Supplementary Information for: The real-world association between digital markers of circadian disruption and mental health risks

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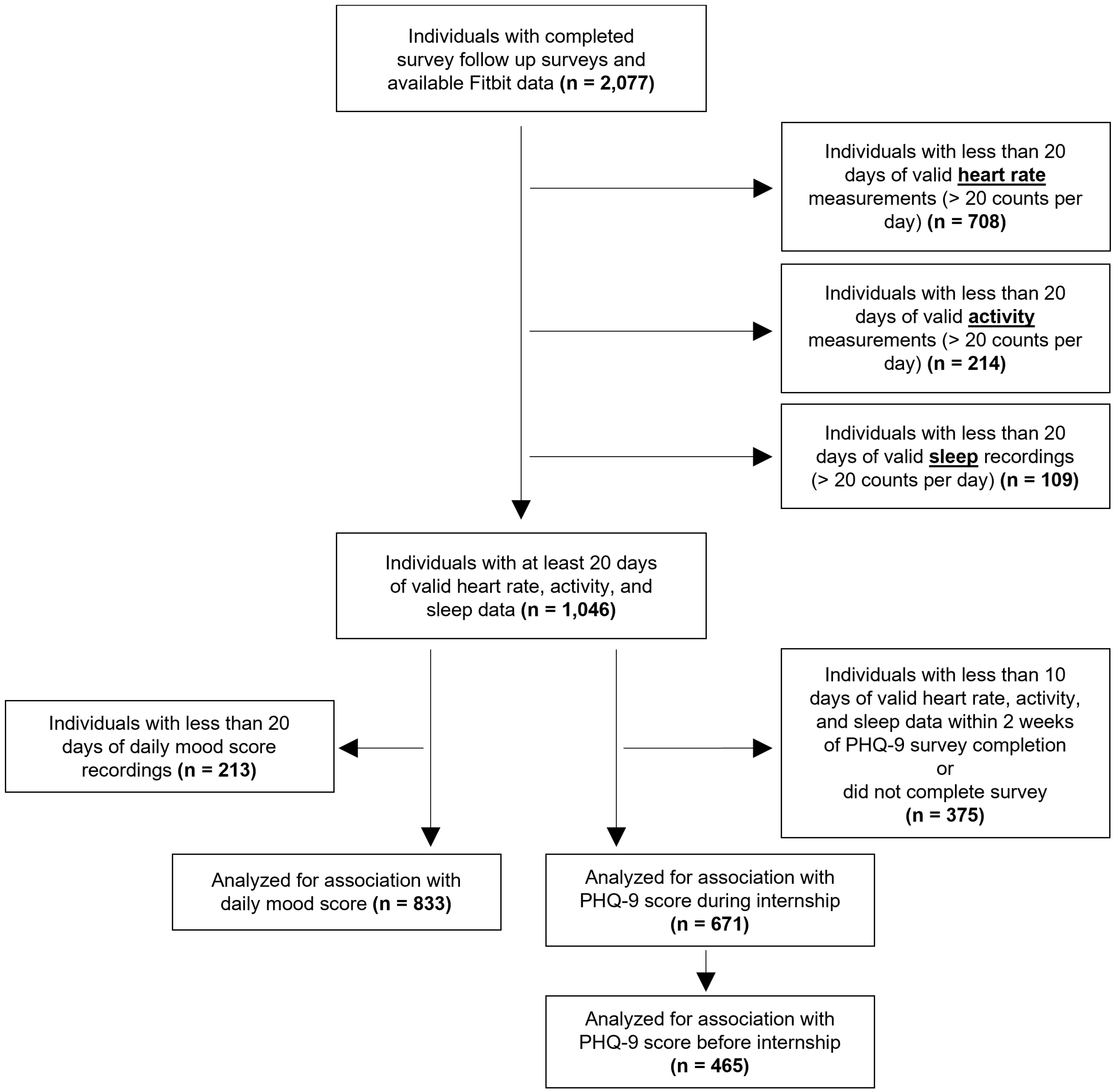
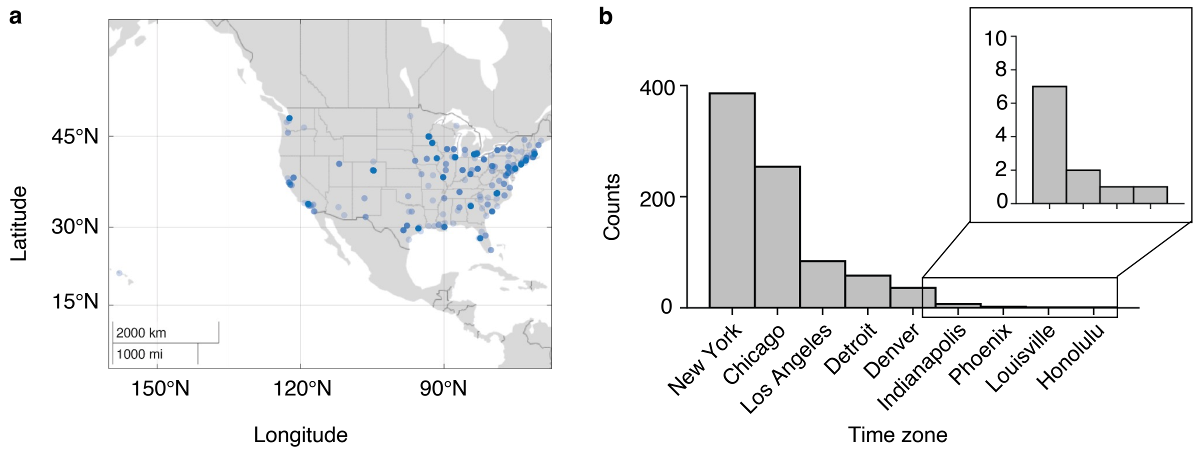
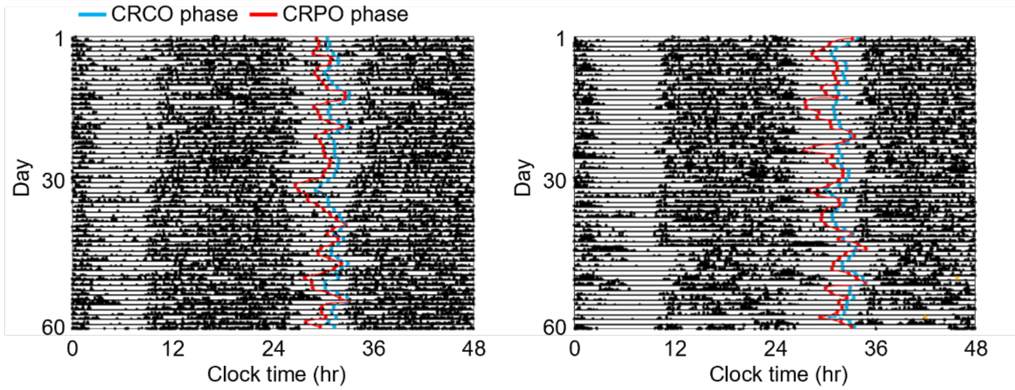


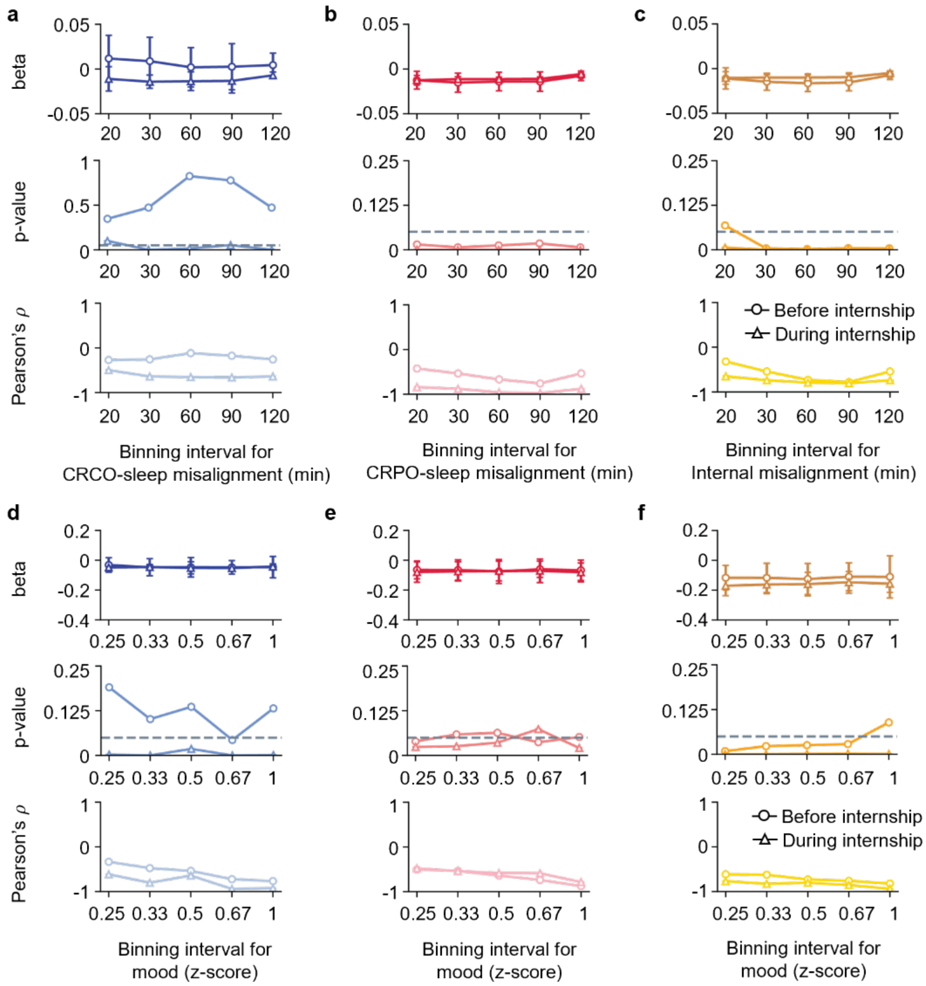
Supplementary Figure 1. Flow diagram of subject exclusion based on data availability. All analyzed data were from the Intern Health Study, a multisite prospective cohort study of depression among training physicians. For all subjects, Fitbit Charge 2™ was used to collect wearable activity, heart rate, and sleep data. See Methods section in the main text for details.



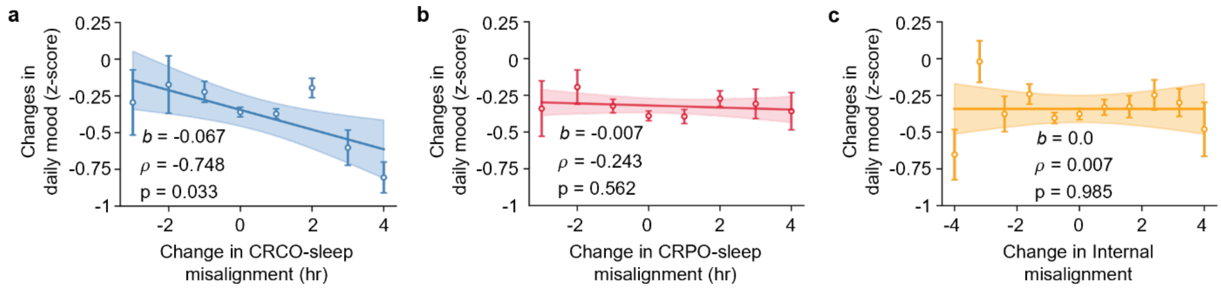
Supplementary Figure 2. Distribution of geographical location (a) and corresponding time zone information (b) of the analyzed subjects. Here, geographic information from 832 subjects, rather than 833, is reported because one subject in the daily mood analysis did not provide demographic information.



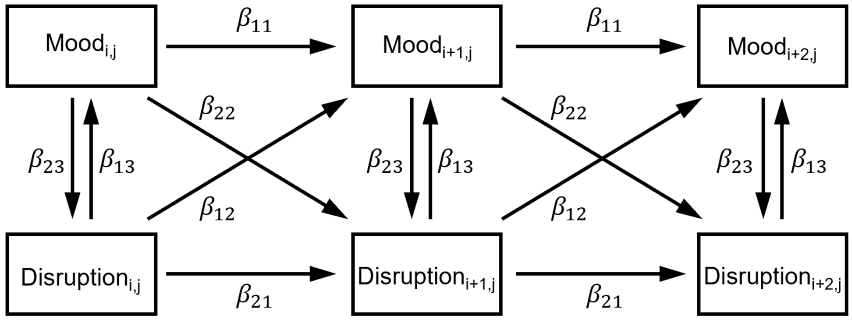
Supplementary Figure 3. Double-plotted actogram for two subjects in the Intern Health Study generated from Fitbit data. The estimates of CRCO phase (blue) and CRPO phase (red) are overlaid on the daily activity patterns (black).



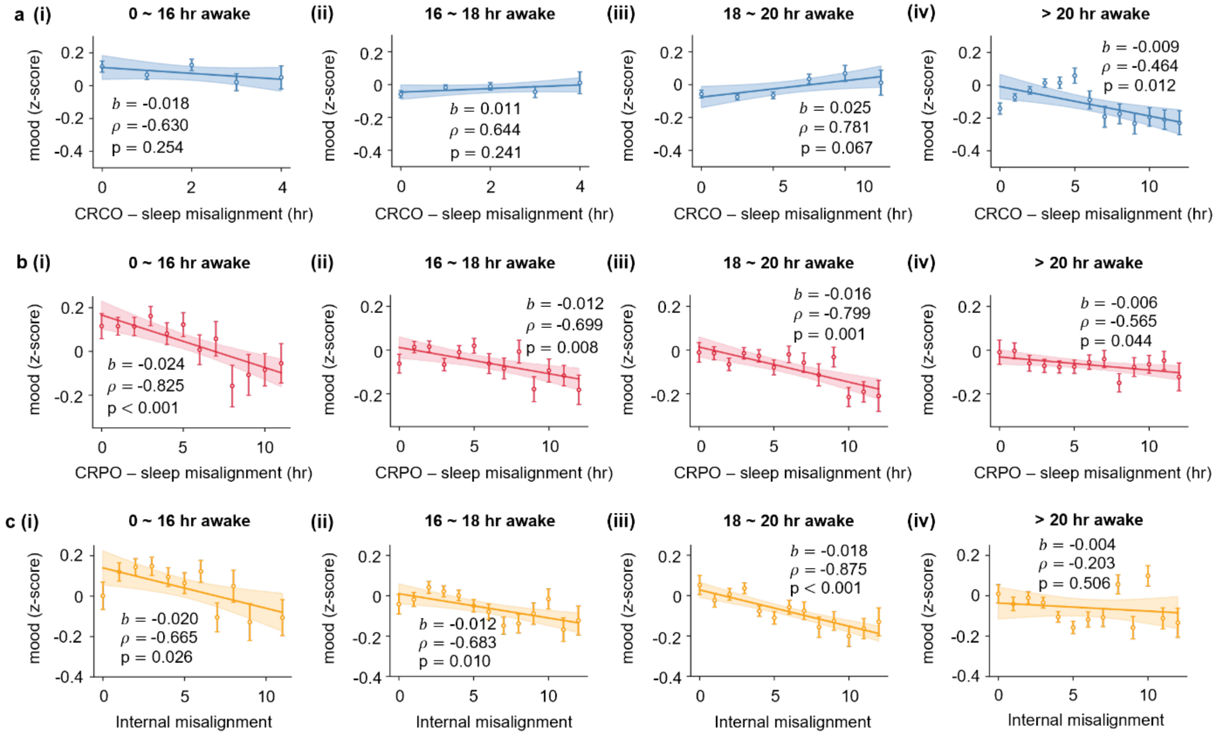
Supplementary Figure 4. The effect of binning on the relationship between circadian disruption measures and daily mood. (a-c) The effect of binning intervals on the relationship between CRCO-sleep (a), CRPO-sleep (b), and internal (c) misalignment and next-day mood before (circle markers) and during (triangle markers) internship. Here, we used the weighted least squares regression to report the beta values denoting the changes in the circadian disruption measure (subjective mood) per unit change in the subjective mood score (circadian disruption measure), their 95% confidence intervals (C.I.), corresponding p-values, and calculated Pearson's correlation coefficient. **(d-f)** Similar analyses were repeated for current-day mood z-score and next-day CRCO-sleep (d), CRPO-sleep (e), and internal (f) misalignment before and during the internship by varying the binning intervals of the current-day mood z-score. Here, the gray dashed lines represent a p-value of 0.05. Overall, the binning interval had minimal impact on the association between circadian disruption levels and daily mood.



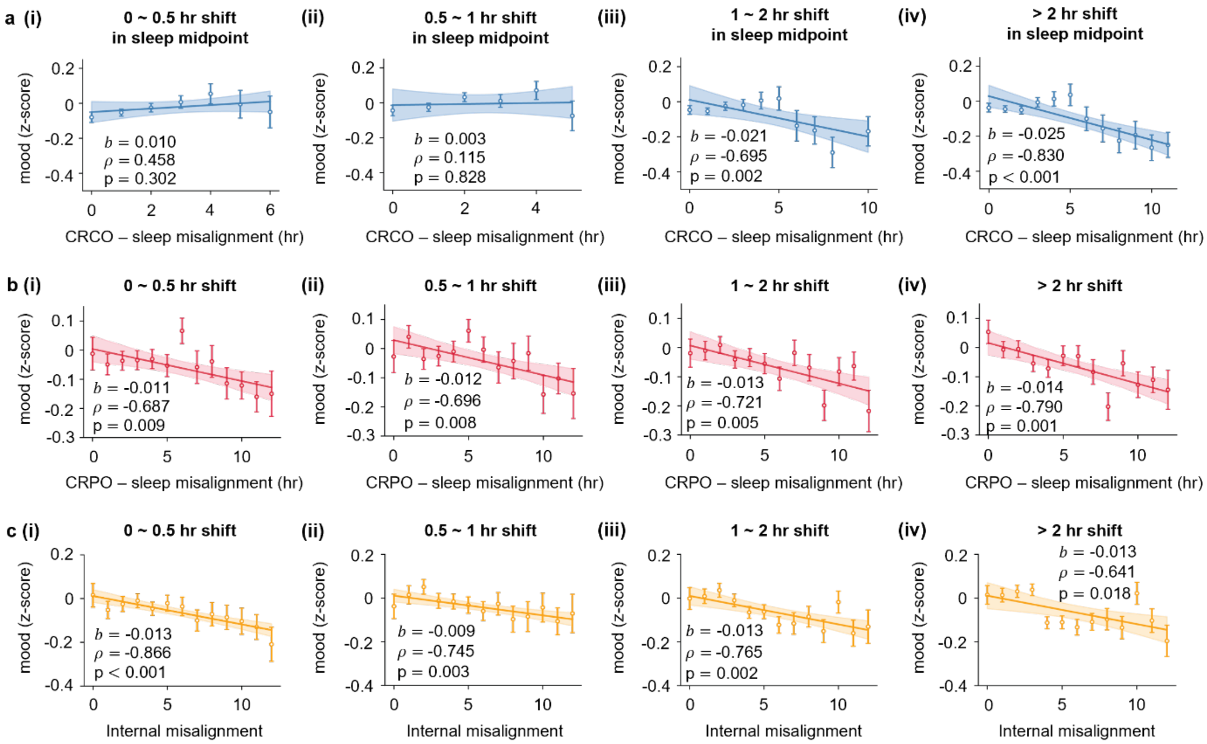
Supplementary Figure 5. The relationship between changes in circadian disruption measures before and during the internship and changes in daily mood. (a) The correlation between changes in CRCO-sleep misalignment level before and during the internship and changes in mood score. As the CRCO-sleep misalignment level increased during the internship compared to before the internship, mood scores tended to decrease during the internship. **(b, c)** Unlike CRCO-sleep misalignment, changes in CRPO-sleep (b) and internal (c) misalignments were not statistically significantly associated with changes in daily mood scores before and during internship. Here, to quantify the changes in mood and misalignment levels before and during the internship, we subtracted their average subjective mood scores (and misalignment levels) before the internship from those during the internship. Changes in mood scores were binned by each change in misalignment level. Bin edges were computed every 1 hour, and the mean and standard error of the changes in mood scores were plotted against the midpoint of each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively, obtained by applying linear least squares regression to the binned data. b, ρ, and p denote the beta estimate, Pearson's correlation coefficient, and p-value, respectively. A two-tailed Wald t-test was used to compute p-values and assess statistical significance.



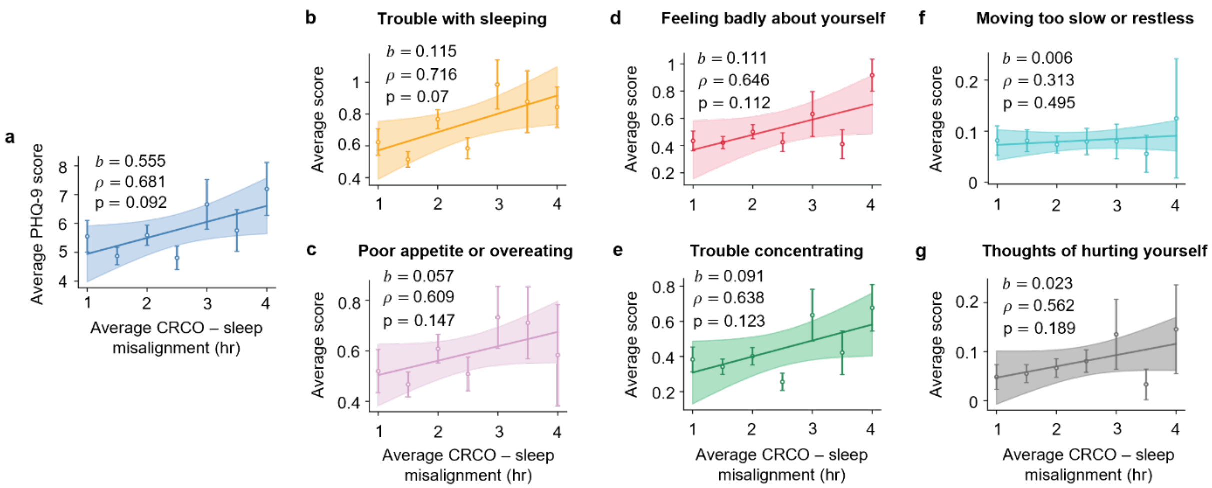
Supplementary Figure 6. A schematic diagram of the cross-lagged panel model describing the reciprocal relationship between a circadian disruption measure and daily mood. For each circadian disruption measure, a cross-lagged panel model was fitted to estimate the autoregressive effects (β_{11} and β_{21}), cross-lagged effects (β_{12} and β_{22}), and synchronous correlation effects (β_{13} and β_{23}). Note that demographic and geographic variables were adjusted for, as done in the linear mixed-effects model analysis. See Methods for details.



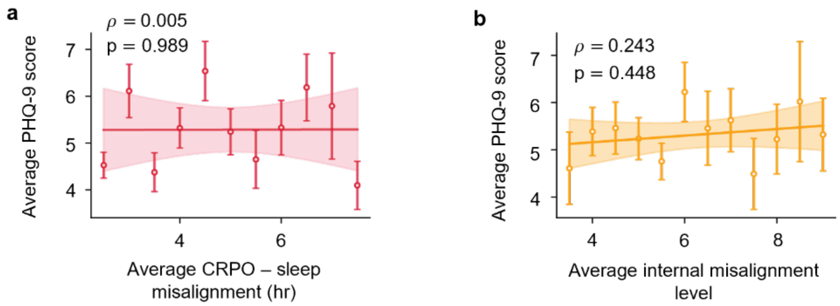
Supplementary Figure 7. The effect of time awake on the relationship between circadian disruption measures on the current-day and daily mood on the subsequent-day during the internship. (a) The association between current-day CRCO-sleep misalignment level and mood score on the following day was assessed for interns who spent 0~12 hr awake (i) (n = 3,499), 12~16 hr awake (ii) (n = 8,589), 16~20 hr awake (iii) (n = 8,994), and greater than 20 hr awake (iv) (n = 8,926). **(b)** The effect of time awake on the association between current-day CRPO-sleep misalignment level and mood score on the following day was similarly investigated. The CRPO-sleep misalignment level was negatively correlated with the next-day mood score regardless of total time awake. **(c)** The effect of time awake on the association between current-day internal misalignment level and mood score on the following day was also examined. The next-day mood scores were binned by each misalignment level. Bin edges were computed every 1 hour, and the mean and standard error of the mean of mood scores were plotted against the midpoint of each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively, obtained by applying linear least squares regression to the binned data. b, ρ, and p denote the beta estimate, Pearson's correlation coefficient, and p-value, respectively. A two-tailed Wald t-test was used to compute p-values and assess statistical significance.



Supplementary Figure 8. The effect of sleep variability on the relationship between circadian disruption measures on the current-day and daily mood on the subsequent-day during the internship. **(a)** The association between current-day CRCO-sleep misalignment level and mood score on the following day was assessed when the sleep midpoint shifted by 0~0.5 hr (i) (n = 6,851), 0.5~1 hr (ii) (n = 5,895), 1~2 hr (iii) (n = 8,360), and greater than 2 hr (iv) (n = 9,598). The negative correlation between CRCO-sleep misalignment level and mood score became pronounced when sleep variability was greater than 2 hours. Here, data points were split into different strata based on sleep variability level, defined as the shift in sleep midpoint relative to the previous day. CRCO-sleep misalignment and mood score were significantly associated only when the sleep midpoint shifted by more than 1 hr. **(b)** The effect of sleep variability on the association between CRPO-sleep misalignment level and next-day mood score was similarly investigated. The CRPO-sleep misalignment level was negatively correlated with the next-day mood score regardless of sleep variability. **(c)** The effect of sleep variability on the association between internal misalignment level and next-day mood was also examined. The internal misalignment level was negatively correlated with the next-day mood score regardless of sleep variability. The next-day mood scores were binned by each misalignment level. Bin edges were computed every 1 hour, and the mean and standard error of the mean of mood scores were plotted against the midpoint of each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively, obtained by applying linear least squares regression to the binned data. b, ρ, and p denote the beta estimate, Pearson's correlation coefficient, and p-value, respectively. A two-tailed Wald t-test was used to compute p-values and assess statistical significance.



Supplementary Figure 9. The average PHQ-9 score can be accurately estimated only when the CRCO-sleep misalignment is obtained using a data assimilation method. (a) When the circadian phase of CRCO was predicted solely based on the mathematical model of the human circadian pacemaker (i.e., without using a data assimilation method) (see Methods for details), the correlation between CRCO-sleep misalignment and average PHQ-9 score was no longer significant, demonstrating the importance of using the data assimilation approach to estimate the phase of CRCO. **(b-g)** The CRCO-sleep misalignment estimated without the data assimilation did not show a significant correlation with the average scores of subitems from PHQ-9 questionnaires. Here, the average misalignment level is binned every 30 minutes, and the mean and standard error of the mean (SEM) of the average PHQ-9 score are reported for each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively. The PHQ-9 score and scores of its six subitems were binned by the average CRCO-sleep misalignment level. Bin edges were computed every 30 minutes, and the mean and standard error of the mean of scores were plotted against the midpoint of each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively, obtained by applying linear least squares regression to the binned data. b, ρ, and p denote the beta estimate, Pearson's correlation coefficient, and p-value, respectively. A two-tailed Wald t-test was used to compute p-values and assess statistical significance.



Supplementary Figure 10. The CRPO-sleep and internal misalignment did not show a correlation with the average PHQ-9 score. (a-b) Unlike CRCO-sleep misalignment, the average CRPO-sleep misalignment level (a) and internal misalignment level (b) and average PHQ-9 score within each participant are not positively correlated. Here, the average misalignment level is binned every 30 minutes, and the mean and standard error of the mean (SEM) of the average PHQ-9 score are reported for each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively. The PHQ-9 score and scores of its six subitems were binned by the average CRPO-sleep and internal misalignment levels. Bin edges were computed every 30 minutes, and the mean and standard error of the mean of scores were plotted against the midpoint of each bin. The line and shaded region represent the best-fitted line and the corresponding 95% confidence band, respectively, obtained by applying linear least squares regression to the binned data. b, ρ, and p denote the beta estimate, Pearson's correlation coefficient, and p-value, respectively. A two-tailed Wald t-test was used to compute p-values and assess statistical significance.

Supplementary Table 1. Summary of demographic information for subjects included in the analysis.

	Male	Female	Total
Daily mood analysis (Fig 2 and 3)	364	468	832
Age	27.9 ± 2.7	27.5 ± 2.4	27.6 ± 2.7
Caucasian	246	304	550
Asian	65	89	154
Mixed	26	39	65
African American	8	21	29
Latino	12	12	24
Arab / Middle Eastern	5	2	7
Other	1	1	2
Information not available	1	0	1
PHQ-9 analysis (Fig 4)	287	384	671
Age	27.8 ± 2.6	27.6 ± 2.5	27.7 ± 2.6
Caucasian	192	251	443
Asian	51	75	126
Mixed	23	31	54
African American	5	17	22
Latino	10	9	19
Arab / Middle Eastern	4	1	5
Other	1	0	1
Information not available	1	0	1

Here, we report the number of subjects in each category of sex and race. The age of the subjects is reported as mean $\pm$ standard deviation. Note that one subject for the daily mood analysis did not report their demographic information. Hence, we report the demographic information from 832, rather than 833, subjects.

Supplementary Table 2. The relationship between circadian disruption levels and mood score using weighted least squares regression.

	Dependent Variables	beta	t-statistics	Pr(>|t|)	95% C.I	Pearson's ρ
Disruption vs next-day mood (Fig 2)						
Before internship	CRCO misalignment	0.002	0.238	0.824	[-0.020, 0.024]	0.118
	CRPO misalignment	-0.014	-2.992	0.012	[-0.024, -0.004]	-0.670
	Internal misalignment	-0.017	-3.879	0.002	[-0.026, -0.007]	-0.732
During internship	CRCO misalignment	-0.014	-2.878	0.015	[-0.024, -0.003]	-0.655
	CRPO misalignment	-0.011	-11.300	< 0.001	[-0.014, -0.009]	-0.960
	Internal misalignment	-0.010	-5.217	< 0.001	[-0.014, -0.006]	-0.794
Mood vs next-day disruption (Fig 3)						
Before internship	Mood (vs CRCO)	-0.047	-1.685	0.136	[-0.112, 0.019]	-0.537
	Mood (vs CRPO)	-0.075	-2.205	0.063	[-0.155, -0.005]	-0.640
	Mood (vs Internal)	-0.125	-2.831	0.025	[-0.230, -0.080]	-0.731
During internship	Mood (vs CRCO)	-0.051	-2.769	0.018	[-0.091, -0.010]	-0.641
	Mood (vs CRPO)	-0.072	-2.392	0.036	[-0.139, -0.006]	-0.585
	Mood (vs Internal)	-0.159	-4.449	0.001	[-0.238, -0.080]	-0.802

The association between current-day circadian disruption and next-day mood score before and during the internship was analyzed after accounting for the differences in the standard error of the mean for the binned data (i.e., the error bars in Fig 2 and Fig 3), where circadian disruption measures were binned every 1 hour. The same analysis was repeated between current-day mood and next-day circadian disruption, except that the current-day subjective mood z-score was binned every 0.5 mood z-score. In all analyses, the weights of the binned data were given as $1/SEM^2$, where SEM denotes the standard error of the mean for each bin. Here, we report the estimates, their 95% confidence intervals (C.I), respective p-values of the fitted intercept, the beta value denoting the change in circadian disruption measure (subjective mood) per unit change in subjective mood score (circadian disruption measure), and the calculated Pearson's correlation coefficient.

Supplementary Table 3. A cross-lagged panel model analysis using next-day mood as the dependent variable.

Dependent variable	Predictors	beta	z-statistics	Pr(>|z|)	95% C.I
Before internship					
$Mood_{i+1}$ (vs CRCO)	$CRCO_{i+1}$	-0.016	-1.916	0.055	[-0.032, -0.000]
	$CRCO_i$	-0.004	-0.493	0.622	[-0.021, 0.012]
	$Mood_i$	0.225	16.583	< 0.001	[0.199, 0.252]
$Mood_{i+1}$ (vs CRPO)	$CRPO_{i+1}$	-0.008	-1.774	0.076	[-0.017, 0.001]
	$CRPO_i$	-0.014	-2.949	0.003	[-0.023, -0.005]
	$Mood_i$	0.223	16.487	< 0.001	[0.197, 0.250]
$Mood_{i+1}$ (vs Internal)	$Internal_{i+1}$	-0.007	-1.788	0.074	[-0.016, 0.001]
	$Internal_i$	-0.012	-2.801	0.005	[-0.020, -0.003]
	$Mood_i$	0.223	16.463	< 0.001	[0.197, 0.250]
During internship					
$Mood_{i+1}$ (vs CRCO)	$CRCO_{i+1}$	-0.001	-0.473	0.636	[-0.007, 0.004]
	$CRCO_i$	-0.007	-2.499	0.012	[-0.013, -0.002]
	$Mood_i$	0.285	43.980	< 0.001	[0.272, 0.297]
$Mood_{i+1}$ (vs CRPO)	$CRPO_{i+1}$	-0.003	-1.213	0.076	[-0.007, 0.002]
	$CRPO_i$	-0.008	-3.837	< 0.001	[-0.013, -0.004]
	$Mood_i$	0.285	43.941	< 0.001	[0.272, 0.297]
$Mood_{i+1}$ (vs Internal)	$Internal_{i+1}$	-0.005	-2.592	0.010	[-0.009, -0.001]
	$Internal_i$	-0.005	-2.445	0.014	[-0.009, -0.001]
	$Mood_i$	0.285	44.034	< 0.001	[0.272, 0.298]

For each circadian disruption measure, a cross-lagged panel model (Fig. S6) was fitted to estimate the synchronous correlation effect, the cross-lagged effect, and the autoregressive effect on the next-day mood. Note that the model adjusted for repeated measures from the same subject, as well as age, sex, race, and time zone information. Here, we report the estimates for β_{21}, β_{22}, and β_{23} as shown in Fig. S6, along with their 95% confidence intervals (C.I.) and the p-value. See Methods for details.

Supplementary Table 4. The relationship between a circadian disruption measure on the current-day and daily mood on the subsequent-day after considering the other two measures as covariates.

	Fixed effects	beta	z-statistics	Pr(>|z|)	95% C.I
Before Internship	CRCO misalignment	-0.011	-1.592	0.111	[-0.024, 0.003]
	CRPO misalignment	-0.002	-0.313	0.754	[-0.013, 0.009]
	Internal misalignment	-0.017	-3.729	< 0.001	[-0.025, -0.008]
During internship	CRCO misalignment	-0.012	-5.515	< 0.001	[-0.017, -0.006]
	CRPO misalignment	-0.002	-0.978	0.328	[-0.007, 0.002]
	Internal misalignment	-0.008	-4.417	< 0.001	[-0.012, -0.004]

The relationship before and during the internship was analyzed using a linear mixed-effects model that estimates the overall influence of one circadian marker on the next-day daily mood across groups with different levels of circadian disruption, while adjusting for random effects from the other two markers to capture variability between groups (see Methods for details). Note that the model also adjusted for repeated measures from the same subject, as well as age, sex, race, and time zone information. Here, we report the beta estimate, its 95% confidence intervals (C.I.), and the p-value.

Supplementary Table 5. A cross-lagged panel model analysis using a next-day circadian disruption measure as the dependent variable.

Dependent variable	Predictors	beta	z-statistics	Pr(>|z|)	95% C.I
Before internship					
$CRCO_{i+1}$	$CRCO_i$	0.286	20.711	< 0.001	[0.259, 0.322]
	$Mood_{i+1}$	-0.014	-0.721	0.471	[-0.052, 0.024]
	$Mood_i$	-0.051	-2.659	0.008	[-0.089, 0.024]
$CRPO_{i+1}$	$CRPO_i$	0.353	26.234	< 0.001	[0.326, 0.379]
	$Mood_{i+1}$	-0.039	-1.106	0.269	[-0.107, 0.030]
	$Mood_i$	-0.116	-3.329	0.001	[-0.184, -0.048]
$Internal_{i+1}$	$Internal_i$	0.447	34.894	< 0.001	[0.422, 0.472]
	$Mood_{i+1}$	-0.020	-0.515	0.606	[-0.098, 0.057]
	$Mood_i$	-0.165	-4.179	< 0.001	[-0.242, -0.087]
During internship					
$CRCO_{i+1}$	$CRCO_i$	0.418	67.469	< 0.001	[0.406, 0.430]
	$Mood_{i+1}$	0.004	0.257	0.797	[-0.024, 0.032]
	$Mood_i$	-0.047	-3.315	0.001	[-0.075, -0.019]
$CRPO_{i+1}$	$CRPO_i$	0.338	52.141	< 0.001	[0.325, 0.351]
	$Mood_{i+1}$	0.028	1.476	0.140	[-0.009, 0.065]
	$Mood_i$	-0.079	-4.154	< 0.001	[-0.009, 0.065]
$Internal_{i+1}$	$Internal_i$	0.487	80.415	< 0.001	[0.475, 0.499]
	$Mood_{i+1}$	-0.004	-0.190	0.849	[-0.047, 0.039]
	$Mood_i$	-0.148	-6.779	< 0.001	[0.475, 0.499]

For each circadian disruption measure, a cross-lagged panel model (Fig. S6) was fitted to estimate the synchronous correlation effect, the cross-lagged effect, and the autoregressive effect on the next-day circadian disruption measure. Note that the model adjusted for repeated measures from the same subject, as well as age, sex, race, and time zone information. Here, we report the estimates for β_{21}, β_{22}, and β_{23} as shown in Fig. S6, along with their 95% confidence intervals (C.I.) and the p-value. See Methods for details.

Supplementary Table 6. The relationship between circadian disruption measures and PHQ-9 scores before the internship.

		Linear regression			Linear mixed effects	
Disruption marker	**Item**	**beta**	**p-value**	**Pearson's ρ**	**beta**	**p-value**
CRCO-sleep misalignment	**PHQ-total**	0.149	0.637	0.219	-0.016	0.928
	PHQ-1	0.112	0.097	0.673	-0.024	0.478
	PHQ-2	-0.084	0.153	-0.601	-0.026	0.398
	PHQ-3	0.173	0.038	0.781	0.034	0.456
	PHQ-4	0.041	0.532	0.287	-0.009	0.822
	PHQ-5	0.078	0.058	0.739	0.010	0.784
	PHQ-6	-0.117	0.026	-0.814	0.018	0.616
	PHQ-7	0.101	0.038	0.781	-0.018	0.606
	PHQ-8	-0.025	0.303	-0.457	-0.003	0.824
	PHQ-9	0.013	0.644	0.215	0.006	0.639
CRPO-sleep misalignment	**PHQ-total**	-0.031	0.678	-0.128	-0.135	0.144
	PHQ-1	-0.008	0.755	-0.096	-0.023	0.189
	PHQ-2	-0.014	0.459	-0.226	-0.022	0.211
	PHQ-3	-0.005	0.782	-0.085	-0.034	0.144
	PHQ-4	-0.005	0.774	-0.089	-0.037	0.071
	PHQ-5	0.032	0.264	0.334	-0.005	0.777
	PHQ-6	0.004	0.902	0.038	-0.006	0.725
	PHQ-7	0.002	0.920	0.031	-0.006	0.749
	PHQ-8	0.018	0.373	0.270	0.003	0.718
	PHQ-9	0.002	0.880	0.047	-0.003	0.640
Internal misalignment	**PHQ-total**	-0.010	0.729	-0.094	-0.046	0.564
	PHQ-1	-0.014	0.533	-0.168	0.000	0.988
	PHQ-2	-0.001	0.955	-0.015	-0.003	0.846
	PHQ-3	-0.032	0.102	-0.424	-0.029	0.147
	PHQ-4	-0.014	0.634	-0.129	-0.022	0.220
	PHQ-5	0.015	0.292	0.281	-0.005	0.774
	PHQ-6	0.011	0.662	0.119	0.008	0.617
	PHQ-7	0.016	0.483	0.189	-0.003	0.870
	PHQ-8	-0.009	0.408	-0.222	0.006	0.336
	PHQ-9	0.011	0.303	0.275	0.002	0.669

The association between circadian disruption markers and PHQ-9 scores before the internship was analyzed using linear regression and linear mixed-effects modeling. For linear regression analysis, the data were binned every 30 minutes for each marker. The beta estimate, representing the change in PHQ-9 scores per unit change in circadian disruption markers, its p-value, and the Pearson's correlation coefficient are reported for linear regression, where a two-tailed Wald *t*-test was used to compute p-values and assess statistical significance. The beta estimate and p-value are reported for linear mixed-effects modeling.

Supplementary Table 7. The relationship between CRCO-sleep misalignment level and PHQ-9 scores analyzed using linear mixed-effects modeling during the internship.

Item	Questions	beta	z-statistics	Pr(>|z|)	95% C.I
PHQ-total	Total score	0.396	2.262	0.024	[0.053, 0.740]
PHQ-1	Little interest or pleasure	0.079	2.633	0.008	[0.020, 0.138]
PHQ-2	Feeling down, depressed, or hopeless	0.042	1.103	0.270	[-0.033, 0.118]
PHQ-3	Trouble sleeping	0.046	1.313	0.189	[-0.023, 0.115]
PHQ-4	Feeling tired or little energy	0.032	0.922	0.356	[-0.036, 0.099]
PHQ-5	Poor appetite or overeating	0.066	1.854	0.064	[-0.004, 0.136]
PHQ-6	Feeling badly about yourself	0.082	2.495	0.013	[0.018, 0.147]
PHQ-7	Trouble concentrating	0.046	1.522	0.128	[-0.013, 0.106]
PHQ-8	Moving too slow or restless	-0.006	-0.404	0.686	[-0.037, 0.024]
PHQ-9	Thoughts of hurting yourself	0.011	0.769	0.442	[-0.017, 0.039]

The association between average circadian CRCO-sleep misalignment and average PHQ-9 scores during the internship was analyzed after accounting for the age, sex, race, and time zone information using linear mixed-effects modeling (see Methods for details). Here, we report the beta estimate, denoting the change in PHQ-9 scores per unit change in CRCO-sleep misalignment, its 95% confidence intervals (C.I), and the p-value.

Supplementary Table 8. The relationship between CRCO-misalignment level and PHQ-9 scores after considering the other two misalignment levels as covariates.

Item	Questions	beta	z-statistics	Pr(>|z|)	95% C.I
PHQ-total	Total score	0.535	2.607	0.009	[0.133, 0.936]
PHQ-1	Little interest or pleasure	0.091	2.629	0.009	[0.023, 0.158]
PHQ-2	Feeling down, depressed, or hopeless	0.066	1.975	0.048	[0.001, 0.132]
PHQ-3	Trouble sleeping	0.049	1.208	0.227	[-0.030, 0.128]
PHQ-4	Feeling tired or little energy	0.042	1.066	0.286	[-0.035, 0.119]
PHQ-5	Poor appetite or overeating	0.080	1.966	0.049	[0.000, 0.160]
PHQ-6	Feeling badly about yourself	0.103	2.725	0.006	[0.029, 0.177]
PHQ-7	Trouble concentrating	0.089	2.588	0.010	[0.022, 0.157]
PHQ-8	Moving too slow or restless	0.003	0.193	0.847	[-0.032, 0.039]
PHQ-9	Thoughts of hurting yourself	0.017	1.016	0.310	[-0.015, 0.049]

The relationship during the internship was analyzed using a linear mixed-effects model that estimates the overall influence of one circadian marker on the average PHQ-9 scores across groups with different levels of circadian disruption, while adjusting for random effects from the other two markers to capture variability between groups (see Methods for details). Note that the model also adjusted for age, sex, race, and time zone information. Here, we report the beta estimate, its 95% confidence intervals (C.I.), and the p-value.