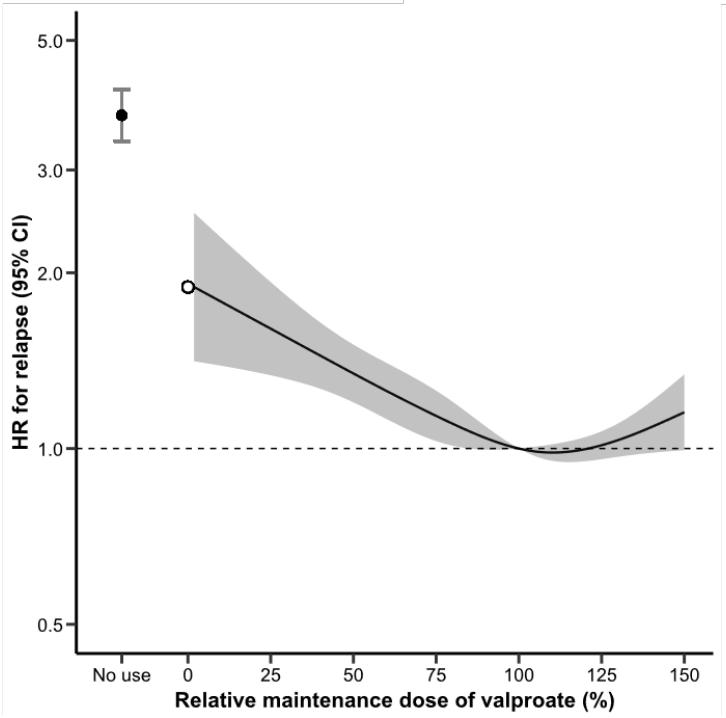

Figure 14. The association between relative maintenance dose of valproate and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, index year, average dose of valproate during the index admission, crude maintenance dose of antipsychotics, crude maintenance dose of mood stabilizers except valproate. PY, person-year; IR, incidence rate.

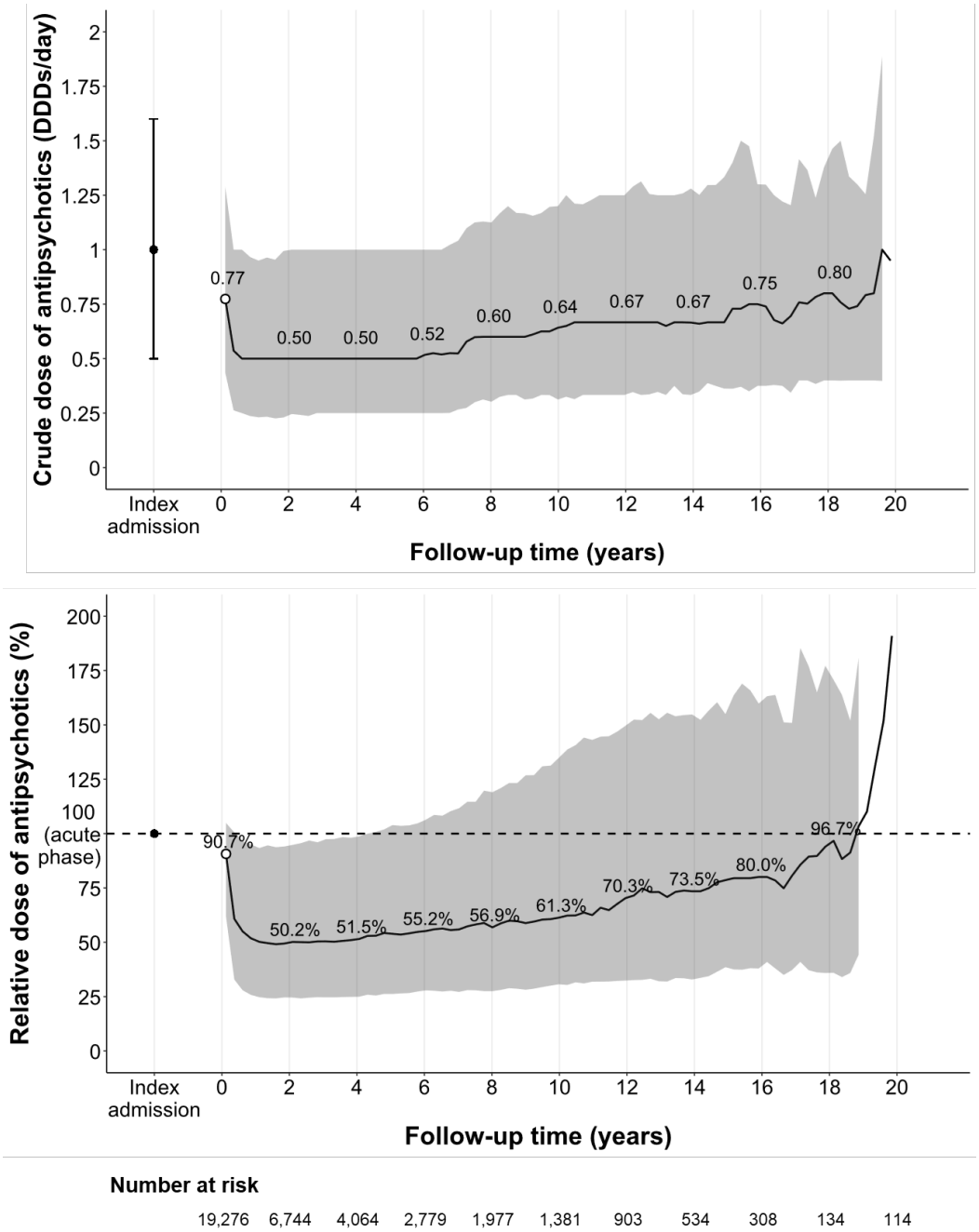

Figure 15. Antipsychotic dose during follow-up in the bipolar disorder-antipsychotic group. The median values (represented by solid lines) and the interquartile ranges (indicated by shaded areas) of maintenance dose of antipsychotics in each 90-day interval were presented.

Incidence rates of relapse were 171.6, 98.2, 84.7, 80.5, and 65.9 per 1,000 person-years in the crude dose categories of no use, <0.5 DDDs/day, 0.5–0.75 DDDs/day, 0.75–1.25 DDDs/day, and ≥1.25 DDDs/day, respectively. Using the dose episode of 0.75–1.25 DDDs/day as the reference, adjusted HRs were 2.43 (95% CI: 2.21–2.67), 1.23 (1.12–1.35), 1.06 (0.95–1.19), and 0.84 (0.74–0.94) in the dose categories of no use, <0.5 DDDs/day, 0.5–0.75 DDDs/day, and ≥1.25 DDDs/day, respectively (Figure 16). In the restricted cubic spline analysis, the relapse risk plateaued in the range of 0.5–1.0 DDDs/day, but below 0.5 DDDs/day, it increased gradually as the crude dose of antipsychotics decreased. In the time-lag analyses, the associations between low maintenance dose and relapse risk grew stronger with longer lag times (<0.5 DDDs/day v. 0.75–1.25 DDDs/day; 14 days, HR=1.40 [95% CI: 1.27–1.54]; 30 days, 1.41 [1.27–1.55]; 60 days, 1.53 [1.38–1.69]; 90 days, 1.52 [1.38–1.67]) (Appendix 12). Sensitivity analyses showed results similar to the primary analysis (Appendix 12).

Figure 17 demonstrated the association between relative maintenance dose of antipsychotics and relapse risk in patients with bipolar disorder. Incidence rates of relapse were 171.6, 95.3, 79.3, 78.2, and 77.7 per 1,000 person-years in the relative dose categories of no use, <50%, 50–75%, 75–125%, and ≥125%, respectively. Using the dose episode of 75–125% as the reference, adjusted HRs were 2.35 (95% CI: 2.13–2.58), 1.16 (1.06–1.27), 0.94 (0.84–1.05), and 1.01 (0.90–1.13) in the dose categories of no use, <50%, 50–75%, and ≥125%, respectively. The restricted cubic spline analysis revealed that the risk of relapse increased as the relative dose decreased below 50%. Similarly with crude dose, the associations between low relative dose and relapse risk increased with long lag times (<50% v. 75–125%; 14 days, HR=1.15 [95% CI: 1.04–1.26]; 30 days, 1.18 [1.07–1.30]; 60 days, 1.21 [1.10–1.33]; 90 days, 1.34 [1.21–1.47]) (Appendix 13).

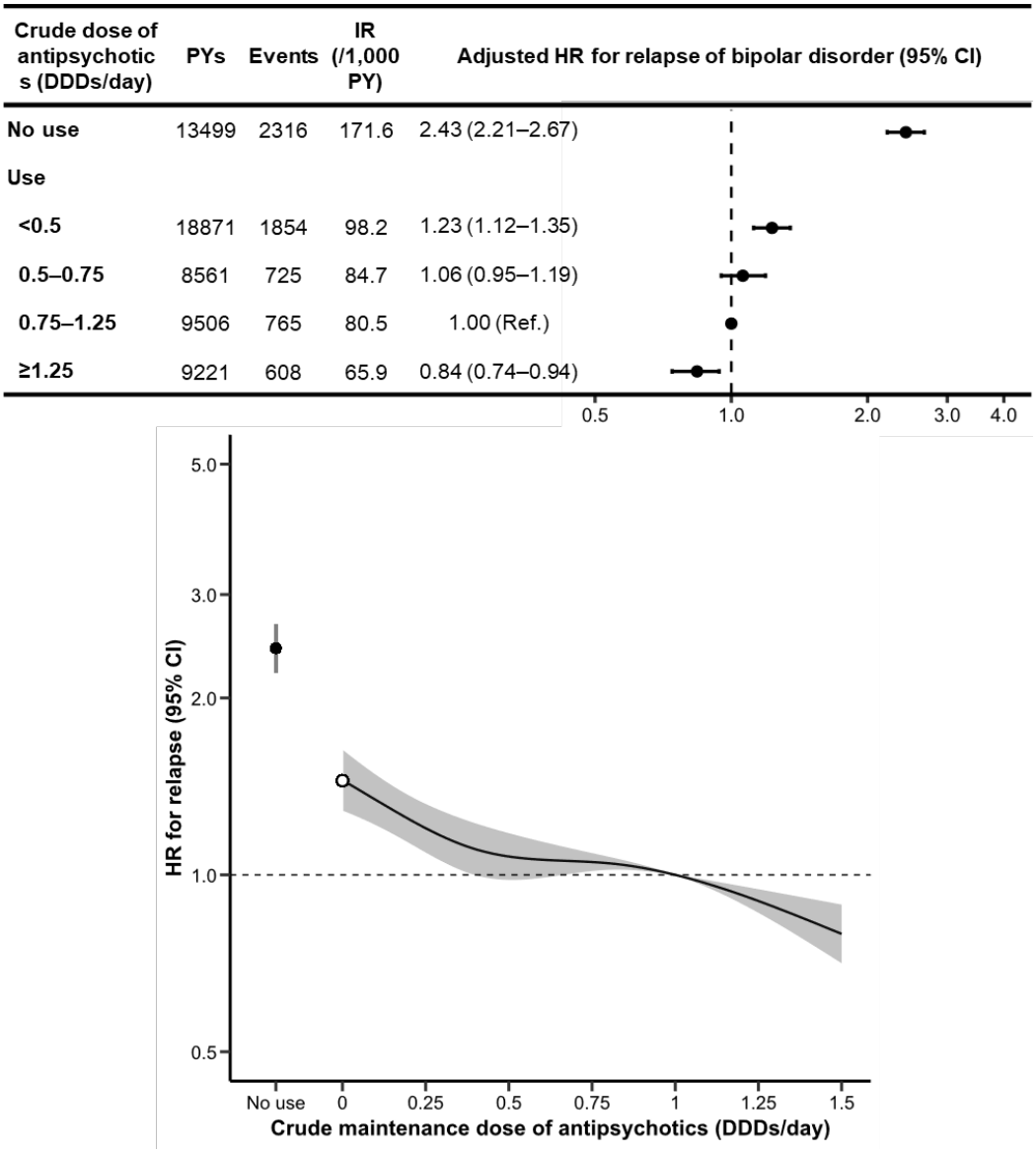

Figure 16. The association between crude maintenance dose of antipsychotics and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission, index year, average dose of antipsychotics during the index admission, polytherapy, and crude maintenance dose of mood stabilizers. PY, person-year; IR, incidence rate; HR, hazard ratio

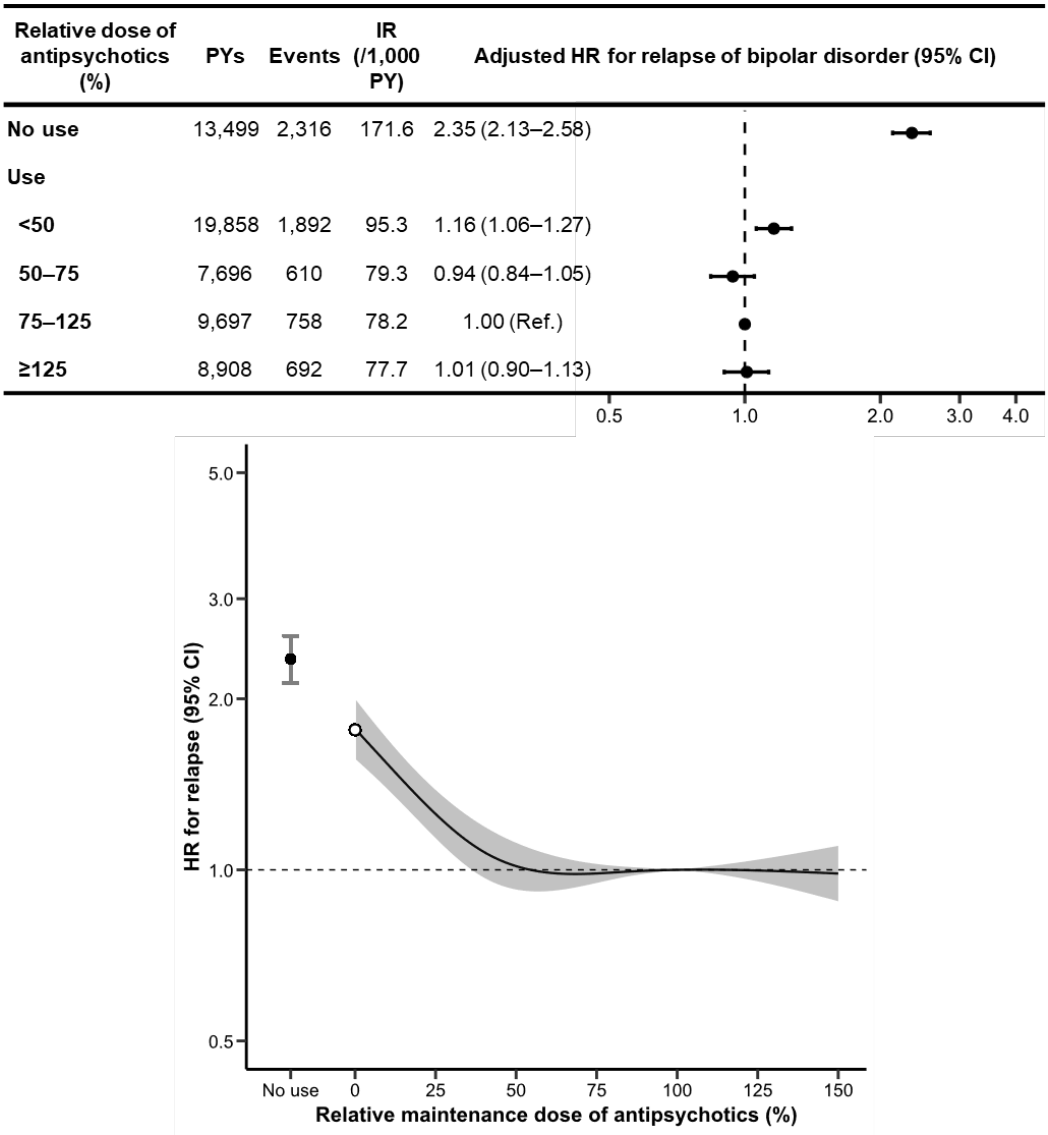

Figure 17. The association between relative maintenance dose of antipsychotics and risk of relapse in patients with bipolar disorder. The model was adjusted for sex, age, household income, substance use disorders, anxiety disorders, obsessive-compulsive disorders, personality disorders, psychiatric developmental disorders, disease duration, duration of the index admission, index year, average dose of antipsychotics during the index admission, polytherapy, and crude maintenance dose of mood stabilizers. PY, person-year; IR, incidence rate; HR, hazard ratio

3.3.3. Interaction between mood stabilizer and antipsychotic dose

In patients with bipolar disorder, the association between the maintenance dose of mood stabilizers and relapse risk was stratified based on a median relative maintenance dose of antipsychotics at 75%, and vice versa. The subgroup of relative maintenance dose of antipsychotics <75% showed a stronger association of low dose of mood stabilizers with relapse risk compared to the subgroup of relative maintenance dose of antipsychotics ≥75% (Table 12 and Figure 18). Similarly, The subgroup of relative maintenance dose of mood stabilizers <75% showed a stronger association of low dose of antipsychotics with relapse risk compared to the subgroup of relative maintenance dose of mood stabilizers ≥75% (Table 12 and Figure 19).

Table 12. Associations of mood stabilizer dose and antipsychotic dose with relapse risk stratified based on maintenance dose of the other medication

Subgroup	Maintenance dose categories, HR (95% CI) with 0.75–1.25 DDDs/day (crude dose) or 75–125% (relative dose) as the reference			
	No use	<0.5 DDDs/day or 50%	0.5–0.75 DDDs/day or 50–75%	≥1.25 DDDs/day or ≥125%
Crude dose of mood stabilizers and relapse risk				
Relative maintenance dose of antipsychotics <75% (N=15,572)	3.01 (2.63-3.45)	1.28 (1.12-1.46)	1.14 (1.00-1.29)	1.27 (1.00-1.60)
Relative maintenance dose of antipsychotics ≥75% (N=2,862)	1.86 (1.34-2.58)	1.11 (0.85-1.44)	0.99 (0.77-1.26)	1.28 (0.86-1.89)
Relative dose of mood stabilizers and relapse risk				
Relative maintenance dose of antipsychotics <75% (N=15,572)	2.82 (2.60-3.07)	1.40 (1.26-1.56)	1.19 (1.08-1.31)	1.07 (0.96-1.18)
Relative maintenance dose of antipsychotics ≥75% (N=2,862)	1.87 (1.44-2.43)	1.20 (0.90-1.61)	1.03 (0.81-1.30)	1.12 (0.92-1.36)
Crude dose of antipsychotics and relapse risk				
Relative maintenance dose of mood stabilizers <75% (N=13,324)	2.69 (2.39-3.03)	1.36 (1.21-1.54)	1.13 (0.98-1.30)	0.76 (0.65-0.89)
Relative maintenance dose of mood stabilizers ≥75% (N=5,952)	2.06 (1.73-2.45)	1.08 (0.93-1.25)	0.99 (0.83-1.17)	0.96 (0.80-1.16)
Relative dose of antipsychotics and relapse risk				
Relative maintenance dose of mood stabilizers <75% (N=13,324)	2.40 (2.13-2.70)	1.18 (1.05-1.33)	0.89 (0.76-1.03)	0.89 (0.77-1.04)
Relative maintenance dose of mood stabilizers ≥75% (N=5,952)	2.16 (1.82-2.57)	1.13 (0.98-1.31)	1.01 (0.85-1.20)	1.17 (0.99-1.39)

DDD, defined daily dose

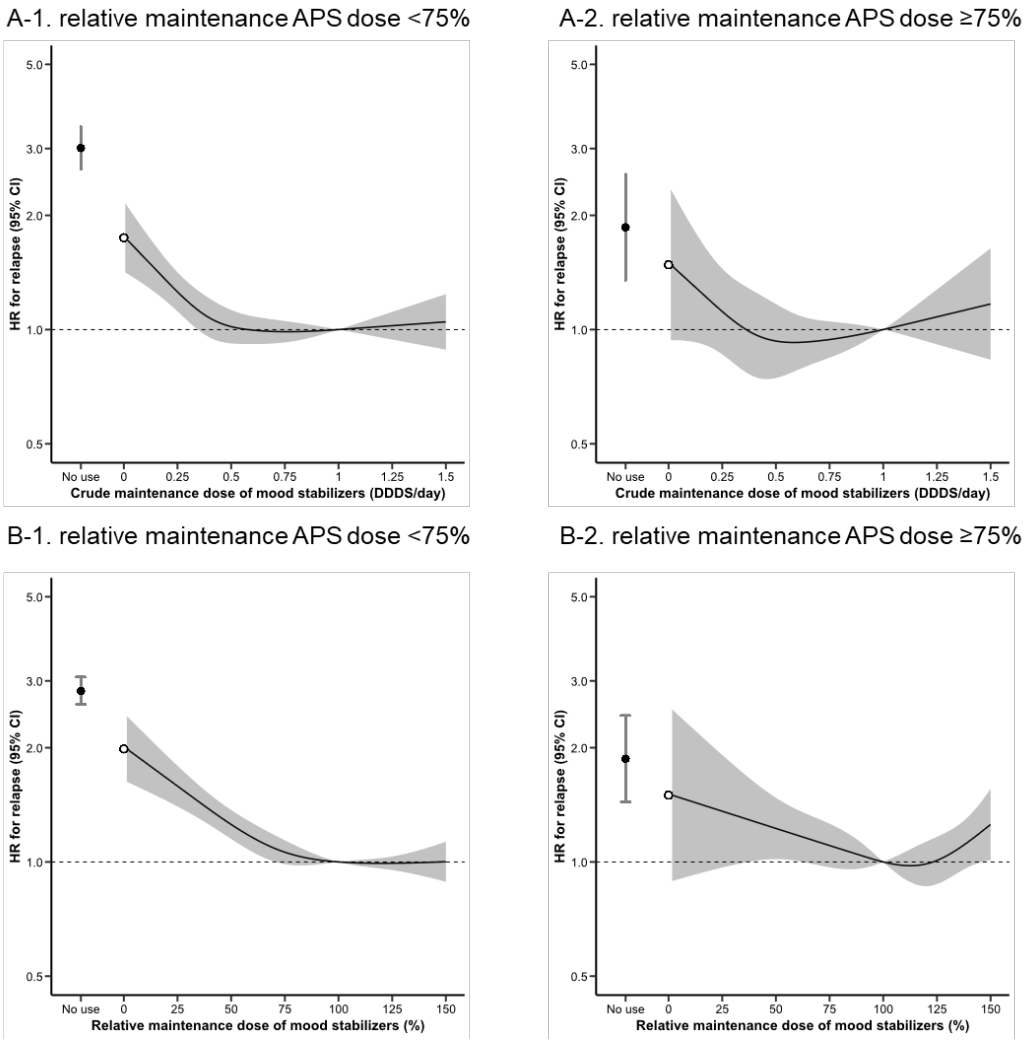

Figure 18. Association between maintenance dose of mood stabilizers and relapse risk in patients with bipolar disorder stratified based on maintenance dose of antipsychotics. A-1, median relative maintenance dose of antipsychotics <75% (crude dose). A-2, median relative maintenance dose of antipsychotics ≥75% (crude dose). B-1, median relative maintenance dose of antipsychotics <75%. (relative dose) B-2, median relative maintenance dose of antipsychotics ≥75% (relative dose). APS, antipsychotics

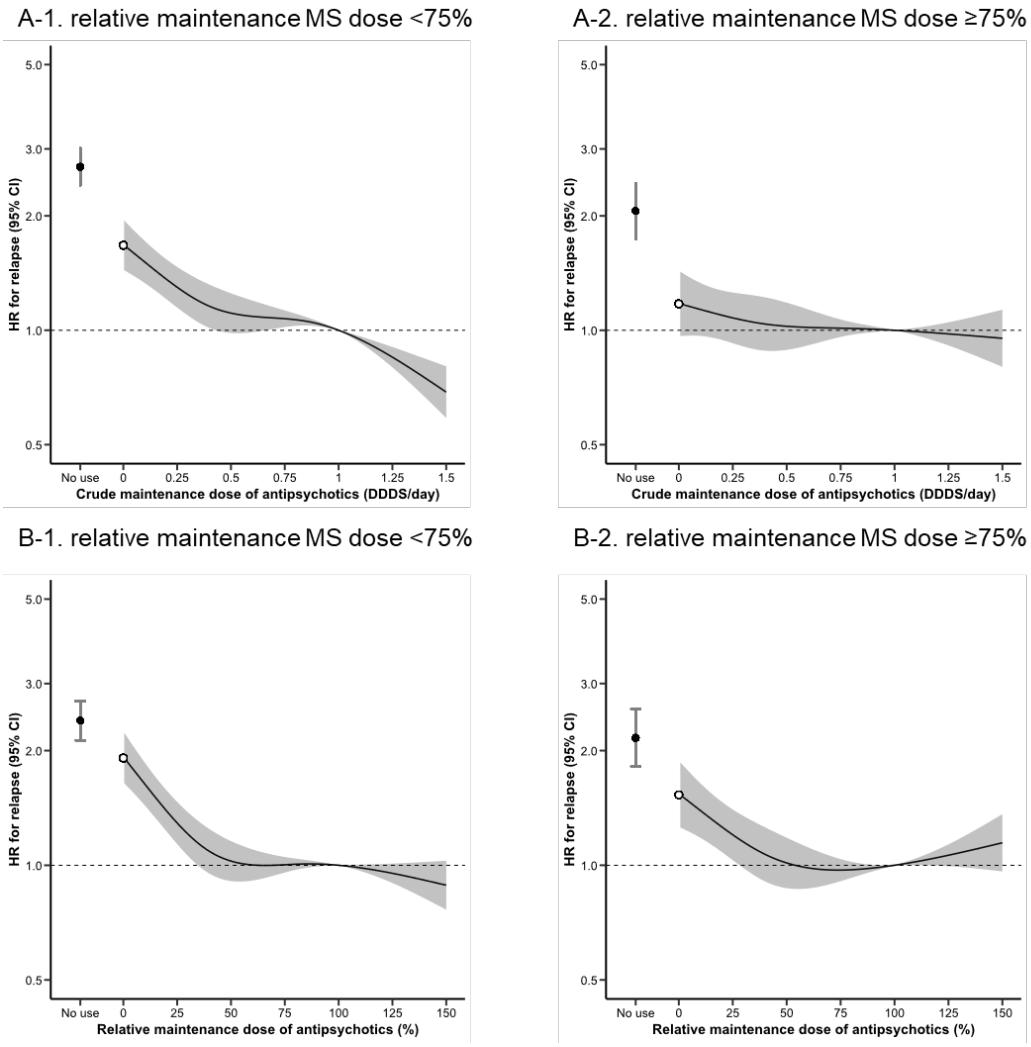

Figure 19. Association between maintenance dose of antipsychotics and relapse risk in patients with bipolar disorder stratified based on maintenance dose of mood stabilizers. A-1, median relative maintenance dose of mood stabilizers <75% (crude dose). A-2, median relative maintenance dose of mood stabilizers ≥75% (crude dose). B-1, median relative maintenance dose of mood stabilizers <75% (relative dose). B-2, median relative maintenance dose of mood stabilizers ≥75% (relative dose). MS, mood stabilizers

4. DISCUSSION

4.1. Validation of case definition and relapse identification

Using SCRAP, case definition algorithms based on claims records for schizophrenia and bipolar disorder were validated. The algorithms for schizophrenia demonstrated considerable validity, with PPVs ranging from 80.5% to 86.5%. For bipolar disorder, the algorithm based on any records, regardless of admission or outpatient care, showed a PPV of 68.5%, while the algorithm based solely on hospitalization records showed a PPV of 84.1%. In a validation study from Canada, case definition algorithms for detecting psychotic disorders had PPVs ranging from 38.4% to 80.8%.[22] The authors of that study concluded that using only hospitalization data was helpful in increasing the PPV of the algorithms. However, since identifying as many cases as possible is necessary to increase the power of analysis, defining schizophrenia using primary diagnostic codes regardless of admission or outpatient care is recommended. Additionally, given that one-third of false cases in the algorithm based on any records were unspecified due to a lack of detailed records, the actual PPV could potentially be higher. For bipolar disorder, as there is a significant difference in PPV depending on whether outpatient records are included, it is recommended to use only hospitalization records if possible. A substantial proportion of false cases in the algorithm based on any records for bipolar disorder were due to misclassifications as depressive disorders and personality disorders, likely contributing to the lower PPV for bipolar disorder.

Relapse identification algorithms based on rehospitalizations for schizophrenia and bipolar disorder showed PPVs of 88.0% and 72.0%, respectively, in validation studies among patients who were hospitalized and re-hospitalized. Given that the PPV for relapse identification inherently includes false cases from the case definition algorithms, the validity for schizophrenia relapse appears to be quite strong. Although the algorithm for bipolar disorder relapse showed reasonably good validity, false cases related to personality disorders may have contributed to the relatively lower PPV. The sensitivity of relapse identification algorithms was 62.8% and 52.2% in the schizophrenia set and bipolar disorder set, respectively. These results imply that approximately half of all relapses can be identified using the algorithm based on rehospitalization. Milder relapse which

can be treated in outpatient care setting might lower the sensitivity of these algorithms.

4.2. Association between maintenance dose and relapse risk

4.2.1. Summary of main findings

In this nationwide, register-based study of patients with schizophrenia or bipolar disorder, the associations between the maintenance dose of primary therapeutic medications and relapse risk were investigated. In patients with schizophrenia, a maintenance dose of antipsychotics below 0.75 DDDs/day was inversely associated with relapse risk, demonstrating a dose-response relationship. In patients with bipolar disorder, an increased relapse risk was linked to a low maintenance dose of mood stabilizers below 0.5 DDDs/day. However, in the subgroup analyses, this association was prominent in the valproate subgroup but not in the lithium subgroup. The maintenance dose of antipsychotics in bipolar disorder showed a significant association with relapse risk at very low doses (Crude dose, <0.5 DDDs/day; relative dose, <50%). Patients with substantial use of both mood stabilizers and antipsychotics showed a weaker association between low doses of either medication and relapse risk.

4.2.2. Clinical relevance of the findings

4.2.2.1. Schizophrenia

In patients with incident schizophrenia who were hospitalized for the first time, the risk of relapse significantly varied depending on the maintenance dose of antipsychotics. An antipsychotic dose around 1 DDD/day was associated with the lowest risk of relapse, and the risk increased as the dose decreased. These results are highly consistent with previous studies. A meta-analysis study of randomized controlled studies, low dose and very low dose of antipsychotics showed increased risks of relapse (low dose: RR=1.44 [95% CI: 1.10–1.87]; very low dose: 1.72 [1.29–2.29]).[29] In a claim data-based study of patients with schizophrenia from Finland, an antipsychotic dose of <0.6 DDDs/day was associated with the lowest risk of first relapse (compared to 0.9–1.1 DDDs/day, HR=1.55 [95% CI: 1.34–1.81]).[27] In this thesis, a high dose (≥1.25 DDDs/day and ≥125%) of antipsychotics was associated with a higher risk of relapse, suggesting the presence of indication bias. Due to this bias, milder patients are more likely to use lower doses of antipsychotics and

experience fewer relapses, thereby weakening the association between lower doses and relapse. Additionally, restricted cubic spline analyses suggested there might be a 'safety zone' (0.75–1.00 DDDs/day or 75–100%) where relapse risk does not increase after dose reduction following the index admission. Given the observed dose-response relationship between low doses of antipsychotics and relapse risk, physicians should strive to maintain the patient's dose at the standard level as much as possible.

4.2.2.2. Bipolar disorder

In patients with incident bipolar disorder, the risk of relapse increased as the maintenance dose of mood stabilizers lower, only at low doses (crude dose, <0.5 DDDs/day; relative dose, <100%). Given that median dose of mood stabilizers during the index admission was 0.5 DDDs/day, these results suggest that the relapse risk would increase in case of even modest dose reduction from the dose in the acute phase.

However, the lithium and valproate sub-groups demonstrated quite different relationships. The relapse risk was similar for low lithium doses and doses during hospitalization, while the dose of valproate showed a significant dose-response relationship with relapse risk. These results are quite similar to the findings from a study analyzing nationwide claims data in Finland.[30] In that study, low-dose lithium and standard-dose lithium demonstrated similar risks of relapse (compared to non-use of mood stabilizers, low dose [<810 mg], HR=0.77 [95% CI: 0.73–0.81]; standard dose [810–990 mg], 0.72 [0.66–0.78]). In contrast, low-dose valproate was associated with a higher risk of relapse than standard-dose valproate (low dose [<900 mg], HR=0.92 [95% CI: 0.88–0.96]; standard dose [900–1100 mg], 0.78 [0.73–0.84]). However, it is difficult to conclude that lithium is safer at low doses than valproate because the incidence rates in the valproate subgroup were generally lower than those in the lithium subgroup. There are some possible explanations for these results. The index year in the valproate subgroup was relatively later than that in the lithium subgroup. Period effects, such as legal issues prohibiting psychiatric hospitalization or the development of non-pharmacological treatments, may explain the difference between the lithium and valproate subgroups. However, since this difference is replicated in the subgroup analyses stratified by index year, it cannot be fully explained by the period effect alone.

The antipsychotic dose in patients with bipolar disorder appears to be associated with relapse risk only at low doses (crude dose, <0.5 DDDs/day; relative dose, 50%). Similar to the findings in the

schizophrenia-antipsychotic group, restricted cubic spline analysis suggested the presence of a 'safe zone' (0.5–1.0 DDDs/day and 50–100%). The dose of antipsychotics in patients with bipolar disorder revealed a rapid reduction after the index admission. These results imply that excessive dose reduction, especially by more than half, may increase the risk of relapse. Additionally, the association between antipsychotic dose and relapse risk strengthened as the lag time increased. This suggests that the maintenance dose of antipsychotics may have delayed effects, such as when a patient on a low dose worsens, prompting dose titration and a shift to a higher dose just before rehospitalization. Therefore, the association between antipsychotic dose and relapse risk in patients with bipolar disorder may be larger than initially estimated.

The use of a considerable dose of antipsychotics or mood stabilizers might mitigate the impact of dose reduction of the other medication on relapse risk. These results suggest a complementary, though not completely substitutable, relationship between mood stabilizers and antipsychotics in the treatment of bipolar disorder. Given the higher risk associated with not using one medication, even when the other is used sufficiently, polytherapy with both mood stabilizers and antipsychotics may be more effective than monotherapy with high doses.

4.3. Strengths and limitations

4.3.1. Validation studies in SCRAP

This is the first study to validate case definition and relapse identification algorithms based on claims data for psychiatric diseases in Korea. By utilizing an extensive hospital-based database, various case identification algorithms could be evaluated. However, there were several limitations to this validation study. First, validations were conducted using data from a tertiary hospital, so the case definition algorithms may not be generalizable to primary care settings. Second, as data were sourced from only a single hospital, true case identification through medical chart review may have led to underdiagnosis. Third, the validation process, particularly the determination of true cases through medical chart review, was conducted by a single researcher. Fourth, until 2014, Gwangju Severance Hospital had a closed ward, while Severance Hospital had only an open ward, which may have resulted in the inclusion of milder cases.

4.3.2. Association between maintenance dose and relapse risk in the NHID

This thesis analyzed nationwide, population-based data to produce real-world evidence, allowing for multiple secondary and sensitivity analyses. Through categorical and continuous analyses of medication doses, the lowest effective doses of antipsychotics and mood stabilizers for patients with schizophrenia and bipolar disorder can be suggested. However, several limitations exist. First, since baseline disease severity cannot be measured in the current data, indication bias for medication dose cannot be ruled out. The use of relative dose as the exposure might mitigate this bias, but it cannot completely eliminate it. Second, as relapses were defined based on hospitalization, milder relapses treated in outpatient care were disregarded. Third, dose categories might be misclassified due to patients' poor adherence. Nevertheless, although the prescribed doses might not accurately reflect the doses actually used by patients, the findings in this thesis can still be applied to physician prescribing practices. Fourth, unmeasured confounding, such as genetic factors, cannot be ruled out.

5. CONCLUSION

A low maintenance dose of antipsychotics or mood stabilizers has been shown to be associated with a higher risk of relapse in patients with schizophrenia and bipolar disorder. The lowest effective doses of antipsychotics and mood stabilizers has been suggested. The observed associations between maintenance dose and relapse risk can provide real-world evidence to assist physicians in making decisions about dose reduction. Further studies on risk prediction models, including variables beyond claim records, are needed.

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APPENDICES

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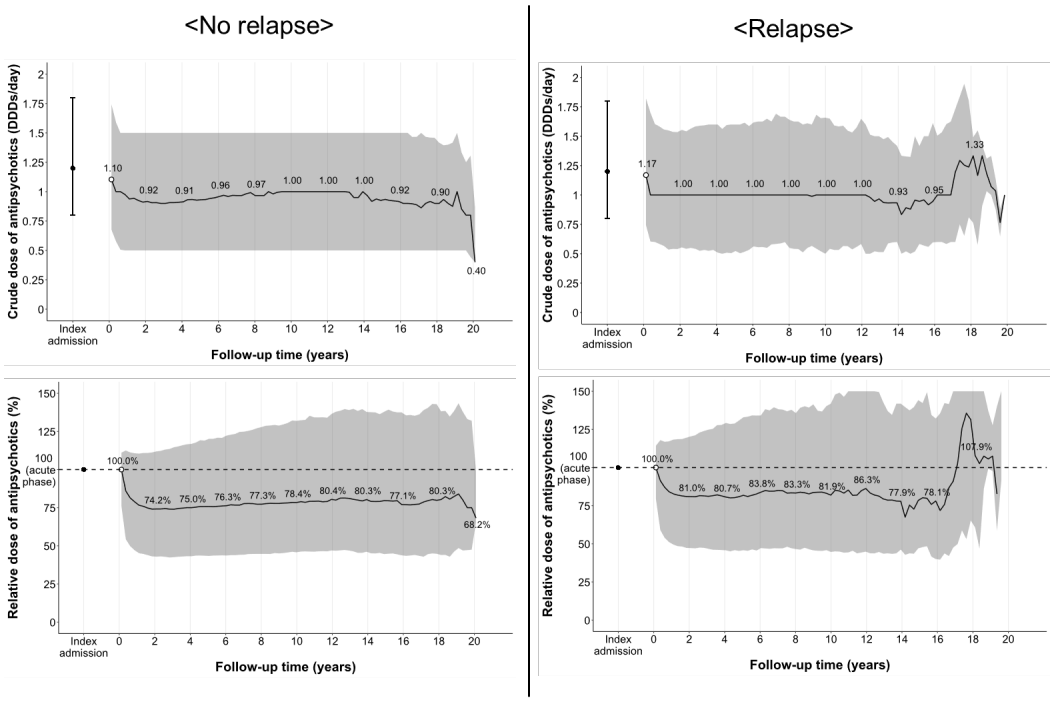
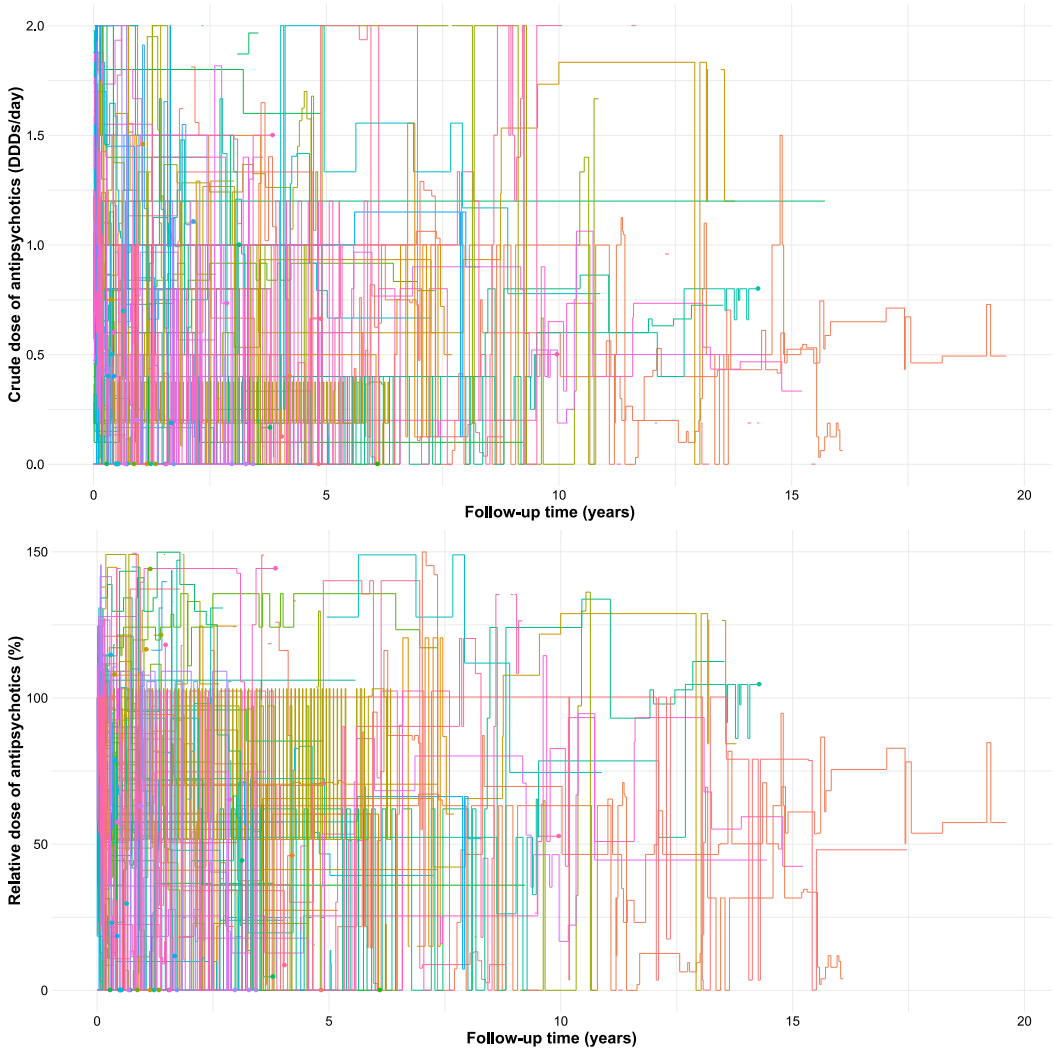
Appendix 1. Variable definitions in the NHID

Variable	ICD-10 codes
Case definitions (hospitalization with main diagnostic codes)	
Schizophrenia	F20, F25
Bipolar disorder	F30, F31
Relapse identification (rehospitalization with main diagnostic codes)	
Schizophrenia	F2.x
Bipolar disorder	F3.x
For exclusion (all diagnostic codes)	
Dementia	F00–03, G30
Schizophrenia	F20, F25
Psychiatric comorbidities (all diagnostic codes)	
Substance use disorders	F1.x
Mood disorders	F3.x
Anxiety disorders	F40, F41
Obsessive-compulsive disorders	F42
Personality disorders	F7.x
Psychiatric developmental disorders	F70–89



Appendix 2. Dose trajectory of antipsychotics stratified according to relapse in patients with schizophrenia. The median values (represented by solid lines) and the interquartile ranges (indicated by shaded areas) of antipsychotic dose in each 90-day interval were presented.



Appendix 3. Spaghetti plot of antipsychotic dose change in patients with schizophrenia. Dose trajectories of 100 randomly sampled patients were presented. Relapses were indicated by colored dots.

Appendix 4. Time-lag analyses and sensitivity analyses of the schizophrenia-antipsychotic group (crude dose)

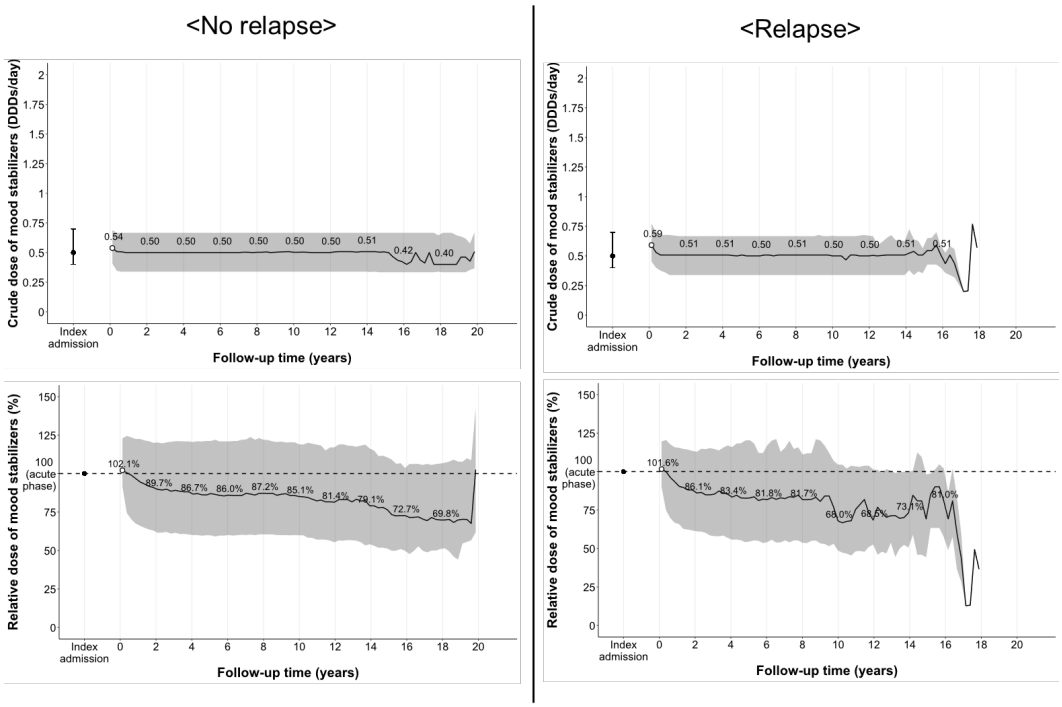
Analysis	Crude maintenance dose categories, HR (95% CI) with 0.75–1.25 DDDs/day as the reference			
	No use	<0.5 DDDs/day	0.5–0.75 DDDs/day	≥1.25 DDDs/day
Primary analysis (N=69,525)	3.37 (3.24-3.50)	1.31 (1.25-1.37)	1.08 (1.03-1.13)	1.11 (1.07-1.15)
Time lag analyses				
14 days (N=70,020)	3.97 (3.83-4.13)	1.26 (1.20-1.32)	1.02 (0.97-1.07)	1.13 (1.08-1.18)
30 days (N=70,647)	3.95 (3.80-4.10)	1.25 (1.20-1.31)	1.03 (0.98-1.08)	1.10 (1.06-1.15)
60 days (N=72,300)	3.63 (3.50-3.77)	1.22 (1.17-1.27)	1.01 (0.97-1.06)	1.08 (1.04-1.12)
90 days (N=73,624)	3.36 (3.24-3.49)	1.22 (1.17-1.28)	1.02 (0.98-1.07)	1.04 (1.00-1.08)
Subgroup analyses				
Men (N=33,388)	3.09 (2.92-3.26)	1.27 (1.19-1.35)	1.11 (1.04-1.19)	1.07 (1.01-1.13)
Women (N=36,137)	3.64 (3.45-3.84)	1.35 (1.27-1.43)	1.06 (0.99-1.13)	1.15 (1.09-1.22)
Age <39 years (N=33,162)	3.60 (3.41-3.79)	1.38 (1.29-1.47)	1.09 (1.02-1.17)	1.07 (1.01-1.13)
Age ≥39 years (N=36,363)	3.11 (2.93-3.29)	1.23 (1.16-1.31)	1.06 (0.99-1.13)	1.15 (1.09-1.21)
Index year <2011 (N=32,413)	3.34 (3.17-3.52)	1.23 (1.15-1.31)	1.04 (0.97-1.11)	1.11 (1.05-1.18)
Index year ≥2011 (N=37,112)	3.42 (3.23-3.62)	1.41 (1.32-1.50)	1.13 (1.06-1.21)	1.11 (1.05-1.18)
Altering grace period				
14 days (N=69,525)	3.34 (3.21-3.47)	1.30 (1.24-1.36)	1.08 (1.03-1.14)	1.13 (1.08-1.17)
60 days (N=69,525)	3.20 (3.08-3.33)	1.31 (1.25-1.36)	1.07 (1.02-1.12)	1.09 (1.05-1.14)
Censoring by medication d/c				
No censored (N=73,624)	1.37 (1.32-1.42)	1.34 (1.29-1.40)	1.11 (1.06-1.16)	1.07 (1.03-1.12)
≥2 years (N=71,062)	2.65 (2.55-2.75)	1.31 (1.26-1.37)	1.08 (1.03-1.13)	1.10 (1.05-1.14)
≥30 days (N=61,833)	1.22 (1.15-1.29)	1.05 (0.99-1.11)	1.18 (1.12-1.24)	0.90 (0.87-0.94)
F/U restriction				
1 years (N=69,525)	2.97 (2.80-3.15)	1.30 (1.21-1.40)	1.07 (1.00-1.16)	1.07 (1.00-1.14)
3 years (N=69,525)	3.28 (3.14-3.43)	1.33 (1.26-1.39)	1.06 (1.01-1.12)	1.08 (1.03-1.14)
5 years (N=69,525)	3.29 (3.16-3.43)	1.30 (1.24-1.37)	1.07 (1.01-1.12)	1.10 (1.05-1.15)

DDD, defined daily dose; d/c, discontinuation; F/U, follow-up

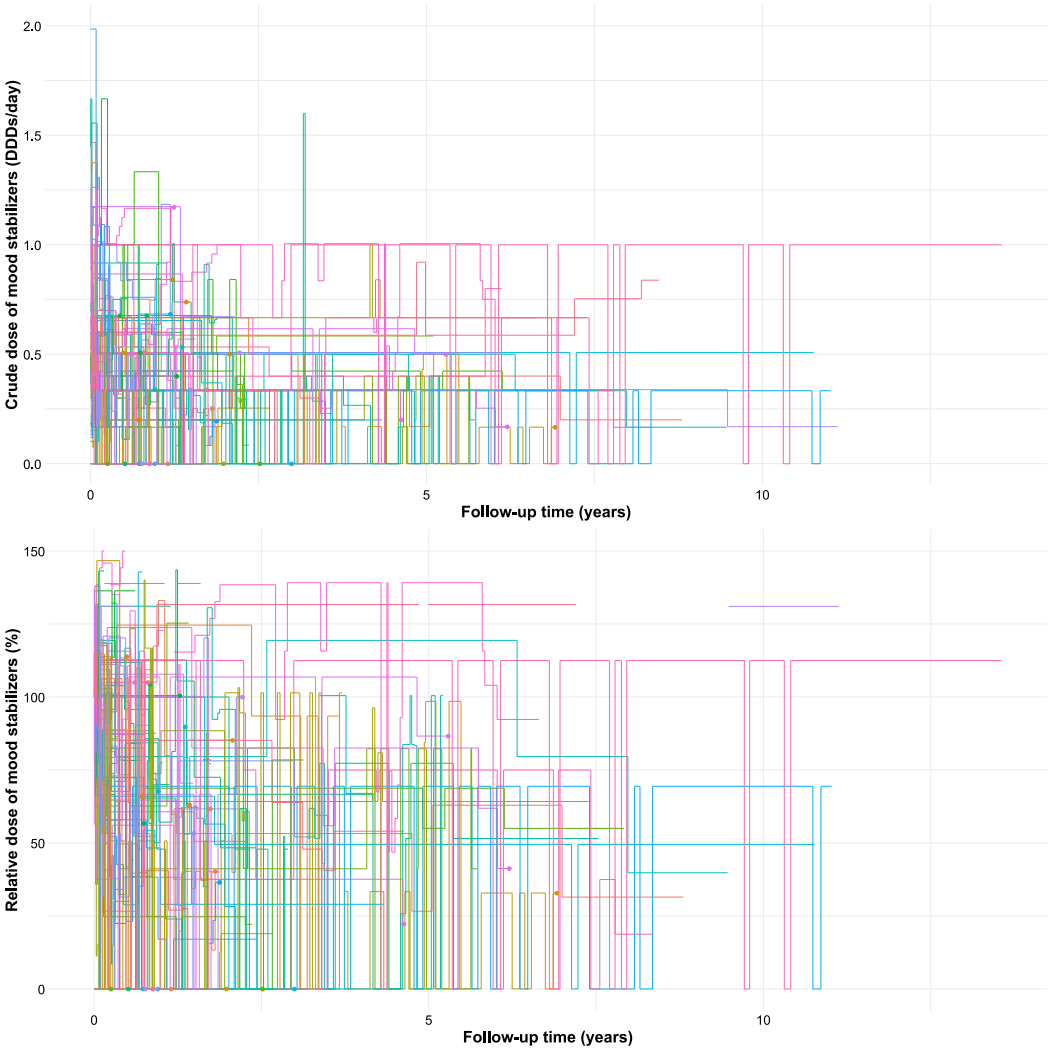
Appendix 5. Time-lag analyses and sensitivity analyses of the schizophrenia-antipsychotic group (relative dose)

Analysis	Relative maintenance dose categories, HR (95% CI) with 75–125% as the reference			
	No use	<50%	50–75%	≥125%
Primary analysis (N=69,525)	3.51 (3.38-3.64)	1.31 (1.25-1.36)	1.02 (0.97-1.06)	1.33 (1.28-1.38)
Time lag analyses				
14 days (N=70,020)	4.05 (3.91-4.21)	1.20 (1.15-1.25)	0.98 (0.94-1.02)	1.31 (1.26-1.36)
30 days (N=70,647)	4.05 (3.91-4.21)	1.21 (1.16-1.26)	0.99 (0.94-1.03)	1.29 (1.24-1.34)
60 days (N=72,300)	3.74 (3.61-3.88)	1.18 (1.14-1.23)	0.98 (0.93-1.02)	1.25 (1.20-1.30)
90 days (N=73,624)	3.57 (3.44-3.71)	1.24 (1.20-1.30)	1.02 (0.98-1.07)	1.24 (1.19-1.29)
Subgroup analyses				
Men (N=33,388)	3.21 (3.04-3.39)	1.29 (1.22-1.36)	1.04 (0.98-1.11)	1.32 (1.25-1.40)
Women (N=36,137)	3.63 (3.44-3.83)	1.28 (1.21-1.36)	0.98 (0.92-1.04)	1.32 (1.25-1.40)
Age <39 years (N=33,162)	3.75 (3.55-3.95)	1.33 (1.25-1.41)	1.02 (0.95-1.08)	1.29 (1.22-1.37)
Age ≥39 years (N=36,363)	3.26 (3.09-3.44)	1.29 (1.21-1.36)	1.02 (0.96-1.09)	1.36 (1.29-1.44)
Index year <2011 (N=32,413)	3.50 (3.32-3.68)	1.26 (1.19-1.33)	1.00 (0.94-1.06)	1.29 (1.22-1.36)
Index year ≥2011 (N=37,112)	3.52 (3.33-3.72)	1.35 (1.28-1.43)	1.03 (0.97-1.10)	1.37 (1.30-1.45)
Altering grace period				
14 days (N=69,525)	3.45 (3.32-3.58)	1.29 (1.23-1.34)	1.01 (0.96-1.05)	1.35 (1.29-1.40)
60 days (N=69,525)	3.35 (3.22-3.48)	1.31 (1.26-1.36)	1.02 (0.97-1.06)	1.30 (1.26-1.36)
Censoring by medication d/c				
No censored (N=73,624)	1.47 (1.41-1.52)	1.34 (1.29-1.40)	1.04 (1.00-1.09)	1.36 (1.31-1.42)
≥2 years (N=71,062)	2.77 (2.67-2.87)	1.30 (1.25-1.36)	1.02 (0.98-1.07)	1.33 (1.28-1.38)
≥30 days (N=61,833)	1.25 (1.19-1.32)	0.98 (0.92-1.03)	1.36 (1.30-1.43)	0.91 (0.88-0.94)
F/U restriction				
1 years (N=69,525)	3.12 (2.95-3.30)	1.29 (1.21-1.38)	1.02 (0.95-1.09)	1.39 (1.30-1.47)
3 years (N=69,525)	3.47 (3.33-3.62)	1.32 (1.26-1.39)	1.04 (0.98-1.09)	1.37 (1.31-1.43)
5 years (N=69,525)	3.46 (3.32-3.60)	1.30 (1.25-1.36)	1.03 (0.98-1.08)	1.35 (1.30-1.41)

DDD, defined daily dose; d/c, discontinuation; F/U, follow-up



Appendix 6. Dose trajectory of mood stabilizers stratified according to relapse in patients with bipolar disorder. The median values (represented by solid lines) and the interquartile ranges (indicated by shaded areas) of mood stabilizers in each 90-day interval were presented.



Appendix 7. Spaghetti plot of mood stabilizer dose change in patients with bipolar disorder. Dose trajectories of 100 randomly sampled patients were presented. Relapses were indicated by colored dots.

Appendix 8. Time-lag analyses and sensitivity analyses of the bipolar disorder-mood stabilizer group (crude dose)

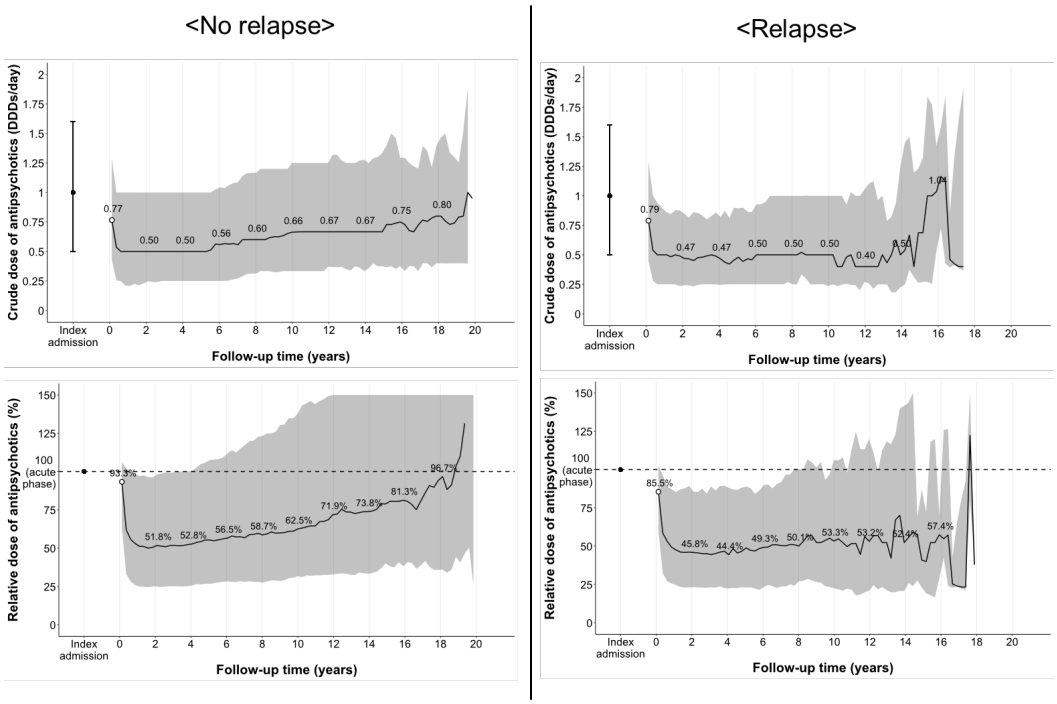
Analysis	Crude maintenance dose categories, HR (95% CI) with 0.75–1.25 DDDs/day as the reference			
	No use	<0.5 DDDs/day	0.5–0.75 DDDs/day	≥1.25 DDDs/day
Primary analysis (N=18,434)	2.86 (2.53-3.23)	1.26 (1.12-1.42)	1.12 (1.00-1.25)	1.26 (1.04-1.54)
Time lag analyses				
14 days (N=18,680)	3.62 (3.20-4.09)	1.22 (1.08-1.38)	1.05 (0.94-1.18)	1.16 (0.94-1.42)
30 days (N=19,058)	3.88 (3.43-4.38)	1.21 (1.07-1.36)	1.03 (0.91-1.15)	1.14 (0.93-1.40)
60 days (N=19,995)	4.25 (3.77-4.81)	1.33 (1.18-1.50)	1.16 (1.03-1.30)	1.14 (0.93-1.41)
90 days (N=20,886)	4.00 (3.55-4.51)	1.25 (1.11-1.41)	1.12 (1.01-1.25)	0.99 (0.80-1.22)
Subgroup analyses				
Men (N=8,548)	2.90 (2.46-3.43)	1.53 (1.31-1.80)	1.23 (1.06-1.43)	1.25 (0.97-1.62)
Women (N=9,886)	2.62 (2.18-3.13)	1.01 (0.85-1.21)	0.97 (0.82-1.15)	1.31 (0.96-1.80)
Age <36 years (N=8,939)	2.81 (2.38-3.31)	1.27 (1.07-1.49)	1.13 (0.97-1.32)	1.36 (1.04-1.78)
Age ≥36 years (N=9,495)	2.86 (2.40-3.42)	1.24 (1.04-1.47)	1.09 (0.92-1.28)	1.19 (0.88-1.61)
Index year <2011 (N=7,886)	3.07 (2.61-3.62)	1.36 (1.16-1.60)	1.19 (1.02-1.38)	1.42 (1.10-1.83)
Index year ≥2011 (N=10,548)	2.60 (2.17-3.11)	1.14 (0.96-1.36)	1.03 (0.87-1.21)	1.09 (0.78-1.52)
Index mood stabilizer dose <0.5 DDDs/day (N=9,297)	3.02 (2.36-3.86)	1.30 (1.02-1.65)	1.21 (0.96-1.53)	1.18 (0.71-1.95)
Index mood stabilizer dose ≥0.5 DDDs/day (N=9,137)	2.79 (2.42-3.22)	1.28 (1.11-1.47)	1.06 (0.93-1.21)	1.30 (1.04-1.62)
Altering grace period				
14 days (N=18,434)	2.73 (2.41-3.09)	1.24 (1.10-1.40)	1.10 (0.98-1.23)	1.26 (1.02-1.55)
60 days (N=18,434)	2.86 (2.53-3.22)	1.28 (1.14-1.43)	1.11 (0.99-1.24)	1.25 (1.03-1.52)
Censoring by medication d/c				
No censored (N=20,886)	0.72 (0.64-0.80)	1.30 (1.17-1.46)	1.12 (1.01-1.24)	1.17 (0.97-1.42)
≥2 years (N=19,087)	2.07 (1.85-2.32)	1.24 (1.11-1.39)	1.09 (0.98-1.22)	1.20 (0.99-1.46)
≥30 days (N=16,316)	1.29 (1.11-1.51)	1.11 (0.96-1.28)	1.35 (1.06-1.71)	0.96 (0.87-1.04)
F/U restriction				
1 years (N=18,434)	2.59 (2.14-3.14)	1.30 (1.08-1.56)	1.03 (0.86-1.23)	1.20 (0.87-1.66)
3 years (N=18,434)	2.86 (2.50-3.27)	1.26 (1.10-1.43)	1.10 (0.97-1.25)	1.19 (0.95-1.50)
5 years (N=18,434)	2.81 (2.48-3.19)	1.22 (1.08-1.38)	1.09 (0.97-1.23)	1.21 (0.98-1.50)

DDD, defined daily dose; d/c, discontinuation; F/U, follow-up

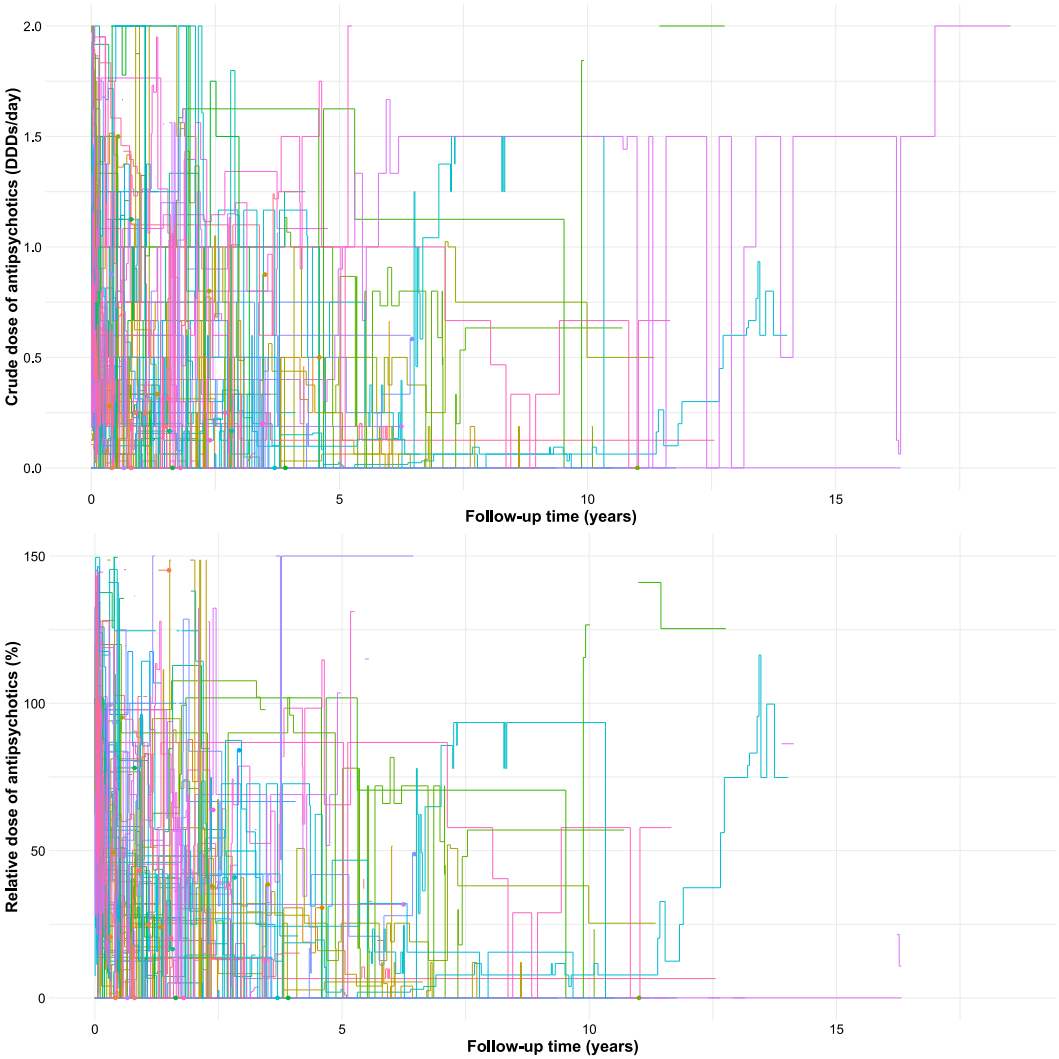
Appendix 9. Time-lag analyses and sensitivity analyses of the bipolar disorder-mood stabilizer group (relative dose)

Analysis	Relative maintenance dose categories, HR (95% CI) with 75–125% as the reference			
	No use	<50%	50–75%	≥125%
Primary analysis (N=18,434)	2.69 (2.49-2.90)	1.38 (1.25-1.52)	1.16 (1.07-1.27)	1.05 (0.96-1.15)
Time lag analyses				
14 days (N=18,680)	3.43 (3.19-3.69)	1.34 (1.21-1.49)	1.06 (0.97-1.16)	1.01 (0.92-1.11)
30 days (N=19,058)	3.70 (3.44-3.98)	1.28 (1.16-1.42)	1.07 (0.97-1.17)	1.02 (0.93-1.12)
60 days (N=19,995)	3.64 (3.38-3.91)	1.24 (1.12-1.38)	1.10 (1.01-1.20)	0.94 (0.86-1.04)
90 days (N=20,886)	3.56 (3.31-3.83)	1.25 (1.13-1.39)	1.07 (0.98-1.17)	0.97 (0.89-1.07)
Subgroup analyses				
Men (N=8,548)	2.47 (2.20-2.77)	1.46 (1.27-1.69)	1.23 (1.08-1.39)	1.03 (0.90-1.17)
Women (N=9,886)	2.87 (2.59-3.18)	1.30 (1.14-1.49)	1.10 (0.98-1.25)	1.07 (0.95-1.21)
Age <36 years (N=8,939)	2.67 (2.39-2.97)	1.46 (1.27-1.67)	1.17 (1.03-1.33)	1.04 (0.92-1.18)
Age ≥36 years (N=9,495)	2.70 (2.42-3.01)	1.29 (1.12-1.49)	1.16 (1.03-1.31)	1.06 (0.93-1.20)
Index year <2011 (N=7,886)	2.68 (2.41-2.97)	1.30 (1.14-1.49)	1.17 (1.03-1.31)	1.01 (0.89-1.14)
Index year ≥2011 (N=10,548)	2.68 (2.39-3.00)	1.46 (1.26-1.69)	1.16 (1.02-1.32)	1.10 (0.97-1.25)
Index mood stabilizer dose <0.5 DDDs/day (N=9,297)	2.57 (2.30-2.89)	1.41 (1.17-1.71)	1.12 (0.96-1.32)	1.08 (0.96-1.22)
Index mood stabilizer dose ≥0.5 DDDs/day (N=9,137)	2.79 (2.52-3.10)	1.36 (1.21-1.53)	1.17 (1.05-1.30)	1.14 (0.98-1.34)
Altering grace period				
14 days (N=18,434)	2.65 (2.45-2.86)	1.40 (1.26-1.54)	1.19 (1.09-1.30)	1.08 (0.99-1.19)
60 days (N=18,434)	2.66 (2.46-2.87)	1.36 (1.24-1.50)	1.16 (1.06-1.26)	1.05 (0.96-1.14)
Censoring by medication d/c				
No censored (N=20,886)	0.66 (0.62-0.71)	1.35 (1.23-1.48)	1.18 (1.09-1.28)	1.09 (1.00-1.18)
≥2 years (N=19,087)	1.96 (1.83-2.10)	1.34 (1.22-1.47)	1.15 (1.06-1.25)	1.04 (0.96-1.13)
≥30 days (N=16,316)	1.30 (1.12-1.50)	1.18 (1.05-1.32)	1.07 (0.96-1.21)	0.95 (0.87-1.04)
F/U restriction				
1 years (N=18,434)	2.46 (2.18-2.79)	1.20 (0.99-1.45)	1.28 (1.10-1.48)	1.07 (0.92-1.23)
3 years (N=18,434)	2.69 (2.47-2.92)	1.34 (1.20-1.51)	1.18 (1.07-1.30)	1.05 (0.95-1.16)
5 years (N=18,434)	2.70 (2.48-2.93)	1.35 (1.20-1.51)	1.18 (1.07-1.31)	1.05 (0.95-1.16)

DDD, defined daily dose; d/c, discontinuation; F/U, follow-up



Appendix 10. Dose trajectory of antipsychotics stratified according to relapse in patients with bipolar disorder. The median values (represented by solid lines) and the interquartile ranges (indicated by shaded areas) of antipsychotic dose in each 90-day interval were presented.



Appendix 11. Spaghetti plot of antipsychotic dose change in patients with bipolar disorder. Dose trajectories of 100 randomly sampled patients were presented. Relapses were indicated by colored dots.

Appendix 12. Time-lag analyses and sensitivity analyses of the bipolar disorder-antipsychotic group (crude dose)

Analysis	Crude maintenance dose categories, HR (95% CI) with 0.75–1.25 DDDs/day as the reference			
	No use	<0.5 DDDs/day	0.5–0.75 DDDs/day	≥1.25 DDDs/day
Primary analysis (N=19,276)	2.43 (2.21-2.67)	1.23 (1.12-1.35)	1.06 (0.95-1.19)	0.84 (0.74-0.94)
Time lag analyses				
14 days (N=19,572)	3.75 (3.40-4.13)	1.40 (1.27-1.54)	1.10 (0.98-1.24)	0.87 (0.77-0.99)
30 days (N=20,006)	4.19 (3.80-4.62)	1.41 (1.27-1.55)	1.13 (1.01-1.27)	0.84 (0.74-0.96)
60 days (N=21,062)	4.38 (3.97-4.84)	1.53 (1.38-1.69)	1.18 (1.05-1.33)	0.91 (0.80-1.04)
90 days (N=21,981)	4.17 (3.78-4.60)	1.52 (1.38-1.67)	1.18 (1.05-1.32)	0.85 (0.75-0.97)
Subgroup analyses				
Men (N=8,657)	2.24 (1.95-2.58)	1.13 (0.99-1.30)	1.04 (0.89-1.21)	0.81 (0.68-0.96)
Women (N=10,619)	2.58 (2.26-2.94)	1.32 (1.16-1.50)	1.09 (0.94-1.27)	0.86 (0.73-1.01)
Age <36 years (N=9,372)	2.52 (2.21-2.87)	1.28 (1.12-1.46)	1.05 (0.90-1.22)	0.78 (0.66-0.92)
Age ≥36 years (N=9,904)	2.33 (2.03-2.68)	1.18 (1.04-1.34)	1.07 (0.92-1.25)	0.91 (0.77-1.09)
Index year <2011 (N=7,958)	2.70 (2.35-3.11)	1.40 (1.22-1.61)	1.10 (0.94-1.30)	0.91 (0.76-1.09)
Index year ≥2011 (N=11,318)	2.23 (1.96-2.54)	1.12 (0.99-1.26)	1.04 (0.90-1.20)	0.78 (0.66-0.91)
Altering grace period				
14 days (N=19,276)	2.51 (2.28-2.76)	1.20 (1.09-1.32)	1.06 (0.95-1.19)	0.84 (0.75-0.95)
60 days (N=19,276)	2.31 (2.10-2.54)	1.25 (1.14-1.37)	1.08 (0.97-1.20)	0.82 (0.73-0.93)
Censoring by medication d/c				
No censored (N=21,981)	0.73 (0.68-0.80)	1.30 (1.19-1.41)	1.09 (0.99-1.20)	0.79 (0.70-0.88)
≥2 years (N=20,210)	1.66 (1.52-1.82)	1.23 (1.13-1.34)	1.06 (0.96-1.17)	0.81 (0.72-0.91)
≥30 days (N=16,456)	1.09 (0.96-1.23)	0.96 (0.83-1.11)	0.94 (0.81-1.10)	0.97 (0.88-1.07)
F/U restriction				
1 years (N=19,276)	1.88 (1.61-2.19)	1.10 (0.95-1.28)	1.00 (0.84-1.19)	0.92 (0.76-1.11)
3 years (N=19,276)	2.33 (2.09-2.59)	1.20 (1.08-1.33)	1.05 (0.93-1.19)	0.89 (0.78-1.02)
5 years (N=19,276)	2.33 (2.09-2.59)	1.20 (1.08-1.33)	1.05 (0.93-1.19)	0.89 (0.78-1.02)

DDD, defined daily dose; d/c, discontinuation; F/U, follow-up

Appendix 13. Time-lag analyses and sensitivity analyses of the bipolar disorder-antipsychotic group (relative dose)

Analysis	Relative maintenance dose categories, HR (95% CI) with 75–125% as the reference			
	No use	<50%	50–75%	≥125%
Primary analysis (N=19,276)	2.35 (2.13-2.58)	1.16 (1.06-1.27)	0.94 (0.84-1.05)	1.01 (0.90-1.13)
Time lag analyses				
14 days (N=19,572)	3.28 (2.99-3.61)	1.15 (1.04-1.26)	0.88 (0.78-0.99)	0.98 (0.87-1.10)
30 days (N=20,006)	3.71 (3.38-4.08)	1.18 (1.07-1.30)	0.88 (0.78-0.99)	0.99 (0.88-1.12)
60 days (N=21,062)	3.69 (3.36-4.05)	1.21 (1.10-1.33)	0.87 (0.78-0.99)	0.95 (0.84-1.07)
90 days (N=21,981)	3.82 (3.47-4.20)	1.34 (1.21-1.47)	0.94 (0.84-1.06)	0.99 (0.88-1.12)
Subgroup analyses				
Men (N=8,657)	2.29 (1.98-2.65)	1.13 (0.98-1.30)	0.96 (0.81-1.14)	1.17 (0.99-1.38)
Women (N=10,619)	2.34 (2.06-2.65)	1.19 (1.05-1.34)	0.93 (0.80-1.08)	0.88 (0.76-1.03)
Age <36 years (N=9,372)	2.47 (2.15-2.83)	1.23 (1.08-1.40)	0.88 (0.74-1.03)	0.94 (0.80-1.11)
Age ≥36 years (N=9,904)	2.24 (1.96-2.57)	1.10 (0.97-1.25)	1.01 (0.86-1.17)	1.08 (0.93-1.27)
Index year <2011 (N=7,958)	2.24 (1.95-2.57)	1.08 (0.94-1.23)	0.90 (0.76-1.06)	0.91 (0.77-1.08)
Index year ≥2011 (N=11,318)	2.46 (2.15-2.82)	1.26 (1.11-1.43)	0.99 (0.85-1.15)	1.09 (0.94-1.28)
Altering grace period				
14 days (N=19,276)	2.46 (2.23-2.71)	1.16 (1.05-1.28)	0.95 (0.84-1.06)	1.02 (0.90-1.14)
60 days (N=19,276)	2.22 (2.02-2.44)	1.18 (1.08-1.29)	0.94 (0.84-1.05)	0.99 (0.89-1.11)
Censoring by medication d/c				
No censored (N=21,981)	0.71 (0.65-0.78)	1.22 (1.12-1.32)	0.95 (0.86-1.05)	1.03 (0.92-1.14)
≥2 years (N=20,210)	1.61 (1.47-1.76)	1.16 (1.06-1.26)	0.94 (0.84-1.05)	0.99 (0.89-1.10)
≥30 days (N=16,456)	1.06 (0.94-1.20)	0.86 (0.74-1.00)	1.08 (0.93-1.25)	0.98 (0.89-1.08)
F/U restriction				
1 years (N=19,276)	1.76 (1.53-2.03)	0.96 (0.83-1.11)	0.86 (0.72-1.02)	1.10 (0.92-1.30)
3 years (N=19,276)	2.23 (2.01-2.48)	1.09 (0.98-1.21)	0.95 (0.84-1.08)	1.10 (0.97-1.25)
5 years (N=19,276)	2.35 (2.13-2.60)	1.13 (1.02-1.25)	0.93 (0.83-1.05)	1.08 (0.95-1.21)

DDD, defined daily dose; d/c, discontinuation; F/U, follow-up

Abstract in Korean

중증정신질환에서 재발 예방을 위한 유지약물치료 전략

서론: 조현병과 양극성 장애는 개인의 삶에 일생에 걸쳐 상당한 장애를 유발하는 중증 정신 질환이다. 이들 질환의 기능 저하를 가속화하는 반복되는 재발을 막기 위해서 유지치료가 필수적이며, 항정신병 약제와 기분 안정제가 주된 치료 약제다. 이러한 약물의 종류와 제형에 따른 재발 위험은 무작위 시험과 대규모 관찰 연구를 통해 널리 연구되어 왔다. 그러나 이들 약물의 최적 용량은 임상가의 시행착오를 통해 얻어지는 것이 보통이며, 유지 용량과 재발 위험의 연관성에 대한 근거는 아직 부족한 실정이다. 이에 본 학위논문에서는 조현병 및 양극성 장애 환자의 유지 약제 용량과 재발 위험 간의 연관성을 분석하여 임상 현장에 실증 데이터 기반 근거(Real-world evidence)를 제공하는 것을 목표로 한다.

방법: 본 학위논문에서는 사례 정의와 재발 식별 알고리즘에 대한 타당성 연구와 유지 약제 용량과 재발 위험 간의 연관성 분석이 수행되었다. 첫 번째 연구를 위해 세브란스병원의 SCRAP (Severance Clinical Research Analysis Portal) 데이터가 사용되었다 2005.11.01~2023.12.31 사이의 기간 동안 개별 알고리즘에 따라 식별된 환자들 중 의무 기록 검토를 통해 확인한 실제 사례의 비율 (양성예측도)을 토대로 타당성을 비교/평가하였다. 두 번째 연구를 위해 국민건강보험공단에서 구축한 맞춤형연구 DB 가 사용되었다. 2002.01.01~2022.12.31 사이의 기간 동안에 입원치료를 받은 초발 조현병 및 초발 양극성 장애 환자들을 식별하였다. 발병 후 첫번째 입원이 기준 입원으로 설정되었다. 이들 중, 질환과 관심 약제에 따라 5개의 그룹이 구축되었다 (조현병-항정신병약제, 양극성 장애-기분 안정제, 양극성 장애-lithium, 양극성 장애-valproate, 양극성 장애-항정신병약제). 각 그룹은 기준 입원 기간 동안 관심 약제를 사용한 환자로 구성되었다. 유지 용량 삽화는 약제 처방 데이터 (약제 종류, 용량, 횟수, 기간)을 이용하여 구축되었으며, 서로 다른 약물들의 용량 합산은 defined daily dose (DDD)를 기준으로 이루어졌다. 유지 용량은 절대

용량과 상대 용량 (절대 유지 용량을 기준 입원 동안의 용량으로 나눈 비율)으로 각각 계산되었다. 대상자들은 기준 입원의 퇴원 일자로부터 재발, 1년 이상의 약제 중단, 사망, 2022.12.31 중 가장 먼저 발생하는 날까지 추적되었다. 통계적 모델로는 유지 용량을 시간 종속 변수로 포함한 확장된 Cox 회귀분석을 사용하였다.

결과: SCRAP 을 사용한 타당성 연구에서 조현병 사례 정의 알고리즘은 80.5~86.5%의 우수한 양성예측도를 보였다. 양극성 장애의 경우, 입원 기록만을 기반으로 한 알고리즘이 84.1%의 양성예측도를 보였다. 조현병과 양극성 장애에 대한 재발 식별 알고리즘은 각각 88.0%와 72.0%의 양성예측도를 보였다. 건강보험공단 자료를 이용한 연관성 분석에서는, 조현병-항정신병약 코호트에서 낮은 항정신병약 용량과 재발 위험 간에 유의한 연관성이 나타났다 (<0.5 vs. 0.75–1.25 DDD/일, HR=1.31 [95% CI: 1.25–1.37]); 50% vs. 75–125%, HR=1.31 [95% CI: 1.25–1.36]). 양극성 장애-기분 안정제 그룹에서는 낮은 유지 용량이 재발 위험 증가와 연관이 있었다(<0.5 vs. 0.75–1.25 DDD/일, HR=1.26 [95% CI: 1.12–1.42]); 50% vs. 75–125%, HR=1.38 [95% CI: 1.25–1.52]). 이 연관성은 특히 valproate 하위 그룹에서 두드러졌지만, lithium 하위 그룹에서는 잘 나타나지 않았다. 양극성 장애-항정신병약 그룹에서는 낮은 항정신병약 용량과 재발 위험 간의 비교적 약한 연관성이 관찰되었다 (<0.5 vs. 0.75–1.25 DDD/일, HR=1.23 [95% CI: 1.12–1.35]); 50% vs. 75–125%, HR=1.16 [95% CI: 1.06–1.27]). 양극성 장애의 유지치료 동안 기분 안정제를 충분히 사용한 경우(≥75%) 낮은 항정신병약 용량과 재발 위험 간의 연관성이 약화되었으며, 그 반대도 마찬가지였다.

결론: 조현병 및 양극성 장애 환자에서 치료 약물의 유지 용량이 낮을수록 재발 위험이 높아지는 것으로 나타났으며, 질환별, 약제별로 다양한 연관성 패턴을 보였다. 이를 통해 약제 부작용 및 환자의 요청을 이유로 약제 용량을 줄일 때 재발 위험을 정량적으로 고려하는 데 도움을 줄 수 있을 것으로 사료된다. 앞으로 청구자료 뿐만 아니라 여러 계층의 변수들을 포함한 재발 위험 예측 모델에 대한 연구가 도움이 될 것이다.

핵심되는 말 : 조현병; 양극성 장애; 재발; 약물역학