Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Adherence to Antipsychotics and Job Acquisition in Patients with First-episode Schizophrenia: A 10-year Follow-up Using the Korean National Health Information Database

HyeYoung Kwon
Mokwon University
Jinyeong Bae
Arizona State University
Yongpyo Lee
Catholic University of Korea
Rachel F. Rodgers
Northeastern University
Eric Bui
Université de Caen Normandie
Yongjoo Kim
yongjoo.kim@mail.harvard.edu

Sangji University

Research Article

Keywords: Schizophrenia, Medication Adherence, Antipsychotic Agents, Employment, National Health Insurance Service

Posted Date: June 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9406344/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose: Schizophrenia substantially impairs social and occupational functioning; however, whether adherence to antipsychotic medication facilitates employment attainment remains uncertain. We aimed to investigate the association between adherence to antipsychotics and subsequent job acquisition among individuals with schizophrenia and to examine potential effect modification by age, sex, socioeconomic status and antipsychotic dose intensity.

Methods: The Korean National Health Insurance Service database (January 1, 2014 to December 31, 2023) was used. Individuals aged 25-54 years with first-episode schizophrenia and non-employed insurance status on the index date were followed until job acquisition, death, or study termination. Adherence to antipsychotics was measured by proportion of days covered (PDC) and classified as high (PDC ≥ 0.8) or low (PDC<0.8). Cox proportional hazards models adjusted for age, sex, income quintile, prior job experience, clinical severity, and concurrent psychotropics use.

Results: Among 6,499 participants (mean age, 39.6 [8.5] years; 3644 women [56.0%]), 2,961 were classified as a high-level adherence and 3,538 a low-level adherence. By follow-up, 1,327 (44.8%) of high-adherence participants and 1,344 (38.0%) of low-adherence participants had attained employee-insured paid work. High versus low adherence was associated with a greater likelihood of employment (adjusted hazard ratio [AHR], 1.17; 95% CI, 1.07-1.29). The association was stronger in men (AHR, 1.29; 95% CI, 1.13-1.46) than in women (AHR, 1.07; 95% CI, 0.96-1.20). However, there was no significant heterogeneity across age groups, economic status, or dose categories.

Conclusions: These findings support integrating adherence-focused pharmacologic management with tailored vocational support to promote functional recovery in schizophrenia.

Introduction

Social recovery of individuals diagnosed with schizophrenia is a significant global public health challenge. Globally, more than 13 million individuals suffer from schizophrenia and related disorders (Charlson et al. 2018; Velligan and Rao 2023). Major clinical features of schizophrenia include positive symptoms (e.g., hallucinations, delusions, and thought disorders), negative symptoms (e.g., apathy and social withdrawal), and cognitive decline (Charlson et al. 2018; Velligan and Rao 2023). Moreover, individuals with schizophrenia experience subsequent diminished work functionality and loss of employment, imposing additional productivity loss and economic burdens to individuals, family, and society (Chafi et al. 2020; Holm et al. 2021; Inada et al. 2024; Song et al. 2024).

According to a longitudinal population-based study of Finish adults, only about 10% of individuals with schizophrenia were employed five years after the first diagnosis, substantial decrease from 24% employed before illness onset (Holm et al. 2021). Globally, unemployment rates among individuals with schizophrenia range from 70%-90%, in which the majority rely on disability pensions instead a formal job (Collins et al. 2023; Hakulinen et al. 2020; Holm et al. 2021; Marwaha et al. 2007; Perala et al. 2008). In

South Korea, the prevalence of schizophrenia is estimated as 0.40–0.45% for one-year prevalence, 0.51–0.54% for three-year cumulative, and 0.75% for ten-year cumulative from 2008 through 2017 (Cho et al. 2020; Jung et al. 2021). Among individuals with schizophrenia, less than 20% reported having a job, which was significantly lower than the population employment rate of 60% in the given year of 2005 (Chang et al. 2008). These necessitate effective approaches for social recovery and job acquisition for individuals with schizophrenia.

Existing research has shown that appropriate use of antipsychotics, reduced symptom severity and relapses, and vocational intervention can improve employment outcomes among individuals with schizophrenia. Razzano and colleagues (2005) found that psychiatric medications can reduce symptom severity, which in turn lead to fewer work absences and increased working hours over time (Razzano et al. 2005). Other studies also revealed that antipsychotic use was associated with improved employment outcomes by stabilizing symptoms, enhancing cognitive function, and better social adaptability (Lindstrom and Lundberg 1997; Littrell 1995).

However, studies have also found that only a limited proportion of individuals diagnosed with schizophrenia adhere to antipsychotics medication with adherence rates ranging from 47.8% to 78.3% depending on measures, time frame considered, and populations (Garcia et al. 2016; Lacro et al. 2002; Novick et al. 2010). In this regard, a growing body of studies have documented that adherence (vs. non-adherence) to antipsychotic medication provides beneficial effects on various clinical (e.g., symptom remission, relapse, and re-hospitalization), behavioral (e.g., substance abuse and cognitive functioning), and social outcomes (e.g., violence and suicidality) (Ascher-Svanum et al. 2006; Haddad et al. 2014; Higashi et al. 2013; Novick et al. 2010).

Nonetheless, only a few studies have examined the effects of adherence to antipsychotic medication on employment. Ascher-Svanum and colleagues (2006) conducted a prospective cohort study of 1906 US individuals (Ascher-Svanum et al. 2006). The study did not find a statistically significant association between the adherence status (non-adherence vs. adherence) in the first year and unemployed status over the second-to-third years (Ascher-Svanum et al. 2006). However, the directionality of the effects estimate suggested potential harmful influences of non-adherence (Ascher-Svanum et al. 2006). Nonetheless, they included both those employed and unemployed at baseline and analyzed difference in prevalences of employed status across the two time points at the group level (Ascher-Svanum et al. 2006). This approach limits the prospective causal understanding at the individual level and thus necessitates further investigation based on an incidence-framework above and beyond prevalence-scale.

Given this gap in the current knowledge, our study aimed to investigate whether adherence to antipsychotics was prospectively associated with subsequent job acquisition among individuals with schizophrenia. To determine causal relationships, we specifically focused on those who were under unemployed status at the time of schizophrenia diagnosis based on a large nationally representative sample from the Korean National Health Insurance Database (NHID), in which diagnostic information

and employment-based beneficiary type were measured with a 10-year of follow-up period. We hypothesized that those with a high-level adherence would be more likely to attain employment over the follow-up, compared to their counterparts with a low-level adherence.

Methods

Data source

The Korean National Health Information Database (NHID) has been established by the National Health Insurance Service (NHIS) since 2012 (Cheol Seong et al. 2017; Lim and Jang 2025). The NHID covers the entire Korean population, who used healthcare services within the national healthcare system, and comprises five different databases: entitlement, national health screening, healthcare utilization based on health insurance claims, long-term care insurance, and healthcare providers. These databases can be interlinked by de-identified join keys (Cheol Seong et al. 2017; Lim and Jang 2025). Medical service utilizations create episode-based claims information, including visit date, visiting facility, diagnosis with the International Classification of Diseases Tenth Revision (ICD-10) codes, ambulatory or inpatient service treated, medicines and services prescribed, length of days for services, cost of the medical services, and patients' copayment (Cheol Seong et al. 2017; Lim and Jang 2025). Of these gigantic databases, we focused on the entitlement and healthcare utilization databases for a given 10 years, from 2014 through 2023.

Cohort Selection

As of 2014, the total population in the NHID was 48,354,089. People diagnosed under the main diagnosis codes of F20-F29 (based on ICD-10) for psychiatric inpatient or outpatient visits and administrated antipsychotics were extracted from the NHID. Those with subsequent ICD-10 codes of F00-F09 (organic mental disorders including dementia) or F10-F19 (disorders related to psychoactive substance use) were excluded. To select first-episode schizophrenia patients as of 2014, those who had been diagnosed with the same ICD-10 code or had been on any prescribed antipsychotics in the previous three consecutive years were excluded.

Based on this group, we selected individuals aged 25–54 who were considered as the major group of the economically active population. Those who had a job at the time of their initial diagnosis were excluded because we focused on the incidence of job acquisition as an outcome of interest. This resulted in 8,594 individuals being identified. Among them, those who had never utilized outpatient services for the condition during the follow-up period were excluded from the analysis, considering their adherence levels would be calculated as 1.0 (perfect adherence) due to the controlled in-patient care setting. The exclusion led to a final cohort of 6,499 individuals, who were tracked until December 31, 2023 (Fig. 1).

This study used de-identified, anonymized secondary data drawn from the National Health Information Database (NHID), provided by the National Health Insurance Service (NHIS), and no personal identifiers

were accessed. Thus, patient consent was waived. This study was approved by the Institutional Review Board of Mokwon University in South Korea (no. 2024-002).

Outcome

Using the National Health Insurance (NHI) eligibility file, we extracted each participant's insurance type. The NHI-classified beneficiaries into six groups: (a) employee-insured members and their dependents, (b) self-employed-insured members and their dependents, and (c) tax-funded medical aid beneficiary group (household head and dependents) (NHIS 2025). The employee-insured category was the outcome indicator of this study. Follow-up for each participant started from the index date, and censoring was performed when the participants experienced (a) transition to employee-insured status (first day of coverage after securing paid employment), (b) death, or (c) study termination (December 31, 2023), whichever came first.

Primary Exposure

We used the Proportion of Days Covered (PDC) as our primary exposure of interest. PDC has been widely used as a measure of medication adherence in claims-based pharmaco-epidemiology research (Ho et al. 2025; Shin et al. 2025). First, according to the World Health Organization's (WHO) anatomical therapeutic classification (ATC) code (www.whoatc.int), we identified 23 ingredients listed in the National Health Insurance Reimbursement Drug List from 2014 to 2023 (Supplementary Table 1). Then, we extracted all episodes in which the participants were prescribed antipsychotic medications associated with diagnosis codes F20-F29 (schizophrenia and related disorders) from the index date to the follow-up endpoint. Using this data, we calculated the Proportion of Days Covered (PDC) for patients' prescriptions, as shown in Eq. 1 (Leslie 2007; Loucks et al. 2022; Shah et al. 2023; Steiner and Prochazka 1997).

$$PDC = \frac{\text{Number of Days Covered}}{\text{Number of Days Observed}} \qquad (Equation\ 1)$$

For long-acting injectable antipsychotics, the dosing days were adjusted based on injection intervals of 1–3 months. Based on previous research, adherence to antipsychotic medication was categorized as "high" (≥ 0.8) or "low" (< 0.8) according to the PDC value (Blecker et al. 2025; Loucks et al. 2022; Shah et al. 2023).

Dose intensity of antipsychotics

During the observation period, the dosage of antipsychotics was calculated using the Defined Daily Dose (DDD) provided by the WHO (Supplement Table 2). To standardize the amount consumed, we adjusted the prescribed dosage according to the DDD of each medication. The total prescribed dose was

converted into DDDs and divided by the total number of observation days to determine the average daily dose (Eq. 2).

Table 2
Unadjusted hazard ratios of adherence to antipsychotics, dose intensity of antipsychotics, and exposure to typical antipsychotics and other co-prescribed psychoactive drugs for job acquisition

Variables	HR (95% CI)	p
Adherence to antipsychotics		
Low	1 (reference)	
High	1.32 (1.21, 1.41)	< 0.001
Dose intensity of antipsychotics		
Low	1 (reference)	
Moderate	1.06 (0.96, 1.16)	NS
High	0.89 (0.78, 0.01)	0.071
Exposure to concurrent non-antipsychotic psychotropic medications		
Antiepileptics (≥ 80% vs. <80%)	0.88 (0.79, 0.99)	0.034
Antidepressants (≥ 80% vs. <80%)	0.88 (0.78, 0.99)	0.039
Psychostimulants (≥ 80% vs. <80%)	1.48 (0.37, 5.91)	NS
Antiparkinson drugs (≥ 80% vs. <80%)	1.05 (0.96, 1.16)	NS
Anxiolytics (≥ 80% vs. <80%)	0.95 (0.87, 1.04)	NS
Hypnotics & Sedatives (≥ 80% vs. <80%)	0.72 (0.58, 0.9)	0.003

$$Dose\ intensity = \frac{\text{Total volumes prescribed in DDD}}{\text{Total Days Observed}} \qquad (Equation\ 2)$$

If the value was greater than 1, it indicated that the prescription exceeded the DDD, suggesting that a high-dose treatment was being administered. Conversely, if the value was less than 1, this reflected either suboptimal dosing or inconsistent medication use during the follow-up period. The intensity of antipsychotic medication use was categorized as “low” (less than 1), “moderate” (from 1 to less than 2), or “high” (2 or greater). These classifications reflect the relative dosage level based on the DDD.

Severity indicators: hospitalization & length of hospital stay

Based on the previous evidence showing that the severity of schizophrenia symptoms affects employment status (Martini et al. 2018), we included the following two variables: (a) hospitalization (vs.

outpatient) at the first episode of psychosis, and (b) the total length of hospital stays during the observation period. Hospitalization days were classified as high (90 days or more) and low (less than 90 days) based on the distribution of the variable among the sample.

Concurrent non-antipsychotic psychotropic medications

Together with antipsychotics, agents affecting the central nervous system (CNS) are often co-prescribed for schizophrenia. These include antidepressants (N06A), antiparkinsonian (N04), anticonvulsants (N03A), anxiolytics (N05AB), hypnotics and sedatives (N05C) and psychostimulants (N06B) [Supplement Table 3].

Table 3
Adjusted hazard ratios for job acquisition from Cox proportional hazard analysis across three models

	Model 1		Model 2		Model 3	
	AHR (95% CI)	**p**	**AHR (95% CI)**	**p**	**AHR (95% CI)**	**P**
Adherence to antipsychotics						
High (vs. Low)	1.30 (1.21, 1.41)	< 0.001	1.16 (1.07, 1.27)	0.0005	1.17 (1.07, 1.29)	0.001
Sex						
Female (vs. Male)	1.02 (0.95, 1.11)	NS	0.94 (0.87, 1.02)	NS	0.94 (0.87, 1.02)	NS
Age						
25 ~ 34 years	1 (Reference)		1 (Reference)		1 (Reference)	
35 ~ 44 years	0.69 (0.63, 0.75)	< 0.001	0.69 (0.63, 0.75)	< 0.001	0.69 (0.63, 0.75)	< 0.001
45 ~ 54 years	0.50 (0.45, 0.55)	< 0.001	0.52 (0.47, 0.58)	< 0.001	0.52 (0.47, 0.58)	< 0.001
Income level						
Underprivileged group	1 (Reference)		1 (Reference)		1 (Reference)	
Others	1.10 (1.10, 1.21)	NS	1.01 (0.92, 1.11)	NS	1.01 (0.92, 1.11)	NS
Prior job experience						
None	1 (Reference)		1 (Reference)		1 (Reference)	
Yes	2.51 (2.31, 2.72)	< 0.001	2.46 (2.27, 2.67)	< 0.001	2.46 (2.26, 2.67)	< 0.001
First intervention						
Ambulatory			1 (Reference)		1 (Reference)	
Hospitalized			0.80 (0.73, 0.86)	< 0.001	0.80 (0.74, 0.87)	< 0.001

AHR, Adjusted Hazard Ratio; PDC, Proportion of Days Covered

	Model 1		Model 2		Model 3	
	AHR (95% CI)	**p**	**AHR (95% CI)**	**p**	**AHR (95% CI)**	**P**
Length of hospital stay						
< 90 days			1 (Reference)		1 (Reference)	
≥ 90days			0.31 (0.27, 0.34)	< 0.001	0.31 (0.27,0.34)	< 0.001
Dose intensity of antipsychotics						
Low			1 (Reference)		1 (Reference)	
Moderate			1.20 (1.08, 1.33)	0.0007	1.19 (1.07, 1.32)	0.0013
High			1.02 (0.89, 1.17)	NS	1.03 (0.89, 1.10)	NS
Exposure to concurrent non-antipsychotic psychotropic medications						
Antiepileptics					0.98 (0.87, 1.10)	NS
Antidepressants					0.92 (0.81, 1.05)	NS
Antiparkinson					0.99 (0.89, 1.10)	NS
Anxiolytics					1.04 (0.94, 1.16)	NS
Hypnotics & sedatives					0.87 (0.70, 1.09)	NS
AHR, Adjusted Hazard Ratio; PDC, Proportion of Days Covered						

We computed each patient's exposure to these medications using Eq. 3. The minimum value was 0, indicating no prescription of these medications. The maximum value may exceed 1 depending on the frequency of prescriptions, meaning that the patient was frequently prescribed these medications. A higher value indicated a longer duration of medication use. To incorporate the exposure to such

concurrent non-antipsychotic psychotropic medications into our analysis, we created a dummy variable based on a threshold of 0.8, indicating high (≥ 0.8) and low (< 0.8) exposures to those medications.

$$Exposure = \frac{\text{Number of Days Prescribed}}{\text{Number of Days Observed}} \qquad (Equation\ 3)$$

Other Covariates

We considered demographic factors such as age, gender, socioeconomic status, and prior employment experience based on previous evidence.(Elie et al. 2010)

Statistical analysis

To investigate the association between adherence to antipsychotics and subsequent job acquisition, we performed multivariable Cox proportion hazard models, estimating adjusted hazard ratios (AHRs) of adherence (high vs. low) on time-to-employment. Potential confounders included age, sex, socioeconomic status, previous job experience, severity of schizophrenia (hospitalization at first episode and lengths of hospital stays during follow-up), dose intensity of antipsychotics, and exposure to other co-prescribed psychoactive drugs. The Kaplan-Meier approach and log-rank test were used to evaluate the time taken for job acquisition after schizophrenia diagnosis (Supplement Fig. 1). Proportional hazard assumption tests and subgroup analyses were performed. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and significance level was considered as 0.05 (two-sided).

Results

Cohort characteristics

Table 1 presents the baseline characteristics of the study population across the level of medication adherence (high vs. low). The total person-years contributed to the analysis were 24,144 person-years for the low adherence group (N = 3,538) and 18,105 person-years for the high adherence group (N = 2,961). The means and standard deviations (SDs) of the follow-up period were 6.82 years (3.51) for low adherence group and 6.11 (3.93) years for high adherence group. Over the follow-up, 1,344 individuals (38.0%) in low adherence group and 1,327 individuals (44.8%) in high adherence group acquired full-time employment.

Table 1
Selected baseline characteristics of participants with low and high levels of adherence to antipsychotics among the study participants (N = 6,499)

Variables		Adherence to Antipsychotics				p
		Low (N = 3,538)		High (N = 2,961)		
N	(%)	N	(%)			
Sex	Male	1,545	(43.7)	1,310	(44.2)	NS
	Female	1,993	(56.3)	1,651	(55.8)	
Age	Mean (SD)	40.15	(8.57)	38.86	(8.35)	< 0.001
Age group	25 ~ 34 years	1,089	(30.8)	1,037	(35.0)	< 0.001
	35 ~ 44 years	1,188	(33.6)	1,070	(36.1)	
	45 ~ 54 years	1,261	(35.6)	854	(28.8)	
Income (quantile)	Underprivileged	848	(24.0)	685	(23.1)	NS
	Others	2690	(76.0)	2276	(76.9)	
NHI entitlement	Self-employed	2,125	(60.1)	1,637	(55.3)	< 0.001
	Employed-dependent	1,399	(39.5)	1,316	(44.4)	
	Medical-Aid	14	(0.4)	8	(0.3)	
First episode	Hospitalized	2,146	(60.7)	1,673	(56.5)	< 0.001
intervention	Ambulatory	1,392	(39.3)	1,288	(43.5)	
Medical institution	Tertiary Hospital	630	(17.8)	749	(25.3)	< 0.001
on first episode	General Hospital	830	(23.5)	669	(22.6)	
	Hospital	2,078	(58.7)	1,543	(52.1)	
Length of hospital stay	≥90 days	1240	(35.1)	788	(26.6)	< 0.0001
	< 90days	2,298	(65.0)	2,173	(73.4)	
PDC, Mean (SD)		0.36	(0.26)	0.95	(0.06)	< 0.001
Dose intensity of antipsychotics	Mean (SD)	0.53	(0.76)	1.39	(1.38)	< 0.001
Dose intensity of antipsychotics	Low	2,964	(83.78)	1,428	(48.23)	< 0.001
	Moderate	398	(11.25)	945	(31.91)	
	High	176	(4.97)	588	(19.86)	

Variables			Adherence to Antipsychotics				p
			Low (N = 3,538)		High (N = 2,961)		
N	(%)	N (%)					
Prior job experience		Yes	1,737	(49.1)	1,513	(51.1)	NS
		No	1,801	(50.9)	1,448	(48.9)	
Job acquired during the follow-up period		Yes	1,344	(38.0)	1,327	(44.8)	< 0.001
		No	2,194	(62.0)	1,634	(55.2)	
Death		Yes	309	(8.7)	217	(7.3)	0.039
		No	3,229	(91.3)	2,744	(92.7)	
Follow-up years, Mean (SD)			6.82	(3.51)	6.11	(3.93)	< 0.001
SD, Standard Deviations; NHI, National Health Insurance; PDC, Proportion of Days Covered							

Bivariate analysis

Table 2 shows the unadjusted hazard ratios (HR) of antipsychotics adherence for subsequent job acquisition among the study sample. Overall, individuals with high adherence to antipsychotics were 1.32 times more likely to find a job than those with low adherence over the follow-up period (unadjusted HR, 1.32; 95% CI, 1.21–1.41).

Multivariable Cox proportional hazard models

Table 3 presents the results of multivariable Cox proportional hazard regression analysis. Overall, high (vs. low) adherence to antipsychotic medication was associated with an increased likelihood of subsequent job acquisition over the follow-up period across models. The AHR estimates ranged from 1.30 in Model 1 to 1.16 in Model 3: (a) AHR, 1.30; 95% CI, 1.21–1.41 in Model 1 adjusting for age, sex, income, and prior job experience, (b) AHR, 1.16; 95% CI, 1.07–1.27 in Model 2 further adjusting for disease severity and dose intensity of antipsychotics, and (c) AHR, 1.17; 95% CI, 1.07–1.29 in Model 3 further adjusting for co-prescribed psychoactive medications.

Interaction and subgroup analyses

We examined potential interactions by demographic (e.g., age, sex, income) and clinical (e.g., dose intensity) characteristics and further performed subgroup analysis across such variables. We found a statistically significant interaction between adherence and sex (interaction p = 0.04), in which the magnitude of the effects was stronger among men (AHR, 1.29; 95% CI, 1.13–1.46) than women (AHR, 1.07; 95% CI, 0.96–1.20) (Supplement Table 4).

However, there was no significant interaction by age (interaction p = 0.07) in the association between antipsychotics adherence and job acquisition (Supplement Table 5). Similarly, we found no significant interaction between adherence and income (interaction p = 0.77) (Supplement Table 6), and between adherence and dose intensity (interaction p = 0.73) (Supplement Table 7). These suggest that the beneficial effects of antipsychotics adherence on job acquisition were generally consistent across age groups and the levels of dose intensity.

Discussion

This study investigated the effects of adherence to antipsychotics on subsequent job acquisition after diagnosis of first-episode schizophrenia among 6,499 individuals aged 25–54 years using a 10-year cohort of the 2014–2023 Korean National Health Insurance Database (NHID). We performed multivariable Cox proportional hazard modeling analysis and found that individuals with high-level adherence to antipsychotic medication (PDC ≥ 0.8) exhibited nearly 16% higher likelihood of subsequent job acquisition during the follow-up period, compared to their counterparts with low-level adherence (PDC < 0.8), when adjusting for sociodemographic and medical conditions. Our analysis also showed that, while a more pronounced relationship was found among men than women, the effects of adherence are generally consistent across age groups, socioeconomic status, and dose intensity of antipsychotic. To our knowledge, this is first to examine such a relationship by using a time-to-event analytic approach, in which only those without a job at study entry were included thereby estimating the association upon a “incidence-scale” rather than “prevalence-scale”, based on a large-size nationally representative sample of Korean populations.

Previous studies have consistently pointed to the importance of adherence to antipsychotic medications across various outcomes. Thus, compared to those who were non-adherent, individuals who were adherent to antipsychotic medications were associated with generally favorable clinical (e.g., symptom severity, relapse, or re-hospitalization), behavioral (e.g., substance abuse and cognitive functioning) and social outcomes (e.g., violence, crime, and suicidality) (Ascher-Svanum et al. 2006; Haddad et al. 2014; Higashi et al. 2013; Novick et al. 2010).

For instance, Ascher-Svanum and colleagues (2006) conducted a multi-site prospective cohort study of 1906 individuals from the US Schizophrenia Care and Assessment Program (SCAP) with a 3-year’s follow-up between 1997 and 2003.(Ascher-Svanum et al. 2006) Adherence status was measured with both (a) patients’ self-report using the SCAP Health Questionnaire and (b) medication possession ratio (MPR, the total number of days prescribed divided by the full number of observation days) based on the prescription data.(Ascher-Svanum et al. 2006). The study found that individuals with non-adherence (vs. adherence) were more likely to use mental healthcare services (e.g., emergency psychiatric service use or hospitalization), engage in negative social behaviors (e.g., substance use, alcohol-related problems, violence, victimizations, or arrests), and decreased mental functioning and quality of life (e.g., satisfaction with basic needs, social life or life in general) (Ascher-Svanum et al. 2006). However, the study did not find a statistically significant association between the non-adherence (vs. adherence) in

the first year and unemployed status over the second-to-third years, while the directionality of the effect estimates suggested harmful effects of non-adherence on employment status (Ascher-Svanum et al. 2006).

More broadly, our findings are in line with existing evidence that generally indicate beneficial effects of adherence to antipsychotic medications on various clinical, behavioral, and social outcomes. Although Ascher-Svanum's study did not find a significant association between non-adherence and unemployment, smaller sample size or mixed employment status at baseline (including both those employed and unemployed) might affect the results. Building on previous efforts and evidence, we extended the investigation by looking at the incident job acquisition among those who were under unemployed status at study entry. Moreover, we further investigated potential moderations and documented that the harmful effects of medication non-adherence were generally consistent across age groups, socioeconomic status, and dose-intensity, except for the more pronounced effects detected among men than women.

Plausible mechanisms linking adherence to antipsychotics with subsequent job acquisition may include the benefits of antipsychotic medications on clinical, cognitive and behavioral domains. For instance, the use of antipsychotics has shown to reduce positive and negative symptoms, resulting in decreased risks of relapse and rehospitalization, which in turn can improve social and occupational functionality (Haddad and Correll 2018; Lindstrom and Lundberg 1997; Littrell 1995; Razzano et al. 2005). Network meta-analyses showed small but significant improvements in global cognitive functioning, including attention and working memory, among individuals who were prescribed with and taking antipsychotics (Efthimiou et al. 2024). Some other studies demonstrated improved quality of life and social functioning among individuals taking antipsychotics compared to placebo control (Feber et al. 2025; Goff et al. 2017; Haime et al. 2021; Leucht et al. 2020; Leucht et al. 2024).

Our study has several limitations that need to be considered when interpreting the findings. First, we calculated antipsychotic adherence based on prescription records, which may not capture actual medication intake of the users. However, the approach of estimating medication adherence based on prescription records is widely used (Shah et al. 2023; Steiner and Prochazka 1997). Second, while the severity of schizophrenia may affect prognosis and social recovery, due to the nature of the claims data, we were not able to measure disease severity directly. Third, the prescription of other psychoactive drugs could not be fully explored, despite the well-known concern of polypharmacy among those with schizophrenia (Kamei 2022; Kodaka et al. 2023; Tiihonen et al. 2012). Lastly, our observational design cannot rule out unmeasured confounding and thereby limiting causality.

Despite these limitations, our study has several strengths. To the best of our knowledge, this is first to investigate such association based on an "incidence-scale", focusing on individuals with first-episode schizophrenia who did not have job at study entry and analyzing with time-to-event analytic methods over the follow-up period. Moreover, we used a large nationally representative sample drawn from the Korean NHI claims database. Additionally, we considered an extensive range of covariates including

sociodemographic factors and concurrent non-antipsychotic psychotropic medications. These approaches incorporated in our study design, together, enable to estimate the prospective causal association, which can plausibly reflect the relationship among the entire Korean population. Further research is needed to consider the potential roles and interplay among subtypes of antipsychotics and co-prescribing medications.

Conclusions

Our findings suggest that adherence to antipsychotic medication is beneficial in job attainment among individuals with first-episode schizophrenia regardless of their sociodemographic and medical conditions. This is first to document such findings using an incidence-framework among individuals without a job at study entry based on a nationally representative sample of Korean populations. While further investigation is warranted, the findings of our study inform public health and clinical approaches that can incorporate education and support programs to improve medication adherence and thereby empowering the marginalized population to better function as a member of a family and more broadly of a society.

Declarations

CRediT authorship contribution statement

Hye-Young Kwon: Conceptualization, Formal analysis, Writing – original draft preparation

Jinyeong Bae: Writing – original draft preparation

Yong-Pyo Lee: Conceptualization

Rachel F. Rodgers: Writing – review & editing

Eric Bui: Writing – review & editing

Yongjoo Kim: Formal analysis, Writing – original draft preparation

Financial Disclosure

No funding was received for conducting this study.

Ethical Approval

This study was approved by the Institutional Review Board of Mokwon University in South Korea (no. 2024-002).

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Author Contribution

H.K. and Y.L. conceived the study design. H.K. and Y.K. conducted data analysis. J.B., H.K., and Y.K. drafted the manuscript. E.B. and R.F.R. edited the manuscript. All authors approved the finalized manuscript.

Acknowledgement

We express our gratitude to the Korean National Health Insurance Service (NHIS), which provided access to the Korean National Health Information Database (NHID) under license (no. REQ202401325-003) for the project titled “Effect of Antipsychotics on Job Acquisition among Schizophrenia”

Data Availability

All data generated or analyzed in this study were strictly restricted by the Korean National Health Insurance Service (NHIS). Access to data for the current study was granted under the NHIS license. Hence, these data are not publicly available.

References

1. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW (2006) Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry 67(3):453–460. https://doi.org/10.4088/jcp.v67n0317
2. Blecker S, Mann DM, Martinez TR, Belli HM, Zhao Y, Ahmed A, Fitchett C, Wong C, Bearnot HR, Voils CI, Schoenthaler AM (2025) Medication Adherence in Hypertension: A Cluster Randomized Clinical Trial. JAMA Cardiol 10(9):914–921. https://doi.org/10.1001/jamacardio.2025.2155
3. Chafi YK, Amare T, Haile K, Damene W, Tesfaye G, Minichil W (2020) Prevalence and correlates of job loss among schizophrenia outpatients at St. AmanuelMental Specialized Hospital, Addis Ababa, Ethiopia; cross sectional study. PLoS ONE 15(12):e0242352. https://doi.org/10.1371/journal.pone.0242352
4. Chang SM, Cho SJ, Jeon HJ, Hahm BJ, Lee HJ, Park JI, Cho MJ (2008) Economic burden of schizophrenia in South Korea. J Korean Med Sci 23(2):167–175. https://doi.org/10.3346/jkms.2008.23.2.167
5. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Whiteford HA (2018) Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of

Disease Study 2016. Schizophr Bull 44(6):1195–1203. https://doi.org/10.1093/schbul/sby058

6. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, Do CH, Song JS, Hyon Bang J, Ha S, Lee EJ, Ae Shin S (2017) Data Resource Profile: The National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 46(3):799–800. https://doi.org/10.1093/ije/dyw253
7. Cho SJ, Kim J, Kang YJ, Lee SY, Seo HY, Park JE, Kim H, Kim KN, Lee JY, Sohn JH (2020) Annual Prevalence and Incidence of Schizophrenia and Similar Psychotic Disorders in the Republic of Korea: A National Health Insurance Data-Based Study. Psychiatry Investig 17(1):61–70. https://doi.org/10.30773/pi.2019.0041
8. Collins DE, Luther L, Raugh IM, Condray R, Allen DN, Strauss GP (2023) The Role of Disability Benefits as an Environmental Factor Contributing to Negative Symptoms. Schizophr Bull 49(1):1–4. https://doi.org/10.1093/schbul/sbac077
9. Efthimiou O, Taipale H, Radua J, Schneider-Thoma J, Pinzon-Espinosa J, Ortuno M, Vinkers CH, Mittendorfer-Rutz E, Cardoner N, Tanskanen A, Fusar-Poli P, Cipriani A, Vieta E, Leucht S, Tiihonen J, Luykx JJ (2024) Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. Lancet Psychiatry 11(2):102–111. https://doi.org/10.1016/S2215-0366(23)00366-8
10. Elie D, Poirier M, Chianetta J, Durand M, Grégoire C, Grignon S (2010) Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. J Psychopharmacol 24(7):1037–1044. https://doi.org/10.1177/0269881108100777
11. Feber L, Peter NL, Chiocchia V, Schneider-Thoma J, Siafis S, Bighelli I, Hansen WP, Lin X, Prates-Baldez D, Salanti G, Keefe RSE, Engel RR, Leucht S (2025) Antipsychotic Drugs and Cognitive Function: A Systematic Review and Network Meta-Analysis. JAMA Psychiatry 82(1):47–56. https://doi.org/10.1001/jamapsychiatry.2024.2890
12. Garcia S, Martinez-Cengotitabengoa M, Lopez-Zurbano S, Zorrilla I, Lopez P, Vieta E, Gonzalez-Pinto A (2016) Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review. J Clin Psychopharmacol 36(4):355–371. https://doi.org/10.1097/JCP.0000000000000523
13. Goff DC, Falkai P, Fleischhacker WW, Girgis RR, Kahn RM, Uchida H, Zhao J, Lieberman JA (2017) The Long-Term Effects of Antipsychotic Medication on Clinical Course in Schizophrenia. Am J Psychiatry 174(9):840–849. https://doi.org/10.1176/appi.ajp.2017.16091016
14. Haddad PM, Brain C, Scott J (2014) Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas 5:43–62. https://doi.org/10.2147/PROM.S42735
15. Haddad PM, Correll CU (2018) The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. Ther Adv Psychopharmacol 8(11):303–318. https://doi.org/10.1177/2045125318781475

16. Haime Z, Watson AJ, Crellin N, Marston L, Joyce E, Moncrieff J (2021) A systematic review of the effects of psychiatric medications on social cognition. BMC Psychiatry 21(1):597. https://doi.org/10.1186/s12888-021-03545-z
17. Hakulinen C, Elovainio M, Arffman M, Lumme S, Suokas K, Pirkola S, Keskimaki I, Manderbacka K, Bockerman P (2020) Employment Status and Personal Income Before and After Onset of a Severe Mental Disorder: A Case-Control Study. Psychiatr Serv 71(3):250–255. https://doi.org/10.1176/appi.ps.201900239
18. Higashi K, Medic G, Littlewood KJ, Diez T, Granstrom O, De Hert M (2013) Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol 3(4):200–218. https://doi.org/10.1177/2045125312474019
19. Ho PM, Glorioso TJ, Allen LA, Blankenhorn R, Glasgow RE, Grunwald GK, Khanna A, Magid DJ, Marrs JC, Novins-Montague S, Orlando S, Peterson P, Plomondon ME, Sandy LM, Saseen JJ, Trinkley KE, Vaughn S, Waughtal J, Bull S (2025) Personalized Patient Data and Behavioral Nudges to Improve Adherence to Chronic Cardiovascular Medications: A Randomized Pragmatic Trial. JAMA 333(1):49–59. https://doi.org/10.1001/jama.2024.21739
20. Holm M, Taipale H, Tanskanen A, Tiihonen J, Mitterdorfer-Rutz E (2021) Employment among people with schizophrenia or bipolar disorder: A population-based study using nationwide registers. Acta Psychiatr Scand 143(1):61–71. https://doi.org/10.1111/acps.13254
21. Inada K, Saito Y, Baba K, Fukui D, Masuda Y, Inoue S, Masuda T (2024) Factors associated with death, hospitalization, resignation, and sick leave from work among patients with schizophrenia in Japan: a nested case-control study using a large claims database. BMC Psychiatry 24(1):22. https://doi.org/10.1186/s12888-023-05474-5
22. Jung YS, Kim YE, Go DS, Yoon SJ (2021) The prevalence, incidence, and admission rate of diagnosed schizophrenia spectrum disorders in Korea, 2008–2017: A nationwide population-based study using claims big data analysis. PLoS ONE 16(8):e0256221. https://doi.org/10.1371/journal.pone.0256221
23. Kamei H (2022) Polypharmacy Management of Antipsychotics in Patients with Schizophrenia. Med (Kaunas) 58(11). https://doi.org/10.3390/medicina58111584
24. Kodaka F, Ohi K, Yasuda Y, Fujimoto M, Yamamori H, Hasegawa N, Ito S, Fukumoto K, Matsumoto J, Miura K, Yasui-Furukori N, Hashimoto R (2023) Relationships Between Adherence to Guideline Recommendations for Pharmacological Therapy Among Clinicians and Psychotic Symptoms in Patients With Schizophrenia. Int J Neuropsychopharmacol 26(8):557–565. https://doi.org/10.1093/ijnp/pyad037
25. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV (2002) Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry 63(10):892–909. https://doi.org/10.4088/jcp.v63n1007

26. Leslie RS (2007) Using Arrays to Calculate Medication Utilization. SAS Global Forum 2007, Orlando, FL, USA. Available at http://www2.sas.com/proceedings/forum2007/043-2007.pdf
27. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM (2020) Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry 177(4):342–353. https://doi.org/10.1176/appi.ajp.2019.19010034
28. Leucht S, Priller J, Davis JM (2024) Antipsychotic Drugs: A Concise Review of History, Classification, Indications, Mechanism, Efficacy, Side Effects, Dosing, and Clinical Application. Am J Psychiatry 181(10):865–878. https://doi.org/10.1176/appi.ajp.20240738
29. Lim SJ, Jang SI (2025) Leveraging National Health Insurance Service Data for Public Health Research in Korea: Structure, Applications, and Future Directions. J Korean Med Sci 40(8):e111. https://doi.org/10.3346/jkms.2025.40.e111
30. Lindstrom L, Lundberg T (1997) Long-term effect on outcome of clozapine in chronic therapy-resistant schizophrenic patients. Eur Psychiatry 12(5):353s–355s. https://doi.org/10.1016/S0924-9338(97)83579-1
31. Littrell K (1995) Maximizing schizophrenia treatment outcomes: A model for reintegration. Psychiatr Rehabil J 19(1):75
32. Loucks J, Zuckerman AD, Berni A, Saulles A, Thomas G, Alonzo A (2022) Proportion of days covered as a measure of medication adherence. Am J Health-System Pharm 79(6):492–496
33. Martini LC, Barbosa Neto JB, Petreche B, Fonseca AO, Santos FVD, Magalhães L, Marques AG, Soares C, Cordeiro Q, Attux C, Bressan RA (2018) Schizophrenia and work: aspects related to job acquisition in a follow-up study. Braz J Psychiatry 40(1):35–40. https://doi.org/10.1590/1516-4446-2016-2128
34. Marwaha S, Johnson S, Bebbington P, Stafford M, Angermeyer MC, Brugha T, Azorin JM, Kilian R, Hansen K, Toumi M (2007) Rates and correlates of employment in people with schizophrenia in the UK, France and Germany. Br J Psychiatry 191:30–37. https://doi.org/10.1192/bjp.bp.105.020982
35. NHIS (2025) Population Coverage. Available at https://www.nhis.or.kr/english/wbheaa02400m01.do (accessed 2025)
36. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM (2010) Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res 176(2–3):109–113. https://doi.org/10.1016/j.psychres.2009.05.004
37. Perala J, Saarni SI, Ostamo A, Pirkola S, Haukka J, Harkanen T, Koskinen S, Lonnqvist J, Suvisaari J (2008) Geographic variation and sociodemographic characteristics of psychotic disorders in Finland. Schizophr Res 106(2–3):337–347. https://doi.org/10.1016/j.schres.2008.08.017
38. Razzano LA, Cook JA, Burke-Miller JK, Mueser KT, Pickett-Schenk SA, Grey DD, Goldberg RW, Blyler CR, Gold PB, Leff HS, Lehman AF, Shafer MS, Blankertz LE, McFarlane WR, Toprac MG, Ann Carey M (2005) Clinical factors associated with employment among people with severe mental illness: findings from the employment intervention demonstration program. J Nerv Ment Dis 193(11):705–713. https://doi.org/10.1097/01.nmd.0000185939.11282.3e

39. Shah KK, Touchette DR, Marrs JC (2023) Research and scholarly methods: Measuring medication adherence. J Am Coll Clin Pharm 6(4):416–426
40. Shin W, Lee DH, Hong M, Kim MK, Yoo H, Lee YS, Jung S (2025) Increased Anticholinergic Agent Use With Co-prescription of CYP2D6-Inhibiting SSRIs and Risperidone, but not Aripiprazole: A Nationwide Cohort Study. Schizophr Bull. https://doi.org/10.1093/schbul/sbaf189
41. Song J, Zhang YX, Qin MN, Ren JX, Jia YN, Yu H, Zhou YQ (2024) Experiences of returning to work in patients with schizophrenia after treatment: A longitudinal qualitative study. Int J Soc Psychiatry 70(3):588–600. https://doi.org/10.1177/00207640231223423
42. Steiner JF, Prochazka AV (1997) The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 50(1):105–116. https://doi.org/10.1016/s0895-4356(96)00268-5
43. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P (2012) Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry 69(5):476–483. https://doi.org/10.1001/archgenpsychiatry.2011.1532
44. Velligan DI, Rao S (2023) The Epidemiology and Global Burden of Schizophrenia. J Clin Psychiatry 84(1). https://doi.org/10.4088/JCP.MS21078COM5

Figures

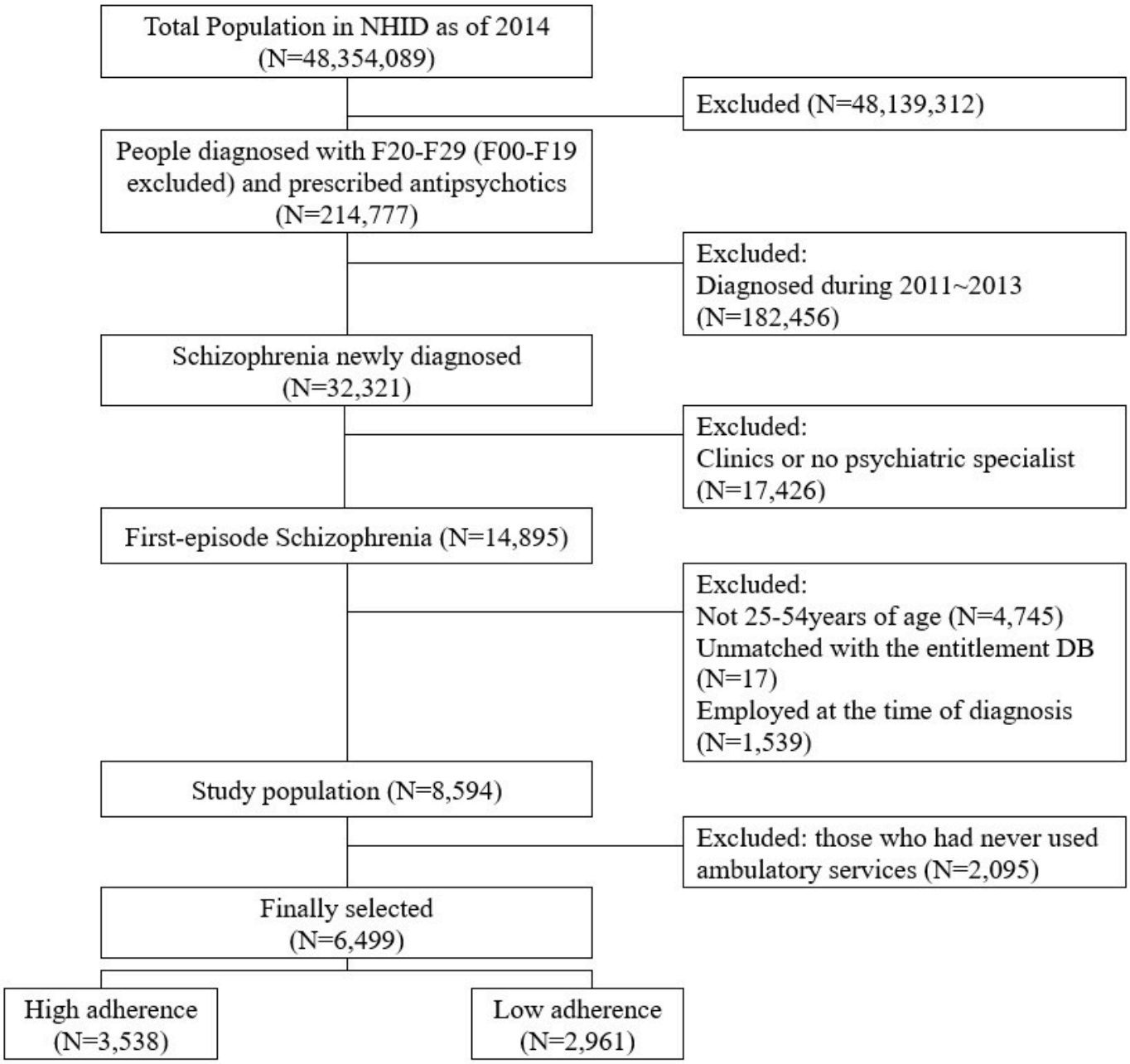


Figure 1

Flow chart of the study cohort selection

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 07tables.docx
- 09supplementarytablesfigures.docx