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Cross-sectional and within-subject seasonality and regularity of hospitalizations: A population study in mood disorders and schizophrenia

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Abstract

Background: Seasonal peaks in hospitalizations for mood disorders and schizophrenia are well recognized and often replicated. The within-subject tendency to experience illness episodes in the same season, that is, seasonal course, is much less established, as certain individuals may temporarily meet criteria for seasonal course purely by chance.

Aims: In this population, prospective cohort study, we investigated whether between and within-subject seasonal patterns of hospitalizations occurred more frequently than would be expected by chance.

Methods: Using a compulsory, standardized national register of hospitalizations, we analyzed all admissions for mood disorders and schizophrenia in the Czech Republic between 1994 and 2013. We used bootstrap tests to compare the observed numbers of (a) participants with seasonal/regular course and (b) hospitalizations in individual months against empirical distributions obtained by simulations.

Results: Among 87 184 participants, we found uneven distribution of hospitalizations, with hospitalization peaks for depression in April and November ($X^2(11) = 363.66$, $P < .001$), for mania in August ($X^2(11) = 50.36$, $P < .001$) and for schizophrenia in June ($X^2(11) = 70.34$, $P < .001$). Significantly more participants than would be expected by chance, had two subsequent rehospitalizations in the same 90 days in different years (7.36%, bootstrap $P < .01$) or after a regular, but non-seasonal interval (6.07%, bootstrap $P < .001$). The proportion of participants with two consecutive hospitalizations in the same season was below chance level (7.06%).

Conclusions: Psychiatric hospitalizations were unevenly distributed throughout the year (cross-sectional seasonality), with evidence for regularity, but not seasonality of hospitalizations within subjects. Our data do not support the validity of seasonal pattern specifier. Season may be a general risk factor, which increases the risk of hospitalizations across psychiatric participants.

KEYWORDS
bipolar affective disorders, depressive disorders, regularity of hospitalizations, schizophrenia, seasonal course, seasonality

1 | INTRODUCTION

For more than 2000 years, seasonal influences have been enduring themes in writing about mood disorders and have played a significant role in theories of pathogenesis and treatment. Seasonal changes in mood disorders noticed already by ancient Greek physicians were replicated in case descriptions from the late 19th and early 20th centuries (for reviews see References [1,2]). This historical record is consistent with modern observations about seasonality.

Seasonality can be studied on different levels. The risk of recurrences or hospitalizations may vary throughout the year, with peaks in some seasons and troughs in others. Controlled studies in the 20th century confirmed seasonal peaks in hospitalizations for mania, mixed episodes, depression[2] but also for schizophrenia.[3-6] Utilization of services for major psychiatric disorders also varies throughout the year, with seasonal peaks in antidepressant prescriptions,[7] emergency visits,[8] or involuntary admissions.[9] We will call this uneven distribution of hospitalizations throughout the year a *cross-sectional seasonality*.

Alternatively, some individuals with major mood disorders may experience episodes of illness always in the same season. This within-subject tendency to have only seasonal recurrences has been recognized in the Diagnostic and Statistical Manual of Mental Disorders (DSM) since the DSM-III-R as a "seasonal pattern" in the course of mood disorders. The prevalence of seasonal course ranges from 0.8% to 38% based on the design, type, and stringency of criteria.[10] The largest study, which was based on the retrospective assessment in the National Comorbidity Survey reported that depending on the definitions, between 2% and 17.9% of patients with mood disorders met criteria for seasonal course specifier.[11] The longitudinal Zurich cohort study showed that 3.44% participants had repeated winter major depressive episodes.[12] We will call this tendency for seasonal recurrences within the same individual a *seasonal course*.

Whereas evidence for the cross-sectional seasonality, especially in mood disorders, is robust and has been replicated in many independent studies, we know much less about the seasonal course/within-subject seasonality and the findings are much more heterogeneous. For example, over time, the seasonal course appears transient in most participants.[13] In addition, even in case of random fluctuations in cycle length, certain individuals may temporarily meet criteria for seasonality purely by chance. Furthermore, it is not clear whether the seasonal peaks in psychiatric hospitalizations/recurrences are driven by specific subjects who show seasonal course or whether the season represents an additional risk factor, which increases the risk of hospitalizations across participants. Considering these unresolved questions, it is not surprising that some have even questioned the very existence of seasonal affective disorders/seasonal course.[14,15]

In addition, the studies investigating the within-subject seasonal course are typically small, retrospective and based on selected participants usually from tertiary centers. Consequently, their generalizability may be limited. Furthermore, retrospective studies may inflate the proportions of participants meeting seasonal course specifier due to recall and confirmation biases, especially if they specifically ask about seasonal effects.[16] Many studies of seasonality base the diagnosis on the Seasonal Pattern Assessment Questionnaire (SPAQ) questionnaire and not on DSM or International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria. Many of the participants diagnosed with seasonal affective disorders based on SPAQ actually do not meet DSM or ICD-10 criteria either for major depressive episode or for seasonal course specifier.[17] Aside from diagnostic inconsistency, investigating seasonal patterns in participants who do not meet DSM criteria for major depressive episodes will markedly inflate the estimates of seasonality, as prominent seasonal difficulties with energy levels, sleep, appetite appear in 10%-20% of subjects from the general population.[18]

Consequently, we designed this study to address some of these issues and to separately study cross-sectional seasonality, that is, uneven distribution of hospitalizations throughout the year, as well as the seasonal course, that is, individual tendency to show seasonal episodes. We investigated both of these phenomena on population level. In order not to mix syndromal and subsyndromal presentations, we focused on hospitalizations for major psychiatric disorders. To eliminate biases, we used a compulsory registry, which records every single psychiatric hospitalization in the whole of Czech Republic. Last but not least, to minimize the recall and confirmation bias, the data about hospitalizations were collected prospectively. Of note, during the study period (1994-2013), the Czech mental health system, which has previously been described in detail,[19,20] has continued to rely strongly on inpatient treatment.[21]

The specific questions we addressed in this sample were as follows: Are there cross-sectional seasonal peaks in hospitalizations for major psychiatric disorders? How many participants meet criteria for seasonal course based on psychiatric hospitalizations? Do the participants who show within-subject seasonal pattern of hospitalizations significantly contribute to the cross-sectional seasonal variations of hospitalizations?

2 | METHODS

2.1 | Description of the registry

We analyzed data from the compulsory National Register of Hospitalised Patients in Czech Republic between 1 January 1994 and 31 December 2013. While the register was originally introduced in 1960, it initially underwent multiple changes in methodology and switched to ICD10 in 1994. Thus, to maintain methodological and diagnostic consistency, we included only data since 1994. The register is based on mandatory, standardized reports about every hospitalization anywhere in the Czech Republic, which are routinely collected at the point of discharge by the Institute of Health Information and Statistics of the Czech Republic. The number of hospitalizations for the diagnoses of

interest has remained stable across the study period, see Figure S1. Each registry record contains dates of admission and discharge, age, sex, discharge diagnosis and a unique anonymized personal identification number, which allowed us to track hospitalizations prospectively for each participant. Please note that all our analyses were based on discharge diagnosis, which takes into account all information including examinations, consultations, laboratory tests and course in the hospital. We analyzed only admission dates, as date of discharge does not closely correspond with symptom/episode remission and is determined by many other factors. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects were approved by Ethics committee of the National Institute of Mental Health, case no. 105/18. No informed consent was obtained due to the character of the study.

2.2 | Selection criteria

Seasonality is most frequently described in schizophrenia and mood disorders. We therefore focused on these diagnostic categories and included participants with (a) unipolar depression (F32 and F33), (b) bipolar depression (F31.3, F31.4, and F31.5), (c) mania (F30, F31.0, F31.1, and F31.2) and (d) schizophrenia (F20). For the analyses of cross-sectional seasonality, we included all hospitalizations for these diagnoses.

To systematically study the seasonal course, we selected participants with three or more hospitalizations (recurrent sample), as only two hospitalizations would not allow us to assess for repeated seasonal patterns. Each of the hospitalizations had to be for one of the above listed diagnoses. For the numbers of included participants and their sequence of diagnoses, see Table S1. Additionally, participants, who had first admission due to brief psychotic disorder (F23) and subsequent hospitalizations for any of the other previously mentioned diagnoses, were also included in the recurrent sample. Participants with any rehospitalization in less than 6 months were excluded from the analysis, as this might indicate rehospitalization for the same episode. We did not apply any other criteria regarding age or duration of hospitalizations.

2.3 | Definitions of within-subject seasonal course

To identify subjects with a seasonal course in the recurrent sample, we used three definitions of seasonality, which were operationalized as follows:

1. Same 90-day periods: The admission dates of the second and third hospitalization are not more than ±45 days apart from the admission date of the first hospitalization, ignoring the number of years between hospitalizations, that is, ((T1 + 45) modulo 365) < 90 AND ((T2 + 45) modulo 365) < 90, where T1 and T2 are time intervals between the subsequent admissions for given participant in days. This conforms to the ICD-10 criteria for seasonality, defining that episode onset must occur within separate 90-day periods.[22]
2. Same season: The admission dates of the three hospitalizations all fall within the same season, that is, (a) Dec-Feb, (b) Mar-May, (c) Jun-Aug and (d) Sep-Nov. This conforms to the "Rosenthal's criteria"[23] for seasonal affective disorders, requiring at least two consecutive, seasonally recurring episodes. It is also similar to the DSM-IV criteria (https://www.ncbi.nlm.nih.gov/pubmed/7846253) for the seasonal specifier, that is, "…there has been a regular temporal relationship between the onset of major depressive episodes and a particular time of the year (eg, regular appearance of the major depressive episode in autumn or winter)."
3. Regular cycle length: The time interval between the admission for the first and second hospitalization does not differ from the interval between the second and the third hospitalization by more than ±30 days. Computation: T1-30<=T2 AND T2<=T1 + 30, where T1 and T2 are the time intervals between the first and second and the second and third admission for given participant in days. This definition captures cycle regularity, rather than seasonality per se.

2.4 | Data preprocessing

There was a systematic bias in the raw data, with fewer admissions in December, as many wards close for Christmas, which was compensated for in the first ca. 3 weeks of January. Specifically, compared to other months, there were 22.11% less hospitalizations in December and 15.73% more hospitalizations in January. To correct this, we (a) filtered all hospitalizations that occurred during the first 3 weeks of the year, (b) chose a random sample of 20% of these hospitalizations and (c) mirrored these hospitalizations to December (ie, a hospitalizations that occurred on Jan 1, Jan 5, Jan 10 were mirrored to Dec 31, Dec 27 and Dec 22 of the previous year, respectively).

2.5 | Statistical analyses

2.5.1 | Cross-sectional seasonality

To assess the cross-sectional seasonality, we used a Monte Carlo test. In each iteration, we added a random number of days to each of the hospitalizations, drawn from a uniform distribution in the interval <0, 365> and computed the number of hypothetical hospitalizations in each month. The process was repeated 10 000 times, producing a null hypothesis distribution of hospitalization counts for each month. Finally, we computed the Bonferroni-corrected (N = 12, as there were 12 months), two-sided 95% confidence interval for each month and compared it to the observed distributions in the data.

2.5.2 | Seasonal course

To test whether the proportion of participants who met criteria for seasonal course was greater than chance, we carried out a nonparametric permutation test with N = 10 000 samples for each of the three seasonality definitions. Specifically, we generated simulated patient samples as follows: the admission date of the first hospitalization was held fixed, while the two inter-hospitalization times were permuted randomly and independently among all subjects. For each simulated sample, we calculated the number of patients conforming to each statistic. We repeated the process 10 000 times and subsequently compared the observed frequencies to the quantiles of the simulated null hypothesis distribution.

To evaluate the typical interval between admissions, we performed admixture analyses for participants with regular cycle length. The data were left-truncated due to the minimum rehospitalization period of 6 months and we additionally truncated all rehospitalizations above 18 months as these represented a sparsely sampled heavy tails that would require separate modelling. The best fitting candidate models consisted of one and two components of the truncated log-normal distribution (modelled using the *truncdist* R package https://cran.r-project.org/web/packages/truncdist/truncdist.pdf). Both candidate models were fit using the maximum likelihood method and we evaluated the goodness of fit using the Akaike information criterion (AIC).

We compared the proportions of participants meeting the above-mentioned criteria for seasonal course between diagnoses using chi-square test. Similar to the approach described above, we used nonparametric bootstrap-based test to investigate whether the hospitalizations in participants meeting the above-mentioned criteria were evenly distributed throughout the year.

We performed all statistical analyses in R, version 3.5.0, https://www.R-project.org/.

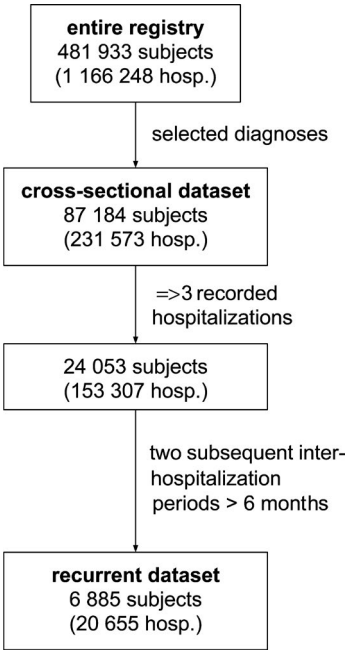

FIGURE 1 Overview of the data

3 | RESULTS

3.1 | Distributions of hospitalizations throughout the year: cross-sectional seasonality

Out of the 481 933 participants (1 166 248 hospitalizations) included in the registry between 1994 and 2013, 87 184 participants were hospitalized for the diagnoses of interest (231 573 hospitalizations), that is, schizophrenia (35 268 participants), bipolar disorders (9872 participants) and unipolar depression (46 226 participants). In all, 4077 participants (4.7%) received different diagnoses at different hospitalizations, see Figure 1 and the supplement (Table S1, Figure S2) for more information.

Hospitalizations for mood disorders or schizophrenia were unevenly distributed throughout the year. In other words, the observed numbers of hospitalizations in certain months significantly differed from the expected numbers. This was most pronounced in unipolar depression ($X^2(11) = 363.66$, $P < .001$), which showed peaks in hospitalizations in April (increase by 10.56% relative to expected number of hospitalizations) and November (increase by 5.60% relative to expected number of hospitalizations), with significantly lower rates of hospitalizations than expected in August (decrease by 12.05%), see Figure 2.

Admissions for bipolar depression or mania peaked in April (11.28% more than expected number of hospitalizations) and August (9.97% more than expected number of hospitalizations), respectively.

Participants with schizophrenia also showed uneven distribution of hospitalizations throughout the year ($X^2(11) = 70.34$, $P < .001$), but the peaks in individual months were small, up to 3.04% more than the expected number of hospitalizations in June.

3.2 | Within-subject patterns of hospitalizations: seasonal course

Out of the 481 933 patients included in the registry between 1994 and 2013, 114 618 patients had three or more hospitalizations. Out of these participants, 24 053 were hospitalized at least three times with only the diagnoses of interest, that is, schizophrenia, bipolar disorders and unipolar depression, out of which 6885 had both inter-hospitalization periods longer than 6 months and were included in the analyses, see Figure 1; Table S1.

Significantly more participants than would be expected by chance, had (a) two subsequent rehospitalizations in the same 90 days period in different years and (b) the same interval (±1 month) between the three hospitalizations, that is, regular cycle length. The number of patients with two consecutive hospitalizations in the same season did not exceed chance level (see Table 1A).

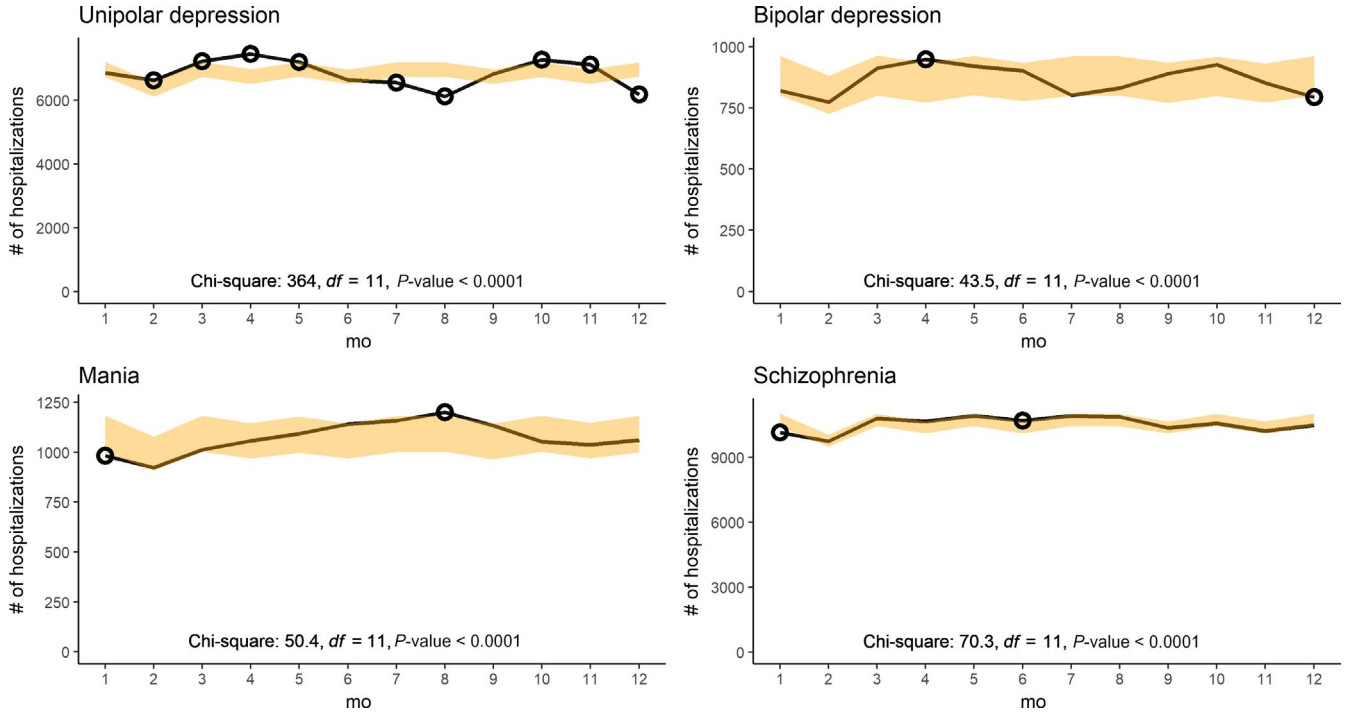

FIGURE 2 Distribution of hospitalizations throughout the year for individual diagnoses (black line) and the 95% confidence interval for expected number of hospitalizations per month (orange band). Circles indicate significant differences between observed and expected numbers of hospitalizations

TABLE 1 Individual seasonal course bootstrap results

A) All subjects (N = 6885)	Observed value	Expected value (bootstrap p95%)	*P* value	*P* value (FWER)[a]
Same 90-day period	507 (7.36%)	487.05 (7.07%)	.001	.003
Same season	486 (7.06%)	485.00 (7.04%)	.04	.12
Regular cycle	418 (6.07%)	353.00 (5.13%)	<.001	<.001
B) Schizophrenia (N = 4461)	**Observed value**	**Expected value (bootstrap p95%)**	***P* value**	***P* value (FWER)[a]**
Same 90-day period	313 (7.02%)	307 (6.88%)	.01	.04
Same season	302 (6.77%)	305 (6.84%)	.07	.22
Regular cycle	242 (5.42%)	220 (4.93%)	<.001	.01
C) Affective disorders (N = 2424)	**Observed value**	**Expected value (bootstrap p95%)**	***P* value**	***P* value (FWER)[a]**
Same 90-day period	194 (8.00%)	192 (7.92%)	.03	.08
Same season	184 (7.59%)	192 (7.92%)	.16	.47
Regular cycle	176 (7.26%)	147 (6.06%)	<.001	<.001

[a]Bonferroni correction for family-wise error (n = 3), B) ad C) were considered post-hoc.

The interval between hospitalizations in the participants with regular cycle length, showed bimodal log-normal distribution, see Figure 3, which was a better fit than unimodal distribution (bimodal with *df* = 5: AIC = −226.91, unimodal with *df* = 2: AIC = −213.24). The more dominant distribution, representing 94.00% of data had mean $e^{\mu 1}$ = 0.66 (sd 0.54) years, 95% CI = 0.51-1.41 years (ie, 26.52-73.22 weeks). The second, less dominant distribution representing 6.00% of data showed mean $e^{\mu 2}$ = 0.99 (sd 0.03) years, 95% CI = 0.94-1.05 years (ie, 48.93-54.34 weeks).

We observed no evidence for uneven distribution of hospitalizations throughout the year among participants who met any of the three criteria for within-subject seasonality/regularity—see the supplement (Table S2) for details.

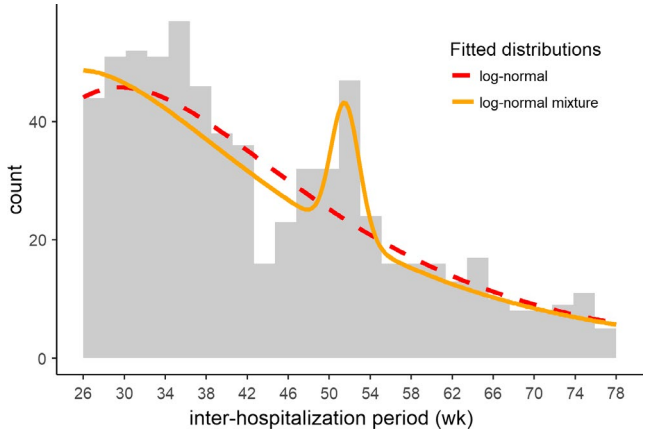

FIGURE 3 Histogram of inter-hospitalization periods within the subjects with the regular interval (±1 mo) between hospitalizations. The apparent peak around 1 y is confirmed by the fitted distributions where the mixture of two log-normal distributions (orange) showed better fit than unimodal log-normal distribution (dashed red)

3.3 | Effects of diagnosis

We repeated the within-subject analyses separately for the participants with affective disorders (N = 2424) and schizophrenia (N = 4461). In either schizophrenia or affective disorders, significantly more participants than would be expected by chance met criteria for regular cycle length. Significantly more participants with schizophrenia had two subsequent rehospitalizations in the same 90-day period in different years. This was only a trend among participants with affective disorders, likely due to lower statistical power, as there were 1.84 times more participants with schizophrenia than affective disorders in the sample. The number of patients with two consecutive hospitalizations in the same season did not exceed chance level in either diagnostic group, please see Table 1(B) and (C).

The proportion of participants with regular cycle length was greater in affective disorders than in schizophrenia, whereas the proportion of participants rehospitalized twice in the same season or in the same 90 days did not differ between these two diagnostic categories, see Table 2.

We observed no association between sex and the proportion of participants who had two subsequent rehospitalizations after a regular interval (X2(1) = 1.43, *P* = .23), in the same season (X2(1) = 1.12, *P* = .29) or in the same 90 days in different years (X2(1) = 0.02, *P* = .89).

TABLE 2 Distribution of diagnostic categories in individual seasonal course criteria

	Schizophrenia (N = 4 461)	Affective disorders (N = 2 424)	χ^2	*P*
Same 90-day period N (%)	313 (7.02%)	194 (8.00%)	2.1	.15
Same season N (%)	302 (6.77%)	184 (7.59%)	1.49	.22
Regular cycle N (%)	242 (5.42%)	176 (7.26%)	8.96	.01

4 | DISCUSSION

In this population study of 87 184 participants, we found that hospitalizations for mood disorders and schizophrenia were unevenly distributed throughout the year. This was more pronounced for mood disorders than schizophrenia. Peaks in hospitalizations for depression occurred in the spring and hospitalizations for mania and schizophrenia were most frequent in the summer. However, the extent of these increases was small, that is, 3%-11% relative to the expected numbers of admissions per month. For the first time, we also systematically studied within-subject variations in patterns of hospitalizations. These analyses suggested some tendency for regularity of hospitalizations within certain individuals. Specifically, among those with at least three hospitalizations, 7.36% of participants had two subsequent rehospitalizations in the same 90 days period in different years and 6.07% of participants had a regular interval between two subsequent hospitalizations, which is significantly more than would be expected by chance. However, the number of patients with two consecutive hospitalizations in the same season did not exceed chance levels.

With 231 573 hospitalizations, this is currently the largest study investigating seasonal patterns in mood and psychotic disorders. Our results closely replicate the findings of previous large studies, which also found increased rates of admissions for mania in the summer,[2] especially in August.[24] It is also in keeping with registry studies describing peaks in depressive symptoms, antidepressants prescriptions or emergency visits for depressions in spring or fall.[7,8,16] The excellent agreement of our findings with previous studies shows good face validity of our methods. Also, providing replications of previous findings decreases the risk of false positives.

However, the most interesting and original feature of the study is the focus on within-subject patterns of hospitalizations. This is the first report which attempted to mathematically model the within-subject definitions of seasonality in hospitalization data. It is important to note that even if there is no seasonality and the patterns of hospitalizations are completely random, some participants may experience repeated admissions in the same season purely by chance. Based on our simulations, this chance occurrence of seasonal pattern may happen in up to 7.06% of participants with recurrent course. Aside from reporting the proportions of patients who meet seasonal course criteria, future studies should attempt to estimate whether the observed rates exceeded chance levels or not.

In this study, we mostly saw evidence for within-subject regularity of hospitalizations, which however did not specifically fall into particular seasons. The pattern of hospitalizations which most differed from the chance levels was regular hospitalizations after the same interval (±30 days). However, as the most typical rehospitalization interval in these participants was 0.66 years,

the rehospitalizations did not fall into the same season. The proportion of participants with repeated hospitalizations in the same season did not exceed chance levels. 7.36% of participants with recurrent hospitalizations met a somewhat broader definition of seasonality—they had repeated rehospitalizations within the same 90 days window in different years, which would be partly in keeping with the ICD-10 definition. This was significantly more than the 7.07%, which would be expected by chance. On the whole, we saw more evidence of within-subject regularity of cycles than of within-subject seasonality.

Regularity of hospitalizations may be explained by biological, treatment adherence, but also social factors, that is, renewal of disability/taxes, shelter seeking. The pattern of regular hospitalizations may also be related to organization of services or preventive strategies aimed at decreasing the relapse. The typical cycle lengths could better allow us to interpret the findings. The hospitalization intervals among participants with regular hospitalizations showed bimodal distribution, which in 94.00% of participants centered at 0.66 years, that is, 34 weeks and the remainder belonged to a distribution with average of 1-year interval. We are not aware of any benefits, treatment or preventive approaches in the Czech Republic, which would require hospitalization every 34 weeks or even annually. As the regularity was not tied to seasons, it does not seem likely that patients would be seeking regular admissions to gain shelter during the cold seasons. Although we cannot rule out biological explanations, that is, regular cycling of some latent biological processes, considering the most frequent intervals and the lack of links to specific seasons, these may be less likely. Also, these patterns did not differ between males and females. Perhaps this is more related to medication noncompliance. Most participants with schizophrenia discontinue their medications before 18 months, with median of 6 months.[25] The mean time to exacerbation or relapse following discontinuation of antipsychotics is 235 days,[26] which broadly falls within the most dominant distribution for rehospitalizations interval, as observed here. On the whole, the reasons for regularity of hospitalizations in these participants remain unclear, but do not seem to be related to seasonal effects.

Another original and interesting feature of the study is the discrepancy between the robust findings of cross-sectional seasonality and the weak findings regarding within-subject seasonality/seasonal course. There is little doubt that seasonal peaks of hospitalizations for major psychiatric disorders occur; however, these peaks do not seem to be driven by a subgroup of individuals, who demonstrate regular seasonal course of illness. Instead, our data suggest that season may be a nonspecific, general risk factor which increases the risk of hospitalizations across psychiatric participants and diagnoses, which is in line with conclusions of a recent review.[16] Consequently, planning of mental health services should take into considerations the seasonal peaks in hospitalizations, but this may be of limited help in predicting individual clinical course.

Last but not least, we demonstrated that even participant with schizophrenia showed seasonal peaks in hospitalizations and some tendency for within-subject regular re-admissions. These between- and within-subject seasonal patterns were relatively small and much smaller than in mood disorders, which is in keeping with other studies.[4] Consequently, these effects could have been missed in smaller previous studies. Interestingly, in keeping with our findings, a recent large scale, hospitalization-based investigation also demonstrated summer peaks in hospital utilization for schizophrenia.[6] Other studies have shown summer peaks in first admissions for schizophrenia.[3-5] In addition, involuntary admissions, which may often be associated with schizophrenia, peak in spring and summer, especially in June.[9] A recent genetic meta-analysis provided evidence for genetic overlap in risk between schizophrenia and seasonality, which was even larger than overlap between BD and seasonality.[27] All in all, seasonal variations in hospitalizations do not appear to be specific to mood disorders, but are also evident in schizophrenia.

The main limitation of the study is the absence of information about episodes which did not require hospitalizations. This could have led to overestimation of seasonal or regular cycles, as milder episodes in those identified as seasonal, could have broken the regularity/seasonality. At the same time, this would not lead to false negative findings. If someone clearly showed hospitalizations in different seasons, he clearly would not meet criteria for seasonal course, even if we added milder episodes. Overall, it is more likely that focusing only on hospitalizations would more likely lead to false-positive than false-negative results. Thus, our findings about absence of within-subject seasonal regularity of episodes seem robust. Another issue is that most participants were receiving prophylactic medication, which may alter the course of illness. Population-level medication data corresponding to the investigated period were not available, as comprehensive national reporting of medication information in Czech Republic started only on 1 January 2018. At the same time in this era, it would be impossible to obtain population based data in untreated patients. Future studies may benefit from deeper analyses of rehospitalizations in relation to service organizations, and the characteristics of mental health services within the country. Moreover, comparing involuntary versus voluntary treatment would be of great interest, but was not possible from our database.

Our study was based on hospital admission date, not on the first onset of acute episode. Also, we could not isolate first episode subjects from available data. As we investigated hospitalizations for fully syndromic psychiatric disorders, we cannot make conclusions about seasonal affective disorders, that is, seasonal variations in mood and energy, which may not necessarily meet full diagnostic criteria for mood disorders. We did not include offset of symptoms, but as a more stringent definition would further decrease the rates of participants with seasonal course, this does not change our conclusions, that seasonal course is rare and may represent random variations in cycle length.

The main advantages of our approach include the large sample size and the highly generalizable dataset. As we included all psychiatric hospitalizations in the whole of Czech Republic, there was no selection bias. Importantly, we obtained information about episodes

from prospectively collected hospitalization records and not based on retrospective recall by the participants. Consequently, we also avoided any recall and confirmation biases, which may arise when participants are specifically asked about seasonality of their episodes. The focus on hospitalizations prevented the mixing of syndromal and subsyndromal presentations. Unlike other studies, we also compared the proportions of seasonal patterns against empirical distributions acquired by simulations.

To conclude, this study adds to the growing body of evidence showing that hospitalizations for mood disorders and to a lesser degree also for schizophrenia are unevenly distributed throughout the year. We also found some tendency for regularity of admissions within some participants, which however was not seasonal. Specifically, more participants than would be expected by chance had two subsequent rehospitalizations in the same 90-day period in different years or after a regular interval (±1 month), but not in the same season. We also demonstrated that two subsequent seasonal episodes may occur by chance, in up to 7.04% of participants with recurrent illness. Furthermore, the between subject seasonality/uneven hospitalization rates could not be explained by the small number of participants with seasonal course. On the whole, our data put to doubt the validity of seasonal pattern specifier and suggest that season may be a nonspecific, general risk factor which increases the risk of hospitalizations across psychiatric participants and diagnoses.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

All authors met ICMJE criteria for authorship. Specifically, TH, EB, FS, KM, and PW contributed to the conception and design of the study, EB, TH, KM, EF, and DM contributed to the statistical analyses and checking the accuracy and integrity of the data, EB, KM, EF, DM, and PW contributed to data collection and preprocessing, TH, EB, EF, MK, FS, and JK contributed to interpretation of the results. All authors contributed to writing of the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The authors have full access to the study data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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