

## RESEARCH ARTICLE

# Unraveling the interplay of circadian rhythm and sleep deprivation on mood: A Real-World Study on first-year physicians

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## Abstract

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**Data Availability Statement:** Data used in this manuscript is located on GitHub in the repository “Interplay of Circadian Rhythm and Sleep Deprivation on Mood” which can be accessed using the following url: <https://github.com/Benhs143/Interplay-of-Circadian-Rhythm-and-Sleep-Deprivation-on-Mood>.

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The interplay between circadian rhythms, time awake, and mood remains poorly understood in the real-world. Individuals in high-stress occupations with irregular schedules or nighttime shifts are particularly vulnerable to depression and other mood disorders. Advances in wearable technology have provided the opportunity to study these interactions outside of a controlled laboratory environment. Here, we examine the effects of circadian rhythms and time awake on mood in first-year physicians using wearables. Continuous heart rate, step count, sleep data, and daily mood scores were collected from 2,602 medical interns across 168,311 days of Fitbit data. Circadian time and time awake were extracted from minute-by-minute wearable heart rate and motion measurements. Linear mixed modeling determined the relationship between mood, circadian rhythm, and time awake. In this cohort, mood was modulated by circadian timekeeping ( $p < 0.001$ ). Furthermore, we show that increasing time awake both deteriorates mood ( $p < 0.001$ ) and amplifies mood’s circadian rhythm non-linearly. These findings demonstrate the contributions of both circadian rhythms and sleep deprivation to underlying mood and show how these factors can be studied in real-world settings using Fitbits. They underscore the promising opportunity to harness wearables in deploying chronotherapies for psychiatric illness.

## Author summary

Our body has an internal clock that controls much of our physiology. New smartwatch technology allows researchers to study this clock without limiting subjects to a specific environment. In this study, we examine how daily mood in first-year doctors changes based on their internal clock and sleep/wake cycle. Over a two-year period, we collected daily mood survey scores and Fitbit data from more than 2,500 first-year doctors. We discovered that mood follows a rhythm connected to this clock, and the clock’s influence on

design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** I have read the journal's policy, and the authors of this manuscript have the following competing interests: DBF is the CSO of Arcascope, and both he and the University of Michigan own equity in Arcascope. Arcascope did not sponsor this research.

mood increases as someone stays awake longer. This study highlights the significant role our body's clock plays in mood and introduces wearable technology as an exciting new way to explore these factors in mental health issues.

## Introduction

Internal 24-hour (circadian) biological clocks regulate many physiological processes in an organism such as metabolism, hormone secretion, and the sleep-wake cycle. Circadian rhythms are any physiological process that follows a 24-hour cycle and are primarily regulated by these biological, or circadian, clocks. Clock genes have been found to be expressed in cells throughout the body and these cells express an internal rhythm that in turn induce regulatory circadian rhythms on local tissue and organs [1–3]. The central clock within the human body resides in the suprachiasmatic nucleus of the brain and acts to synchronize all these peripheral clocks [4].

Circadian rhythms are distinct from sleep-wake cycles or sleep deprivation because of their primary regulation through biological clocks rather than environmental cues. These rhythms endure even in the absence of external cues or environmental influences as they are inherently driven by internal mechanisms. The difference is illustrated with the flexibility of sleep/wake schedules in night shift workers. In these individuals, circadian clocks measured through endogenous temperature and plasma melatonin levels do not always re-align to match the shift work schedule [5, 6].

Circadian rhythms, sleep-wake cycles, and sleep deprivation all affect physiology. Misalignment of these rhythms can lead to adverse health outcomes such as psychiatric and metabolic disorders, cardiovascular disease, and cancer [7, 8].

One important aspect of our physiology which is under the control of circadian timekeeping is mood. Mood is the constantly changing emotional lens which we see and interact with our environment. Adverse mood can lead to many health challenges including cardiovascular disease, diabetes, and suicide [9–11]. Thus, a careful understanding of mood is important for optimal health.

There has been much interest in connecting mood, circadian rhythms, and time awake in healthy individuals. It has been shown that there is a diurnal variation in mood and that mood deteriorates with sleep deprivation [12–15]. Furthermore, it has been demonstrated that mood varies with circadian phase and that, depending on the phase, mood either improved or worsened based on time awake [16]. However, such studies were in controlled conditions, had smaller number of subjects, or may not have used recent statistical methods [12, 17–20].

Additional evidence highlighting the close relationship between mood and the circadian pacemaker can be observed in individuals experiencing mental health conditions marked by mood disturbances. In such cases, circadian rhythms have been found to be disrupted, with the type of this impact differing based on the specific disorder. In the case of depression, cortisol and temperature measurements have indicated a phase delay accompanied by a reduction in rhythmic amplitude [21, 22]. Mood displays an alternative diurnal variation in these individuals. Instead of peaking in the late afternoon as seen in healthy individuals, it progressively rises throughout the evening [15, 23]. Mania, which is marked by a significant decrease in sleep requirement along with an abnormally heightened mood, has been linked to a phase advance in the biological clock [24].

Recently, genetic risk factors for affective disorders have been identified. The a-kinase anchoring protein 11 (AKAP11) gene emerged as a risk factor for bipolar disorder with this

variant occurring 7 times higher in this population [25]. AKAP11 interacts with glycogen synthetic kinase 3 (GSK3B) which is a key component of the circadian clock that modulates neuronal excitability through the regulation of persistent sodium channels [26].

Studying circadian rhythms in humans has previously required invasive laboratory monitoring such as minute by minute rectal temperature measurements or frequent blood draws [27]. These measurements can require participants to be confined to a laboratory setting for days or even weeks. While some of the methods have been adapted to non-laboratory settings, they still require subjects to spend hours in darkness and costly and time-consuming biochemical assays. Such methods can remove many social factors that could affect mood and circadian timekeeping. However, it is unclear how being removed from society could affect mood. Additionally, such biochemical assays cannot scale to understand population levels interactions between sleep, circadian rhythms and mood.

In the real-world, individuals encounter a myriad of daily social challenges that are absent in laboratory settings. Due to the numerous confounding factors, it remains uncertain whether a significant relationship between circadian rhythm, time awake, and mood can be established in everyday life.

Investigations into peripheral rhythms have shown a circadian rhythm of heart rate and heart rate variability [28–33]. Data collection in these studies required either a sleep laboratory or portable electrocardiograms placed with clinical supervision. Advances in wearable technology have made continuous heart rate, sleep stage, and activity monitoring possible for the general population. Algorithms created by Bowman et al. have further allowed extraction of circadian phase from wearable data without the need for invasive temperature or laboratory monitoring [34]. The ability to measure circadian rhythm noninvasively has provided an opportunity to investigate the relationship between the biological clock and mood amidst the unpredictable and tumultuous nature of daily life.

Here, we study the relationship between circadian timekeeping, sleep and mood using this new mobile and wearable technology. A key question is whether historical laboratory findings in clinical settings would generalize to real-world settings. This technology could help in the treatment of mood; if mood is unduly lowered by sleep deprivation or circadian timekeeping, simple circadian or sleep interventions would be appropriate. It could also indicate abnormal mood patterns, even when sleep and circadian rhythms are accounted for, to inform psychiatric diagnosis, suicide prediction, and treatment decisions.

## Methods

### Participants

The Intern Health Study is a multicenter study across the United States involving first year physicians [35]. Physician interns were recruited for this study through emails that were sent to both their medical school and upcoming place of internship. Recruitment lasted from April through June prior to the start of their internship. Participants were required to have an iPhone and were incentivized by receiving a Fitbit Charge 2 device and up to US \$125, split into 5 distributions for continued participation [36]. Interns recruited in years 2018 and 2019 were included in this study.

Participants downloaded a mobile application which would prompt them with daily ecological momentary assessments [37]. Users were sent a daily push notification at a user-specified time between 5pm and 10pm reminding them to complete the once daily assessment. The assessment contained one question asking the user 'on a scale of 1–10 how was your mood today?' with a slider to select the score. While users received a push notification at a designated time, they had the ability to complete the survey at any point in the day. [S1 Fig](#) displays the

**Table 1. Demographic breakdown of sample.** The number of participants analyzed in this study was 2,602. Baseline characteristic proportions are rounded to nearest percentage.

| Baseline Characteristic |                  | Sample Proportion |
|-------------------------|------------------|-------------------|
| Sex                     | Female           | 55%               |
|                         | Male             | 45%               |
| Ethnicity               |                  |                   |
|                         | Caucasian        | 61%               |
|                         | Asian            | 21%               |
|                         | African American | 5%                |
|                         | Latino           | 4%                |
|                         | Mixed            | 9%                |
| Age                     | Under 25         | 2%                |
|                         | 25 to 29         | 80%               |
|                         | 30 to 34         | 15%               |
|                         | 35 and above     | 3%                |

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mood scale. In addition, minute by minute sleep, heart rate, and step counts were collected while they wore the provided Fitbit device [38, 39].

A total of 489,523 surveys from 4,919 participants were collected. Of those, survey scores that did not contain at least 24 hours of abutting wearable data were removed. Participants were included in the study if they had at least one survey score with wearable data. A total of 168,311 survey scores met these criteria across 2,602 participants. Demographic data of age, sex, and ethnicity were collected by self-reporting on enrollment and displayed in Table 1 for these participants.

This raw data was automatically uploaded from participant Fitbit devices to a secure server at regular intervals during collection. The data was analyzed post-hoc on these servers after collection was completed using MATLAB [35] and Python [40] scripts. This study was approved by the University of Michigan IRB and all subjects were provided informed consent after receiving a complete description of the study.

## Statistical analysis

Bowman et. al. developed a model of heart rate informed by a comprehensive literature review that depicts heart rate as the combination of influences from physical activity, a 24-hour rhythm, and a standardized model of error [34].

$$HR_t = a - b \cdot \cos\left(\frac{\pi}{12}(t - c)\right) + d \cdot activity + \varepsilon_t$$

The model of heart rate at time  $t$  ( $HR_t$ ) is governed by six physiological parameters—basal heart rate ( $a$ ), amplitude of a 24-hour circadian oscillation in heart rate ( $b$ ), time of the circadian heart rate minimum ( $c$ ), increase in heart rate per step ( $d$ ), and an autoregressive error function ( $\varepsilon_t$ ). The error function accounts for both the inaccuracies of the wearable device [41] and external factors such as cortisol and other hormones [42] which are driven by stimuli such as light, sleep cycles, stress levels, and meals [43–47].

To utilize Bowman et. al.'s model, heart rate and step data were averaged into 5-minute bins and data was separated by periods of sleep more than 2 hours in length. The model was then fit using Goodman and Weare affine invariant Markov chain Monte Carlo algorithm [48] to two wake-sleep intervals at a time. Each mood survey score was subsequently paired with an

individual's circadian heart rate minimum during the day of survey completion and their duration of prior time awake.

Circadian phase was then computed as the angle between the heart rate minimum and the time of survey completion. Circadian phase is the current state of the body's internal clock. It is measured from  $0^\circ$  to  $360^\circ$  with  $0^\circ$  representing the heart rate minimum. On someone habituated to normal day-night conditions (entrained) this minimum occurs at the midpoint of sleep. A total of 168,311 survey scores were paired from 2,602 participants. For each score, a standardized mood z score was calculated.

To assess if mood changes based on circadian phase and time awake, linear mixed modeling was applied. Linear mixed modeling was chosen given the unbalanced study design and the serial mood measurements. Subjects were considered a random effect with fixed slope and random intercept. Given the circular nature of circadian phase, e.g.  $0^\circ = 360^\circ$ , phase was modeled as the additive process of a sine and cosine wave. For each subject, mood was then modeled as the sum of the fixed effects of circadian phase, time awake, age, sex, and ethnicity.

$$\text{Mood}_{ij} = \gamma_{00} + \gamma_{10} \cos(\text{phase}_{ij}) + \gamma_{20} \sin(\text{phase}_{ij}) + \gamma_{30}(\text{cumulative time awake}_{ij}) + \gamma_{40}(\text{age}_j) + \gamma_{50}(\text{sex}_j) + \gamma_{60}(\text{ethnicity}_j) + u_{0j} + e_{ij}$$

Where  $i$  represents each survey nested to subject  $j$ .  $\gamma$  is the coefficient for each fixed effect of the model with  $u$  denoting the random component of the intercept.

Using R packages lme4 and lmerTest [49, 50], coefficients and their p-values were calculated. The model was compared to one without the fixed effects of age, sex, and ethnicity. Using the R anova function, the fit of the model including demographic data was compared against one without.

To help understand the nonlinear relationship of time awake and circadian phase on mood, survey scores were broken into 4 strata. Strata were set at less than 6 hours, 6 to 12 hours, 12 to 18 hours, and 18 to 24 hours of time awake. Each stratum was then fit with its own model, however, now without the fixed effect of time awake.

$$\text{Mood}_{ij} = \gamma_{00} + \gamma_{10} \cos(\text{phase}_{ij}) + \gamma_{20} \sin(\text{phase}_{ij}) + u_{0j} + e_{ij}$$

where  $i$  represents each survey nested to subject  $j$ .  $\gamma$  is the coefficient for each fixed effect of the model with  $u$  denoting the random component of the intercept.

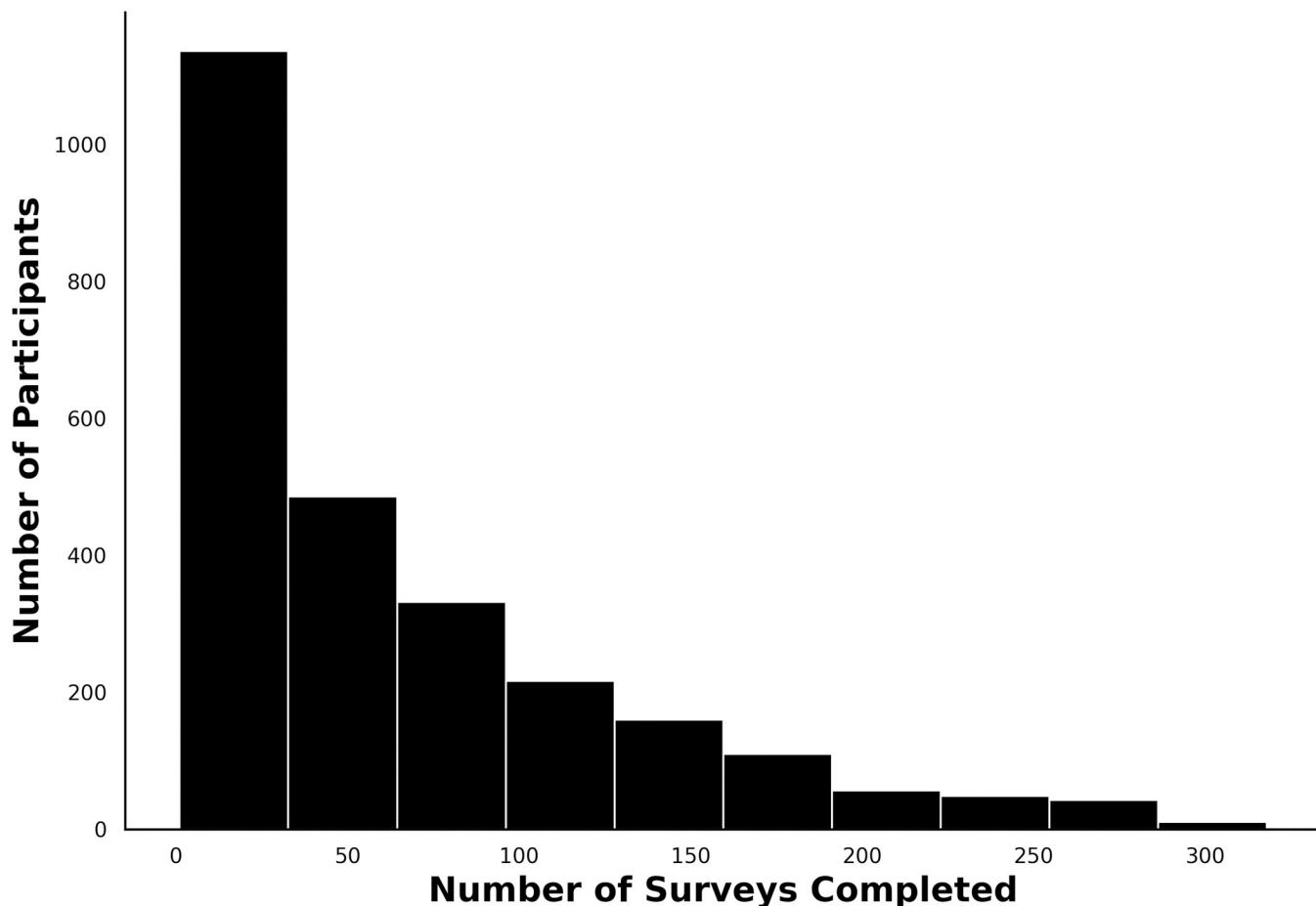
The coefficients and the associated p-values were calculated in each stratum. Using only the fixed effect components of each model, we calculated the corresponding function amplitudes, minimums, and intercepts.

## Results

We analyzed a total of 168,311 survey scores from 2,602 participants. The sample was 55% female and 60% Caucasian. The majority of the subjects, 80%, were between the ages of 25 and 29. A comprehensive demographic breakdown is provided in Table 1 for further illustration.

Each subject completed an average of 64.7 surveys. A histogram of the number of surveys per participant is displayed in Fig 1. The mean of the median time difference between successive surveys per participant was 2.58 days with a standard deviation of 2.41 days and mode of 1 day. Raw mood survey scores ranged from 1 to 10 with an overall mean of 7.3 and standard deviation of 1.5. Individual average mood scores spanned from 1.7 to 10 with standard deviation ranging from 0.07 to 3.09.

Demographic data of age, sex, and ethnicity did not provide any additional explanatory value ( $p = 0.22$ ) and were removed from the model. Average participant standardized mood



**Fig 1. Distribution of Surveys Completed per Participant**, showcasing the number of surveys each participant completed that were used in the statistical analysis of this study.

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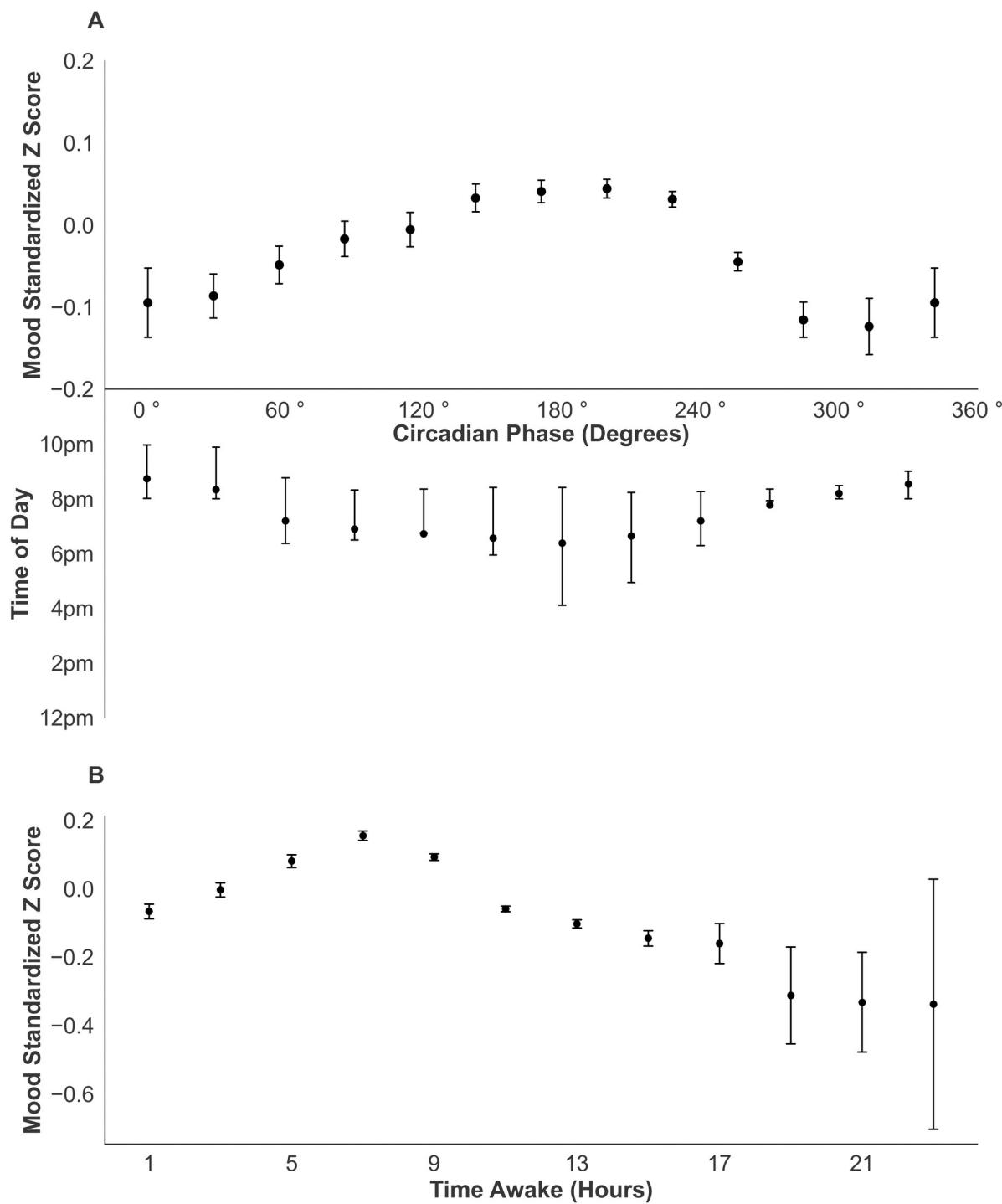
scores were plotted against circadian phase in Fig 2A and against time awake in Fig 2B. Both circadian phase ( $p < 0.001$ ) and time awake ( $p < 0.001$ ) were significantly associated with mood scores (Table 2).

The association between circadian phase and mood was rhythmic. In the fitted model, mood peaked at 198°, or approximately 5 pm on an entrained clock, and a nadir at 18°, or approximately 5 am. A significant association was also found between time awake and mood, where mood deteriorates with increasing time awake.

Mood scores were subsequently split into strata: 0–6, 6–12, 12–18, and 18–24 hours of time awake at survey completion. The strata had 24698, 108405, 34747, and 451 survey results respectively. Fig 3 displays each fitted model plotted with the corresponding raw data binned by circadian phase.

The median time of survey completion was calculated for each circadian phase bin. For 0–6 hours awake the median time of survey completion ranged from 1:30 pm to 8:47 pm, 6–12 hours ranged from 7:23 pm to 8:43 pm, 12–18 hours ranged from 8:44 pm to 9:43 pm, and 18–24 hours ranged from 8:42 pm to 9:46 pm.

Circadian phase was found to be significantly associated with mood in a rhythmic form for the first three strata with  $p = 0.006$ ,  $<0.0001$ , and  $<0.0001$  respectively (Table 3). The fourth stratum was trending towards significance with  $p = 0.06$  yet explained the most variance out of



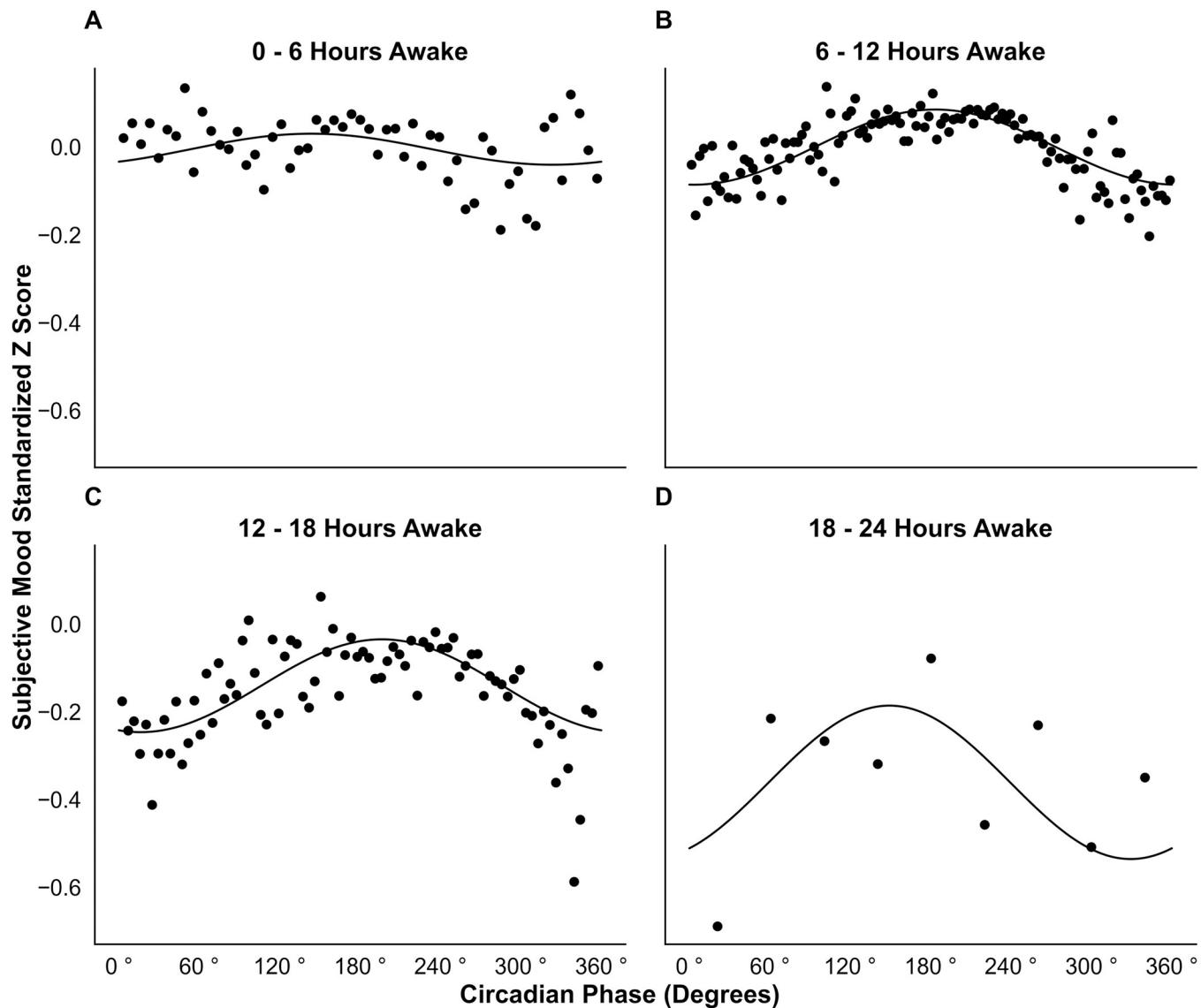
**Fig 2. Variation in Mood with Circadian Phase and Time Awake.** (A) Each mood score was paired with the circadian phase at time of submission. Bin edges were computed every 30° and the average standardized mood survey score was plotted against the midpoint of each bin. The median time of survey completion and interquartile range was calculated for each circadian phase bin and plotted beneath the x-axis. Bin sizes were as follows: 345°-15°: 3517, 15°-45°: 4910, 45°-75°: 6705, 75°-105°: 7463, 105°-135°: 8188, 135°-165°: 11892, 165°-195°: 18494, 195°-225°: 26778, 225°-255°: 39290, 255°-285°: 29436, 285°-315°: 8503, 315°-345°: 3135 B) Each mood score was paired with the corresponding number of hours the participant has been awake at survey submission. Bin edges were computed every 2 hours, and the average standardized mood survey score was plotted against the midpoint of each bin. Bin sizes were as follows: 0–2 hours: 7425, 2–4 hours: 7560, 4–6 hours: 9713, 6–8 hours: 18617, 8–10 hours: 38372, 10–12 hours: 51416, 12–14 hours: 26236, 14–16 hours: 7402, 16–18 hours: 1119, 18–20 hours: 246, 20–22 hours: 180, 22–24 hours: 25.

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Table 2. Coefficients Fit to the Aggregate Linear Mixed Effects Model. This model tests if participant mood scores are associated with circadian phase and time awake.

| Fixed Effect Coefficient     | Estimate | t Value | Pr(> t ) | Confidence Interval |
|------------------------------|----------|---------|----------|---------------------|
| Intercept ( $\gamma_{00}$ )  | 0.119    | 15.4    | <0.001   | [0.103, 0.133]      |
| Cos(phase) ( $\gamma_{10}$ ) | -0.076   | -17.4   | <0.001   | [-0.085, -0.067]    |
| Sin(phase) ( $\gamma_{20}$ ) | -0.024   | -6.3    | <0.001   | [-0.032, -0.017]    |
| Time Awake ( $\gamma_{30}$ ) | -0.016   | -21.4   | <0.001   | [-0.018, -0.015]    |

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**Fig 3. Variation in Mood with Circadian Phase Stratified by Time Awake.** Survey scores were split into 4 categories of wake time: < 6 hours (A), 6–12 hours (B), 12–18 hours (C), and 18–24 hours (D). Each category was binned by circadian phase and edges computed using the Freedman Diaconis Estimator [70]. Bin resolution and average number of samples per bin for each graph are as follows: 6.5° and 449 samples (A), 3.0° and 919 samples (B), 4.5° and 434 samples (C), and 40° and 50 samples (D). The average mood z score for each bin was plotted against the bin midpoint. Linear mixed models were fit to each category. Predictions using the fixed effects of each model were plotted.

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**Table 3. Mixed Linear Effects Model Fit to Each Strata.** A linear mixed model was fit to 4 different groups of survey data: 0–6 hours, 6–12 hours, 12–18 hours, and 18–24 hours of wake time. This model tests if participant mood scores are associated with circadian phase without assuming a linear relationship with time awake.

| Fixed Effect Coefficient     | Estimate | t Value | Pr(> t ) | 95% Confidence Interval |
|------------------------------|----------|---------|----------|-------------------------|
| 0–6 Hours                    |          |         |          |                         |
| Intercept ( $\gamma_{00}$ )  | -0.005   | -0.586  | 0.558    | [-0.023, 0.012]         |
| Cos(phase) ( $\gamma_{10}$ ) | -0.028   | -2.774  | 0.006    | [-0.049, -0.008]        |
| Sin(phase) ( $\gamma_{20}$ ) | 0.021    | 2.199   | 0.028    | [0.002, 0.040]          |
| Amplitude                    | 0.071    |         | $R^2$    | 0.0355                  |
| 6–12 Hours                   |          |         |          |                         |
| Intercept ( $\gamma_{00}$ )  | 0        | -0.101  | 0.919    | [-0.009, 0.008]         |
| Cos(phase) ( $\gamma_{10}$ ) | -0.085   | -15.2   | <0.001   | [-0.097, -0.074]        |
| Sin(phase) ( $\gamma_{20}$ ) | -0.005   | -1.07   | 0.285    | [-0.015, 0.004]         |
| Amplitude                    | 0.171    |         | $R^2$    | 0.008                   |
| 12–18 Hours                  |          |         |          |                         |
| Intercept ( $\gamma_{00}$ )  | -0.141   | 16.774  | <0.001   | [-0.158, -0.125]        |
| Cos(phase) ( $\gamma_{10}$ ) | -0.102   | -9.909  | <0.001   | [-0.122, -0.081]        |
| Sin(phase) ( $\gamma_{20}$ ) | -0.03    | -3.264  | 0.001    | [-0.047, -0.012]        |
| Amplitude                    | 0.211    |         | $R^2$    | 0.04                    |
| 18–24 Hours                  |          |         |          |                         |
| Intercept ( $\gamma_{00}$ )  | -0.361   | -5.992  | <0.001   | [-0.158, -0.125]        |
| Cos(phase) ( $\gamma_{10}$ ) | -0.15    | -1.868  | 0.0625   | [-0.122, -0.081]        |
| Sin(phase) ( $\gamma_{20}$ ) | 0.089    | 1.3     | 0.1942   | [-0.047, -0.012]        |
| Amplitude                    | 0.35     |         | $R^2$    | 0.39                    |

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all the models ( $R^2 = 0.39$ ). The average mood standardized z scores, represented by model intercepts, were near 0 for the first two strata (-0.005 and 0.000) then progressively declined to -0.141 in the third stratum and -0.361 in the fourth stratum. Amplitude increased in a near linear fashion between models ( $R^2 = .97$ ) from 0.07 in the first stratum to 0.350 in the fourth stratum. In the first three strata, the nadir of mood shifted later (323°, 3°, 16° respectively) with increasing time awake.

## Discussion

Rigorous measures of circadian rhythms were previously restricted to laboratory settings. These measures included tracking core body temperature, melatonin levels, or cortisol levels [27]. Collecting this data required frequent rectal temperature measurements or consecutive blood draws. To obtain the serial measurements and avoid external environmental confounders, past studies often required participants to be confined in conditions far from what would be experienced in the natural environment. These conditions would reduce biases by controlling environmental cues such as participant caloric intake, meal timing, and ambient lighting which all can affect these measures [45, 51, 52].

Outside the laboratory, measuring temperature trends is difficult to implement as one needs to measure core body temperature throughout the day and subsequently fit an individualized oscillatory model to the collected data [53]. Using cortisol to determine circadian rhythm poses similar constraints as temperature except frequent blood draws would be needed rather than core body temperatures [54]. Dim-light melatonin onset (DLMO) has been the most promising measurement of circadian rhythm that may be extended outside the laboratory setting. In this procedure, several consecutive saliva sample can be used to determine circadian rhythm. However, this test requires the participant to sit in standardized dim lighting

conditions (<20 lux) for several hours [55] which is both inconvenient and difficult to replicate in a non-laboratory setting [56].

Amplitude changes and phase shifts in temperature, cortisol, and melatonin have been utilized experimentally as markers of affective illness and treatment response [18, 57, 58]. However, the application in clinical practice has been limited due to both the inconvenience of these measurement tools and the concern that rhythmic changes can not accurately be measured in uncontrolled settings [59]. Chronotherapies have therefore been limited to broad based interventions that do not require knowledge of an individualized circadian rhythm such as total and partial sleep deprivation [60], interpersonal and social rhythms therapy for bipolar disorder which regularizes daily routines [61], and nighttime melatonin for insomnia [62].

In this study we analyzed minute by minute step, heart rate, and sleep data from 2,602 medical interns across a total of 168,311 days collected using Fitbits. From this real-world or non-laboratory data, we were able to calculate the daily circadian rhythm for each participant, information that previously would have required laboratory-based minute by minute rectal temperature monitoring or daily intravenous blood draws. Despite using these new noninvasive measures and the uncontrolled and chaotic environment of participants, we extend historic laboratory findings that mood is dependent on cumulative wake time and circadian phase in a non-linear way. We also show that measuring circadian rhythms via heart rate through wearables, or laboratory rectal temperature measurements yields similar results. More work needs to better delineate these and other circadian markers.

Our study demonstrates a clear circadian variation in mood, with peak mood occurring in the evening and troughing in the early morning. As waking hours accumulate, there is a significant decrease in mood. The circadian rhythm's impact on mood becomes more pronounced with longer periods of wakefulness, leading to a greater rhythmic amplitude of mood.

There were several limitations to our study design. First, the mixed effects model serves as a generalized model of mood in medical interns. On an individual basis, the model only accounts for the differing variance and average mood of an individual. The inter-individual variation of mood is more complex than this and is dependent on factors such as social dynamics, schedules, and temperaments [63–65]. Second, due to the real-world nature of this data, there were minimal samples over 18 hours of time awake (N = 451), decreasing the power of the fourth model. Third, no validated emotional rating scales such as the Depression Anxiety Stress Scale or clinical screening tools were utilized in our analysis. Emotional screening tools could help identify intra participant outliers and clinical screening tools would help account for potential confounding effects of affective and anxiety disorders. Fourth, circadian phases at survey completion were not equally distributed with 66% of survey results having a circadian phase between 180° and 300° which weighted these phases higher when the model was fit. Lastly, to aid in the simplicity of our model, we left out factors such as sleep time and variability which have been recently shown to affect mood [66].

Despite these limitations, the results of our study highlight the critical role played by the circadian pacemaker in regulating mood, even during the challenging and unpredictable nature of medical internship. More so, our research shows that measuring the circadian influence on mood can be achieved noninvasively, without the need for stringent experimental conditions.

These findings have important implications in evaluating for psychopathology. It indicates clinicians should be particularly attentive to a patient's sleep-wake cycle and the time of day of an evaluation. This raises the question of whether multiple assessments throughout various times of day may be beneficial and highlights the potential for time-of-day biases in existing literature.

The ability to measure circadian rhythm using wearable holds significant clinical promise. Psychiatric patients can be provided with a Fitbit and their circadian rhythm tracked.

Treating clinicians can monitor for circadian phase shifts as an indicator of the onset of a depressive or manic episode [67, 68] and proactively begin treatment. Furthermore, treatment response can be gauged by circadian re-alignment [24] in addition to more subjective patient reports currently utilized [69]. Chronotherapies such as social rhythms therapy and oral melatonin can be timed more accurately based on an individual's current circadian phase.

Further work can integrate our general model of mood into more personalized mathematical models of mood. Individualized models of mood would allow clinicians to detect anomalies in patients' emotional patterns. Clinicians could use such a model to anticipate potential mood shifts and devise intervention strategies proactively. With the combination of technology and clinical insights, such a model can pave the way for a new era in mental health care, one that is predictive, personalized, and preemptive in its approach.

## Supporting information

### S1 Fig. Mood survey prompt.

(DOCX)

## Author Contributions

**Conceptualization:** Daniel Forger.

**Data curation:** Yu Fang.

**Formal analysis:** Benjamin Shapiro, Daniel Forger.

**Project administration:** Srijan Sen, Daniel Forger.

**Resources:** Yu Fang, Srijan Sen.

**Writing – original draft:** Benjamin Shapiro, Daniel Forger.

**Writing – review & editing:** Benjamin Shapiro, Yu Fang, Srijan Sen, Daniel Forger.

## References

1. Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. *Nat Rev Neurosci*. 2003 Aug; 4(8):649–61. <https://doi.org/10.1038/nrn1177> PMID: 12894240
2. Albrecht U. The mammalian circadian clock: a network of gene expression. *Front Biosci*. 2004 Jan 1; 9:48–55. <https://doi.org/10.2741/1196> PMID: 14766343
3. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol*. 2010; 72:517–49. <https://doi.org/10.1146/annurev-physiol-021909-135821> PMID: 20148687
4. Richards J, Gumz ML.. Advances in understanding the peripheral circadian clocks. *FASEB J*. 2012 Sep; 26(9):3602–13. <https://doi.org/10.1096/fj.12-203554> PMID: 22661008
5. Smith MR, Fogg LF, Eastman CI. Practical interventions to promote circadian adaptation to permanent night shift work: study 4. *J Biol Rhythms*. 2009 Apr; 24(2):161–72. <https://doi.org/10.1177/0748730409332068> PMID: 19346453
6. Kervezee L, Cuesta M, Cermakian N, Boivin DB. Simulated night shift work induces circadian misalignment of the human peripheral blood mononuclear cell transcriptome. *Proc Natl Acad Sci U S A*. 2018 May 22; 115(21):5540–5. <https://doi.org/10.1073/pnas.1720719115> PMID: 29735673
7. Ingram KK. Circadian rhythm sleep-wake disorders (CRSWDs): Linking circadian misalignment to adverse health outcomes. *EBioMedicine*. 2020 Dec; 62:103142. <https://doi.org/10.1016/j.ebiom.2020.103142> PMID: 33254025
8. Baron KG, Reid KJ. Circadian misalignment and health. *Int Rev Psychiatry*. 2014 Apr; 26(2):139–54. <https://doi.org/10.3109/09540261.2014.911149> PMID: 24892891

9. Raic M. Depression and Heart Diseases: Leading Health Problems. *Psychiatr Danub.* 2017 Dec; 29 Suppl 4(Suppl 4):770–7. PMID: [29278623](#)
10. Kang HJ, Kim SY, Bae KY, Kim SW, Shin IS, Yoon JS, et al. Comorbidity of depression with physical disorders: research and clinical implications. *Chonnam Med J.* 2015 Apr; 51(1):8–18. <https://doi.org/10.4068/cmj.2015.51.1.8> PMID: [25914875](#)
11. Orsolini L, Latini R, Pompili M, Serafini G, Volpe U, Vellante F, et al. Understanding the Complex of Suicide in Depression: from Research to Clinics. *Psychiatry Investig.* 2020 Mar; 17(3):207–21. <https://doi.org/10.30773/pi.2019.0171> PMID: [32209966](#)
12. Short MA, Louca M. Sleep deprivation leads to mood deficits in healthy adolescents. *Sleep Med.* 2015 Aug; 16(8):987–93. <https://doi.org/10.1016/j.sleep.2015.03.007> PMID: [26141007](#)
13. Monk TH, Buysse DJ, Reynolds CF 3rd, Jarrett DB, Kupfer DJ. Rhythmic vs homeostatic influences on mood, activation, and performance in young and old men. *J Gerontol.* 1992 Jul; 47(4):P221–7. <https://doi.org/10.1093/geronj/47.4.p221> PMID: [1624698](#)
14. Emens JS, Berman AM, Thosar SS, Butler MP, Roberts SA, Clemons NA, et al. Circadian rhythm in negative affect: Implications for mood disorders. *Psychiatry Res.* 2020 Nov; 293:113337. <https://doi.org/10.1016/j.psychres.2020.113337> PMID: [32777620](#)
15. Murray G. Diurnal mood variation in depression: a signal of disturbed circadian function? *J Affect Disord.* 2007 Sep; 102(1–3):47–53. <https://doi.org/10.1016/j.jad.2006.12.001> PMID: [17239958](#)
16. Boivin DB. Influence of sleep-wake and circadian rhythm disturbances in psychiatric disorders. *J Psychiatry Neurosci.* 2000 Nov; 25(5):446–58. PMID: [11109296](#)
17. Tomaso CC, Johnson AB, Nelson TD. The effect of sleep deprivation and restriction on mood, emotion, and emotion regulation: three meta-analyses in one. *Sleep.* 2021 Jun 11; 44(6).
18. Monk TH, Buysse DJ, Frank E, Kupfer DJ, Dettling J, Ritenour AM. Nocturnal and circadian body temperatures of depressed outpatients during symptomatic and recovered states. *Psychiatry Res.* 1994 Mar; 51(3):297–311. [https://doi.org/10.1016/0165-1781\(94\)90016-7](https://doi.org/10.1016/0165-1781(94)90016-7) PMID: [8208875](#)
19. Brendel DH, Reynolds CF 3rd, Jennings JR, Hoch CC, Monk TH, Berman SR, et al. Sleep stage physiology, mood, and vigilance responses to total sleep deprivation in healthy 80-year-olds and 20-year-olds. *Psychophysiology.* 1990 Nov; 27(6):677–85. <https://doi.org/10.1111/j.1469-8986.1990.tb03193.x> PMID: [2100353](#)
20. Angus RG, Heslegrave RJ, Myles WS. Effects of prolonged sleep deprivation, with and without chronic physical exercise, on mood and performance. *Psychophysiology.* 1985 May; 22(3):276–82. <https://doi.org/10.1111/j.1469-8986.1985.tb01601.x> PMID: [4011797](#)
21. Souetre E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B, et al. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res.* 1989 Jun; 28(3):263–78. [https://doi.org/10.1016/0165-1781\(89\)90207-2](https://doi.org/10.1016/0165-1781(89)90207-2) PMID: [2762432](#)
22. Lewy AJ, Rough JN, Songer JB, Mishra N, Yuhas K, Emens JS. The phase shift hypothesis for the circadian component of winter depression. *Dialogues Clin Neurosci.* 2007; 9(3):291–300. <https://doi.org/10.31887/DCNS.2007.9.3/alewy> PMID: [17969866](#)
23. Wirz-Justice A. Diurnal variation of depressive symptoms. *Dialogues Clin Neurosci.* 2008; 10(3):337–43. <https://doi.org/10.31887/DCNS.2008.10.3/awjustice> PMID: [18979947](#)
24. Moon JH, Cho CH, Son GH, Geum D, Chung S, Kim H, et al. Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder. *EBioMedicine.* 2016 Sep; 11:285–95. <https://doi.org/10.1016/j.ebiom.2016.08.019> PMID: [27543154](#)
25. Palmer DS, Howrigan DP, Chapman SB, Adolfsson R, Bass N, Blackwood D, et al. Exome sequencing in bipolar disorder identifies AKAP11 as a risk gene shared with schizophrenia. *Nat Genet.* 2022 May; 54(5):541–7. <https://doi.org/10.1038/s41588-022-01034-x> PMID: [35410376](#)
26. Paul JR, DeWoskin D, McMeekin LJ, Cowell RM, Forger DB, Gamble KL. Regulation of persistent sodium currents by glycogen synthase kinase 3 encodes daily rhythms of neuronal excitability. *Nat Commun.* 2016 Nov 14; 7:13470. <https://doi.org/10.1038/ncomms13470> PMID: [27841351](#)
27. Hofstra WA, de Weerd AW. How to assess circadian rhythm in humans: a review of literature. *Epilepsy Behav.* 2008 Oct; 13(3):438–44. <https://doi.org/10.1016/j.yebeh.2008.06.002> PMID: [18588999](#)
28. Vandewalle G, Middleton B, Rajaratnam SM, Stone BM, Thorleifsdottir B, Arendt J, et al. Robust circadian rhythm in heart rate and its variability: influence of exogenous melatonin and photoperiod. *J Sleep Res.* 2007 Jun; 16(2):148–55. <https://doi.org/10.1111/j.1365-2869.2007.00581.x> PMID: [17542944](#)
29. Hayter EA, Wehrens SMT, Van Dongen HPA, Stangherlin A, Gaddameedi S, Crooks E, et al. Author Correction: Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nat Commun.* 2021 Dec 8; 12(1):7284. <https://doi.org/10.1038/s41467-021-27498-9> PMID: [34880252](#)

30. Malpas SC, Purdie GL. Circadian variation of heart rate variability. *Cardiovasc Res*. 1990 Mar; 24(3):210–3. <https://doi.org/10.1093/cvr/24.3.210> PMID: 2346954
31. Black N, D'Souza A, Wang Y, Piggins H, Dobrzynski H, Morris G, et al. Circadian rhythm of cardiac electrophysiology, arrhythmogenesis, and the underlying mechanisms. *Heart Rhythm*. 2019 Feb; 16(2):298–307. <https://doi.org/10.1016/j.hrthm.2018.08.026> PMID: 30170229
32. Boudreau P, Yeh WH, Dumont GA, Boivin DB. A circadian rhythm in heart rate variability contributes to the increased cardiac sympathovagal response to awakening in the morning. *Chronobiol Int*. 2012 Jul; 29(6):757–68. <https://doi.org/10.3109/07420528.2012.674592> PMID: 22734576
33. Massin MM, Maeys K, Withofs N, Ravet F, Gerard P. Circadian rhythm of heart rate and heart rate variability. *Arch Dis Child*. 2000 Aug; 83(2):179–82. <https://doi.org/10.1136/adc.83.2.179> PMID: 10906034
34. Bowman C, Huang Y, Walch OJ, Fang Y, Frank E, Tyler J, et al. A method for characterizing daily physiology from widely used wearables. *Cell Rep Methods*. 2021 Aug 23; 1(4). <https://doi.org/10.1016/j.crmeth.2021.100058> PMID: 34568865
35. MATLAB. 2020a ed. Natick, MA: The Math Works, Inc; 2020.
36. Fitbit. Fitbit Charge 2 User Manual. [cited 2022]; Available from: [https://staticcs.fitbit.com/content/assets/help/manuals/manual\\_charge\\_2\\_en\\_US.pdf](https://staticcs.fitbit.com/content/assets/help/manuals/manual_charge_2_en_US.pdf).
37. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol*. 2008; 4:1–32. <https://doi.org/10.1146/annurev.clinpsy.3.022806.091415> PMID: 18509902
38. Sen S, Kranzler HR, Krystal JH, Speller H, Chan G, Gelernter J, et al. A prospective cohort study investigating factors associated with depression during medical internship. *Arch Gen Psychiatry*. 2010 Jun; 67(6):557–65. <https://doi.org/10.1001/archgenpsychiatry.2010.41> PMID: 20368500
39. NeCamp T, Sen S, Frank E, Walton MA, Ionides EL, Fang Y, et al. Assessing Real-Time Moderation for Developing Adaptive Mobile Health Interventions for Medical Interns: Micro-Randomized Trial. *J Med Internet Res*. 2020 Mar 31; 22(3):e15033. <https://doi.org/10.2196/15033> PMID: 32229469
40. Van Rossum GaD, Fred L and others. Python reference manual: Centrum voor Wiskunde en Informatica Amsterdam; 1995.
41. Al-Kaisey AM, Koshy AN, Ha FJ, Spencer R, Toner L, Sajeev JK, et al. Accuracy of wrist-worn heart rate monitors for rate control assessment in atrial fibrillation. *Int J Cardiol*. 2020 Feb 1; 300:161–4. <https://doi.org/10.1016/j.ijcard.2019.11.120> PMID: 31787389
42. Gnocchi D, Bruscalupi G. Circadian Rhythms and Hormonal Homeostasis: Pathophysiological Implications. *Biology (Basel)*. 2017 Feb 4; 6(1). <https://doi.org/10.3390/biology6010010> PMID: 28165421
43. Koch CE, Leinweber B, Drengberg BC, Blaum C, Oster H. Interaction between circadian rhythms and stress. *Neurobiol Stress*. 2017 Feb; 6:57–67. <https://doi.org/10.1016/j.ynstr.2016.09.001> PMID: 28229109
44. Jung CM, Khalsa SB, Scheer FA, Cajochen C, Lockley SW, Czeisler CA, et al. Acute effects of bright light exposure on cortisol levels. *J Biol Rhythms*. 2010 Jun; 25(3):208–16. <https://doi.org/10.1177/0748730410368413> PMID: 20484692
45. Wehrens SMT, Christou S, Isherwood C, Middleton B, Gibbs MA, Archer SN, et al. Meal Timing Regulates the Human Circadian System. *Curr Biol*. 2017 Jun 19; 27(12):1768–75 e3. <https://doi.org/10.1016/j.cub.2017.04.059> PMID: 28578930
46. Smyth N, Thorn L, Hucklebridge F, Evans P, Clow A. Detailed time course of the cortisol awakening response in healthy participants. *Psychoneuroendocrinology*. 2015 Dec; 62:200–3. <https://doi.org/10.1016/j.psyneuen.2015.08.011> PMID: 26318630
47. Follenius M, Brandenberger G, Hietter B. Diurnal cortisol peaks and their relationships to meals. *J Clin Endocrinol Metab*. 1982 Oct; 55(4):757–61. <https://doi.org/10.1210/jcem-55-4-757> PMID: 7202017
48. Goodman J, Weare J. Ensemble Samplers with Affine Invariance. *Comm App Math Com Sc*. 2010; 5(1):65–80.
49. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*. 2017 12/06; 82(13):1–26.
50. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015 10/07; 67(1):1–48.
51. Brobeck JR. Food intake as a mechanism of temperature regulation. *Yale J Biol Med*. 1948 Jul; 20(6):545–52. PMID: 18872321
52. Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van Reen E, et al. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metab*. 2011 Mar; 96(3):E463–72. <https://doi.org/10.1210/jc.2010-2098> PMID: 21193540

53. Waterhouse J, Drust B, Weinert D, Edwards B, Gregson W, Atkinson G, et al. The circadian rhythm of core temperature: origin and some implications for exercise performance. *Chronobiol Int*. 2005; 22(2):207–25. <https://doi.org/10.1081/cbi-200053477> PMID: 16021839
54. Oster H, Challet E, Ott V, Arvat E, de Kloet ER, Dijk DJ, et al. The Functional and Clinical Significance of the 24-Hour Rhythm of Circulating Glucocorticoids. *Endocr Rev*. 2017 Feb 1; 38(1):3–45. <https://doi.org/10.1210/er.2015-1080> PMID: 27749086
55. Molina TA, Burgess HJ. Calculating the dim light melatonin onset: the impact of threshold and sampling rate. *Chronobiol Int*. 2011 Oct; 28(8):714–8. <https://doi.org/10.3109/07420528.2011.597531> PMID: 21823817
56. Pullman RE, Roepke SE, Duffy JF. Laboratory validation of an in-home method for assessing circadian phase using dim light melatonin onset (DLMO). *Sleep Med*. 2012 Jun; 13(6):703–6. <https://doi.org/10.1016/j.sleep.2011.11.008> PMID: 22445311
57. Avery DH, Wildschiodtz G, Rafaelsen OJ. Nocturnal temperature in affective disorder. *J Affect Disord*. 1982 Mar; 4(1):61–71. [https://doi.org/10.1016/0165-0327\(82\)90020-9](https://doi.org/10.1016/0165-0327(82)90020-9) PMID: 6461688
58. Koenigsberg HW, Teicher MH, Mitropoulou V, Navalta C, New AS, Trestman R, et al. 24-h Monitoring of plasma norepinephrine, MHPG, cortisol, growth hormone and prolactin in depression. *J Psychiatr Res*. 2004 Sep-Oct; 38(5):503–11. <https://doi.org/10.1016/j.jpsychires.2004.03.006> PMID: 15380401
59. Crnko S, Schutte H, Doevedans PA, Sluijter JPG, van Laake LW. Minimally Invasive Ways of Determining Circadian Rhythms in Humans. *Physiology (Bethesda)*. 2021 Jan 1; 36(1):7–20. <https://doi.org/10.1152/physiol.00018.2020> PMID: 33325813
60. Ioannou M, Wartenberg C, Greenbrook JTV, Larson T, Magnusson K, Schmitz L, et al. Sleep deprivation as treatment for depression: Systematic review and meta-analysis. *Acta Psychiatr Scand*. 2021 Jan; 143(1):22–35. <https://doi.org/10.1111/acps.13253> PMID: 33145770
61. Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biol Psychiatry*. 2000 Sep 15; 48(6):593–604. [https://doi.org/10.1016/s0006-3223\(00\)00969-0](https://doi.org/10.1016/s0006-3223(00)00969-0) PMID: 11018230
62. Fatemeh G, Sajjad M, Niloufar R, Neda S, Leila S, Khadijeh M. Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. *J Neurol*. 2022 Jan; 269(1):205–16. <https://doi.org/10.1007/s00415-020-10381-w> PMID: 33417003
63. Chellappa SL, Morris CJ, Scheer F. Circadian misalignment increases mood vulnerability in simulated shift work. *Sci Rep*. 2020 Oct 29; 10(1):18614. <https://doi.org/10.1038/s41598-020-75245-9> PMID: 33122670
64. Rihmer Z, Akiskal KK, Rihmer A, Akiskal HS. Current research on affective temperaments. *Curr Opin Psychiatry*. 2010 Jan; 23(1):12–8. <https://doi.org/10.1097/YCO.0b013e32833299d4> PMID: 19809321
65. Hao Y, Farah MJ. The affective neuroscience of socioeconomic status: implications for mental health. *BJPsych Bull*. 2020 Oct; 44(5):202–7. <https://doi.org/10.1192/bjb.2020.69> PMID: 32611462
66. Fang Y, Forger DB, Frank E, Sen S, Goldstein C. Day-to-day variability in sleep parameters and depression risk: a prospective cohort study of training physicians. *NPJ Digit Med*. 2021 Feb 18; 4(1):28. <https://doi.org/10.1038/s41746-021-00400-z> PMID: 33603132
67. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol*. 2008 Oct; 23(7):571–85. <https://doi.org/10.1002/hup.964> PMID: 18680211
68. Takaesu Y. Circadian rhythm in bipolar disorder: A review of the literature. *Psychiatry Clin Neurosci*. 2018 Sep; 72(9):673–82. <https://doi.org/10.1111/pcn.12688> PMID: 29869403
69. Haberer JE, Trabin T, Klinkman M. Furthering the reliable and valid measurement of mental health screening, diagnoses, treatment and outcomes through health information technology. *Gen Hosp Psychiatry*. 2013 Jul-Aug; 35(4):349–53. <https://doi.org/10.1016/j.genhosppsych.2013.03.009> PMID: 23628162
70. Freedman D, Diaconis P. On the histogram as a density estimator: L 2 theory. *Zeitschrift für Wahrscheinlichkeitstheorie und verwandte Gebiete*. 1981; 57(4):453–76.