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Seasonality in schizophrenia—An analysis of a nationwide registry with 110,735 hospital admissions

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Research Article

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Abstract

Background. Seasonal patterns in hospitalizations have been observed in various psychiatric disorders, however, it is unclear whether they also exist in schizophrenia. Previous studies found mixed results and those reporting the presence of seasonality differ regarding the characteristics of these patterns. Further, they are inconclusive whether sex is an influencing factor. The aim of this study was therefore to examine if seasonal patterns in hospitalizations can be found in schizophrenia, with special regard to a possible influence of sex, by using a large national dataset.
Methods. Data on all hospital admissions within Austria due to schizophrenia (F20.0–F20.6) for the time period of 2003–2016 were included. Age standardized monthly variation of hospitalization for women and men was analyzed and the level of significance adjusted for multiple testing.
Results. The database comprised of 110,735 admissions (59.6% men). Significant seasonal variations were found in the total sample with hospitalization peaks in January and June and a trough in December ($p < 0.0001$). No significant difference in these patterns was found between women and men with schizophrenia ($p < 0.0001$).
Conclusion. Our study shows that schizophrenia-related hospitalizations follow a seasonal pattern in both men and women. The distribution of peaks might be influenced by photoperiod changes which trigger worsening of symptoms and lead to exacerbations in schizophrenia. Further research is necessary to identify underlying factors influencing seasonal patterns and to assess whether a subgroup of patients with schizophrenia is especially vulnerable to the impact of seasonal variations.

Introduction

In various psychiatric disorders, especially mood disorders, the presence of seasonal patterns was found to profoundly affect the clinical course and to be a risk factor for increased severity with higher rates of mood episodes, younger age of onset and increased prevalence of psychiatric comorbidities [1–5]. However, inconsistent results exist regarding the influence of seasonality on schizophrenia which is a severe and often chronic mental disorder affecting 20 million people worldwide [6]. Since the end of the 18th century, seasonal patterns in symptom severity as well as in the course of hospitalizations of patients suffering from schizophrenia have been observed [7,8]. Nevertheless, controversy about whether, and to which extent, a seasonality effect in schizophrenia exists continues: While some studies reported a significant increase of admissions due to schizophrenia in spring and summer [9–12], others negated such seasonal variations [2,13]. Further, in an Irish study summer peaks were observed for first time admissions only, but no seasonal effects found for readmissions [14], while results from a community-based hospital in New York City claimed such variation for readmissions only [15]. Variations in the occurrence of psychosis along the course of the year were assumed to underlie climatic conditions [12,14] and their influence on biological mechanisms including melatonergic and serotonergic interactions [16]. Previous studies also suggested an association between hospitalization rates and duration of photoperiod [17,18] and a possible influence of public holidays and religious festivities [18–20]. Besides previous inconsistent results regarding seasonal hospitalization patterns in patients with schizophrenia in general, there has been some evidence for sex-specific seasonal patterns in hospitalizations due to schizophrenia [11,18,21,22].

For a more comprehensive understanding of seasonal hospitalization patterns in patients with schizophrenia, we examined a large national dataset on hospital admissions for schizophrenia over a 14-year time period. With regard to the number of included hospital admission data

combined with the length of observation, this is, to the best of our knowledge, the largest study so far, as previous studies consisted of individual, but relatively small patient samples.

Material and Methods

Data source

In this study, hospital discharge data of all counties in Austria were analyzed for individuals diagnosed with schizophrenia (F20.0–F20.6) between 2003 and 2016. After the selection of cases according to the inclusion and exclusion criteria defined by the authors, the dataset was provided in anonymized form by Statistics Austria, the national statistics agency which collects data from the Austrian health system and provides data access for scientific research. The dataset includes sex, age schizophrenia subtype (F20.0–F20.6), month of discharge and length of hospital inpatient stay in days.

Population

Aiming to examine hospitalization patterns for a homogeneous sample of patients with schizophrenia, individuals with other psychotic disorders including "schizotypal disorder" (F21), "persistent delusional disorder" (F22), "acute and transient psychotic disorders" (F23), "induced delusional disorder" (F24), "schizoaffective disorders" (F25) as well as "other nonorganic psychotic disorders" (F28), and "unspecified nonorganic psychosis" (F29) were excluded from analysis. Due to lacking specificity of categorization within schizophrenia-spectrum disorders, patients with the diagnosis "other schizophrenia" (F20.8) ($n = 881$) and "unspecified schizophrenia" (F20.9) ($n = 2{,}848$) were also excluded. Furthermore, a subsample of patients with a duration of hospitalization ≥400 days ($n = 937$), representing a group of extremely ill patients, was also excluded from further analysis as well as patients younger than 15 years ($n = 184$) who were assumed to represent a rather specific cohort of individuals with very early-onset schizophrenia. Inclusion and exclusion criteria were carefully discussed and determined within the research team with the consent of all members.

Statistics

The number of admissions was described by frequency tables and compared between men and women by Chi-squared test. Seasonality patterns were shown by presenting observed and expected percentage of hospitalizations by month within a year. Expected percentage by month was calculated by multiplying the sum of all admissions by proportion of days of a specific month compared to the total sum of days. Age at admission was described by mean and standard deviation. Comparison of age between men and women was done by Wilcoxon signed rank test. The effect of sex was shown by calculating the ratio of admission rate men to women within age groups (10 years) along with 95% confidence intervals. The significance level was adjusted to account for multiple testing ($p < 0.001$). Analysis was performed using SAS (SAS Institute Inc., Cary, NC).

Results

The database comprised 110,735 schizophrenia-related hospital admissions. The overall admission estimate rate for all schizophrenia subtypes was 107.5 per 100,000 residents per year (see Table 1). For hospital admission rates and estimates for subtypes see Table 1. The mean age of patients in our dataset was 41.2 years (SD = 14.1). On average, men were 5 years younger (mean = 37.5 years; SD = 13) than women (42.5 years; SD = 14.7). In total, 59.6% ($n = 65{,}955$) of the admissions were men, which were also significantly more often diagnosed within all subtypes ($p < 0.0001$) (see Table 2). Mean length of hospital stay was significantly shorter in women (mean = 21.55 days, SD = 30.39) when compared to men (mean = 22.03 days, SD = 34.07) ($p < 0.0001$).

Seasonality of hospitalizations

Seasonal patterns for hospitalizations due to schizophrenia were revealed in the total sample ($p < 0.0001$). When data was examined according to sex, significant deviations in observed hospitalizations were found for both women and men from the expected number of hospitalizations revealing maximum peaks for January and June, with hospitalizations exceeding the expected numbers by up to 10% in both groups ($p < 0.0001$). The largest negative deviation from the expected rate of hospitalizations was found for December, again in both sexes ($p < 0.0001$) (Figures 1 and 2). No significant differences between sexes were found regarding seasonality patterns.

Discussion

Hospital admission peaks were found in January and June with a continuous decline from summer to December for both sexes individually as well as combined. The largest trough in schizophrenia-related hospitalizations was found in December for both sexes. In line with previous data [23,24], men were overrepresented in the total sample and all subgroups. Contrary to our hypothesis based on previous studies reporting hospitalization peaks for female patients with schizophrenia in summer [11] and spring [21] and for male patients with schizophrenia in winter with a trough in hospitalization rates in summer [18], no significant sex differences regarding seasonal patterns in hospitalizations due to schizophrenia were found in our study.

As no conclusive result has been reported yet, a multitude of possible factors might be associated with the observed hospitalization patterns in patients with schizophrenia including genetic variations, sociocultural factors as well as meteorological factors [12,17,19,20,25–27].

Addressing the interplay of sunlight, photoperiod time, vitamin D and melatonin, it has been observed that people born in winter and early spring are more likely to develop schizophrenia later on in life [26]. These findings have been hypothesized to be also caused by a shorter photoperiod and thus sunlight exposure at time of birth and the following months, subsequently causing lower vitamin D levels in patients with schizophrenia [25–28]. Examining the effect of sunlight exposure, it is important to note that vitamin D and melatonin are thought to exert inhibitory effects on each other, and literature has described psychotic exacerbations in patients due to increases of melatonin [29]. Furthermore, secretion of melatonin is reported to peak in January and July [29–31]. Yet, the role of melatonin is still unclear since significant changes in melatonin levels and melatonin circadian rhythm were found in patients with schizophrenia. Furthermore, potential benefits of an adjunctive use of melatonin along with vitamin D were suggested for patients with schizophrenia by preventing side effects of typical and atypical antipsychotics and potentially attenuating the development and severity of psychotic disorders. Melatonin's impact on the tryptophan catabolic pathway was also discussed via its effect on cortisol secretion and stress response, thus influencing cognition, amygdala associated affect and striatal motivational processing [32].

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Table 1. Mean annual admission rates per 100,000 population with 95% CI for schizophrenia (total sample and subgroups).

Schizophrenia subgroup	Observed events	Estimated rate per 100,000 person years	Lower CI	Upper CI
F20.0	89,469	86.35	85.79	86.92
F20.1	2,955	2.38	2.73	2.93
F20.2	1,676	1.64	1.56	1.72
F20.3	1,753	1.68	1.60	1.76
F20.4	481	0.48	0.44	0.52
F20.5	13,429	13.63	13.40	13.87
F20.6	972	0.93	0.87	0.99
F20.0–F20.6	110,735	107.50	106.90	108.20

Abbreviation: CI, confidence intervals.

Table 2. Number and percentage of admissions for schizophrenia (total sample and subgroups) according to sex.

	Schizophrenia subgroups							Total
	F20.0	F20.1	F20.2	F20.3	F20.4	F20.5	F20.6	F20.0–F20.6
Male	53,370	1,900	871	1,016	291	7,925	582	65,955
	59.7%	64.3%	52%	58%	60.5%	59%	59.9%	59.6%
Female	36,099	1,055	805	737	190	5,504	390	44,780
	40.3%	35.7%	48%	42%	39.5%	41%	40.1%	40.4%
Total	89,469	2,955	1,676	1,753	481	13,429	972	110,735

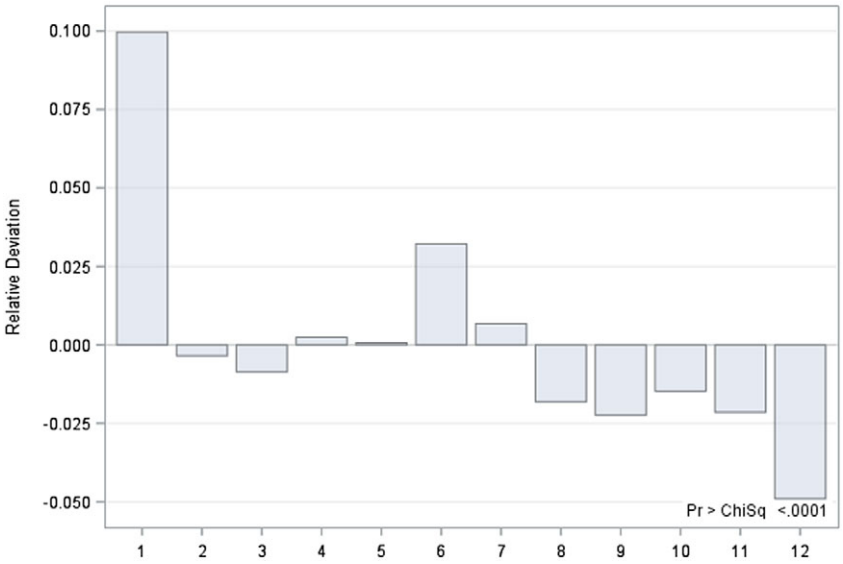

Figure 1. Deviations (in percentage) of expected from observed number of hospitalization of male patients by month.

While previous publications have suggested the change in temperature to be responsible for deterioration of mental health status in schizophrenia [33,34], we assume that temperature changes are a proxy-variable for changes in photoperiod. This hypothesis is strengthened by findings revealing hospitalization peaks during periods of lower temperature and shorter photoperiod: For the population of Australia, hospitalization peaks due to schizophrenia for July/August—representing winter and thus the shortest photoperiod per day on the southern hemisphere—were reported [18,22]. Recent studies from China also published agreeing results revealing significantly higher rates of hospitalizations in patients with schizophrenia following shorter photoperiods [17,35]. As Austria is situated in the northern hemisphere, the photoperiod continuously shortens from July onwards until the end of December. Thereafter, following the winter solstice, the photoperiod significantly increases again in January and continues this trend until June, when it again, following the summer solstice, reverses the trend [36]. This data is congruent with our results,

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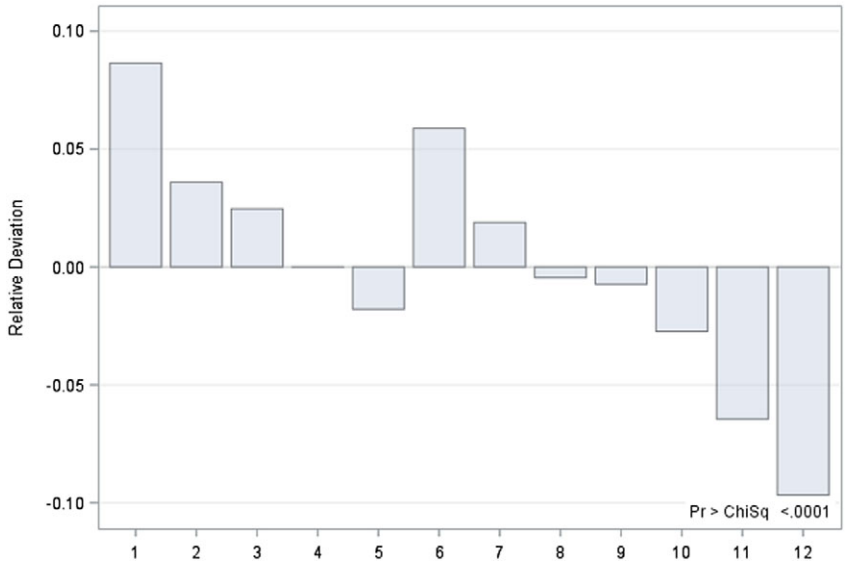

Figure 2. Deviations (in percentage) of expected from observed number of hospitalization of female patients by month.

revealing hospitalization peaks in patients suffering from schizophrenia in January as well as June and a continuous decline from August to December, which leads us to conclude that the change in relative duration of photoperiod may be an important influencing factor in triggering psychotic exacerbations and hereby leads to increased numbers of hospitalizations.

When investigating genetic factors associated with a seasonal variation in hospitalizations due to schizophrenia, Byrne et al. [27] reported possible risk factors in genome-wide association studies, as in schizophrenia the genetic profile score was associated with the highest global seasonality score compared to bipolar disorder and major depressive disorder. In the last decades, a multitude of risk factors including genetic factors could be identified concerning the etiology and course of schizophrenia [37–39]. It is known from previous studies that specific neuroanatomical markers of genetic liability to psychosis exist, grey matter reductions in the anterior cingulate were shown to be potential markers of genetic liability to psychosis while reductions in the superior temporal gyrus and cerebellum were interpreted as markers of a first onset of psychosis [40]. It should be noted, that a focus on genetic explanations of the etiology of psychotic disorders was found to be more often associated with stigmatizing attitudes [41]. However, until now we have no further knowledge about specific markers regarding the influence of seasonality on the etiology and course of schizophrenia. Thereof, the biopsychosocial model continues as highly relevant approach to the etiology and treatment of schizophrenia by embracing the role of biological, psychological, and social factors contributing to the disorder [42].

Besides genetic factors, neurobiological factors might influence seasonal patterns in schizophrenia-related hospitalizations. Significantly higher cortisol levels and higher rates of dexamethasone test nonsuppression were found in male patients with schizophrenia in winter compared to female patients with schizophrenia and patients with depression [28]. Significant seasonal variations in rates of dexamethasone test nonsuppression were found only in patients with schizophrenia in comparison to healthy controls [29].

In addition to genetic and neurobiological factors, a possible interpretation of the significant decrease in hospitalizations in December may be that during a time of religious festivities in countries with a Christian majority celebrating Christmas, a possible reduction in staff presence may necessitate a reduction of admission rates in December which then may increase thereafter in January [18,20]. Similar results were found in a study examining hospitalization patterns during Passover, the most widely celebrated holiday in Israel, reporting a significant reduction in first admissions for men with schizophrenia, but not for female patients or readmissions [19]. Yet, this interpretation does not explain the peak of hospitalizations due to schizophrenia in June.

Analyzing periods of decreased hospital admissions might help to understand the role of potential protective factors in preventing or delaying hospitalizations due to specific social factors. Addressing the overlap of genetic and neurobiological risk factors between seasonality and schizophrenia, further investigation is warranted at genetic, environmental and clinical levels aiming for the development of specific markers and potential new treatment options of schizophrenia.

Limitations

A study based on national health care data has several limitations, including possible misclassifications and potential over-selection of severely ill patients. Since identification of individuals within this data set is technically impossible, calculations of the number of inpatient stays per individual patient, and assessments of comorbid diagnoses or psychopharmacological treatment were unfortunately not feasible. Nevertheless, administrative discharge data have been shown to be sufficiently robust to support their use in research [43,44]. For psychotic disorders, administrative data has been found to be predictive of true diagnosis with high reliability, especially for the clinical diagnosis of schizophrenia [45,46].

Conclusion

To the best of our knowledge, covering more than 110,000 hospitalizations over a time period of 14 years, this is the largest population-based study on hospitalization patterns in schizophrenia. By revealing a distinct and significant seasonal variation in

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hospitalizations due to schizophrenia for both sexes, it can be concluded that seasonality is profoundly influencing the clinical course in men and women with schizophrenia leading to worsening of the mental health status and subsequently causing the necessity of an inpatient stay. The distribution of hospitalization peaks can be hypothesized to be influenced by photoperiod changes which hereby trigger worsening of symptom severity in patients with schizophrenia. A better understanding of the underlying factors influencing these seasonal patterns could help to identify subgroups of individuals with schizophrenia who are more prone to exacerbations due to seasonal variations and the development of specific markers of the disorder. Further research is warranted to identify underlying influencing factors and their mechanisms triggering seasonal patterns in patients with schizophrenia.

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Conflict of Interest. The authors report no conflict of interest.

Data Availability Statement. The data that support the finding of this study are available from Statistik, Austria (https://www.statistik.at/).

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