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The association between season of birth, age at onset, and clozapine use in schizophrenia

Kim JS, Park CM, Choi JA, Park E, Tchoe HJ, Choi M, Suh JK, Kim YH, Won SH, Chung YC, Bae KY, Lee SK, Park SC, Lee SH. The association between season of birth, age at onset, and clozapine use in schizophrenia.

Objective: This study aimed to determine whether the rate of clozapine use, an indicator of refractoriness in schizophrenia, is associated with the season of birth and age at onset in patients with schizophrenia based on nationwide data.
Methods: Patients with schizophrenia (n = 114 749) who received prescriptions for antipsychotic medication between 2008 and 2014 were retrospectively identified from the Korean National Health Insurance Service database. The study population was divided into three groups based on their age at the onset of schizophrenia (early, middle, and late onset). We assessed differences in the month of birth between patients and the general population. In addition, the cumulative clozapine use was calculated.
Results: Compared to the late-onset schizophrenia group, the early- and middle-onset groups showed a higher probability of birth during the winter season. In addition, the early-onset group showed the highest cumulative clozapine use rate. In the middle-onset group, the initiation of clozapine use was significantly earlier for patients born in winter compared to those born in summer.
Conclusion: Our results indicate that the age at onset is an important factor in predicting the prognosis of schizophrenia patients. The season of birth also affects the prognosis, but with less robustness. Specifically, it appears that early disease onset and winter birth might be associated with poor outcomes in Korean patients with schizophrenia.

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Key words: schizophrenia; seasonal birth; age at onset; clozapine use rate; prognosis

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Significant outcomes

- Patients with early-onset schizophrenia showed the highest clozapine prescription rate independent of season of birth patterns.
- The clozapine prescription rate was higher in the middle-onset group for patients that were born in winter.
- Both the age at onset and season of birth are important factors associated with the prognosis of schizophrenia patients.

Limitations

- This study was conducted on data obtained from the Korean population and caution should be exercised when generalizing our findings to other ethnicities.
- The clozapine treatment as a proxy definition for treatment resistance is too narrow to capture all patients with treatment-resistant schizophrenia due to the possible underuse of clozapine in high-income countries.
- The study was restricted to new users of antipsychotics and did not include prodromal patients.

Introduction

A seasonal risk for schizophrenia according to the season of birth has been established. The probability of winter and spring births has been shown to exceed that of summer or autumn births by 5–8% in patients with schizophrenia (1, 2). A meta-analysis found this seasonality effect to be consistent but not large in terms of relative risk. (3) Additionally, Suvisaari et al. reported that the intensity of the factors causing the seasonal variation of births in schizophrenia may be decreasing (4). Cheng et al. reported that the deviant season of birth in winter and spring was found in female but not male patients with schizophrenia (5). The factors underlying this deviant season of birth have not been fully established but may include viral infection, cold weather, stress, vitamin D deficiency, nutritional deficiencies, external toxins, and susceptibility gene interactions (2, 6, 7). Whether treatment refractoriness in schizophrenia is associated with season of birth remains to be elucidated. Sorensen et al. reported that autumn birth was associated with an increased probability of clozapine treatment in Danish patients with schizophrenia (8). Additionally, this study suggested that early exposures to the winter flu season and low vitamin D levels might be causative factors for this phenomenon.

Numerous studies suggest that the course and outcome are relatively worse in schizophrenia that begins at an early age compared to that beginning at an adult age (9–12). In particular, some studies on patients with early-onset schizophrenia (age < 13 years) have revealed a considerably worse prognosis for early-onset than late-onset disease (12, 13). Other studies have found no differences in symptoms and functioning between early-onset and adult-onset schizophrenia patients (14, 15). On the contrary, a long-term follow-up study by Amminger et al. showed that patients with early-onset schizophrenia had fewer symptoms and superior functioning than those with a later onset (16). However, the majority of these studies have been conducted on a relatively small number of patients. Therefore, to achieve a reliable prognosis for schizophrenia based on the age at onset, further studies involving a larger number of patients are required.

Clozapine remains the drug of choice for patients with treatment-refractory schizophrenia (17) because of its unique effectiveness and ability to significantly reduce suicidal behaviour (18, 19). However, clozapine use is associated with serious side-effects, such as agranulocytosis and fever. In addition, clozapine use must be monitored closely using frequent obligatory blood evaluations. Because of these characteristics, clozapine is generally prescribed for refractory schizophrenia (8, 20, 21).

There is insufficient evidence to conclude whether season of birth and age at onset are important prognostic factors for patients with schizophrenia. In the present study, the national administrative claim data in Korea were analyzed. The age at onset was defined as the first date of prescription of antipsychotic medication for the treatment of schizophrenia. The information on prescriptions was available in our National Insurance Health Service data. Moreover, we investigated the relationship between age at onset and season of birth in schizophrenia. We hypothesized that season of birth, age at onset, and the combination of these two parameters are associated with the prognosis of schizophrenia.

Methods

Data source

The present study is based on the Statistics Korea and National Health Insurance Service (NHIS) databases. To estimate the birth rate by month among patients with schizophrenia, we obtained birth month data from the Statistics Korea database. The number of patients diagnosed with schizophrenia was obtained from the NHIS database (NHIS-2015-4-004). The use of the NHIS

database to estimate the proportions of specific subpopulations of patients and to quantify treatment use has several advantages (22). First, South Korea provides universal health insurance coverage. NHIS covers the entire population of South Korea (50.6 million) and therefore is representative of the Korean population (22). Second, the NHIS data include diagnostic information. Patients are diagnosed according to the International Classification of Diseases, 10th Edition (ICD-10). In addition, the data on procedures, prescriptions (drug name, formula, dose, duration of prescription, and costs), and demographics are provided. Therefore, using the NHIS database, it is possible to monitor the diagnosis and treatment usage in a specific disease in routine clinical practice. These databases have been used in previous studies (23, 24). This study was approved by the Institutional Review Board at the National Evidence-based Healthcare Collaborating Agency (NECAIRB 14-017).

Subjects

This retrospective population-based analysis used the NHIS database to identify patients with schizophrenia between January 1, 2008, and December 31, 2014. Incident cases of schizophrenia were identified according to the following steps: First, we selected subjects with a diagnostic code for schizophrenia (ICD-10, F20) and selected those who were prescribed antipsychotic medications (WHO Anatomical Therapeutic Chemical, ATC, code N05AA01, N05AA02, N05AA05, N05AB03, N05AC02, N05AC03, N05AD01, N05 AD06, N05AE02, N05AE04, N05AF01, N05A F03, N05AF04, N05AF05, N05AG02, N05AH01, N05AH02, N05AH03, N05AH04, N05AL01, N05 AL05, N05AX08, N05AX11, N05AX12, N05A X13, Nemonapride and Blonanserin) between January 1, 2008, and December 31, 2014. Second, among all subjects who satisfied the first criterion, new users of antipsychotics were defined as those who had received no prescriptions for antipsychotic medication for schizophrenia treatment in the previous 4 years. A total of 114 749 new users of antipsychotics with schizophrenia aged 15–64 years were included in this study (Table 1). The study population was divided into three groups according to the age at onset: early-onset corresponded to 15–20 years of age, middle-onset to 21–44 years of age, and late-onset to 45–64 years of age (25). The age at onset was defined as the date of the first prescription for antipsychotic medication to treat symptoms of schizophrenia.

Statistical analysis

To assess differences in the season of birth rate between patients with schizophrenia and the general population, we performed a chi-squared test. Differences between the observed and expected number of patient births are expressed as a percentage excess or deficit for each month. In patients with schizophrenia, the expected number of births was calculated based on the number observed in the general population. We classified births by meteorological season as follows: March to May as spring, June to August as summer, September to November as fall, and December to February as winter (5). Our data were also analyzed using the astronomical definition of seasons as follows: April to June as spring, July to September as summer, October to December as fall, and January to March as winter. We estimated the time from the age at onset of schizophrenia to the first prescription of clozapine as a pragmatic measure of treatment resistance (8). A Walter–Elwood test was used to assess a possible season of birth in the clozapine prescription rate (26). The cumulative incidence of clozapine use from the time of schizophrenia onset was analyzed using the Kaplan–Meier method and log-rank test. We considered the death rate when estimating and plotting the cumulative incidence. The total number of deaths was 7753, and the death rate was 18.4 (per 1000 person-years). All data manipulation and statistical analyses were performed using SAS 9.1.3 (SAS Institute, Cary, NC, USA), except for the Walter–Elwood test and graphing, which were performed using R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Differences in distributions with a P-value <0.05 were considered statistically significant.

Results

Effects of season of birth in schizophrenia

Table 2 displays the actual vs. expected births by month in patients with schizophrenia. The expected number of births was calculated by applying the proportion in the general population for each of the three groups classified by age at onset (early, middle, and late onset).

First, patients with schizophrenia showed an excess of births in January and February (Jan and Feb). In terms of age at onset, the early- and middle-onset groups showed higher excess percentages in winter (Jan and Feb) compared to the late-onset group (6.3% and 26.4% for early onset, 8.5% and

Table 1. Baseline characteristics of the study population

	Total		Initiation of Antipsychotics						
			Early (15–20)		Middle (21–44)		Late (45–64)		
	n = 114 749		*n* = 12 811		*n* = 56 309		*n* = 45 629		*P*-value
Sex									
Male	56 691	49.4%	7896	61.6%	27 909	49.6%	20 886	45.8%	<0.0001
Female	58 058	50.6%	4915	38.4%	28 400	50.4%	24 743	54.2%	
Age of onset of antipsychotics									
Mean ± SD	39.6	14.0	17.9	1.5	32.7	6.9	54.2	5.6	<0.0001
Min, max	16	64	16	20	21	44	45	64	
Calendar year of onset									
2008	18 223	15.9%	1879	14.7%	9257	16.4%	7087	15.5%	<0.0001
2009	18 756	16.3%	1953	15.2%	9162	16.3%	7641	16.7%	
2010	15 343	13.4%	1757	13.7%	7631	13.6%	5955	13.1%	
2011	16 305	14.2%	1904	14.9%	7885	14.0%	6516	14.3%	
2012	22 084	19.2%	2591	20.2%	10 783	19.1%	8710	19.1%	
2013	19 784	17.2%	2188	17.1%	9439	16.8%	8157	17.9%	
2014	4254	3.7%	539	4.2%	2152	3.8%	1563	3.4%	
Type of beneficiary									
Insured	38 802	33.8%	616	4.8%	18 888	33.5%	19 298	42.3%	<0.0001
Dependents	75 947	66.2%	12 195	95.2%	37 421	66.5%	26 331	57.7%	
Type of medical insurance									
Industrial workers	52 455	45.7%	4550	35.5%	26 962	47.9%	20 943	45.9%	<0.0001
Self-employed	62 294	54.3%	8261	64.5%	29 347	52.1%	24 686	54.1%	
Season of birth (Meteorological)									
Spring	28 227	24.6%	3106	24.2%	13 091	23.2%	12 030	26.4%	<0.0001
Summer	26 311	22.9%	2893	22.6%	12 725	22.6%	10 693	23.4%	
Fall	27 557	24.0%	3109	24.3%	13 762	24.4%	10 686	23.4%	
Winter	32 654	28.5%	3703	28.9%	16 731	29.7%	12 220	26.8%	
Season of birth (Astronomical)									
Spring	25 816	22.5%	2924	22.8%	12 271	21.8%	10 621	23.3%	<0.0001
Summer	27 291	23.8%	2996	23.4%	13 327	23.7%	10 968	24.0%	
Fall	28 045	24.4%	3098	24.2%	14 060	25.0%	10 887	23.9%	
Winter	33 597	29.3%	3793	29.6%	16 651	29.6%	13 153	28.8%	

27.1% for middle onset, for Jan and Feb respectively). The late-onset group showed the highest excess birth rate in March (Mar; 10.6%). Figure 1 shows the monthly birth percentages by age at onset in patients with schizophrenia. A clear peak can be observed in Jan and Feb for patients with early- and middle-onset disease.

The effect of the clozapine treatment rate on age at onset and season of birth

Figure 2 shows the cumulative incidence of clozapine prescription according to the age at onset. A significant difference in the cumulative incidence of clozapine use was observed based on the age at onset ($P < 0.001$). The early-onset group showed the highest cumulative incidence of clozapine use ($P < 0.001$). Moreover, significant differences in clozapine use were observed depending on season of birth ($P = 0.01$). The winter birth group showed a significantly higher incidence of clozapine use than the summer birth group (winter group = 0.037, summer group = 0.031; $P = 0.01$). Figure 3 displays the cumulative incidence of clozapine use by season of birth for each disease onset classification. The middle-onset group showed a significantly earlier initiation of clozapine use in patients born in winter and fall than in those born in summer (winter = 0.040, fall = 0.037, summer = 0.03; $P = 0.03$). There was no significant association between age at onset and clozapine use when births were classified by astronomical season (Supplementary Figure 1).

Discussion

In the present study, Korean patients with early- and middle-onset schizophrenia had a distinctive season of birth pattern, showing a steep increase in winter births. Interestingly, patients with early-onset schizophrenia showed the highest clozapine prescription rate independent of season of birth patterns. The clozapine prescription rate was higher for winter births in the middle-onset group. Overall, our results indicate that both patient age at onset and season of birth are important factors for the prognosis for schizophrenia.

In this study, we showed that the early- and middle-onset groups exhibited birthdate peaks in the

Table 2. Proportion of patients with schizophrenia by month of birth from 2008 to 2014 by onset age (n = 114 749)

		January	February	March	April	May	June	July	August	September	October	November	December	Total
Schizophrenia														
Early onset	*n*	1306	1379	1108	1059	939	926	1012	955	1029	1059	1021	1018	12 811
	%	10.2%	10.8%	8.6%	8.3%	7.3%	7.2%	7.9%	7.5%	8.0%	8.3%	8.0%	7.9%	100%
Middle onset	*n*	5856	6093	4702	4122	4267	3882	4357	4486	4484	4793	4485	4782	56 309
	%	10.4%	10.8%	8.4%	7.3%	7.6%	6.9%	7.7%	8.0%	8.0%	8.5%	8.0%	8.5%	100%
Late onset	*n*	4330	4137	4686	3598	3746	3277	3534	3882	3552	3714	3420	3753	45 629
	%	9.5%	9.1%	10.3%	7.9%	8.2%	7.2%	7.7%	8.5%	7.8%	8.1%	7.5%	8.2%	100%
Total	*n*	11 492	11 609	10 496	8779	8952	8085	8903	9323	9065	9566	8926	9553	114 749
	%	10.0%	10.1%	9.1%	7.7%	7.8%	7.0%	7.8%	8.1%	7.9%	8.3%	7.8%	8.3%	100%
Expected number														
All births of Korea population in 2000–2009	%	9.6%	8.5%	9.3%	8.5%	8.2%	7.5%	7.9%	8.1%	8.4%	8.5%	8.0%	7.6%	100%
Early onset	*n*	1228	1091	1190	1083	1054	966	1007	1037	1078	1088	1024	967	12 811
Middle onset	*n*	5398	4794	5230	4759	4632	4245	4424	4556	4738	4781	4500	4252	56 309
Late onset	*n*	4374	3885	4238	3856	3753	3440	3585	3692	3839	3874	3646	3446	45 629
Total	*n*	11 000	9770	10 658	9698	9438	8650	9016	9285	9655	9743	9170	8666	114 749
Relative excess or decrease														*P*-value*
Early onset	%	6.3%	26.4%	−6.9%	−2.2%	−10.9%	−4.1%	0.5%	−7.9%	−4.5%	−2.6%	−0.3%	5.2%	<0.0001
Middle onset	%	8.5%	27.1%	−10.1%	−13.4%	−7.9%	−8.5%	−1.5%	−1.5%	−5.4%	0.3%	−0.3%	12.5%	<0.0001
Late onset	%	−1.0%	6.5%	10.6%	−6.7%	−0.2%	−4.7%	−1.4%	5.1%	−7.5%	−4.1%	−6.2%	8.9%	<0.0001
Total	%	4.5%	18.8%	−1.5%	−9.5%	−5.2%	−6.5%	−1.3%	0.4%	−6.1%	−1.8%	−2.7%	10.2%	<0.0001

*Chi-square test to compare birth rate of general population to birth rate of schizophrenia patients regarding to each month.

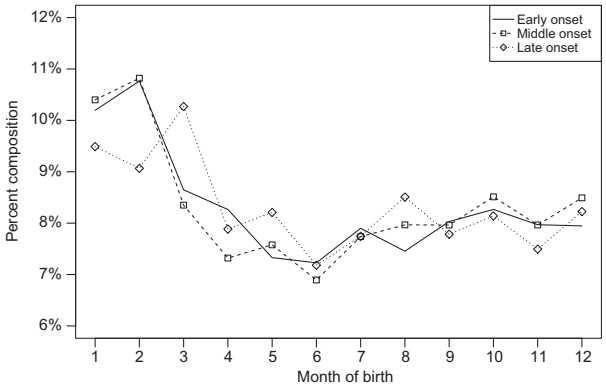

Fig. 1. Seasonality of birth in patients with schizophrenia. Comparison of early-onset (15–20 years of age), middle-onset (21–44 years of age), and late-onset (45–64 years of age) disease.

winter months. This deviant season of birth (in winter and spring) in patients with schizophrenia is concordant with previous findings (1–3). Evidence suggests that patients with schizophrenia in the northern hemisphere exhibit peaks in birth between January and April (3, 5). Korea is also located in the northern hemisphere. Accordingly, the observed season of birth distributions in Korean patients with schizophrenia is similar to those reported in North America, Europe, Japan, and Taiwan (1, 2, 5, 7). While the excess of winter or spring births was around 5–15% in previous studies (1–3), our data showed an excess of February births of 26–27% in the early- and middle-onset groups. In contrast to previous studies, we considered the age at onset of schizophrenia in addition to the month of birth, which may explain the larger difference observed in our study. Interestingly, the distribution of season of birth in the group of patients with late-onset schizophrenia followed a different pattern: These patients showed an increased percentage of births in early spring, particularly in March. It has been suggested that the season of birth pattern with a winter peak appears predominantly in early- and middle-onset groups; this result is plausible considering that onset of schizophrenia occurs most frequently in late adolescence and early adulthood (27). A previous Taiwanese study did not find an association between the month of birth and late-onset schizophrenia (28). A Finnish study reported an association between autumn birth and a later disease onset (4). Although our sample size is larger than that of these two studies, further research is needed to validate and replicate our results. In accordance with our results, Pulver et al. (29) have provided evidence for a winter birth excess in early-onset schizophrenia. Assuming the validity of our results, we cautiously speculate that the early- and middle-onset groups might constitute separate subgroups, with a different pathophysiology related to season of birth and a different prognosis compared to the late-onset group.

In the present study, patients with early-onset schizophrenia showed the highest rate of clozapine prescription regardless of the season of birth. Early-onset schizophrenia appears to have poorer outcomes compared with late-onset schizophrenia (9, 10, 12). Our findings corroborate the results of a recent study by Wimberley et al. (30), which showed that an earlier age at initial diagnosis was associated with an increased rate of treatment-resistant schizophrenia. Furthermore, possible biological markers for a poor prognosis have been found in early-onset schizophrenia. Patients who

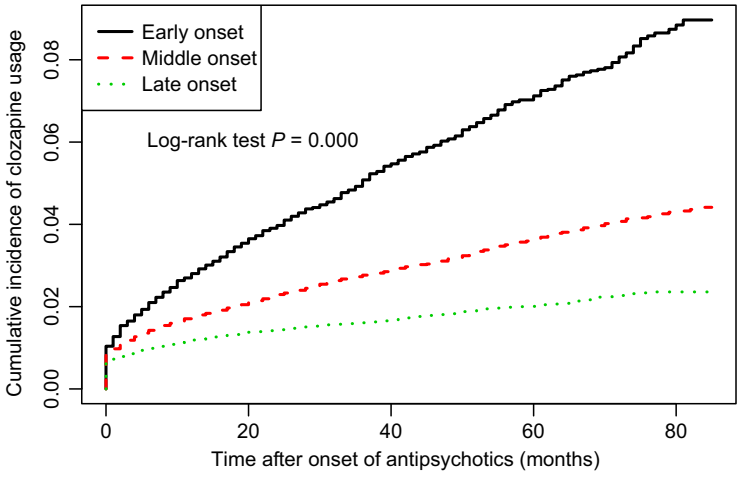

Fig. 2. Cumulative incidence of clozapine use from the time of onset of antipsychotics. Comparison of early-onset (15–20 years of age), middle-onset (21–44 years of age), and late-onset (45–64 years of age) schizophrenia. [Colour figure can be viewed at wileyonlinelibrary.com]

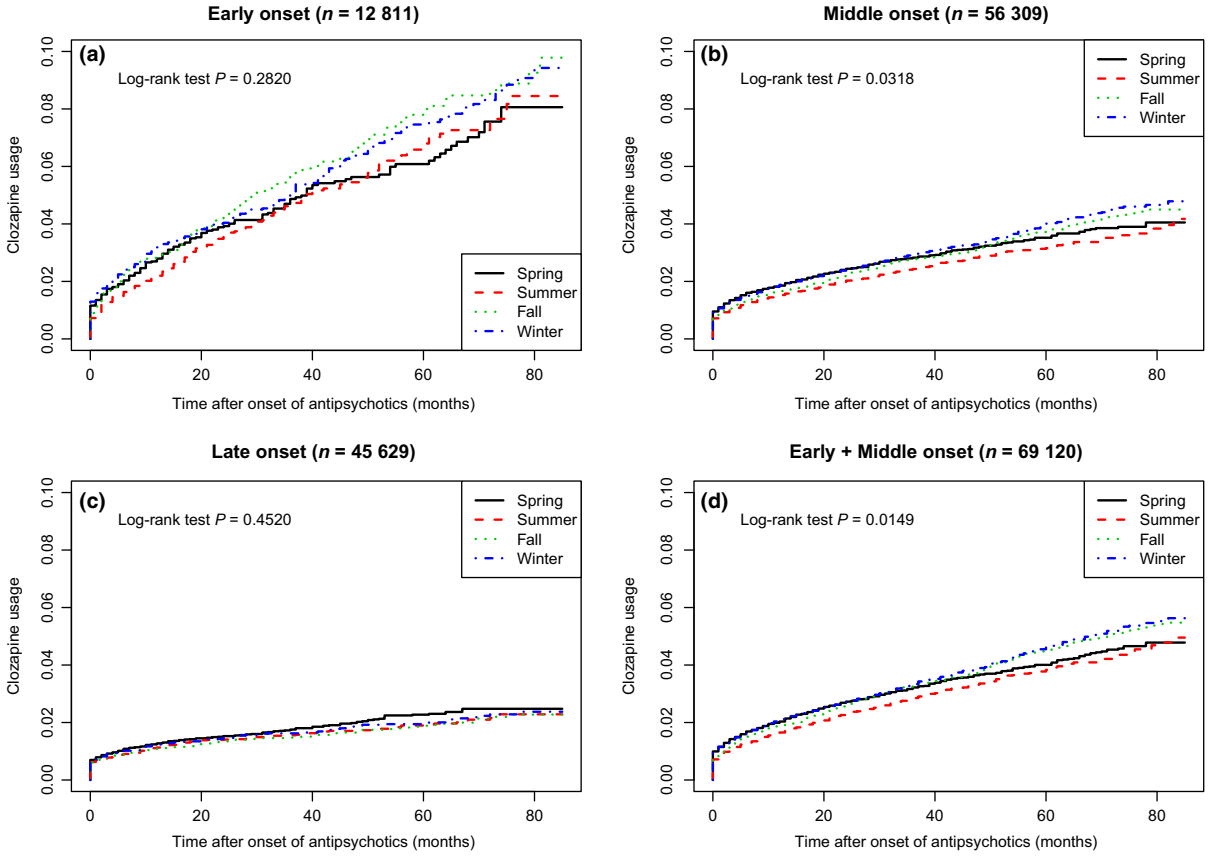

Fig. 3. Cumulative incidence of clozapine use from the onset of antipsychotic use by birth seasonality. (a) The clozapine usage according to time after onset of antipsychotics in the early onset group. (b) The middle-onset group showed an earlier initiation of clozapine use for winter and fall births than for summer births (Log-rank test $P = 0.0318$). (c) The clozapine usage according to time after onset of antipsychotics in the late onset group. (d) Early- and middle-onset groups showed an earlier initiation of clozapine use for winter and fall births than for summer births (log-rank test $P = 0.0149$). [Colour figure can be viewed at wileyonlinelibrary.com]

had their first episode before age 15–20 showed a significantly decreased volume and thickness of the frontal lobe, a decreased volume of the temporal lobe, and an enlarged volume of the ventricular system and the basal ganglia (31). Pauly et al. reported that patients with adolescent-onset schizophrenia showed altered patterns of activation in the thalamo-cortical network during the interaction of emotion and cognition (32). These structural and functional changes may explain the poor prognosis of early-onset schizophrenia. Our results support the hypothesis that an early onset itself may be a significant associating factor for clozapine use in schizophrenia.

Interestingly, patients in the middle-onset group that were born in winter were prescribed clozapine earlier than the rest of the patients in the middle-onset group. In fact, the incidence of clozapine use was higher for patients born in winter than in summer regardless of the age at schizophrenia onset. Therefore, both early onset and winter birth may be associated with negative prognostic factors for patients with schizophrenia. Despite intensive research on the relationship between season of birth and schizophrenia prognosis, the current evidence is inconclusive. A number of previous studies have reported a better prognosis for patients born in winter (33–35). However, Watson et al. found a worse prognosis for patients born in winter (36). This inconsistency may be explained by the different definitions of season of birth and different variables used as prognostic factors for schizophrenia among the various studies (33, 35, 37). In addition, none of these studies considered the age at onset of schizophrenia as a moderating prognostic factor in their study design. Only a few studies have examined the relationship between clozapine initiation and birth month, and their results differ from those obtained in our study (8, 30). This difference might be due to the different study populations and different definitions of onset age. While the association of younger onset age with clozapine use is clear and consistent with previous findings (30, 38–41), there was limited evidence for an association between season of birth and clozapine use in the current study. Moreover, our additional analysis restricting

the follow-up to two years showed only trends for an association between season of birth and clozapine use ($P = 0.055$). This finding and the inconsistency of previous results suggest that our study should be interpreted with caution, and further studies should be conducted using a larger group of patients.

The biological mechanisms underlying the relationship between season of birth and schizophrenia may be related to early exposure to perinatal viral infections during the winter flu season and low prenatal vitamin D levels (2, 8, 42). We propose that winter birth might be a negative prognostic factor for patients with a genetic predisposition for schizophrenia. We speculate that environmental risks, such as viral infections or nutritional deficiencies, could worsen the schizophrenia outcome if patients with a genetic predisposition are born in winter. These environmental factors have been proven to modulate the etiology and course of the disease (43). Environmental stress can affect brain structure (44) and immune function (45) by driving coordinated patterned plasticity in different brain areas responsive to stress (43). Nevertheless, the effects of winter birth are likely to involve complex mechanisms. McGrath et al. (46) reported that despite the association of a winter birth excess with schizophrenia, the cognitive functioning in cohorts of children born in winter did not show general deficits. However, Konrath et al. recently demonstrated a similar excess of winter births in schizotypy among the general population (47). This study suggested that individuals born in winter might not display a 'general deficit' in cognitive functioning, but may show a slight increase in signs of schizophrenia proneness such as schizotypy (47). Previous findings concerning season of birth effects on cognitive and physical development vs. those on the risk for schizophrenia in the general population suggest that more complex mechanisms should be investigated. Another theory is that genes that increase the susceptibility toward infections might also play a role in the season of birth pattern. Moreover, we did not find a significant association between age at onset and clozapine use based on the astronomical season. Considering the differences between the meteorological and astronomical seasons might inform our speculations regarding the causative role of environmental factors.

Although the relationship between season of birth, a variety of clinical variables including age of schizophrenia onset, marital status, total duration of hospitalization, and number of hospital admissions (48–50) and prognosis has not yet been established, season of birth does appear to contribute to not only in the development but also the course of the disease for patients with schizophrenia.

Moreover, our results showed that the clozapine usage pattern in real life did not follow the clinical guidelines. Clinicians face barriers in prescribing clozapine due to concerns about compliance, tolerance, and patient refusal to comply with the blood monitoring requirements (51). Substantial delays in clozapine initiation remain a problem and affect the pattern of clozapine intake.

Our study has several limitations. First, our study was conducted on data obtained from the Korean population. Therefore, caution should be exercised when generalizing our findings to other ethnicities. Second, we considered only one factor (the clozapine prescription rate) as an indicator of the schizophrenia outcome. Further studies are needed to explore the relationship of season of birth with other clinical variables such as illness severity, negative symptoms, and functional outcomes. Third, although almost all previous studies have considered clozapine treatment as a proxy for treatment resistance, this proxy definition is too narrow to capture all patients with treatment-resistant schizophrenia due to the possible underuse of clozapine in high-income countries (30). Moreover, Howes et al. reported that substantial delays in the initiation of clozapine treatment remain, and antipsychotic polypharmacy and high doses are common prior to clozapine use in 34–36% of patients (52). Considering that the rate of clozapine use is generally about 3–8% (52, 53), it is highly likely that the rate of clozapine use does not fully reflect the prevalence of treatment resistance. To minimize this limitation, Wimberley et al. (30) used the duration of polypharmacy as another proxy definition of treatment resistance. However, the rate of clozapine use has recently increased in South Korea (54), and the Korean Medication Algorithm for schizophrenia prefers clozapine to antipsychotic polypharmacy for refractory schizophrenia (55). One recent study reported that the rate of clozapine use was 16–29% in university-affiliated hospitals in Korea (54, 56). Therefore, this limitation might be minimized in South Korea. As mentioned above, caution should be exercised when generalizing our findings to other ethnicities because of the relatively high rate of clozapine use in South Korea. Next, our study population did not cover prodromal patients as we restricted to new users of antipsychotics, and it is important to notice that 'age at onset' in the present study refers to the age of first antipsychotic prescription which does not precisely translate to the age at onset of schizophrenia. Considering that the average duration of untreated illness in Korea is about 13 months (57), the

temporal gap between the 'onset of illness' and the 'onset of first antipsychotics prescription' may be small, and the trend of these two points is quite similar. Lastly, our results might be biased due to residual confounding factors, such as marital status, substance abuse diagnosis, socioeconomic status, premorbid social adjustment and personality, family support, stressful life events, and duration of untreated psychosis (58). These variables should be considered in future studies.

Despite these limitations, our study is the first nationwide study to assess the association between the season of birth and the prognosis for schizophrenia patients in the Korean population. Our results suggest that the season of birth and age at onset may play important roles in determining the course, refractoriness, and development of schizophrenia. Furthermore, our results have important implications for the primary and secondary prevention of schizophrenia in Korea (3, 59). Our results indicate that clinicians need to consider not only the season of birth, but also the age at disease onset to be associated with a viable prognosis for patients with schizophrenia.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Cumulative incidence of clozapine use from the onset of antipsychotic use classified by astronomical season.