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Effects of Age, Sex, Index Admission, and Predominant Polarity on the Seasonality of Acute Admissions For Bipolar Disorder: A Population-Based Study

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Bipolar disorder seasonality has been documented previously, though information on the effect of demographic and clinical variables on seasonal patterns is scant. This study examined effects of age, sex, index admission, and predominant polarity on bipolar disorder seasonality in a nationwide population. An inpatient cohort admitted to hospital exclusively for mental illness was derived from the Taiwan National Health Insurance Research Database for 2002–2007. The authors identified 9619 inpatients with bipolar disorder, who had generated 15 078 acute admission records. An empirical mode decomposition method was used to identify seasonal oscillations in bipolar admission data, and regression and cross-correlation analyses were used to quantify the degree and timing of bipolar admission seasonality. Results for seasonality timing found that manic or mixed episodes peak in spring or summer, and depressive episodes peak in winter. Analysis for degree of seasonality revealed that (1) the polarity of patients' index admission predicted the seasonality of relapse admissions; (2) seasonality was significant in female admissions for depressive episodes and in male admissions for manic episodes; (3) young adults displayed a higher degree of seasonality for acute admissions than middle-aged adults; and (4) patients with predominantly depressive admissions displayed a higher degree of seasonality than patients with predominantly manic admissions. Demographic and clinical variables were found to affect the seasonality of acute admissions for bipolar disorders. These findings highlight the need for research on identification and management of seasonal features in bipolar patients. (Author correspondence: ccyang@physionet.org)

Keywords: Age, Bipolar disorder, Empirical mode decomposition, Gender, Hospital admissions, Hospitalization, Seasonality, Sex, Time-series analysis

INTRODUCTION

Seasonal influences on human mood have been well documented since the time of Hippocrates, who observed variations in the seasonal incidence of melancholy and mania (Jones, 1868). The seasonal patterns of affective illness have interested clinicians since (Wehr & Rosenthal, 1989). Although contemporary research on the seasonality of affective illness has yielded relatively inconsistent results (Daniels et al., 2000; Whitney et al., 1999), studies worldwide have generally found that unipolar depression is likely to occur during winter (Eastwood & Peacocke, 1976; Eastwood & Stiasny, 1978), whereas mania is likely to occur during spring and summer (Avasthi et al., 2001; Lee et al., 2007; Parker & Walter, 1982; Shand et al., 2011; Shapira et al., 2004; Silverstone et al., 1995; Simonsen et al., 2011).

Most studies on the seasonality of affective illness have focused on the association between clinical visit data and weather variables. This approach may demonstrate a correlation between clinical data and meteorological factors, but offers limited insight into how much variance in the data from a patient cohort can be explained by seasonal variation. Identification of intrinsic seasonal variation was of clinical interest and was measured using a seasonality questionnaire for a clinical sample (Avasthi et al., 2003; Choi et al., 2011; Shand et al., 2011). Moreover,

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the effect of demographic variables and clinical subtypes of illness on the seasonality of affective disorders remains largely unexplored.

Patients with bipolar disorders often experience repeated hospitalizations throughout their lifetime, thus understanding the clinical factors associated with seasonal patterns of hospital admissions for bipolar disorders may shed light on prevention and early intervention for such distressing mood episodes. This study hypothesized that seasonality may account for differences in bipolar disorder admissions stratified by demographic variables, episode at the index admission, and clinical subtypes. We attempted to identify intrinsic seasonal oscillations in acute admissions for bipolar disorder in a nationwide population-based sample derived from the National Health Insurance claims data in Taiwan. To overcome the limitations of previous studies, we used the empirical mode decomposition (EMD) method to identify seasonal oscillations embedded in the acute admission time series, by detrending the time series into a set of intrinsic oscillations termed intrinsic mode functions (IMFs) (Huang et al., 1998; Wu et al., 2007). Each IMF had a characteristic time scale, which enabled the identification of the seasonal IMF and removing unwanted or nonstationary oscillations (e.g., secular trends).

The EMD approach allows for the study of the degree of seasonality (Yang et al., 2010a), that is, the amount of variance that can be accounted for by the identified seasonal oscillations in the admission data, using regression analysis. We also employed cross-correlation analysis to measure the timing of seasonality (i.e., admission peaks) using a daily temperature time series as the reference for seasons. We generalized the seasonality analysis to various time-series models of acute admissions for bipolar disorder.

MATERIALS AND METHODS

Health Insurance Claim Data

The Taiwan National Health Insurance (NHI) program was initiated on March 1, 1995, and currently covers 98% of the Taiwanese population (Cheng & Chiang, 1997). Claims data for the reimbursement of medical costs dating from 1996 onward was transferred from the Bureau of NHI to the National Health Research Institute (NHRI) to establish a National Health Insurance Research Database (NHIRD), which is accessible to academic institutions for research purposes. Information that could be used to identify beneficiaries and medical care providers is scrambled to protect their privacy. The NHIRD includes patients' demographic characteristics, diagnoses, date of visit, medical expenditures, and prescription claims data. All researchers must sign an agreement guaranteeing patient confidentiality before database use. Our use of anonymous NHIRD data was approved by the NHRI (application number: 100053). This study conforms to the international ethical standards (Portaluppi et al., 2010).

Patients

An exclusive inpatient cohort of mental illness was established by the NHRI to identify all patients who had at least one psychiatric hospitalization between 2002 and 2007, and whose discharge diagnosis included certain codes of psychiatric disorder. The codes of 290 to 319 as listed in the International Classification of Diseases (9th revision, Clinical Modification) (ICD-9-CM) were included in this cohort. Patients hospitalized because of psychiatric disorders between 1996 and 2001 were excluded, leaving a cohort of 96 103 inpatients with new incidence of psychiatric hospitalization from 2002 to 2007.

Figure 1 shows the enrollment procedure used in this study to include patients with bipolar disorder. We identified 36 903 insurance claims for bipolar disorder admissions between January 1, 2002, and December 31, 2007. All such claims had as the main diagnosis an ICD-9-CM code of 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, or 296.8. Because each hospitalization record contained information indicating whether the admission was for an acute or chronic psychiatric ward, we excluded 15 884 recurring insurance claims for chronic admissions, and further identified 21 019 acute admissions (representing 11 555 patients) for bipolar disorder. Next, we used the patient's age at first admission (i.e., index admission) to refine our cohort by including only patients with an age at index admission between 18 and 55. We also excluded cases lacking data on sex or where reported birth dates were mismatched among multiple admissions. A final cohort of 9619 bipolar inpatients was established, who among them had generated 15 078 records for acute bipolar disorder admissions. To differentiate among separate episodes in a patient with multiple admissions, we counted only the first

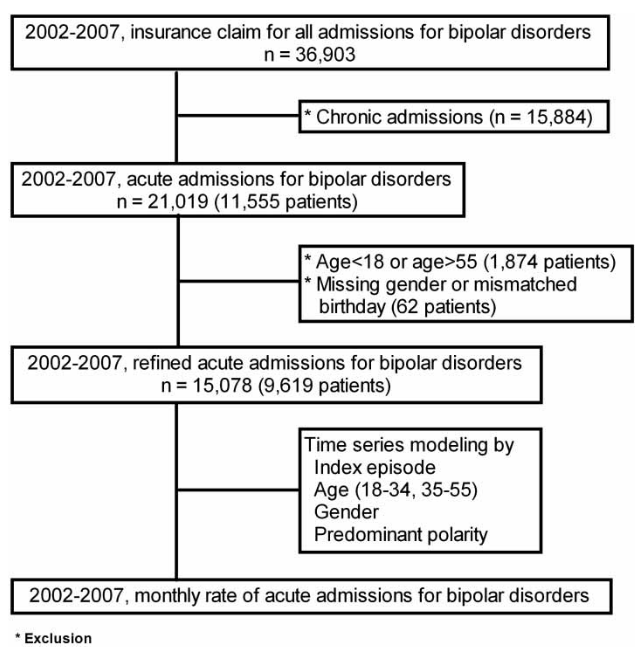

FIGURE 1. Flow chart of sampling procedure of the acute admissions for bipolar disorders.

admission if the patient had been readmitted within an 8-wk period (Lee et al., 2007).

To establish a time-series model of bipolar admissions, we counted the monthly number of bipolar admissions during 2002–2007, and normalized the data according to the annual Taiwanese population. This calculation estimated the bipolar monthly admission rate per 100 000 of the population during the study period. We then stratified the bipolar admission rate time series by the polarity of index admission, age at index admission (18–34, 35–55 yrs), sex, and predominant polarity to generate various bipolar time-series models.

To establish the predominant polarity of a patient's bipolar disorder, namely manic or depressive, we identified a subset of 1245 patients who had three or more acute admissions. We calculated the number of admissions of each patient attributed to manic (ICD-9-CM: 296.0, 296.1, 296.4), depressive (296.5), or mixed/unspecified episodes (296.6, 296.7, 296.8). The predominant polarity of bipolar disorder in a patient was defined as follows: (1) predominant mania (n = 469): admissions for mania exceeded the total for depressive and mixed/unspecified admissions by two visits; (2) predominant depression (n = 492): admissions for depression or mixed/unspecified episodes exceeded manic admissions by two visits; and (3) unclassified bipolar disorder (n = 284): admissions for mania versus depression versus mixed/unspecified episodes differed by less than two visits.

Empirical Mode Decomposition (EMD)

This study used EMD, the core algorithm of Hilbert-Huang Transform (Huang et al., 1998), to isolate the seasonal fluctuations in time series of bipolar admissions. The EMD method was developed to detrend and decompose the intrinsic oscillations embedded in a time series (Huang et al., 1998). Details on EMD (Huang et al., 1998) and its application to identify intrinsic variations in an epidemiological time series have been described previously (Cummings et al., 2004; Yang et al., 2010a, 2010b, 2012). Briefly, the decomposition was based on the assumption that any time series consists of a finite number of intrinsic components of oscillations. Each oscillation component, termed IMF, was sequentially decomposed from the original time series by a sifting process (Huang et al., 1998).

The sifting process comprised the following steps: (1) connecting the local maxima or minima of a targeted time series to form the upper and lower envelopes by natural cubic spline lines; (2) extracting the first prototype IMF by estimating the difference between the targeted time series and the mean of the upper and lower envelopes; and (3) repeating these procedures to produce a set of IMFs that are represented by a certain frequency-amplitude modulation at a characteristic time scale. The decomposition process is complete when no more IMFs can be extracted, and the residual component is then considered the overall trend of the raw data.

The main advantage of EMD is to identify IMFs of interest embedded in the time series (such as seasonal IMF in the current study), and to remove other irrelevant oscillations. Furthermore, an IMF has a zero-mean distribution, thereby reducing type I statistical error in the subsequent regression analysis. This study used a publicly available EMD algorithm based on MATLAB software (version 2007; The MathWorks, Natick, MA, USA) (http://rcada.ncu.edu.tw/research1.htm).

Seasonality Analysis

Based on seasonal IMF decomposed from the raw bipolar admission time-series data, we assessed two aspects of seasonality: degree and timing. First, the degree of seasonal influence was estimated by regression analysis to measure total variance in bipolar admission time series explained by the identified seasonal IMF. The correlation (r) and r-square (r^2) coefficients reported in the regression analysis were used as indicators of the degree of seasonality. Unlike prior studies of assessing the seasonality using the correlation between admission data and meteorological variables, the quantification of seasonality in this study estimated solely the IMF decomposed from the bipolar admission data that exhibited seasonal variation, thus giving important clinical insights on seasonality of bipolar disorders.

Second, to assess the timing of seasonal influence, we used cross-correlation analysis (Cummings et al., 2004) to estimate the time lag between bipolar admissions and seasonal changes as referenced by average monthly temperature in Taiwan. The temperature time series was used in the analysis as a proxy of determining the timing of seasons (i.e., winter and summer). Taiwan is a subtropical region characterized by a cool winter and a hot summer. The average monthly temperature between 2002 and 2007 reached its lowest point at 16.4°C in January and its highest point at 30.1°C in July. Thus, the timing of seasonality (i.e., months in which bipolar admission peaked) could be determined by examining the lag pattern in the cross-correlation function between the two time series of bipolar admission and temperature.

We generalized the seasonality analysis to different time-series models stratified by age, sex, index admission, and predominant polarity of bipolar disorder. The SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) software was used to perform regression and cross-correlation analysis. A p value of less than .05 (two-tailed test) was required for statistical significance.

RESULTS

Characteristics of Admission Data

Table 1 shows the demographic and clinical characteristics of 9619 bipolar inpatients. A slight majority, 51.2% (n = 4925), experienced index admission during young

TABLE 1. Demographic and clinical characteristics of 9619 inpatients of bipolar disorders

Characteristic	n	%
Age (years at index admission)		
18–34	4925	51.2
35–55	4694	48.8
Sex		
Female	4709	49.0
Male	4910	51.0
Number of admissions		
1–2	8374	87.0
3–5	1067	11.1
≥6	178	1.9
Polarity of episode at index admission		
Manic	5418	56.3
Depressive	1713	17.8
Mixed/unspecified	2488	25.9
Predominant polarity*		
Manic	469	37.7
Depressive	492	39.5
Unclassified	284	22.8

*Based on 1245 patients with equal or more than three times of acute admissions (see Materials and Methods for classification rules).

adulthood (18–34 yrs), and 48.8% (n = 4694) experienced index admission during middle adulthood (35–55 yrs). Women comprised 49.0% (n = 4709) of the cohort. The majority of patients, 87.1% (n = 8374), were admitted to hospital either once or twice during the study period; 11.1% (n = 1067) were admitted three to five times; and 1.9% (n = 178) were admitted more than five times. Manic episodes accounted for the highest number of index admissions (n = 5418; 56.3%), followed by mixed/unspecified episodes (n = 2488; 25.9%) and depressive episodes (n = 1713; 17.8%). The monthly rate of bipolar admission per 100 000 of the population had increased from .57 in January 2002 to 1.01 in December 2007.

Decomposition of Bipolar Admission Time Series

Figure 2 shows the decomposition of raw time series of bipolar admissions. Decomposition yielded five IMFs (IMFs 1–5) and the overall trend. We identified IMF 3 as representing the seasonal oscillations in admission data, and used this seasonal IMF for subsequent analysis. Other IMFs indicated noisy fluctuations (IMF 1), interseasonal influences (IMF 2), or secular oscillations that fluctuated over longer periods (IMFs 4–5). Thus, decomposition removed the effects of noise, interseasonal influences, and secular trends on the time-series data. The trend component of bipolar admission data exhibited a notable upward trend post 2002, which represented the accumulation of new incidences of bipolar admissions.

Quantification of the Timing of Seasonality

Figure 3 shows the cross-correlation analysis of seasonal IMF for bipolar admission and average monthly

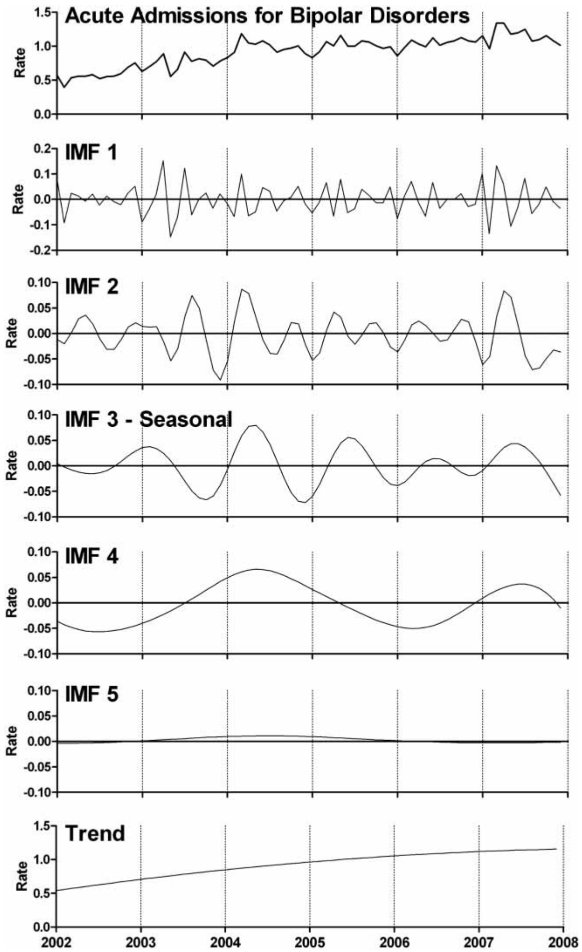

FIGURE 2. Empirical mode decomposition of time series of acute admissions for bipolar disorders. The decomposition yielded five intrinsic mode functions (IMFs) and an overall trend. IMF 3 was identified to be seasonal. Other IMFs were identified as noisy fluctuations (IMF 1) or interseasonal (IMF 2) or secular (IMFs 4–5) oscillation.

temperature time series. Bipolar seasonal IMF showed a lead pattern ahead of the temperature time series; cross-correlation analysis measured the lead to be 2 mos, indicating that bipolar admission peaked in May, that is, 2 mos ahead of the temperature peak in July. On generalizing the seasonal analysis to various bipolar time-series models (Table 2), the analyses of timing in all models consistently showed that manic episodes tend to occur from March to June, depressive episodes from September to January, and mixed/unspecified episodes from May to June.

Effect of Index Admission on the Degree of Seasonal Influence

When considering the polarity of episodes among all admissions, higher seasonality was found in mixed/unspecified episodes (r = .608), followed by manic (r = .436) and then depressive (r = .310) episodes. When analyzing the polarity of the index admissions only, mixed/unspecified episodes demonstrated the highest

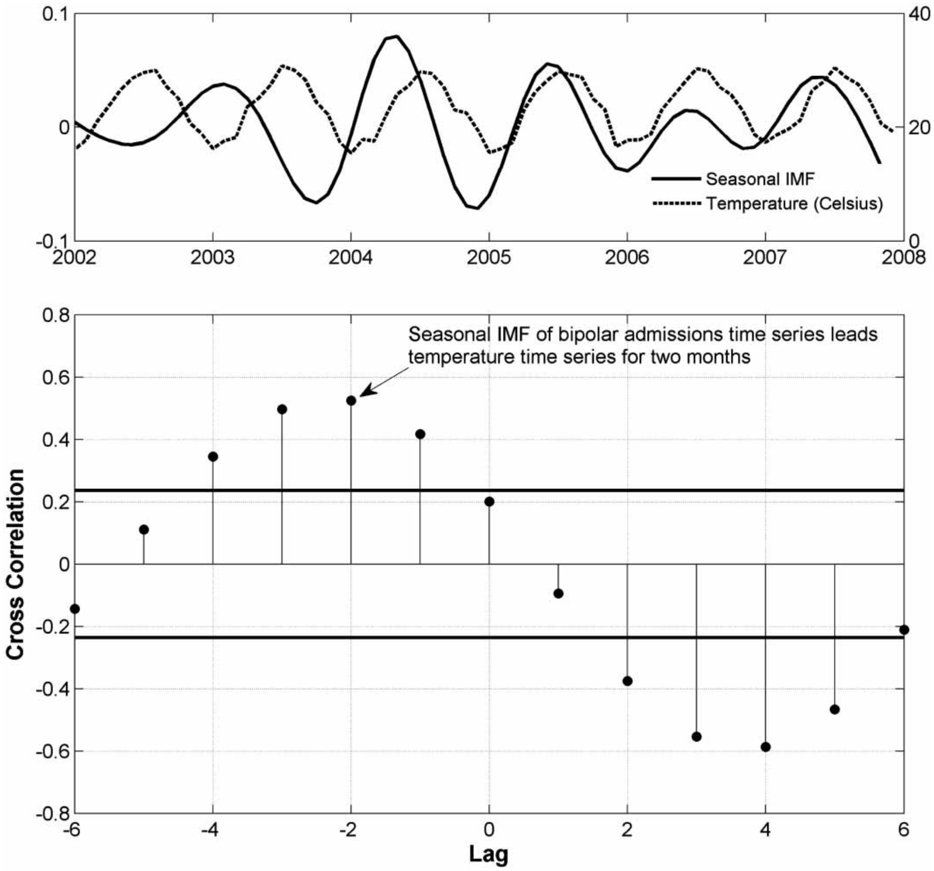

FIGURE 3. Cross–correlation analysis of seasonal IMF derived from acute admissions for bipolar disorders. Temperature time series was used as the reference of seasons. Upper panel: Comparisons of seasonal IMF and temperature time series. Lower panel: Cross-correlation analysis shows that seasonal IMF of bipolar admissions leads temperature time series for 2 mos, suggesting that the peak of bipolar admission occurred at May, 2 mos ahead of temperature peak at July. Of note, bipolar time series was out of phase with temperature time series in years 2002–2003, which was mainly due to few data of new admission incidence in early period of the study. Black horizontal line indicates the 95% confidence interval.

seasonality ($r = .701$), followed by depressive ($r = .645$) and manic ($r = .438$) episodes.

To test whether the polarity of the index admission was related to the seasonality of relapse admissions, we retrieved all admissions records for each patient following the index admission. Patients with an index admission of mixed/unspecified type once more displayed the highest seasonality in subsequent acute admissions ($r = .703$), followed by those with depressive ($r = .615$) and manic ($r = .477$) index admissions.

Effects of Age, Sex, and Predominant Polarity on the Degree of Seasonality

Table 2 summarizes the seasonality of bipolar disorders associated with age, sex, and predominant polarity models. Significant seasonality was found in most bipolar models (all $p < .05$). Sex displayed differential effects on the seasonality of bipolar admissions. Although mixed/unspecified episodes demonstrated the highest seasonality for both female and male patients ($r = .564$ and .610, respectively), women experienced a higher seasonal influence for depressive ($r = .512$) than manic ($r = .438$) episodes. In contrast, male patients experienced a higher seasonality for manic ($r = .531$) than depressive ($r = .281$) episodes.

Age group analysis showed that patients with index admission at young adulthood experienced higher seasonality than those with index admissions at middle age for all types of bipolar episodes (Table 2). Similarly to the total admission model, both age groups had higher seasonality for mixed/unspecified and manic episodes than for depressive episodes.

We classified 1245 patients admitted to the acute ward at least three times into predominantly manic, depressive, or unclassified bipolar disorders (see Materials and Methods). Acute admissions for predominantly depressive episodes showed higher seasonality ($r = .423$) than predominantly manic episodes ($r = .328$). Acute admissions for unclassified bipolar cases showed no significant seasonality.

DISCUSSION

The main findings of this study were as follows: (1) index admissions caused by mixed/unspecified or depressive episodes displayed higher seasonality than those

TABLE 2. Seasonality of acute admissions for bipolar disorders by age, sex, and subtypes

Models	Number of admissions (%)	Seasonality				Peak
		β	SE	r (r^2)	p	
Female						
Total	7580	1.667	.353	.491 (.24)	<.001	May
Manic	4218 (55.6)	1.414	.346	.438 (.19)	<.001	May
Depressive	1392 (18.4)	.924	.185	.512 (.26)	<.001	November
Mixed/unspecified	1970 (26.0)	1.697	.297	.564 (.32)	<.001	May
Male						
Total	7498	1.714	.270	.605 (.37)	<.001	May
Manic	3838 (51.2)	1.312	.250	.531 (.28)	<.001	April
Depressive	1714 (22.8)	1.255	.512	.281 (.08)	.017	September
Mixed/unspecified	1946 (26.0)	1.891	.294	.610 (.37)	<.001	June
Young adult (ages 18–34)						
Total	7513	1.549	.340	.478 (.23)	<.001	June
Manic	4053 (53.9)	1.812	.330	.549 (.30)	<.001	June
Depressive	1416 (18.8)	1.129	.289	.424 (.18)	<.001	October
Mixed/unspecified	2044 (27.3)	1.700	.266	.607 (.37)	<.001	June
Middle adult (ages 35–55)						
Total	7565	1.218	.340	.394 (.16)	<.001	April
Manic	4003 (52.9)	1.044	.281	.405 (.16)	<.001	March
Depressive	1690 (22.3)	1.347	.393	.379 (.14)	.001	December
Mixed/unspecified	1872 (24.7)	1.587	.340	.487 (.24)	<.001	May
Predominant polarity*						
Manic	1933	1.321	.455	.328 (.11)	.005	April
Depressive/mixed	2090	1.231	.315	.423 (.18)	<.001	March
Unclassified bipolar	1046	1.296	.666	.227 (.05)	.056	—

*Based on 1245 patients with equal or more than three times of acute admissions (see Materials and Methods for classification rules).

caused by manic episodes; (2) the polarity of the index admission was associated with the seasonality of relapse admissions; (3) women displayed higher seasonality in acute admissions for depressive than manic episodes, and vice versa for men; (4) patients with index admission at young age showed higher seasonality for acute admissions than those with index admission at middle age; and (5) patients with predominantly depressive admissions showed higher seasonality than those with predominantly manic admissions. This study employed a novel approach based on the EMD method and various time-series models to explore the degree and timing of seasonality in acute admissions for bipolar disorders. The results for the timing of seasonality were consistent with prior studies, and indicated that manic and mixed episodes occur in spring and summer, and depressive episodes in winter. The quantification of the degree of seasonal influence complements prior research, and provides new clinical insight into the seasonality of bipolar disorders.

Effect of Age at Index Admission on the Seasonality of Admission Data

Prior research had not clearly identified the effect of age on the seasonality of bipolar disorder (Takei et al., 1992). Our findings suggested a generally higher seasonality in patients with index admission at young age (ages 18–34) for all types of polarity, compared with those with index admission at middle age (ages 35–55). Of note, the age at the index admission is not a good proxy of the age of onset; bipolar patients tend to begin with the depressive episode and were less likely to be admitted (Etain et al., 2012).

Effect of Sex on the Seasonality of Admission Data

Previous data on the effect of sex in the seasonality of bipolar disorder are limited (Morken et al., 2002; Suhail & Cochrane, 1998). One recent study examining sex differences in diagnostic features among bipolar patients did not find significant differences in seasonality (Nivoli et al., 2011). Another recent study found mixed results for the effect of sex on bipolar disorder (Diflorio & Jones, 2011). Although the female sex has been associated with predominantly depressive polarity, research has also found that male and female patients experience equal rates for lifetime history of rapid cycling and depressive episodes (Baldassano et al., 2005). Our results, based on admission data, showed that opposite patterns occurred for male and female patients regarding the seasonality of manic and depressive episodes.

Effect of Index Admission on the Seasonality of Admission Data

The natural course of bipolar disorder often involves multiple relapses (Goldberg et al., 1995). This study shows that patients with mixed or depressive episode at index admission tended to demonstrate a comparable degree and timing of seasonality in their subsequent admissions. Although an earlier study did not find an association between timing of index episode and subsequent admissions (Hunt et al., 1992), our results based on population data suggest that the two might be linked in certain polarities of bipolar disorder.

Effect of Predominant Polarity on the Seasonality of Admission Data

Our results regarding predominant polarity suggested that patients with predominantly depressive episodes experienced higher seasonality in acute admissions than those with predominant manic episodes. Predominant polarity is a valid prognostic parameter with therapeutic implications (Colom et al., 2006). Manic polarity is more prevalent among bipolar I patients than bipolar II, and vice versa for depressive polarity (Baek et al., 2011). Our findings, though not a proxy for diagnosing bipolar I or II disorder, are comparable to prior data showing that patients with bipolar II disorder are more vulnerable to seasonal changes than patients with bipolar I disorder (Goikolea et al., 2007; Jacobsen & Rosenthal, 1988).

Clinical Insights

The influence of seasonality in bipolar disorder may have implications for treatment strategies. The findings in this study help to operationalize that patients with mixed/depressive episodes at index admission or those with predominant depressive episode may require additional attentions to prevent from seasonal cycling. Early studies have suggested that seasonal cycling in bipolar disorder may be treated with light therapy, particular for the depressive episodes (Lewy et al., 1982; Rosenthal et al., 1983). Recent studies suggested that such predominant depressive episodes may be responded to long-term treatment of lamotrigine treatment (Perlis et al., 2005). Furthermore, although our claim-based data cannot be validated for the diagnosis of bipolar I or II disorder, findings of predominant polarity of depressive episodes in this study may be consistent with the picture of bipolar II disorder, which is known to have more seasonal pattern than bipolar I disorder (Vieta & Suppes, 2008).

Strengths and Limitations

The merits of the current study included the enrollment of new incidence of mental illness among a cohort in the nationwide population-based database; identification of key oscillations related to seasonal variation, and the removal of irrelevant, nonstationary trends by EMD methods; and the stratification of time-series models by various demographic and clinical variables. However, the study has several limitations to consider when interpreting the findings. First, the ecological design was appropriate for identifying associations, but not for establishing causality. Second, admission data may provide a less accurate indication of the onset of mood episodes. Although hospital admissions may be a relatively good indicator of the onset of manic episodes, depressive episodes may not require admission or such admissions may be far from actual onsets and are determined by various psychosocial factors other than symptom exacerbation (Winokur, 1976). Furthermore, the polarity analysis in this study did not take into account for the outpatient record, thus depressive episodes may be underestimated and the polarity calculation may be biased toward manic episodes. Third, the validity of diagnoses based on insurance claims data may be less accurate than diagnoses received in interview-based studies. Fourth, this study did not control for the confounding effect of medication on the seasonality of acute admissions. Fifth, seasonal affective disorder may be related to photoperiod variation throughout the year (Praschak-Rieder et al., 2008), and we used temperature as a proxy of photoperiod to be the reference of the seasons (Yang et al., 2010a). The use of solar radiation data may be of help to validate this study (Bauer et al., 2012). Finally, the mechanism underlying seasonality of bipolar admission remains unclear; one recent study shows that pollen-specific immunoglobulin E positivity is associated with worsening of depression scores in bipolar disorder patients during high-pollen season (Manalai et al., 2012), thus the interaction between mood episode and environmental factors warrants future investigations.

Conclusions

In summary, this study showed that age, sex, index admission, and predominant polarity affect the seasonality of acute admissions for bipolar disorder. These findings highlight the need for future research on the identification and management of seasonal features in patients with bipolar disorder.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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