Causal dynamics of sleep, circadian rhythm, and mood symptoms in patients with major depression and bipolar disorder: insights from longitudinal wearable device data

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Summary

Background Sleep and circadian rhythm disruptions are common in patients with mood disorders. The intricate relationship between these disruptions and mood has been investigated, but their causal dynamics remain unknown.

Methods We analysed data from 139 patients (76 female, mean age = 23.5 ± 3.64 years) with mood disorders who participated in a prospective observational study in South Korea. The patients wore wearable devices to monitor sleep and engaged in smartphone-delivered ecological momentary assessment of mood symptoms. Using a mathematical model, we estimated their daily circadian phase based on sleep data. Subsequently, we obtained daily time series for sleep/circadian phase estimates and mood symptoms spanning >40,000 days. We analysed the causal relationship between the time series using transfer entropy, a non-linear causal inference method.

Findings The transfer entropy analysis suggested causality from circadian phase disturbance to mood symptoms in both patients with MDD (n = 45) and BD type I (n = 35), as 66.7% and 85.7% of the patients with a large dataset (>600 days) showed causality, but not in patients with BD type II (n = 59). Surprisingly, no causal relationship was suggested between sleep phase disturbances and mood symptoms.

Interpretation Our findings suggest that in patients with mood disorders, circadian phase disturbances directly precede mood symptoms. This underscores the potential of targeting circadian rhythms in digital medicine, such as sleep or light exposure interventions, to restore circadian phase and thereby manage mood disorders effectively.

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Keywords: Major depressive disorder; Bipolar disorder; Circadian rhythm; Sleep; Mathematical modelling; Causality

Introduction

Sleep and circadian rhythm are tightly intertwined,[1] and their disruptions are commonly observed in patients with major depressive disorder (MDD) and bipolar disorder (BD).[2] For instance, during depressive episodes in both patients with MDD and those with BD, insomnia or hypersomnia is prevalent,[3,4] while a reduced need for sleep is a prominent feature of manic and hypomanic episodes.[5,6] Patients with MDD typically have lower amplitude on circadian rhythms of locomotor activity, body temperature, norepinephrine, thyroid stimulating hormone, and melatonin levels.[7,8] Furthermore,

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Research in context

Evidence before this study

We searched PubMed for studies on September 15, 2023, using the search ("mood disorder" [Title] OR "depression" [title] OR "bipolar" [title]) AND ("circadian rhythm" OR "circadian" OR "chronobiology" OR "chronobiological"). While prior studies suggest a robust association between circadian rhythms and mood disorders, the precise role of circadian systems in relation to mood disorders remains unclear. Among various aspects of circadian rhythms, circadian phase is notably recognised for its substantial impact on mood disorders. Earlier research has indicated a strong association between delayed sleep phases and late chronotype with mood disorders. Recent investigations have explored individual sleep-wake patterns and their impact on the course of mood disorders using wearable devices. However, these studies have often failed to consider internal circadian rhythms fully. In a noteworthy study that measured rhythms of circadian gene expression and salivary cortisol, patients with bipolar disorder exhibited 4–5 h delayed rhythms during their depressive episodes and 7 h advanced rhythms (equivocal to 17 h delayed) during manic episodes. Notably, these rhythms were normalised following the treatment of mood episodes. Nevertheless, our understanding of the direction of the causal relationship between changes in circadian phase and individual mood at the personal level remains limited.

Added value of this study

We analysed causal relationships between real-world time series data of sleep/circadian phase estimates and mood symptoms, encompassing an average of 290 days. The acquisition of such extensive real-world data was possible by introducing a mathematical model for circadian phase estimation, as well as through advancements in wearable devices and smartphones. This extended dataset enabled robust causality analysis based on transfer entropy, a method capable of capturing non-linear relationships overlooked by conventional approaches like Granger causality. Our findings unveiled a crucial distinction: It was not sleep but circadian phase disruptions that preceded variations in mood symptoms among individuals with MDD and BDI. Furthermore, exploring the dynamic disparities between sleep and circadian phases provided insights into the complex causal dynamics, thus deepening our comprehension of the intricate interplay among sleep, circadian rhythms, and mood disorders.

Implications of all the available evidence

This study explores the complex interplay between sleep disturbances, circadian rhythms, and mood disorders, shedding light on the challenging task of establishing evidence in support of causality. We have elucidated the evidence supporting a causal relationship, aligning with the accumulating body of research in this area. Moreover, the methodology employed to achieve this breakthrough, harnessing mobile apps, wearable technology, and a mathematical model, represents a significant advancement in the real-time assessment of mood episode risks. This, in turn, holds promise for timely interventions focused on regulating circadian rhythms. Such interventions could usher in an innovative approach to the treatment of mood disorders, distinguishing them from conventional digital therapeutics that primarily offer standardised forms of behavioural therapy.

abnormalities in the peak time and amount of melatonin secretion have been observed in patients with BD.[9–12] Additionally, genetic evidence points to a strong relationship between susceptibility to mood disorders and circadian genes, such as CLOCK and TIM.[13,14]

Among the various types of sleep and circadian disturbances, phase disturbances are gaining attention in relation to mood disorders. For instance, social jetlag, determined by the difference between mid-sleep time during weekdays and weekends, positively correlated with depressive symptoms.[15] Both patients with MDD and BD often exhibit a preference for an evening chronotype.[16,17] Phase angle difference between the circadian phase and desired bedtime was associated with depressive severity in individuals with delayed sleep-wake phase disorder.[18] In seasonal affective disorder, phase delay in circadian rhythms was associated with depression.[19–21] Similar associations between circadian misalignment and depression severity have been observed in non-seasonal depression.[22] Furthermore, circadian phase advancement in acute manic episodes and circadian phase delay in acute mixed and depressive episodes were reported among patients with BD.[23] These circadian phase changes were normalised after treating the patients with BD. While strong associations between mood disorders and disturbances in sleep and circadian phases have been found, the causal relationship between these disturbances and mood remains elusive[24–27] (Fig. 1). For instance, sleep or circadian phase disruptions could lead to mood disturbances, or it could be the other way around.

While the causal relationship between circadian/sleep phase disturbance and mood can be inferred from their temporal sequences,[28] their longitudinal monitoring has rarely been performed in existing studies. Fortunately, the widespread usage of smartphones and wearable devices has facilitated the collection of continuous sleep and mood information over extended periods during longitudinal studies.[29,30] However, unlike the sleep phase, direct measurement of the circadian phase in humans is costly and possible only under limited conditions, making it nearly impossible to

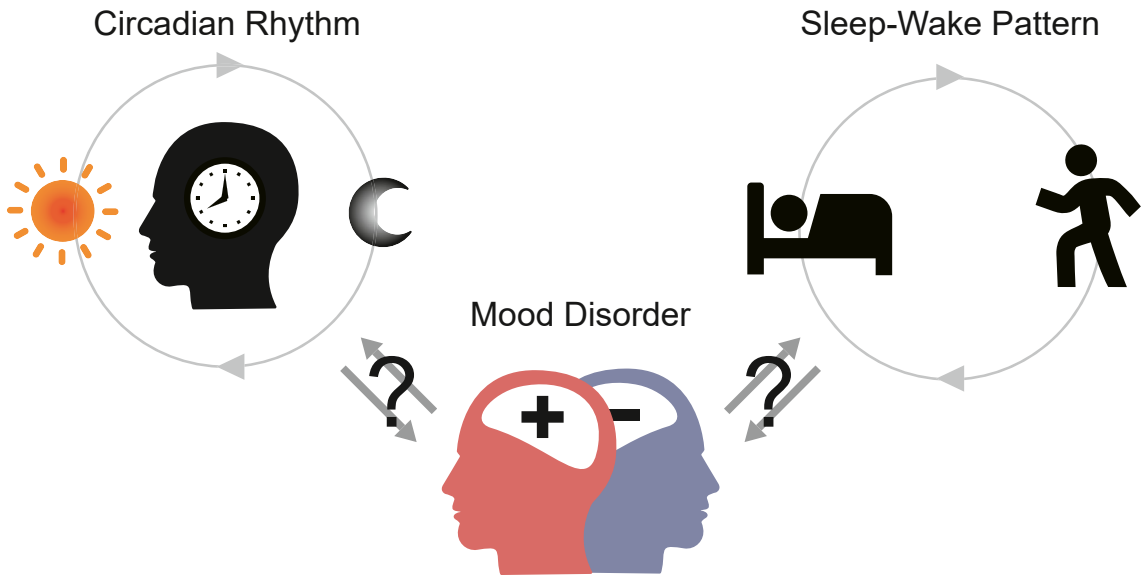

***Fig. 1:* Causal relationships between sleep or circadian phase disturbance and mood disorders remain unclear**. Sleep and circadian phase disturbances are associated with feeling depressed, lack of interest, tiredness, poor concentration and irritability, contributing to the development of mood disorders such as depression and bipolar disorder. However, the details of the causation between these factors are not yet fully understood. In particular, sleep-wake cycle disturbance may directly contribute to mood variations of patients with mood disorders or contribute indirectly through circadian phase disturbance. Conversely, mood variations themselves may disturb sleep and/or circadian phase.

acquire long-term time series data.[31] An alternative approach is indirectly estimating the circadian phase with mathematical models and wearable devices.[32–35] These models describe how the circadian rhythm responds to light exposure. Applying these models to light exposure data continuously obtained or inferred from wearable devices makes it possible to simulate the long-term evolution of the circadian rhythm, thereby generating a time series of the long-term estimates of circadian phase. Among currently known computational approaches in field settings, such as multiple regression models and artificial neural network models, this approach is considered the most effective[36] and has been widely accepted in various studies to track circadian dynamics.[32,36–40]

Previous studies have explored the temporal association and causal relationship between sleep and mood states using autoregressive models or Granger causality.[41,42] However, these approaches assume a linear relationship between the time series,[28] which may not be suitable when considering mood states such as depressive, elevated, and mixed moods. To better understand their causal dynamics, employing a non-linear causal inference method such as transfer entropy (TE) is essential.[43,44] TE quantifies the reduction in uncertainty when predicting the future state of one process based on the knowledge of the current and past states of another process. As a deliberately asymmetric measure, TE is frequently employed to deduce the directionality of information flow and, consequently, the causal relationship between the two processes.[28,45] TE has been proposed as an effective tool for investigating causality within complex systems, especially in computational neuroscience,[44,46–48] and in physiological systems such as cardiorespiratory interactions.[49–53] In particular, TE has also been employed to analyse electroencephalogram signals in individuals with mood disorders.[54–56]

In this study, we aimed to elucidate the direction of causality between circadian/sleep phase disturbances and mood symptoms in patients with mood disorders. We collected information on sleep and subjective mood symptoms over several hundred days using wearable devices and mobile applications. In addition, using a mathematical model, we estimated the daily circadian phase based on the collected sleep data, which indirectly informs the light exposure of patients. This process allowed us to extract time series data of circadian and sleep phase estimates as well as mood symptoms, with an average length of 290 days, from 139 patients with mood disorders. Subsequently, we performed causal inference between these time series using TE, which enabled us to consider the non-linear nature of depressive, elevated, and mixed moods. The analysis suggested causality from circadian phase disturbance to mood symptoms in patients with MDD and BD type I (BDI) but not in patients with BD type II (BDII). However, no causal relationship was suggested between sleep phase disturbance and mood symptoms. Our findings propose that in patients with mood disorders, it is not the sleep phase disturbances but the circadian

phase disturbance that directly precedes variations in mood symptoms. Furthermore, circadian phase disruption could trigger the relapse of mood episodes and, therefore, is a potential target of mood disorder treatment.

Methods

Recruitment

The data used in this study were collected from the Mood Disorder Cohort Research Consortium (MDCRC), a multicenter prospective observational cohort study on early-onset mood disorders in South Korea (ClinicalTrials.gov: NCT03088657).[57,58] Detailed study design and protocol information can be found in a previous publication.[57] In the original cohort study, 495 patients were recruited from March 2015 to April 2019, on a convenience basis, from both outpatient clinics and psychiatric wards. The inclusion criteria were being of an age <35 years and treated for less than two years with the diagnosis of mood disorders (MDD, BDI, and BDII) or age <25 years and diagnosed with mood disorders. Individuals with evidence of intellectual disabilities, organic brain injury, or difficulties with the Korean language were excluded. Most patients were on medications, and this study did not affect their ongoing treatment. Sex identification was self-reported by study participants and eligible patients were all encouraged to participate without restriction on sex. The study received approval from the Institutional Review Boards of all participating hospitals (2015AN0239) and was conducted following the Declaration of Helsinki. All participants provided written informed consent before enrollment after receiving a thorough explanation of the study.

Assessment

The patients were diagnosed by a psychiatrist using the Mini-International Neuropsychiatric Interview. They completed clinical scales, including the Montgomery-Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS). Furthermore, the patients were instructed to engage in daily smartphone-delivered ecological momentary assessment (EMA) of mood symptoms. The EMA questionnaire comprised two types of mood symptoms: depressed and elevated. Patients recorded their daily mood by rating both depressed and elevated moods on a scale ranging from 0 (not at all) to 3 (extremely). The patients were instructed to check both poles to identify a mixed state of mood state if their mood fluctuated frequently throughout the day or if they felt both elevated and depressed. The patients were encouraged to complete the questionnaire at the end of each day to record their overall daily mood symptoms, with a reminder text message sent to all patients at 9 pm daily. The patients were also asked to wear a wearable activity tracker every day (Fitbit Charge HR, 2 or 3, Fitbit Inc.), which records their sleep patterns.

Participants

Among 495 patients enrolled in the MDCRC study, 270 patients providing more than 30 days of lifelog data collected from wearable devices were initially included in the analysis. We excluded any missing instances after aligning the extracted estimates of daily sleep/circadian phase data with the corresponding mood symptoms data. Subsequently, we excluded 110 patients from the analysis whose processed data covered fewer than 28 days, excluding the initial 14 days' data. Additionally, 20 patients were excluded due to their low mood symptom variation. The exclusions were necessary for ensuring the reliable estimation of TE (see the following two sections for details). Finally, one patient was excluded from the analysis due to a change in diagnosis during follow-up evaluations of psychotic disorder. As a result, the final analysis was conducted with 139 patients.

Sleep/circadian phase estimates and mood symptoms extraction

To extract sleep and circadian phase information from the data collected using wearable devices, we analysed the sleep duration and timing (Fig. 2a). We determined the midpoint of each patient's daily main sleep period (Midsleep), a valuable measure for assessing the sleep phase.[59,60] The main sleep period of each day was identified as the most extended continuous period of sleep that overlapped with that specific day. Furthermore, we utilised a light-based circadian pacemaker model (Forger model)[61] to predict the daily DLMO, a widely recognised biomarker of the circadian phase. Specifically, the model simulates the core body temperature rhythm, predicting the core body temperature nadir (CBTmin). As CBTmin is known to occur 7 h after DLMO,[62,63] we can predict DLMO using the model simulations. This approach is substantiated by findings from several preceding studies where mathematical models were validated for predicting circadian phases.[32–35] In particular, the Forger model demonstrated comparable accuracy to other validated models.[35] The applicability of the Forger model to describe circadian rhythm dynamics is further highlighted by its integration into sleep-cycle models, effectively elucidating the alertness dynamics arising from circadian rhythm.[37,38]

To simulate the Forger model, we inferred the light input based on the sleep-wake pattern, using 250 lux for wakefulness and 0 lux otherwise, based on previous studies.[35,64] Specifically, one recent study demonstrated that a light proxy, which includes five light intensity levels (0, 100, 200, 500, and 2000 lux) based on activity levels, leads to more accurate circadian phase prediction for shift workers compared to actual data collected from wearable devices.[35] Moreover, another study indicated

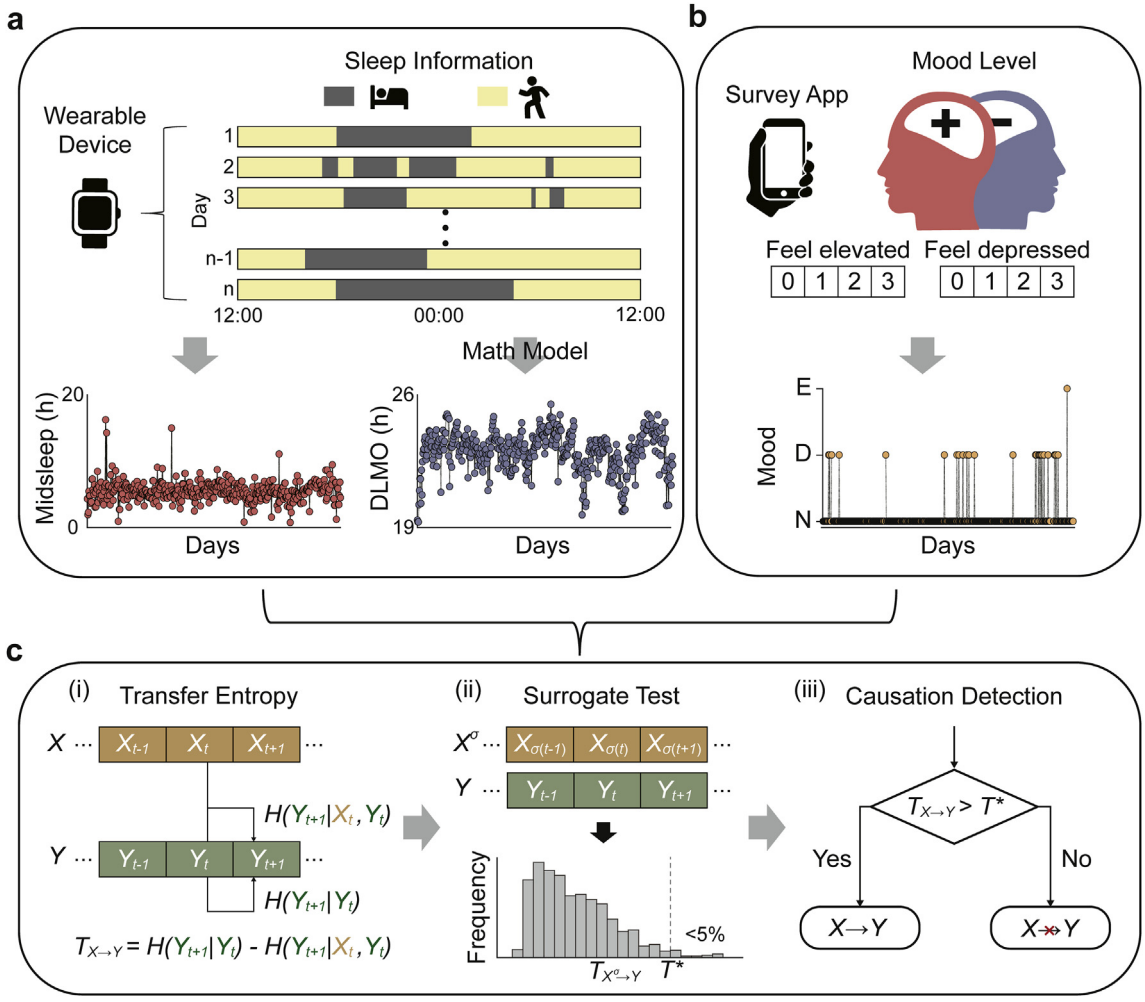

Fig. 2: **A framework for determining the causal relationship between sleep/circadian phase disturbance and mood variation.** **(a)** Sleep information, including duration and timing, was collected from mood disorder patients via wearable devices. The midpoint of the patient's daily sleep period (Midsleep) is used as a measurement of the sleep phase. A mathematical model is applied to the collected data to predict the daily Dim Light Melatonin Onset (DLMO), a golden standard biomarker of the circadian phase. **(b)** Self-reported information on the individual's emotional state was collected via a mobile survey app. The daily emotional states (Mood) are assessed as feeling low or high on a scale ranging from 0 to 3 and further classified into three categories: normal (N; both are 0), depressed (D; only feeling low is >0), and elevated or mixed (E; otherwise). **(c)** The causal relationship between the two daily time series (i.e., between Midsleep/DLMO and Mood) was determined via transfer entropy ($T_{X\to Y}$) (i). $T_{X\to Y}$ measures how much the uncertainty of the future state of the target variable (Y) reduces by knowing the past values of X (i.e., $H(Y_{t+1}|Y_t) - H(Y_{t+1}|X_t, Y_t)$). In order to handle biases of transfer entropy due to limited data size, surrogate testing is performed (ii). Specifically, X is randomly permuted (X^σ), and a transfer entropy value is computed ($T_{X^\sigma\to Y}$). This is repeated 1000 times to generate a distribution of transfer entropy and determine the threshold (T^*), making the proportion of $T_{X^\sigma\to Y}$ exceeding T^* by 5%. If the transfer entropy of the original data ($T_{X\to Y}$) exceeds T^*, causation from X to Y is detected; otherwise, no causation (iii).

that using 250 lux instead of the other positive light intensities does not significantly affect the simulation results of the Forger model.[38] Therefore, employing such two-level light input can effectively predict circadian phase and applies to data collected with the Fitbit Charge, known for its comparable accuracy in sleep evaluation compared to actigraphy.[65]

The initial conditions of the simulations were determined individually, assuming that each individual's average midsleep time during the first seven days corresponded to the initial CBTmin. This approach is based on a prior study that demonstrated high accuracy in predicting circadian phase for shift workers.[33] To further mitigate the impact of uncertainty in the initial conditions, we excluded estimated DLMO from the first two weeks. Additionally, we excluded Midsleep from the first two weeks for pair comparisons with DLMO.

From the collected daily mood symptoms data (measured by the EMA), we obtained time series data on daily mood symptoms (Mood) (Fig. 2b). Specifically, the quantified pairs of feeling depressed and elevated on a scale of 0–3 were classified into three categories: normal (N) when both poles are 0, depressed (D) when only depressed mood is greater than 0, and elevated or mixed (E) for all other cases.

Each day's Midsleep or DLMO data was paired with corresponding Mood data. The days without Midsleep/DLMO or Mood data due to data missing or absence of sleep period were excluded from the time series (see Tables S1–S3 for the time series lengths). Notably, DLMO can be estimated for the day without any sleep period, unlike Midsleep. Thus, the lengths of DLMO and Midsleep can differ, but the difference is at most 11 days.

Causal inference between sleep/circadian phase estimates and mood symptoms time series

The causal relationship between the two daily time series, namely Midsleep/DLMO and Mood, was investigated using TE (Fig. 2c (i)), which was found to be more precise and visually interpretable than Granger causality.[66] TE quantifies the amount by which the uncertainty of the future state of the target variable (Y) decreases when the previous day's value of the source variable (X) is known. It is computed as the difference between the two conditional entropies $H(Y_{t+1}|Y_t)$ and $H(Y_{t+1}|X_t, Y_t)$. Here, $H(Y_{t+1}|Y_t)$ evaluates the amount of information that remains in the next day's state of Y (Y_{t+1}) given the knowledge of its current value (Y_t). Intuitively, this captures the average uncertainty or surprise linked to the outcome of Y when its preceding value is available. If $H(Y_{t+1}|Y_t)$ is high and low, knowing the current value (Y_t) provides large and small amounts of information about future value (Y_{t+1}), respectively. Analogously, $H(Y_{t+1}|X_t, Y_t)$ measures the amount of information remaining in the future state of Y (Y_{t+1}) when the current values of both X (X_t) and Y (Y_t) are known. A positive TE indicates that the current value of X contributes valuable information for predicting the future of Y. Conversely, if it approaches zero, it implies that knowledge of the current values of X does not substantially augment the information obtained from the current values of Y alone. See Supplementary Information for a detailed illustrative calculation of TE.

Theoretically, a TE value of 0 indicates the absence of a causal relationship between two variables. Thus, previous studies have employed the positivity of TE as a criterion to detect causation.[44,67–69] However, this approach lacks reliability because it disregards confidence or statistical significance testing. To address this limitation, a statistical test for TE has recently been developed and incorporated into an R package, widely used for inference.[70] This approach, known as the Markov block bootstrap, requires the reconstruction of the Markov chain transition matrix for each variable to generate sample time series of the two variables without any causality. It is important to note that the reliability of this statistical test has been questioned due to the need for a large dataset and high data variability, particularly when the data has numerous categories or states.[44] To address these concerns, we employed a bin size of three for both source and target time series to reduce the number of states, aiming to enhance the robustness of the analysis. We also considered only 159 patients with MDD and BD among 495 patients whose data size (i.e., length of the time series) was larger than 27, excluding the initial two weeks' data (see the sleep/circadian phase estimates and mood symptom extraction section for details). The 27-day threshold represents the minimum data size required to cover all states in the joint probability of the current target state, the previous day's target state, and the previous day's source state (i.e., $(\text{bin size})^3 = 27$), which is essential for calculating transfer entropy. Moreover, 20 patients whose Mood variations were below 0.05 were excluded when assigning 0 and 1 to the normal and the other states (see Tables S1–S3 for the mood variation of the included data).

Despite implementing precautions, it was observed that the current algorithm for predicting causation still yielded statistically significant results when applied to randomised DLMO time series, which should not exhibit any causation (Fig. S1 for details). To overcome this false-positive prediction, we employed an alternative approach that does not involve the reconstruction of the Markov chain transition matrix. Specifically, we performed surrogate testing (Fig. 2c (ii)), which involves randomly permuting the variable X (X^σ), and calculating the TE value ($T_{X^\sigma \to Y}$). This process is repeated 1000 times to generate a distribution of TE values. From this distribution, a threshold value (T^*) is determined such that the proportion of $T_{X^\sigma \to Y}$ exceeding T^* is 5%. To determine the presence of causation from X to Y, the TE of the original data ($T_{X \to Y}$) is compared to T^* (Fig. 2c (iii)). If $T_{X \to Y}$ surpasses T^*, it indicates the detection of causation from X to Y. Conversely, if $T_{X \to Y}$ falls below T^*, it suggests the absence of causation between the variables. When applying this statistical test to the randomised DLMO data, we observed a significantly reduced number of cases where causation was detected compared to the previous statistical test method (Fig. S1 for details). This demonstrates the improved accuracy and reliability of the alternative approach in distinguishing between actual causation and random fluctuations in the data.

Quantification and statistical analysis

Statistical analysis of study patients' demographic and clinical characteristics was performed using R software (version: 4.3.2, http://www.R-project.org). Measurement data are expressed as the mean ± standard deviation and compared between three diagnostic groups using

analysis of variance. Categorical data are represented as frequencies and percentages (%) and compared between three diagnostic groups using the chi-square test and Fisher's exact test when the value in any of the cells is below five. The annualised relapse rate is calculated with counts of relapse as the numerator and person-years of observation as the denominator. Estimated DLMO and midsleep are expressed as the median and interquartile range. For sleep and DLMO estimation, the data preprocessing was performed with MATLAB 2021a software (Natick, MA, USA). The simulations of the mathematical model to estimate the DLMO were performed using ode15s solver in MATLAB. The TE analysis was performed using RTransferEntropy package for R.

Role of the funding sources

The funder played no role in study design, data collection, analysis and interpretation of data, or the writing of this manuscript.

Results

Among a total of 139 patients included in the analysis, 45 (32.4%) were diagnosed with MDD, 35 (25.2%) had BDI, and 59 (42.4%) had BDII. The obtained time series spanned 29 to 1457 days (mean ± standard deviation (SD) = 290± 297; see Tables S1–S3 for details). Table 1 presents the patients' baseline demographic and clinical characteristics, including their baseline symptoms, comorbidities, and medications. Age, sex, MADRS, and data size exhibited no differences among the three groups, whereas YMRS varied between groups, reflecting their respective diagnoses. The post-hoc analysis indicated a significantly higher baseline YMRS score in BDI compared to MDD, with consideration for Bonferroni's correction. The prevalence of comorbidities, including anxiety disorder, substance use disorder, obsessive-compulsive and related disorder, eating disorder, and posttraumatic stress disorder, did not show differences between groups. However, medications differed between groups, reflecting diagnostic differences, except lithium. Specifically, pairwise comparison with Bonferroni correction revealed that patients with BD used mood-stabilising anticonvulsants more frequently and antidepressants less frequently than patients with MDD. The mean ± SD age of patients with MDD, BDI, and BDII were 23.3 ± 3.9, 24.7 ± 4.4, and 23.0 ± 2.7 years, respectively. The number (percentage) of patients whose mood episodes recurred during the data requisition period were 21 (47%), 23 (66%), and 40 (68%) in MDD, BDI, and BDII, respectively. The mean ± SD durations of data were 266 ± 238, 360 ± 391, and 267 ± 271 days in MDD, BDI, and BDII, respectively. The annualised relapse rates of mood episode recurrence per person-year were as follows: major depressive episodes, 0.48, 0.53, and 0.73 in MDD, BDI, and BDII, respectively; manic episodes, 0.28 in BDI, and hypomanic episodes; 0.15 and 0.33 in BDI and BDII, respectively.

TE analysis suggests the causality between circadian phase disturbance and mood symptoms

We examined the percentages of patients demonstrating causal relationships (% of causality) of each direction within each diagnostic group of MDD, BDI, and BDII (Fig. 3). In particular, we investigated how the % of causality changes as the data size increases, and thus TE estimation becomes more reliable.[44] Thus, the increase in the % of causality as the data size increases can be used as the criteria for the reliability of causality.

As the data size grew from 0, 100 to 200, ..., and 600 days for patients with MDD (Fig. 3a) and BDI (Fig. 3b), the % of causality of DLMO to Mood exhibited a progressive increase. In particular, when considering only patients with a data size larger than 600 days, the % of causality reached 66.7% and 85.7% for patients with MDD and BDI, respectively. However, the opposite direction (Mood to DLMO) showed a consistently low % of causality (Fig. 3d and e), never exceeding 17% regardless of data size. In particular, no causality from Mood to DLMO was observed for MDD. The % of causality of Midsleep to Mood also showed a gradual increase with larger data sizes both for patients with MDD (Fig. 3g) and those with BDI (Fig. 3h). However, this increase was not as pronounced as that of DLMO to Mood, with the % of causality never exceeding 43% in all cases. As for Mood to Midsleep causality, it was nearly 0% regardless of the data size in both patients with MDD (Fig. 3j) and those with BDI (Fig. 3k). Taken together, the analysis suggests strong evidence supporting causality from DLMO to Mood in patients with MDD and BDI, indicating that the circadian phase exerts a more prominent influence on mood symptoms in these diagnostic groups. Conversely, Midsleep did not exhibit such robust evidence supporting a causal relationship with Mood, suggesting a comparatively weaker impact.

On the other hand, patients with BDII displayed a different pattern. The % of causality of DLMO to Mood (Fig. 3c) did not progressively increase with larger data sizes, never exceeding 37%. Additionally, the % of causality from Mood to DLMO (Fig. 3f) was nearly 0% regardless of the data size. Similarly, the % of causality of Midsleep to Mood (Fig. 3i) did not show a clear increasing pattern, with the % of causality never exceeding 37%, and that of Mood to Midsleep (Fig. 3l) was 0% for all the data sizes. These findings suggest a less pronounced causal relationship between DLMO/Midsleep and Mood in patients with BDII, possibly influenced by other factors (see Discussion for details).

Given the utilisation of estimated DLMO through a mathematical model, it is crucial to consider the potential impact of prediction errors on our previous analysis of the causal relationship between DLMO and Mood. To address this concern, we deliberately

Characteristics	Diagnosis			p
	MDD n = 45	BDI n = 35	BDII n = 59	
Demographic characteristics				
Age at baseline, years, mean (SD)	23.3 (3.92)	24.7 (4.37)	23.0 (2.74)	0.62
Sex, n (%)				0.054
Female	18 (40%)	22 (63%)	36 (61%)	
Male	27 (60%)	13 (37%)	23 (39%)	
Clinical characteristics				
Baseline clinical scales				
MADRS	18.3 (11.1)	10.7 (10.1)	17.4 (10.6)	0.86
YMRS	1.22 (2.15)	2.37 (3.33)	3.19 (3.64)	<0.05
Comorbidities				
Anxiety disorder	15 (33%)	5 (14%)	21 (36%)	0.065
Substance use disorder	2 (4.4%)	3 (8.6%)	2 (3.4%)	0.54
OC and related disorder	2 (4.4%)	2 (5.7%)	10 (17%)	0.10
Eating disorder	1 (2.2%)	1 (2.9%)	5 (8.5%)	0.37
PTSD	2 (4.4%)	0	5 (8.5%)	0.22
Somatic symptom and related disorder	1 (2.2%)	0	1 (1.7%)	1
Medications				
Lithium	13 (29%)	19 (54%)	26 (44%)	0.065
Anticonvulsants	10 (22%)	19 (54%)	31 (53%)	<0.05
SSRIs	26 (58%)	1 (2.9%)	10 (17%)	<0.01
Other antidepressants	18 (40%)	0	8 (14%)	<0.01
Annualised relapse rate (person-year)				
MDEs	0.48	0.53	0.73	
MEs		0.28		
HMEs		0.15	0.33	
Sleep measures and circadian estimates				
Data size, days, mean (SD)	266 (238)	360 (391)	267 (271)	0.89
Estimated DLMO, hour, median (IQR)	23.1 (22.0–24.3)	22.2 (21.2–23.3)	23.0 (21.7–24.6)	
Midsleep, hour, median (IQR)	5.02 (3.70–6.97)	4.14 (2.92–5.67)	4.96 (3.37–7.05)	

Data are expressed as mean (standard deviation), number (%), number per year per person or median (interquartile range). Analysis of variance was applied to test for age and data size. Categorical variables were compared using the chi-square test and Fisher's exact test. MDD Major depressive disorder, BDI bipolar I disorder, BDII bipolar II disorder, MADRS Montgomery-Asberg Depression Rating Scale, YMRS Young Mania Rating Scale, OC obsessive-compulsive, PTSD posttraumatic stress disorder, MDE major depressive episode, ME manic episode, HME hypomanic episode, DLMO, dim light melatonin onset, IQR, interquartile range.

Table 1: **Demographic and clinical characteristics of study participants.**

introduced random Gaussian noise into the DLMO time series, mirroring the level of prediction error encountered. Subsequently, we applied transfer entropy analysis to investigate this impact. The magnitude of the noise was determined based on a prior validation study of the mathematical modelling approach.[33] Specifically, the predicted circadian phase shows a linear correlation with the measured values, while the slope is not precisely one. As the current transfer entropy analysis is insensitive to the scaling of the time series, we can regard the residual error of the linear model between predicted and measured circadian phases as the prediction error. From the previously reported r-squared values and the SDs of the measured circadian phases in the previous study,[33] we calculated that the SD of the random noise required to be added to the current DLMO time series is ~0.3 h for day shifts and ~0.6 h for night shifts. Noise of SD 0.6 h was added to the day with a night-shift-like sleep phase, where the Midsleep falls between 10 am and 3 pm, while noise of SD 0.3 h was added to the other days.

This process was repeated 20 times, and we calculated the mean and standard deviation of the % of causality (Fig. S3). Interestingly, as we introduced random noise, the % of causality from DLMO to Mood in patients with MDD remained relatively consistent, while in patients with BDI, it exhibited a significant decrease. However, the overall increasing trend with increasing thresholds persisted. Moreover, these values continued to be notably higher than the % of causality from Mood to DLMO. Importantly, even in this added random noise, the % of causality from DLMO to Mood remained comparable to or even exceeded those observed for Midsleep to Mood (Fig. 3). This suggests

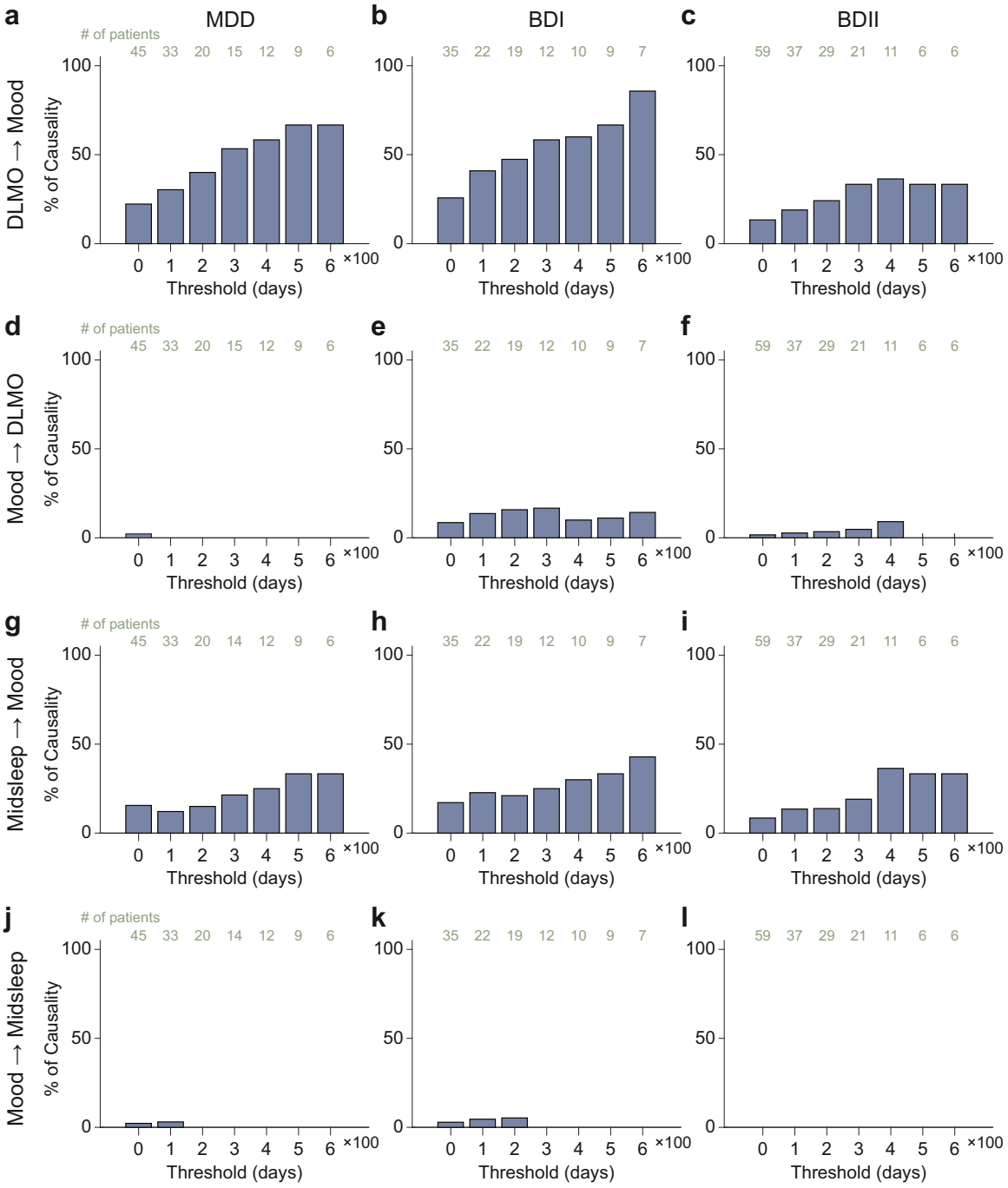

Fig. 3: **Only causation from circadian phase disturbance to mood variation is evident**. **(a–f)** The fractions of causality between circadian phase and mood symptoms among patients with MDD (a, d), BDI (b, e), and BDII (c, f), which were obtained by transfer entropy (TE). In particular, the fraction of causality was calculated by changing the data inclusion threshold for data length (0, 100, 200, ..., 600 days). As more patients with low data size were excluded, and thus the causation detection with TE became more reliable, the causation from DLMO to Mood became more evident in patients with major depressive disorder (MDD; (a)) and bipolar disorder I (BDI; (b)), but not BDII (c). **(g–l)** Unlike DLMO, there is no apparent causation between Midsleep and Mood for all patients with mood disorders (i.e., MDD, BDI, and BDII).

that, despite the existence of prediction errors, their impact was sufficiently minimal to avoid distorting the implication of the previous analysis.

The TE analysis in this study examined causality from a source variable to a target variable by investigating whether knowledge of the previous day's source variable can diminish the uncertainty of the present day's target variable. As depicted in the results (Fig. 3), this analysis highlights evidence supporting the causality of the preceding day's circadian phase change on mood symptoms. This prompts the question of whether the influence of the circadian phase on mood symptoms extends beyond a single day. To explore this, we shifted the source variable time series one day forward and applied TE analysis. This approach allows us to evaluate whether awareness of the source variable from two days prior could reduce the uncertainty of the present day's target variable. Upon shifting the source time series by one day, the overall % of causality decreased compared to the case without a time series shift (Fig. S2). In particular, the % of causality from DLMO to Mood of patients with BDI decreased significantly, and that of patients with MDD no longer shows a progressive increase. This observation suggests that the influence of the circadian phase disturbance from one day prior on mood symptoms is most substantial and diminishes as the delay increases.

Sleep phase disturbance induces circadian phase disturbance, which potentially causes mood episode relapse

Inter-daily circadian phase variations primarily hinge on sleep-wake patterns, notably dictating the most pivotal factor in the circadian rhythm—light exposure pattern. This influence has become especially pronounced in modern society due to the prevalence of artificial light.[71] Nevertheless, our TE analysis suggests that the causal link between circadian phase disruption and mood symptoms is much stronger than that between sleep phase disruption and mood symptoms in patients with MDD and BDI. This raises the question of what specific dynamical differences between circadian and sleep phases contribute to this disparity in causality. To explore this further, we examined the dynamics of Midsleep and DLMO in two sample sleep-wake pattern scenarios: (1) a sudden 4-h delay of sleep periods while maintaining the overall sleep period (Fig. 4a) and (2) a gradual variation in sleep durations while keeping the midpoints of the sleep periods constant (Fig. 4b).

In both scenarios, changes in sleep patterns and the following change in light exposure pattern resulted in alterations in the circadian phase, but their change tendencies differed. Specifically, when sleep periods were suddenly delayed by 4 h, Midsleep also shifted by 4 h immediately, while DLMO exhibited a gradual delay, taking more than six days to shift by 4 h (Fig. 4a). In addition, when sleep durations varied while maintaining a constant Midsleep, DLMO showed variation (Fig. 4b). These distinctive dynamics between Midsleep and DLMO may have contributed to the differential identification of causal relationships. For instance, a chronic sleep phase disruption, which induces a large circadian phase shift, might be more likely to cause mood symptom variation than acute sleep phase disruptions. Moreover, irregular sleep durations might induce significant circadian shifts and contribute to mood symptoms even when the time of midsleep remains almost the same.

Based on these observations, we can conclude the following causal relationships between sleep patterns, circadian phases, and mood disorder: disturbance in the sleep pattern results in circadian phase disruption whose dynamics differ from the sleep phase. This distinct circadian phase disruption ultimately causes mood symptom variation, which potentially results in mood episode relapse in patients with mood disorders (Fig. 4c).

Discussion

Accumulating evidence has shed light on the associations between sleep/circadian phase disturbance and mood disorders,[23,58,72–74] yet unravelling the direction of causality remains challenging (Fig. 1).[26] Our findings based on the application of a mathematical model and the TE analysis (Fig. 2) demonstrated strong evidence supporting causality from circadian but not sleep phase disturbance to mood symptoms for patients with MDD and BDI, whereas no clear evidence supporting causality was observed in patients with BDII (Fig. 3). These results suggest that disturbances in the circadian phase preceding mood symptom variations may trigger relapses of mood episodes in patients with MDD and BDI. Furthermore, we explored the dynamics of the circadian phase estimates, which, although linked to sleep pattern disturbance, exhibited distinctive characteristics that might contribute to the different causal relationships with mood symptoms (Fig. 4a and b). Based on these findings, we hypothesise that sleep phase disturbance indirectly influences mood symptoms through circadian phase disturbances (Fig. 4c).

The absence of evidence supporting causality in BDII may be attributed to several factors. Until recently, it was believed that BDI and BDII could be classified along a spectrum based on the extent, duration, and severity of manic symptoms. However, recent studies report more prominent and longer depressions, more cyclothymic temperament,[75] greater likelihood of mixed features,[76] and higher risk of mood recurrences[77] in BDII than BDI. These findings suggest that mood oscillations in patients with BDII may be more chaotic than in patients with BDI. Consequently, patients with BDII face difficulties accurately assessing their daily mood, which can result in inaccurate mood symptom recordings.

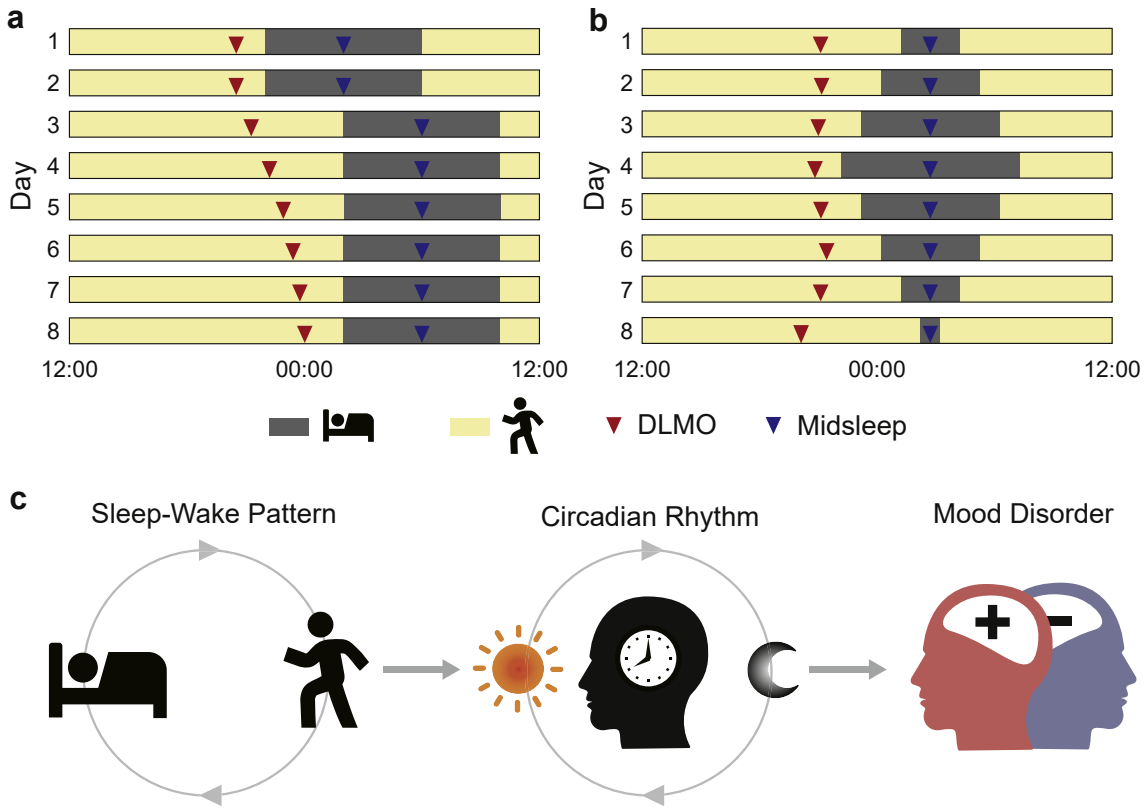

Fig. 4: **Circadian phase disturbance, which results from sleep phase disturbance, causes mood variation, potentially resulting in mood episode relapse**. **(a)** A sudden delay in the sleep period leads to an abrupt delay in Midsleep (blue triangle) but a gradual delay in DLMO (red triangle) over time due to altered light exposure. **(b)** Varying sleep durations does not change the Midsleep but alters DLMO due to altered light exposure. **(c)** Due to these different dynamics of Midsleep and DLMO, although DLMO was determined by sleep phase, which determines light exposure pattern, only the causation from DLMO, not Midsleep to Mood, was detected. Therefore, the accumulation of sleep disruptions and resulting circadian disruption cause mood variation, potentially contributing to the onset of mood episodes.

Moreover, patients with BDII are more likely to have comorbidity with borderline personality disorder (BPD) than BDI.[78] However, differentiating BPD from BDII is a common diagnostic dilemma for clinicians.[79] Whether due to comorbidity or misdiagnosis of BPD, patients with this disorder can complicate the establishment of a causal relationship between the circadian phase and mood symptoms due to their core features, such as affective instability and emotional dysregulation. Interestingly, a recent large study assessing polygenic risk scores (PRS) for sleep traits in association with BD reported that PRS for morningness was associated with a reduced relative risk of BDI compared with the control participants, while the results for BDII compared with the control were not significant.[80] This result aligns with our results and may reflect the characteristics mentioned above of patients with BDII.

The suggested causality from circadian phase to subsequent mood symptoms indicates that disruptions in circadian phase have the potential to lead to the recurrence of mood symptoms in patients with mood disorders. This finding aligns with previous research that found that disturbances of circadian phase were linked to the relapse of mood episodes. For instance, a 12-month prospective study found a significant association between a later timing of baseline circadian activity rhythm and an increased risk of depressive episode relapses in patients with BD.[81] A 48-week prospective study revealed that comorbidity of circadian rhythm sleep-wake disorders was significantly associated with the time to relapse of mood episodes.[74] In contrast, some longitudinal studies found that chronotype was not associated with mood disorders.[82,83] However, a meta-analysis that included these longitudinal studies reported a significant relationship between evening chronotype and mood-related disturbances.[84] The association of chronotype with mood disorders is further supported by a recent large-sample genome-wide association study, which revealed that earlier diurnal preference is associated with a protective effect on the risk of MDD.[85] It is important to note, however, that the previous studies primarily assessed the

inter-individual level effects of circadian rhythm characteristics. Our causality inference framework provides insights into the within-individual-level impact of circadian phase on mood symptoms through gathering longitudinal data, revealing dynamic intra-individual variability of estimated sleep/circadian rhythms and its impact on mood symptoms. Therefore, our framework addresses the limitations of previous research and bridges the gap between circadian rhythm characteristics and future mood episodes.

The suggested causality from circadian disruption to mood symptoms also aligns with prior animal studies.[86,87] The studies involved mice carrying mutated REV-ERB α gene, a circadian clock component, and found that these mice exhibited behaviours akin to elevated, similar to those in BD.[86] In particular, the studies proposed molecular links for this phenomenon by demonstrating that REV-ERB α regulates dopamine and serotonin levels in the midbrain and dorsal raphe, respectively, neurotransmitters known to influence mood.[86,87] Our study significantly supports these prior inquiries by employing a unique approach to establish causality between time series data, distinct from previous animal studies. Taken together, these results emphasise the importance of circadian rhythm in MDD and BD, indicating its potential role in aetiology and treatment.

This study utilised sleep onset and offset data collected through the Fitbit Charge device to estimate sleep and circadian phases. Previous research has indicated that estimating gross sleep parameters such as Total Sleep Time (TST) and Wakefulness After Sleep Onset (WASO) using Fitbit devices can be inaccurate, especially among individuals with psychiatric conditions.[88–90] However, it is worth noting that the Fitbit device model employed in our study was a newer model than the device used in prior research, and newer generations have shown improved performance.[91–93] Moreover, past studies have primarily noted inaccuracies in classifying WASO as sleep, while the estimation of sleep onset and offsets remained reliable.[88–90,94] Hence, the estimated sleep phase (i.e., Midsleep) in our study can be deemed reliable. Additionally, WASO typically occurs in low-light or dark conditions, making it less likely to impact the accuracy of circadian phase estimation using our methodology significantly. Nevertheless, further validation of the current Fitbit model's ability to estimate sleep onset and offset in the psychiatric population is imperative.

Previous studies have demonstrated the effectiveness of mathematical models in simulating circadian rhythm and estimating circadian phase, even in challenging shift work scenarios where sleep patterns are highly irregular. Specifically, while specific investigations have reported reduced accuracy in predicting circadian phases for shift workers compared to non-shift workers,[32,34,35] another study by Stone et al.[33] demonstrated notably higher accuracy, even among shift workers; they achieved circadian phase predictions within ± 1 h for 80% and 68% of individuals on diurnal and night schedules, respectively. This success was attributed to their unique approach of setting initial conditions based on individuals' midsleep phase, deviating from the uniform initial conditions used in previous studies. Inspired by this approach, we also adopted individualised initial conditions recommended by Stone et al. to enhance the accuracy of DLMO prediction. Furthermore, acknowledging the lingering uncertainty associated with initial conditions, we excluded DLMO data from the first two weeks. Taken together, our study's circadian phase estimation is expected to be robust and reliable, even when targeting individuals with disrupted sleep patterns.

The circadian rhythms simulated with the mathematical models have applications in various domains, such as predicting appropriate sleep-wake patterns or daily alertness level variation in shift workers.[32,37,38] This indicates the broad potential of utilising mathematical model-predicted circadian rhythms to uncover the intricate connections between circadian rhythm disturbances and the onset or progression of diverse health conditions, such as neurodegenerative disease.[95] This approach might also be directly applied to data from previous studies that have explored the temporal association between sleep and mood.[41,42,96]

Integration of wearable devices and mathematical models can detect disruptions in circadian rhythms in real time.[35,97,98] This opens up the possibility of assessing the risk of recurring mood episodes in the patient's daily life outside clinical settings. Additionally, it provides an objective measure of the patient's condition, which has been lacking in traditional interview-based psychiatric approaches to mood disorders. Based on these findings, clinicians may be able to intervene early, before daily mood swings develop into full-blown mood episodes. This could include correcting the patient's circadian rhythm through lifestyle modification or administration of light therapy or melatonin.[99–101] In particular, the timing of melatonin administration or light exposure could be optimised based on the patient's calculated DLMO, considering the phase response curve.[101,102] Other zeitgebers, such as mealtime and activity schedules, also have potential as targets for intervention.

In order to make these interventions timely according to patients' dynamic conditions, digital therapeutics (DTs) may be more appropriate than outpatient clinics.[97,100] DTs, a unique class of software applications designed to deliver evidence-based treatments through patients' smartphones, tablets, or computers,[64] are emerging treatment options in mental health.[103] Some DTs, like reSET[104] and Somryst,[105] digitally provide standardised versions of behavioural therapies already employed in traditional clinician-based settings. On the other hand, a DT focused on modulating circadian

rhythms in accordance with their daily fluctuations could offer a distinctive approach to treating mood disorders. However, further clinical trials are imperative to establish robust evidence concerning therapeutic efficacy.

While the current study found evidence supporting a causal link between circadian phase disturbance and mood symptoms, further investigation is needed to determine the exact nature of this relationship. Specifically, it is crucial to explore whether circadian rhythm delay or advance actively contributes to the development of depression or (hypo)mania. Moreover, this study focused only on phase disturbance, while various types of circadian disturbances are known to be associated with mood disorders, such as chronotype, amplitude, and irregularity of sleep/circadian rhythms.[106,107] It would be interesting to apply the same approach as in this study to circadian amplitude and mood symptom variation data. Furthermore, it is essential to acknowledge that other sleep-related factors, like sleep loss, which were not considered in this study, could potentially influence mood symptoms in individuals through non-circadian mechanisms. These unexplored factors might actively contribute to mood symptoms in cases where a causal link between DLMO and mood was not identified in this study. It would be intriguing to conduct further investigations into the causality between various sleep parameters like sleep duration and mood symptoms.

Several limitations in our study methodologies warrant acknowledgement. Firstly, subjective (self-reported) mood symptoms may be susceptible to biases. It is essential to approach the interpretation of subjective mood symptoms with caution, considering the potential for miscommunication or misunderstanding, and maintain a nuanced understanding when assessing their implications in mood disorders. Secondly, our study did not account for the potential effects of medications and comorbidities. Previous research has indicated that lithium treatment in BD was associated with shifts towards morningness and a larger circadian amplitude.[108] Other mood stabilisers, such as valproic acid and even serotonergic antidepressants, are also known to influence circadian rhythms.[109,110] Furthermore, comorbid psychiatric conditions, such as substance use disorder with mood disorders, are recognised for their impact on circadian rhythms.[111,112] The rate of comorbidities in the patient population, except for anxiety disorder, mainly was below 10% (Table 1). Thus, the impact of psychiatric comorbidities on our results is presumed to be negligible. However, a majority of patients in this study were using medications, including lithium, mood-stabilising anticonvulsants, and antidepressants (Table 1). This could potentially influence the study results. Thirdly, depending on sleep onset and offset data collected from Fitbit, which may necessitate further validation in the psychiatric population, poses a potential limitation to the current study. Strengthening the findings may require further validation of our approach by utilising more reliable sleep data. Finally, while the Forger model has been successfully validated in diverse populations, including shift workers, its validation for patients with mood disorders is lacking. Patients with depression have shown hyposensitivity of the circadian system to light,[113] and supersensitivity to light has been proposed as a biomarker of BD.[106] Given potential variations in physiological properties related to circadian rhythms in this patient group compared to non-patients, additional calibration of model parameters may be necessary to enhance the accuracy of circadian phase predictions for individuals with mood disorders.

Contributors

H.J.L. and J.K.K. developed the concept and design. H.J.L., C.H.C., J.B.L., T.L., and J.W.Y. performed the recruitment of participants and data collection. A.A.D.L.R.V., Y.M.S., D.L., and J.K.K. developed the algorithm. Y.M.S., A.A.D.L.R.V., J.J., H.J.L., and J.K.K. performed the analysis of data. Y.M.S., A.A.D.L.R.V., J.J., verified the underlying data. Y.M.S., A.A.D.L.R.V., J.J., H.J.L., and J.K.K. wrote the draft of the manuscript. All authors provided critical feedback on the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

Data sharing statement

The MDCRC data are not deposited into a public repository due to multi-site partnership agreements and conditions for Institutional Review Board approval. The MDCRC data are routinely made available through submission and approval from the cohort executive committee of a data access form. The access to the data was facilitated by one of the corresponding authors of this study, HJ Lee, who served as a principal investigator of the MDCRC study.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105094.

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