TIMING OF DYSREGULATION IN REST-ACTIVITY RHYTHM AND DEPRESSION SYMPTOM SEVERITY IN DEMENTIA CAREGIVERS

by

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ABSTRACT

Introduction: Several studies have shown differences in rest-activity rhythms (RARs) are associated with poor mental health outcomes, like depression. However, few studies have explored how the timing of these differences in RAR patterns influences subclinical depression, a known risk factor for developing future depression. The present study proposes three measures of activity to evaluate the effects of timing on subclinical depression symptom severity (non-sleep items from the Hamilton Rating Scale for Depression (HRSD)) in dementia caregivers (n=57).

Methods: The three proposed measures, calculated within 4-hour time bins, include: absolute mean activity within each time period, standard deviation of mean activity across days in each time bin, and relative activity in each time bin. 4-hour time bins are defined based on proposed 'Person-Time' (clock-time minus wake-up hour). Spearman correlations and linear regressions were used to assess the association between each measure at each time bin and depression, using age and gender as covariates. Group-based trajectory analysis was also used to identify clusters of activity trajectories, which were subsequently tested for associations with depression scores using Analysis of Covariance (ANCOVA).

Results: Spearman correlations showed that 20 to 24 hours after waking, mean activity and relative activity were positively associated with depression score ($\rho = 0.37$, P-value <0.01 and $\rho = 0.35$, P-value $= 0.01$, respectively). Spearman correlations also revealed a

significant negative association between relative activity and depression score (ρ = -0.42, P-value <0.01) 12 to 16 hours after waking. Multiple regression models showed that at 20 to 24 hours after waking, both mean activity (β = 0.96, β P-value <0.01, model P-value = 0.007, adj. R^2 = 0.16) and relative activity (β = 21.81, β P-value <0.01, model P-value = 0.01, adj. R^2 = 0.15) were positively associated with depression score. Standard deviation of mean activity was not significantly associated with depression score across all regression models. Trajectory analyses identified two latent RAR types based on each of the three activity measures. ANCOVA of cluster assignments based on mean activity showed a significant association with depression score (F-value = 5.28, P-value = 0.03), controlling for age and sex.

Conclusion: Results suggested that activity late in a patient's RAR is associated with increased subclinical depression severity in dementia caregivers.

Public Health Significance: These analyses may help inform where in a patient's RAR an activity- or sleep-based interventions should be applied.

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1.0 INTRODUCTION

1.1 ACTIVITY PATTERNS AND HEALTH

Wearable technology offers a unique clinical opportunity for researchers to study patients outside of the laboratory environment. As technological advancements have made wearables more mobile and compact, wearables are being used in a variety of studies as a reliable way to monitor long-term health patterns [1]. Actigraphy is one type of wearable technology that uses accelerometer-based transformations to quantify physical activity. Actigraphy offers several advantages for measuring physical activity. First, actigraphs offer an objective and validated method of measuring activity data, making them immune to self-report biases. Secondly, actigraphs are lightweight, wireless, and can be worn at the wrist, hip, or foot. This allows patients to comfortably wear actigraphs continuously for weeks at a time in their natural environment. Finally, actigraphy is an ideal activity- and sleep-monitoring tool for patients who struggle to reliably complete sleep diaries or adhere to study protocols due to cognitive impairment, disability, or other psychological and physical demands. These advantages make actigraphy particularly useful for evaluating longer-term dysregulations in circadian rhythms, which are often associated with sleep and mood disorders [2, 3]. Previous studies using actigraphy have shown that certain circadian patterns are associated with a variety of physical health outcomes, such as diabetes and coronary artery disease [4, 5].

These circadian patterns are also referred to as rest-activity rhythms (RARs). In adults, RARs are typically characterized by a 24-hour sleep-wake cycle. In addition to the health outcomes mentioned above, actigraphy has also been used to study neuropsychological disorders. These studies have revealed that disturbances in RAR are associated with a number of mental health disorders, such as bipolar disorder [6], major depression [7, 8], and depres-

sion risk [9, 10]. Sleep quality is a known correlate for psychiatric disorders like depression [11]. Research suggests that increasing physical activity can reduce anxiety and depression [12] and correlates with improved sleep quality [13]. In addition to disturbances in RAR, subclinical depression is a known risk factor for developing major depression in the future [14]. Thus, characterizing the RAR patterns associated with subclinical depression symptom severity may help identify patterns of activity that increase the risk of depression and can ultimately inform future activity-based intervention strategies targeting those at risk for depression.

Individuals caring for a family member with a disability or impairment are a particular population that is at a heightened risk for depression. In developed nations, like the United States, up to three-quarters of care provided to the elderly is provided by informal caregivers, such as a spouse or an offspring, and the majority of that assistance is needed seven days a week [15]. Informal caregivers often struggle with physical, psychological, social, and financial demands of care giving, making them at heightened risk for depression [16, 17, 18]. While previous studies have examined the relationship between caregiver burden and depression risk, few studies have specifically used actigraphy to identify how activity patterns relate to depression risk in informal caregivers.

Informal caregivers caring for a spouse with dementia may be particularly at risk for depression. Dementia caregivers report being less physically active than their non-caregiver peers and approximately two-thirds of dementia caregivers report disturbed sleep patterns (for review, [19]), both of which are known risk factor for depression. Only one study to-date has specifically used actigraphy to directly measure and analyze RAR characteristics with depression symptom severity in dementia caregivers [10]. Smagula et al. (2017)[10] found that more time awake after sleep onset (WASO), relatively shortened activity periods, and early evening setting time were associated with depression symptom severity in this group.

1.2 METHODOLOGICAL BACKGROUND

Traditional methods of analyzing actigraphy fall into two broad classes: parametric and nonparametric. A common parametric approach includes fitting a five-parameter extended cosine model to a subjects activity pattern [20]. Estimated parameters from the parametric model includes: α, the relative width of the activity peak; β, the steepness of the curve, which determines how square-like the curve is; mesor, the middle of the height of the curve; and amplitude, the peak of the rhythm (see Figure 1.1). Parametric models also offer a 'pseudo-F' statistic, which can be thought of as a goodness of fit measure. Parametric models are advantageous in that they offer interpretable measures of the shape and size of RARs. However, parametric models have a disadvantage in that they rely on the validity of the assumed cosine model.

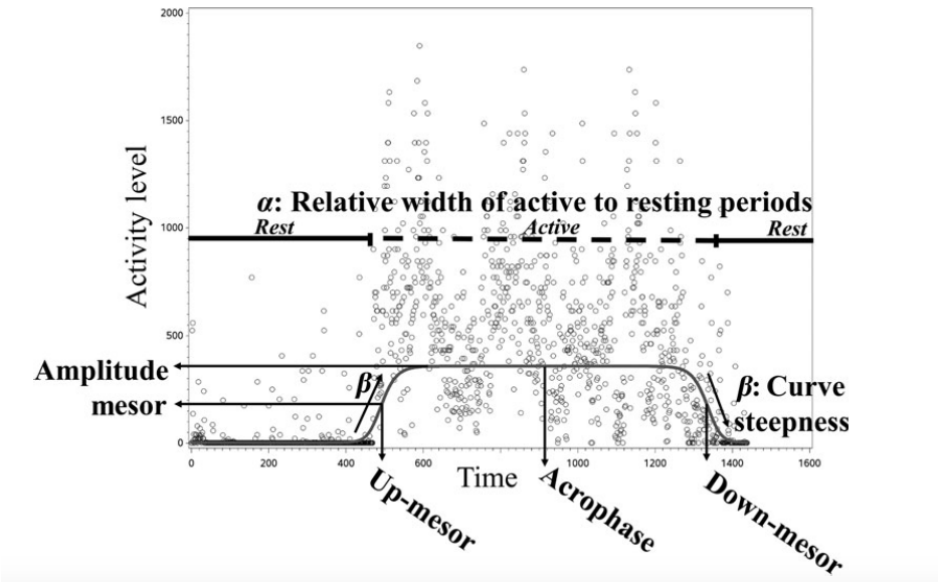


Figure 1.1: Example of a five-parameter extended cosine model.
Taken from Smagula et al. 2017[10]

Nonparametric models, on the other hand, are directly derived from quadratic and linear functions of the time series data [21]. The measures provided from nonparametric models include intradaily variability (IV) and interdaily stability (IS). IV provides an indication

of the fragmentation of the rhythm within a day, or the frequency of transitions between activity and rest. IV is based on hourly values and is defined as the ratio of the mean squares of the difference between consecutive hours and the mean squares around the grand mean (i.e., the overall variance). IS is a a signal-to-noise measure, which can be thought of as the variability across days. IS is defined as the ratio of the average square-error of the of the hourly means relative to the global mean over the total variability. And while freedom from dependence on an assumed model is a strength for nonparametric methods, they offer limited interpretability or understanding of the shape and size of RAR patterns.

Both the parametric and nonparametric methods mentioned above allow us to understand the overall variability or stability of activity across and within days, but neither allow us to understand how RAR variability may change throughout the course of a day and when they changes occur. Exploring the timing of activity patterns may enhance our understanding of the relationship between activity patterns and depression severity. Recent work by Shou et al. (2017)[6] has attempted to identify the timing of disturbance in activity and how it relates to the presence of mood disorders. The authors calculated mean activity at clock-time intervals 00:00-06:00, 06:00-12:00, 12:00-16:00, 16:00-20:00, 20:00-00:00 by collapsing activity across days. They authors then calculated day-to-day variability in each time interval by calculating the standard deviation around mean activity. The authors used Generalized Estimating Equations (GEE) and linear regression models with mood disorder as predictors, demographic information as covariates, and activity as the outcome variable. They authors found that the presence of Bipolar Disorder (BPD) I was significantly negatively associated with activity from 12:00-16:00, 16:00-20:00 and 20:00-00:00 hours, suggesting that the presence of BPD I may dampen activity during these times. This study also showed that BPD II and BPD I were both independently significantly positively associated with standard deviation of activity across days from 00:00-06:00 and 12:00-16:00 respectively, suggesting that the presence of BPD I or II may explain increases in variability across days at these time points.

The study mentioned above is important as it begins to identify ways to measure timing of RAR patterns and dysregulation and their influence on mood disorders. However, analyses techniques from this study could be improved. First, Shou et al. (2017)[6] do not account for

differences in patient wake time or sleep time. RAR cycles within a subject are understood to be consistent in timing, but this specific timing may vary across subjects. For example, one subject may consistently wake at 8am, whereas another subject may wake up at 6am. Without this adjustment, the results imply that all patients with BPD I are likely to have less activity around 12:00, independent of waking time. While informative, this does not account for how subject-specific variations in RAR timing may influence psychopathology. Secondly, treating psychopathology as a independent variables may inhibit the ability to interpret these findings in a prevention/intervention context. And thus, associations should be re-assessed using psychopathology as an outcome of interest. Finally, absolute mean activity *per se* may not be the only indicator of activity level. Instead, a measure of relative activity, such as a ratio of activity between two time intervals or a proportion representing the weight of the activity at one time point compared to all time points, may more accurately reflect the relative importance of activity at certain time points. Relative measures may also provide us with a better understanding of the daily temporal distribution of RAR patterns.

1.3 PRESENT STUDY

As mentioned above, previous research has shown that dysregulation in RAR in dementia caregivers was associated with increased subclinical depression symptom severity [10]. Previous analyses by Smagula et al. (2017)[10], relied on parametric approaches of RAR analysis in order to characterize the differences in activity patterns in this population. Thus, the timing of dysregulation has yet to be characterized in this population.

The present study re-examines RAR patterns of dementia caregivers from Smagula et al. (2017)[10] to understand how changes in the timing of activity patterns and dysregulation relate to depression symptom severity in this population. To meet this end, three measures are proposed that expand upon the recently explored methodological technique utilized by Shou et al. (2017)[6] (above), further bridging gaps in interpretation in both the parametric

and nonparametric methods mentioned above. Finally, group-based trajectory analysis is applied to identify any latent class structures in activity patterns in this dataset and to determine their effects on subclinical depression scores. While group-based trajectory analyses are fairly common in epidemiological research, few studies have used it to characterize RAR patterns specifically in caregivers and only one has been applied to caregiver distress[22].

Coding techniques used to calculate measures of activity used in the present study will be packaged in R and will be made available for public use.

2.0 METHODS

2.1 PARTICIPANTS

Participants were part of the NIH-funded Aging Well, Sleeping Efficiently: Intervention Studies Program Project (P01 AG20677), also known as AgeWise. Study participants were live-in, spousal caregivers for a patient with an advanced form of dementia. The primary goals of the study were intervention-based and emphasized caregiver stress management and sleep habits. Data for AgeWise was collected between November 2003 and June 2008. The present study is a re-examination of the cross-sectional, baseline data analyzed by Smagula et al. (2017)[10].

Inclusion criteria for AgeWise included: aged 50 years or older; disrupted sleep, identified as a score of at least five on the Pittsburgh Sleep Quality Index [11]; and caregiver strain, as indicated by a 'yes' to the question 'it is a significant physical and emotional strain for me to care for my spouse'. Exclusion criteria included: the presence of breathing related sleep disorders; a current psychiatric disorder; a score of less than 24 on the Mini-Mental State Exam [23], indicating cognitive impairment. 60 subjects met these criteria, 57 of whom contributed usable actigraphy data at baseline and are included in the present study. AgeWise was approved by the University of Pittsburgh Institutional Review Board and participants provided written informed consent.

2.2 DATA COLLECTION

2.2.1 Rest-Activity Measurements

Participants were asked to wear an Actiwatch 2® (Philips Respironics, Bend, OR, USA) on their non-dominant wrist for two weeks. Each subject (n=57) had actigraphy measurements (counts) for 60-second epochs over the course of the study period. Only two subjects had missing data, which totaled two hours of lost activity. Activity counts were log transformed by adding one to all activity counts and then taking the natural log. Log(activity + 1) was then treated as a continuous variable.

Previous parametric analyses conducted by Smagula et al. (2017)[10] identified the timing of the up-mesor for each subject. The up-mesor can be thought of as the time a subject's activity began, or a subject's assumed wake-up time. Traditionally, wake-up time has often been identified using sleep diaries. Using modeled up-mesor provides a objective understanding of waking-time, one that is not prone to self-report biases. In order to adjust for subject specific variations in activity timing, up-mesor time was subtracted from each 60-second epoch time (see "Person-Time" column in example dataset below 2.1). The subsequent up-mesor adjusted time is referred to as "Person-Time", and can be interpreted as the number of hours after waking. Standardizing for timing in this way reveals the differences in activity period length or shape without obscuring these patterns within the context of an arbitrary 'clock-time'.

Activity was then assigned to one of six 4-hour time intervals: 00:00-04:00, 04:00-08:00, 08:00-12:00, 12:00-16:00, 16:00-20:00, 20:00-24:00. 4-hour time intervals were chosen *a priori*.

2.2.2 Outcome Measure

Total of non-sleep items from the Hamilton Rating Scale for Depression (HRSD) was the outcome of interest [24] and were obtained at baseline. The HRSD is a 17-item scale, of which three items are sleep-related. Sleep-related questions were removed as objective sleep measurements was acquired using actigraphy. Non-sleep HRSD scores were log(HRSD + 1) transformed, to avoid zero scores, and were treated as continuous.

2.2.3 Covariates

Age and gender were considered potential confounder variables of sleep-wake patterns and depression and thus were included as covariates in all analyses. Age was treated as a continuous variable and gender was treated as a categorical variable.

Table 2.1: Example dataset for one subject.

Date	Time	Activity	Log(Act)	Time (hrs)	Up-mesor (hrs)	Person-Time	Bins (4hrs)
2007-02-27	19:00:00	26	3.30	19.00	6.17	12.83	(12,16]
2007-02-27	19:01:00	4	1.61	19.02	6.17	12.84	(12,16]
2007-02-27	19:02:00	125	4.84	19.03	6.17	12.86	(12,16]
2007-02-27	19:03:00	286	5.66	19.05	6.17	12.88	(12,16]
2007-02-27	19:04:00	212	5.36	19.07	6.17	12.89	(12,16]
2007-02-27	19:05:00	191	5.26	19.08	6.17	12.91	(12,16]

Person-Time = Time(hrs) - Up-mesor(hrs). Bins (4hrs) are the time intervals that each observation epoch falls into. Bin assignments are based on Person-Time. Log(Act) is the log transformation of activity + 1.

2.3 STATISTICAL ANALYSES

2.3.1 Proposed Measures of Timing

The present study proposed three measures to characterize the timing of activity: absolute mean activity, standard deviation of mean activity across days, and relative mean activity. Each of these measures are described below:

1. **Absolute mean activity** was derived by first calculating mean of log transformed activity for each subject at each time-interval on each day. Then, the mean was calculated for each time-interval across days. This created an absolute mean activity value across all days for each time point. This measure can be interpreted as the absolute activity in a given time-interval.
2. **Standard deviation of activity** was defined as the standard deviation around the mean activity across days within a given time point. This was calculated by taking the standard deviation around the mean activity for each subject at each time-interval on each day. This measure can be interpreted as the between-day variability in activity in a given time-interval.
3. **Relative activity** was calculated by taking the ratio of the absolute mean activity at time-interval t to the sum of absolute mean activity over all time points. For example, the relative activity at time-interval [0,4] and be calculated as the absolute mean activity at [0,4] divided by the sum of all absolute mean activity over all time-intervals. This measure represents the proportional weight of activity at time t relative to the whole day. Relative activity can also be interpreted as within-day variability in activity, with higher values indicating a stronger peak at a given time-interval.

An example of the proposed measures of timing calculated for a single subject can be found in Table 2.2.

2.3.2 Analyses

All analyses were conducted using R Studio v.1.0.153 [25]. First, the distribution of the outcome measure, non-sleep HRSD score, was characterized. Secondly, descriptive statistics of demographic variables (age and sex) and RAR patterns based on mean, standard deviation, and relative activity were characterized. Pairwise t-tests with Bonferroni adjusted p-values were conducted to identify any significant differences in activity measures at each time point.

The relationship between activity at each time point and non-sleep HRSD scores was first assessed using Spearman Correlation of each measure at each time point against HRSD. Spearman Correlation was specifically chosen as it does not rely on any distributional as-

sumptions about the relationship between the two variables. To assess the predictive power of activity patterns on subclinical depression symptoms, scatter plots, univariate and multiple linear regression models (using age and gender as covariates) were fit for each activity measure at each time point. Regression assumptions were assessed by reviewing regression diagnostics and by including and testing quadratic terms into each model.

Multivariate regression models treat each time bin as independent. However, this may not accurately reflect the nature of RAR, as activity at a given time point may be correlated with previous or future time points. Thus, group-based trajectory analysis was used to identify any clusters or types of RAR trajectories based on each activity measure. Clusters of RARs were identified for each activity measure (i.e. clusters based on mean, standard deviation, and relative activity, respectively). Analysis of Covariance (ANCOVA) was then used to assess the influence of each cluster on depression scores, with age and gender as covariates.

Group-based trajectory analyses were conducted using R package *kml* [26]. *kml* identifies clusters of RAR trajectories by applying k-means clustering techniques modified specifically to suit longitudinal data. The k-means procedure is unsupervised and works by converting trajectories into a time t-dimensional vector. Each t-dimensional vector is assigned into an initial cluster. The final cluster assignments are found by using an Expectation-Maximization (EM) algorithm. After initializing cluster assignments, the E phase identifies the center (mean) of each cluster. The M phase then identifies the "nearest" cluster to each observation using Euclidean distances and re-assigns each observation to that cluster. This process is iterated repeatedly until there are no changes to cluster assignments.

Identifying the ideal number of clusters is a yet-to-be-solved problem in cluster analysis. Many methods exist to act as heuristics in identifying cluster numbers, all of which offer their own advantages and disadvantages. *kml*, in particular, choses cluster number and identity using Calinski & Harabatz (CH) criterion. CH criterion is essentially the ratio of the between cluster variance and the within cluster variance. Cluster assignments that simultaneously increase between cluster variance and decrease within cluster variance are ideal. Thus, the cluster assignment which maximizes the CH criterion results in the optimal number of clusters.

Table 2.2: Example dataset of proposed measures of timing for one subject.

Subject	Time Bin	No. Days	Mean Activity	SD Activity	Total Activity	Relative Activity
1	[0,4]	17	5.09	0.46	22.72	0.22
1	(4,8]	16	5.78	0.40	22.72	0.25
1	(8,12]	16	5.53	0.34	22.72	0.24
1	(12,16]	17	4.35	0.80	22.72	0.19
1	(16,20]	18	1.01	0.92	22.72	0.04
1	(20,24]	17	0.96	0.57	22.72	0.04

Proposed measures of timing calculated for one subject. Proposed measures include: Mean Activity, Standard Deviation of Activity (SD Activity), and Relative Activity. No. Days = total number of days contributing to the respective time bin. Total Activity = sum of Mean Activity across all time points for each subject. Relative Activity = (Mean at time-interval t)/(Total Activity). Time Bin is based on "Person-Time" and represents the number of hours after waking.

3.0 RESULTS

3.1 DESCRIPTIVE STATISTICS

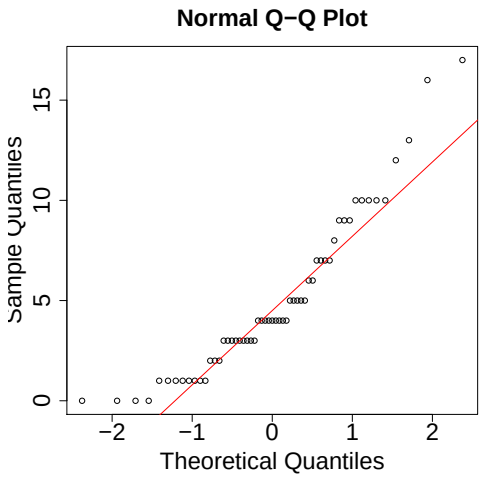
First, the distribution of the outcome measure, non-sleep HRSD score, was characterized. Raw non-sleep HRSD scores were highly skewed (Figure 3.1). After log transformation, histograms and QQplots of HRSD scores appeared roughly normally distributed. However, Shapiro-Wilk test of normality suggested the outcome may not be normally distributed (W = 0.955, P-value = 0.04). In small sample sizes, the Shapiro-Wilk test can be prone to false-rejection and qualitative assessment is preferred. Mean and median of log(HRSD+1) were 1.56 and 1.61 respectively with one standard deviation of 0.73 (Table 3.1, Figure 3.1), and thus log(HRSD+1) was assumed normal.

Based on inclusion criteria listed above, all subjects (n=57) were at least 50 years of age, had disrupted sleep, identified as a score of at least five on the Pittsburgh Sleep Quality Index, and reported that they felt strain as a caregiver of a spouse with dementia. In this cohort, subjects were on average 74±7.4 years of age and the majority were female (77.2%). The average scores for HRSD scales were 6.8±4.3 and 5.0±4.0 for the full scale and the scale removing sleep items, respectively (Table 3.1).

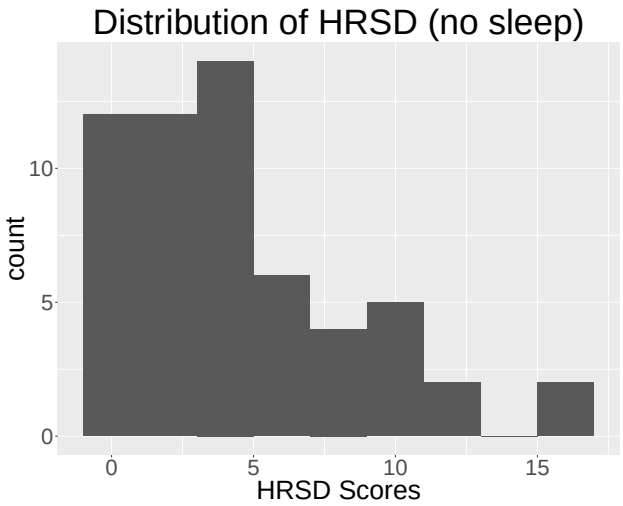
Means and standard deviations of each activity measure at each time point can be found in Table 3.2. On average, across all subjects, there is a stereotypical ramping-up pattern, in which there is increased activity in RARs after waking with a singular peak followed by a decline in activity. There is a peak in mean activity 4 to 8 hours after waking (5.00±0.51), followed by a decline in activity. Standard deviation of activity is highest 0 to 4 hours after waking (0.73±0.26). Minimum standard deviation of activity occurs at 20 to 24 hours after waking (0.53±0.25). Relative activity, similarly to mean activity, peaks at 4 to 8

hours after waking (0.25±0.2) and steadily declines afterwards. We also see that relative activity measurements also have much lower standard deviation values than other measures of activity. Figures summarizing the distribution of mean activity, standard deviation of activity, and relative activity for all subjects can be found in Figures 3.2.

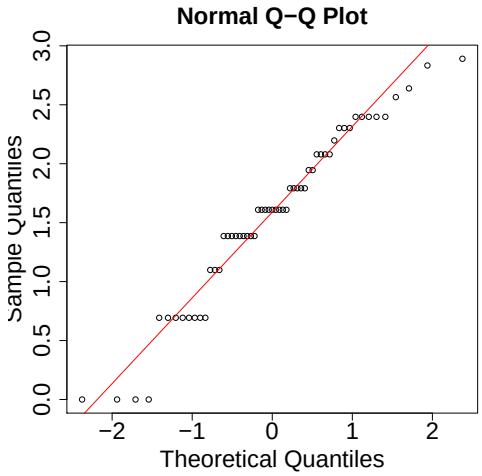
Pairwise t-tests with Bonferroni adjusted P-values were conducted to see if there were significant differences between time points. These analyses show significant differences in mean activity between all pairs of time-bins except for three pairings: [0,4] v. (8,12], (4,8] v. (8,12], and (16,20] v. (20,24]. There were no significant differences in pairwise comparisons of standard deviation of activity except for five pairings: [0,4] v. (4,8], [0,4] v. (16,20], [0,4] v. (20,24], (12,16] v. (16,20], and (12,16] v. (20,24]. And all pairwise comparisons of time points were significant different in relative activity except for two pairings: [0,4] v. (8,12], and (16,20] v. (20,24]. Summary of these results can be found in Table 3.3.



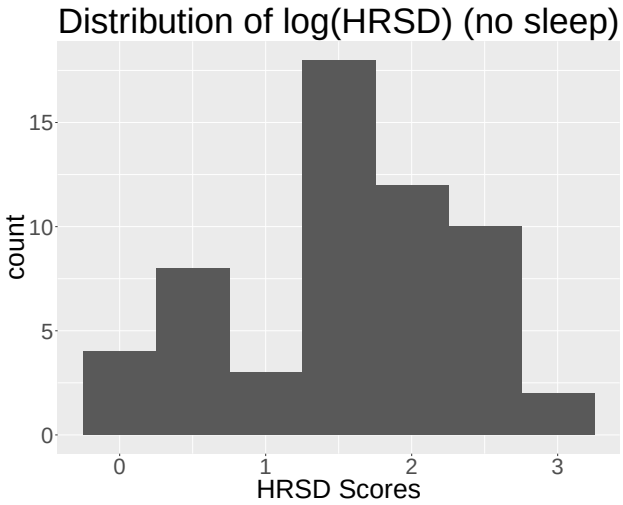
(a) QQ-Plot of HRSD



(b) Histogram: HRSD



(c) QQ-Plot of Log(HRSD + 1)



(d) Histogram: Log(HRSD + 1)

Figure 3.1: Distribution of HRSD and Log(HRSD + 1) scores.

Table 3.1: Descriptive Statistics of Demographic and Outcome Variables.

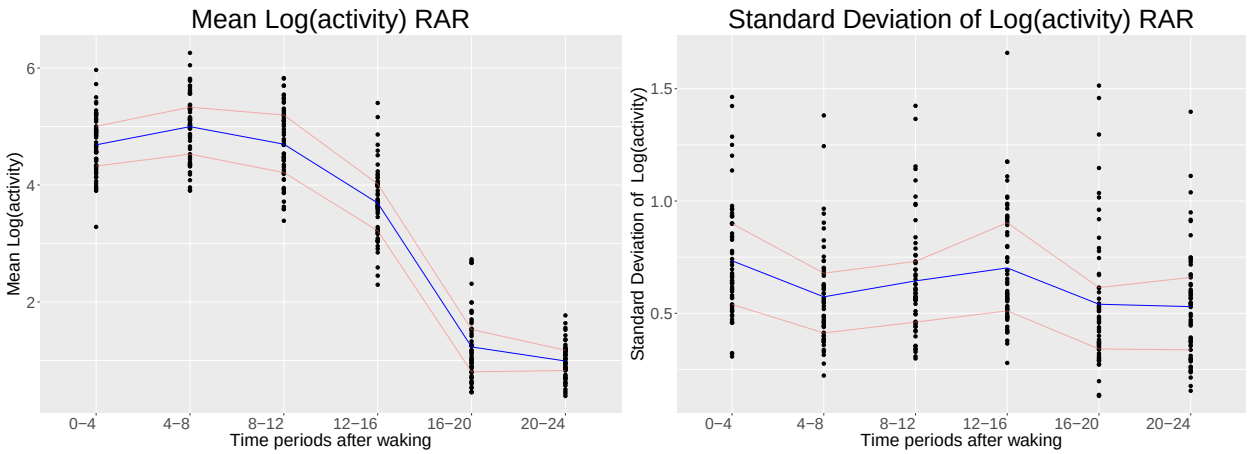
Age	Sex, % (n)	Full HRSD	Non-sleep HRSD	log(HRSD+1), mean, median (sd)
74.0 (7.4)	77.2 (44)	6.8 (4.3)	5.0 (4.0)	1.56, 1.61 (0.73)

Descriptive statistics of demographic and outcome variables (age and sex) and depression scores for the present sample (n=57). HRSD = Hamilton Rating Scale for Depression. Data presented as mean (sd), unless otherwise specified. log(HRSD+1) is log transformation of non-sleep HRSD items.

Table 3.2: Descriptive Statistics of Activity Measures at each Time Point

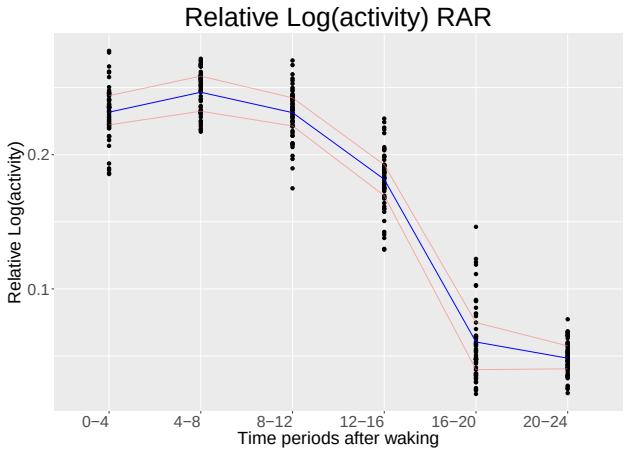
Time Period	Mean Activity	SD Activity	Relative Activity
[0,4]	4.69 (0.51)	0.73 (0.26)	0.23 (0.02)
(4,8]	5.00 (0.56)	0.57 (0.22)	0.25 (0.02)
(8,12]	4.70 (0.64)	0.64 (0.25)	0.23 (0.02)
(12,16]	3.69 (0.63)	0.70 (0.26)	0.18 (0.02)
(16,20]	1.23 (0.59)	0.54 (0.31)	0.06 (0.03)
(20,24]	0.99 (0.30)	0.53 (0.25)	0.05 (0.01)

Gobal mean and standard deviation of Absolute Mean Activity, Standard Deviation of Activity (SD Activity) and Relative Activity at each time period across the entire sample (n=57).



(a) Mean Activity across time

(b) SD Activity across time



(c) Relative Activity across time

Figure 3.2: Activity measures across time.

Each dot represents an individual subject's activity at a given time point. The blue line represents the global mean across subjects at each time point. Red lines represent the 25th and 75th percentiles.

Table 3.3: Pairwise T-tests of Activity Measures at each time period

a) Mean Activity

	[0,4]	(4,8]	(8,12]	(12,16]	(16,20]
(4,8]	0.04				
(8,12]	1.00	0.13			
(12,16]	<0.01	<0.01	<0.01		
(16,20]	<0.01	<0.01	<0.01	<0.01	
(20,24]	<0.01	<0.01	<0.01	<0.01	0.11

b) Standard Deviation of Activity

	[0,4]	(4,8]	(8,12]	(12,16]	(16,20]
(4,8]	0.01				
(8,12]	0.99	1.00			
(12,16]	1.00	0.08	1.00		
(16,20]	0.01	1.00	0.80	0.05	
(20,24]	<0.01	1.00	0.26	0.01	1.00

c) Relative Activity

	[0,4]	(4,8]	(8,12]	(12,16]	(16,20]
(4,8]	<0.01				
(8,12]	1.00	<0.01			
(12,16]	<0.01	<0.01	<0.01		
(16,20]	<0.01	<0.01	<0.01	<0.01	
(20,24]	<0.01	<0.01	<0.01	<0.01	0.06

Bonferonni adjusted p-values for pairwise t-tests of Mean Activity, Standard Deviation of Activity, and Relative Activity.

3.2 ASSOCIATIONS BETWEEN DEPRESSION AND ACTIVITY

Spearman correlations were calculated for each activity measure at each time point against depression symptom severity. Mean activity 20 to 24 hours after waking was significantly positively correlated with non-sleep HRSD score ($\rho = 0.37$, P-value <0.01). Similarly, relative activity was positively correlated with non-sleep HRSD scores (ρ = 0.35, P-value = 0.01) 20 to 24 hours after waking. Relative activity was also negatively correlated with non-sleep HRSD scores (ρ = -0.42, P-value <0.01) 12 to 16 hours after waking (see Table 3.4).

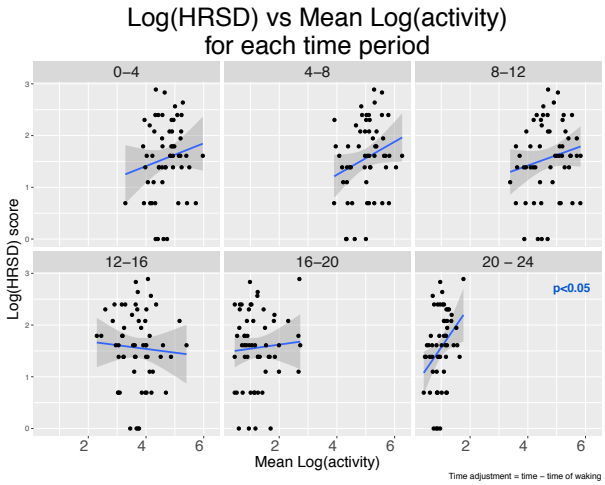
Table 3.4: Spearman Correlations.

Time Period	ρ Mean vs. HRSD	P-value	ρ SD vs. HRSD	P-value	ρ Relative vs. HRSD	P-value
[0,4]	0.17	0.20	0.02	0.86	0.01	0.91
(4,8]	0.24	0.07	-0.09	0.52	0.13	0.35
(8,12]	0.19	0.16	-0.15	0.26	0.09	0.49
(12,16]	-0.09	0.50	0.05	0.72	-0.42	**<0.01**
(16,20]	-0.03	0.83	0.02	0.89	-0.09	0.49
(20,24]	0.37	**<0.01**	0.10	0.46	0.35	**0.01**

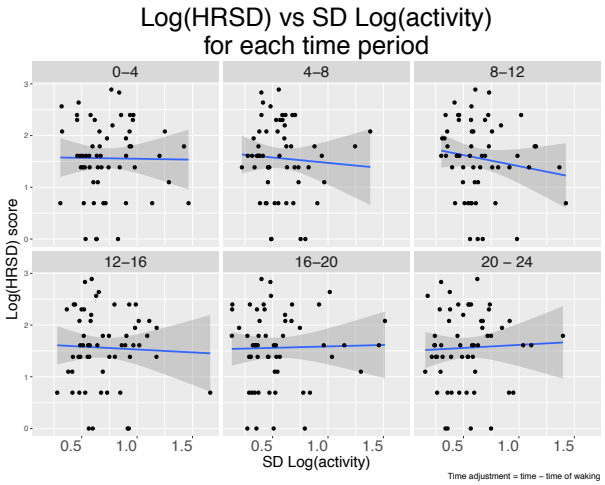
Correlation estimates and corresponding P-values for each activity measure at each time point against non-sleep log(HRSD+1) score.

Scatter plots of activity measures at each can be found below in Figure 3.3. Scatter plots also include a simple linear model fit, indicating the potential direction and strength of the univariate association of each measure against depression score. Scatter plots of mean activity indicated a potential positive association between activity and HRSD scores at almost

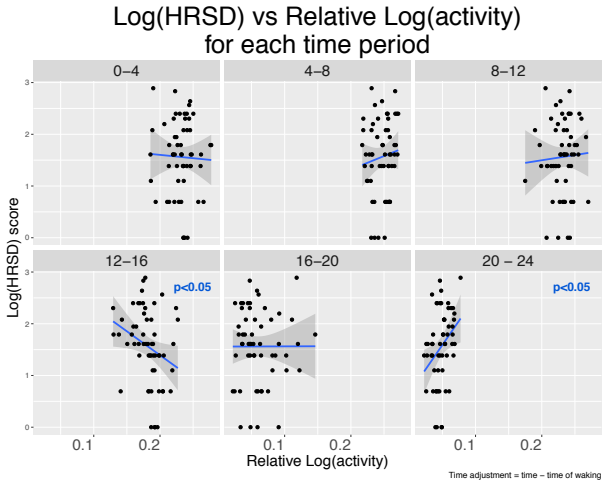
all time points, with a significant linear association in 20 to 24 hours after waking, Figure 3.3a. There was little to no association between standard deviation of activity and HRSD scores, Figure 3.3b. Scatter plots of relative activity showed a significant positive association between relative activity and HRSD at 20 to 24 hours after waking and a significant negative association at 12 to 16 hours after waking, Figure 3.3c.



(a) Scatter plot: Mean Activity against HRSD



(b) Scatter plot: SD Activity against HRSD



(c) Scatter plot: Relative Activity against HRSD

Figure 3.3: Scatter plot of each Activity Measure at each time point against HRSD.
A simple linear regression (in blue) is also fitted with grey indicating the error in the estimate.
Significant univariate associations are indicated by $p<0.05$ in blue.

Summaries for multiple linear regression models including age, sex, and each activity measure at each time point can be found in Tables 3.5 - 3.7. Multiple linear regression models indicate that, after controlling for age and sex, mean activity 20 to 24 hours after waking positively associated with HRSD score (β = 0.96, β P-value<0.01, Model P-value = 0.007, Adj. R^2 = 0.16). No other time points for mean activity showed a significant relationship with HRSD score. Models including standard deviation of activity showed no significant association between standard deviation of activity at any time point against HRSD scores. Relative activity at 20 to 24 hours after waking significantly positively associated with HRSD scores (β = 21.81, β P-value <0.01, Model P-value = 0.01, Adj. R^2 = 0.15). After controlling for age and sex, relative activity at 12 to 16 hours after waking was not significantly associated with HSRD score (β = -7.40, β P-value = 0.11, Model P-value = 0.13, Adj. $R^2 = 0.05$). At 20 to 24 hours after waking, the model using mean activity showed slightly higher adjusted R^2 compared the model using relative activity.

Model diagnostics were performed for all fitted models listed in Tables 3.5 - 3.7 and can be seen in Figures 3.4 - 3.6. Overall, there were no significant patterns in the residuals or any strong indication of violation of regression assumptions. In mean and relative activity models at 20 to 24 hours after waking, there was slight fanning pattern in the Scale-Location plots, indicating a potential violation in homoscedasticity of variances, see Figures 3.4 and 3.6. Heteroscedasticity may indicate a nonlinear association between mean activity and relative activity against HRSD, respectively, and thus quadratic terms were also fit.

Results of quadratic mean models can be found in Tables A1 - A3 and Figures A1 - A3. Across all models, the addition of quadratic terms did not show significant changes in model fit and no quadratic terms were significant. Thus, analyses failed to reject the null that the effect of the quadratic terms were zero and quadratic terms were not retained.

Finally, the effect of waking time was also assessed as a possible confounding variable using multiple linear regression. Recall that up-mesor was derived from the five parameter cosine model fit by Smagula et al. (2017) [10] (see Methods section). Controlling for age and sex, up-mesor did not significantly associate with HRSD score nor improve model fit. Summaries of all models with up-mesor included can be found in Tables A4 - A6. Thus, up-mesor was not included as a covariate in models.

Table 3.5: Multiple Regression Models: Mean Activity at each time point

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	mean activity	0.14	0.49	0.304	0.013
		age	-0.01	0.52	–	–
		sex	0.25	0.34	–	–
2	(4,8]	mean activity	0.27	0.13	0.142	0.046
		age	-0.01	0.56	–	–
		sex	0.23	0.36	–	–
3	(8,12]	mean activity	0.17	0.29	0.233	0.025
		age	-0.01	0.62	–	–
		sex	0.29	0.27	–	–
4	(12,16]	mean activity	-0.02	0.91	0.368	0.004
		age	-0.01	0.40	–	–
		sex	0.25	0.35	–	–
5	(16,20]	mean activity	0.14	0.40	0.276	0.017
		age	-0.01	0.36	–	–
		sex	0.28	0.28	–	–
6	**(20,24]**	**mean activity**	**0.96**	**<0.01**	**0.007**	**0.157**
		age	-0.00	0.73	–	–
		sex	0.47	0.06	–	–

Summary of multiple linear regression models of mean activity at each time point including age and sex in models.

Table 3.6: Multiple Regression Models: Standard Deviation Activity at each time point.

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	sd activity	-0.01	0.98	0.37	0.004
		age	-0.01	0.41	–	–
		sex	0.26	0.32	–	–
2	(4,8]	sd activity	-0.33	0.46	0.296	0.014
		age	-0.01	0.39	–	–
		sex	0.28	0.28	–	–
3	(8,12]	sd activity	-0.49	0.20	0.186	0.034
		age	-0.01	0.44	–	–
		sex	0.30	0.24	–	–
4	(12,16]	sd activity	-0.34	0.38	0.268	0.018
		age	-0.01	0.35	–	–
		sex	0.31	0.25	–	–
5	(16,20]	sd activity	0.02	0.94	0.37	0.004
		age	-0.01	0.41	–	–
		sex	0.26	0.32	–	–
6	(20,24]	sd activity	0.04	0.91	0.368	0.004
		age	-0.01	0.41	–	–
		sex	0.26	0.32	–	–

Summary of multiple linear regression models of standard deviation activity (sd activity) at each time point including age and sex in models.

Table 3.7: Multiple Regression Models: Relative Activity at each time point

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	relative activity	-4.33	0.40	0.275	0.017
		age	-0.01	0.37	–	–
		sex	0.32	0.24	–	–
2	(4,8]	relative activity	1.92	0.78	0.358	0.005
		age	-0.01	0.40	–	–
		sex	0.23	0.40	–	–
3	(8,12]	relative activity	-0.33	0.95	0.37	0.004
		age	-0.01	0.41	–	–
		sex	0.26	0.32	–	–
4	(12,16]	relative activity	-7.40	0.11	0.128	0.05
		age	-0.01	0.52	–	–
		sex	0.16	0.55	–	–
5	(16,20]	relative activity	1.52	0.67	0.344	0.007
		age	-0.01	0.37	–	–
		sex	0.27	0.31	–	–
6	**(20,24]**	**relative activity**	**21.81**	**<0.01**	**0.01**	**0.146**
		age	-0.01	0.66	–	–
		sex	0.45	0.07	–	–

Summary of multiple linear regression models of relative activity at each time point including age and sex in models.

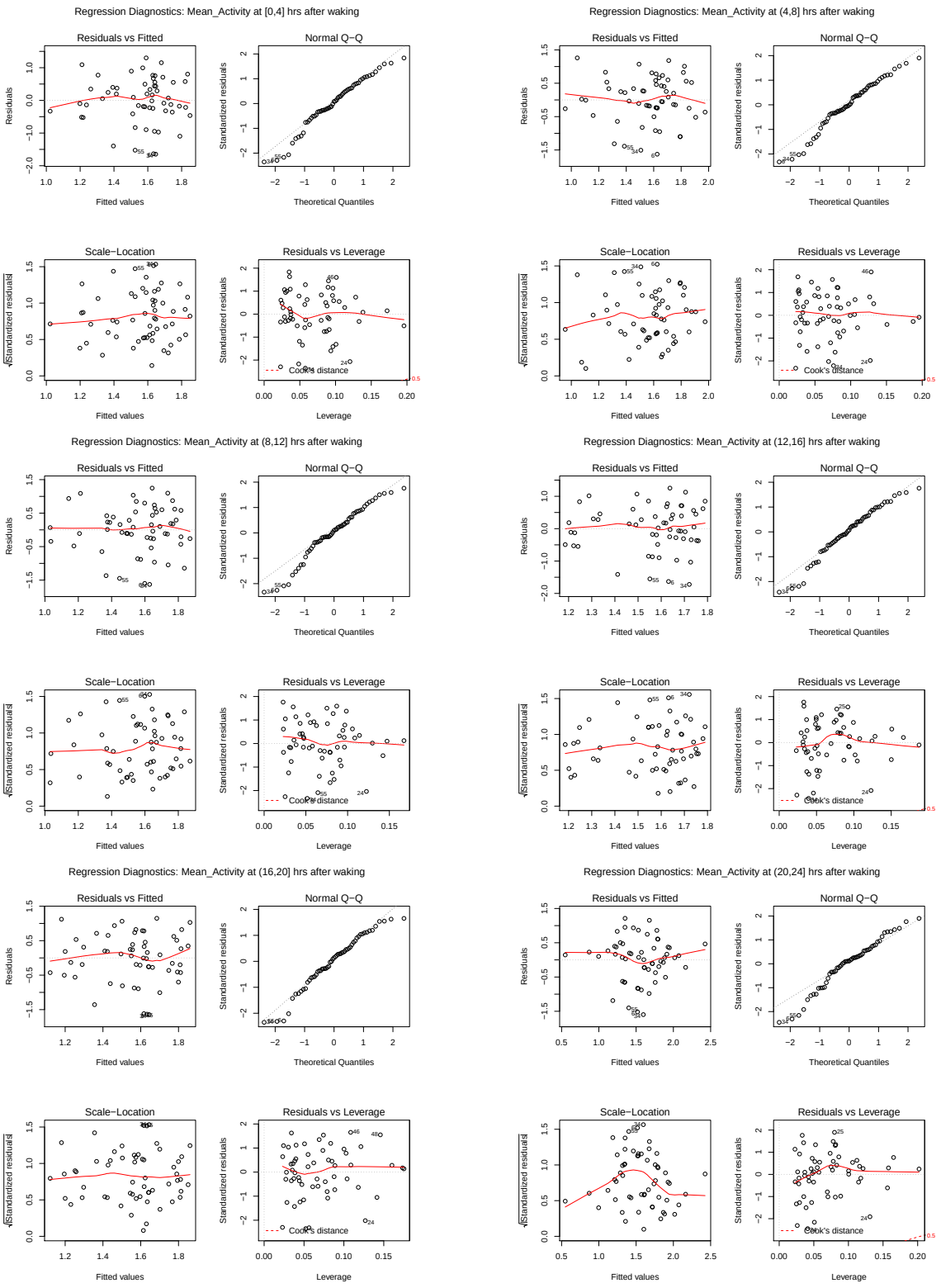


Figure 3.4: Diagnostic plots for Multiple Regression: Mean Activity.

Models: Mean Activity at each time point against HRSD with age and sex as covariates.

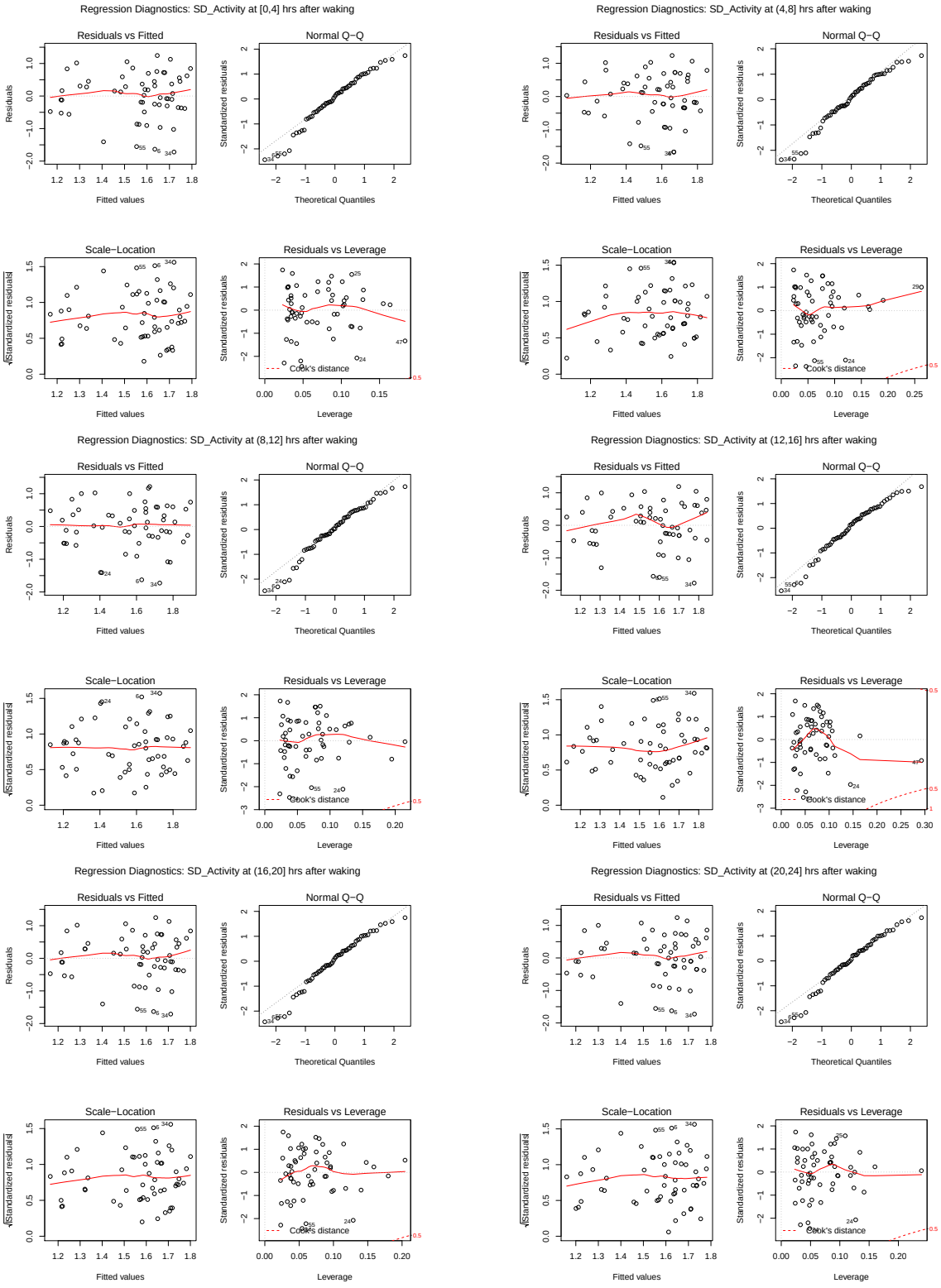


Figure 3.5: Diagnostic plots for Multiple Regression: SD Activity.

Models: SD Activity at each time point against HRSD with age and sex as covariates.

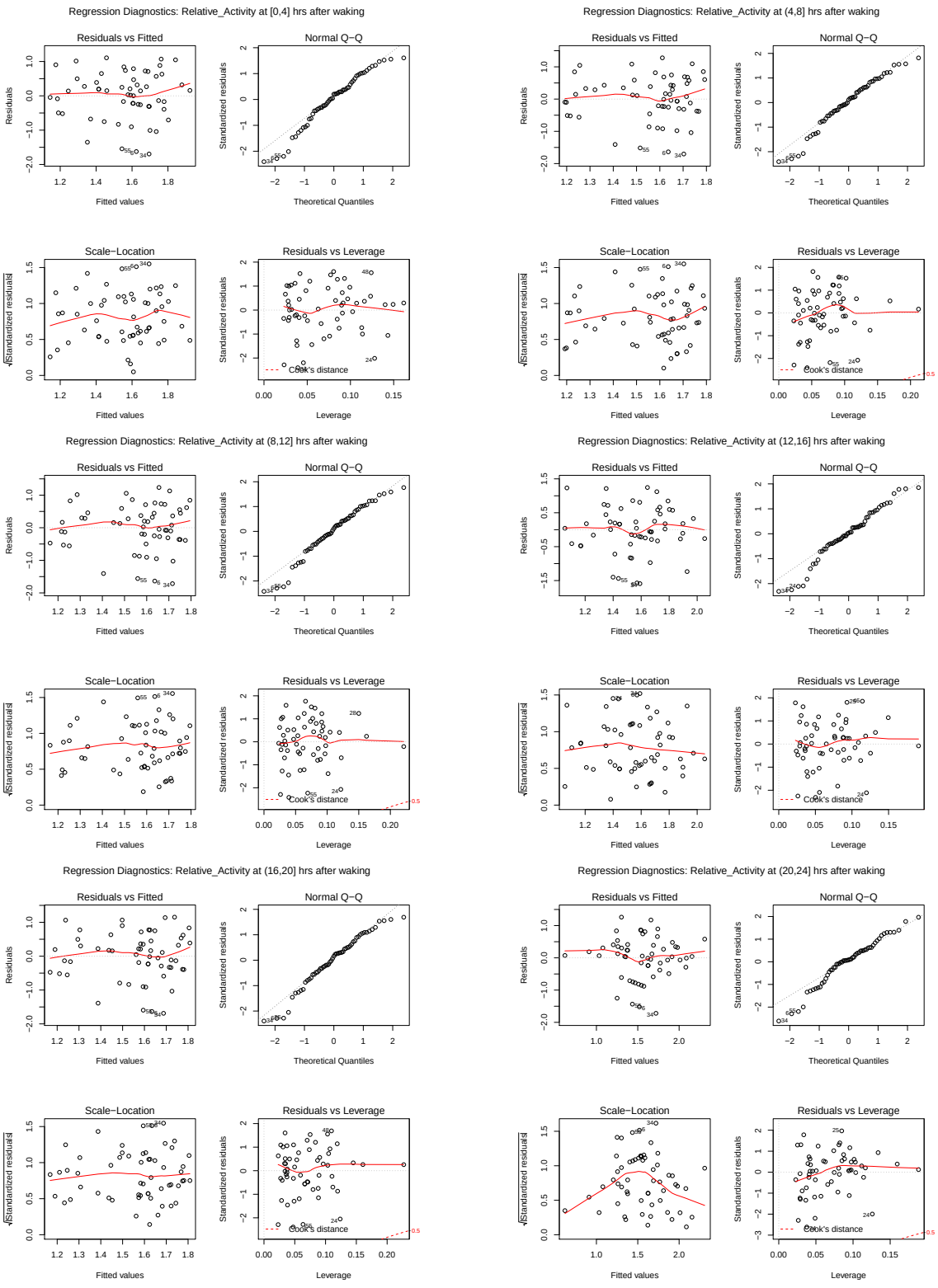


Figure 3.6: Diagnostic plots for Multiple Regression: Relative Activity

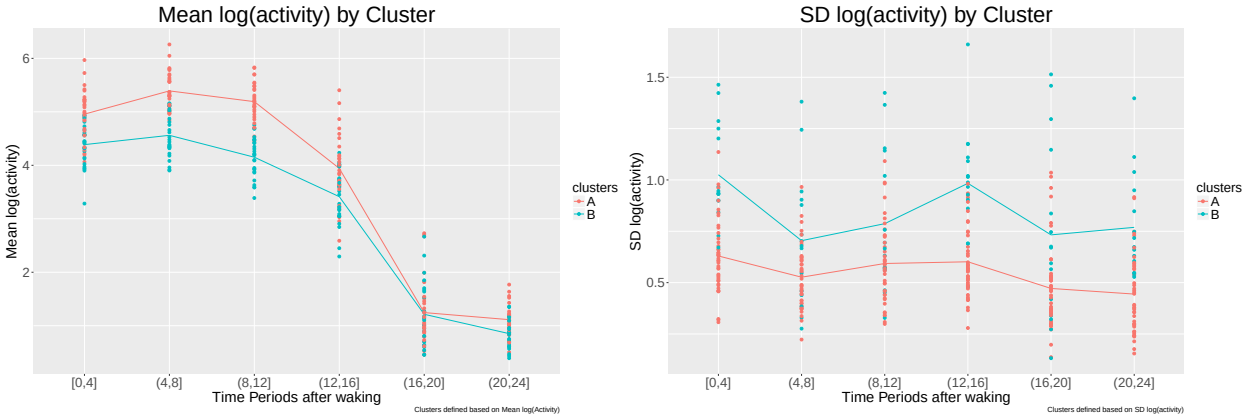
Models: Relative Activity at each time point against HRSD with age and sex as covariates.

3.3 TRAJECTORY ANALYSIS

In mean activity trajectory analysis (Figure 3.7a), cluster A had higher activity at all time points except for 16 to 20 hours after waking. Clusters A and B comprised of 52.6% (n=30) and 47.4% (n=27) of the sample, respectively. Additionally, mean non-sleep HRSD scores in clusters A and B were 1.76 and 1.34, respectively. An Analysis of Covariance (ANCOVA) of cluster assignments against non-sleep HRSD scores showed significant differences in HRSD scores based on clusters (F-value = 5.28, P-value = 0.03, df=1, Table 3.8). These results indicate that subjects with mean activity RARs in cluster A have significantly higher depression scores than subjects with RARs in cluster B.

As in the mean activity trajectory analysis, trajectory analysis based on standard deviation of activity resulted in two clusters, in which cluster B showed higher standard deviation across all time points (Figure 3.7b). Clusters A and B comprised of 73.7% (n=42) and 26.3% (n=15) of the sample, respectively. Mean non-sleep HRSD scores in clusters A and B were 1.52 and 1.69, respectively. ANCOVA results show no significant association between non-sleep HRSD scores and cluster assignment (F-value = 0.42, P-value = 0.52, df=1, Table 3.8).

Trajectory analysis of relative activity identified two clusters, in which cluster A had higher relative activity in early time points and lower activity after 8 to 12 hours after waking (Figure 3.7c). Clusters A and B comprised of 57.9% (n=33) and 42.1% (n=24) of the sample, respectively. Mean non-sleep HRSD scores in clusters A and B were 1.61 and 1.50, respectively. ANCOVA results show no significant association between non-sleep HRSD scores and cluster assignment (F-value = 0.28, P-value = 0.60, df=1, Table 3.8).



(a) Mean Activity by Cluster

(b) SD Activity by Cluster

(c) Relative Activity by Cluster

Figure 3.7: Trajectory Analysis.

RAR patterns for cluster assignments based on Mean Activity, Standard Deviation of Activity, and Relative Activity.

Table 3.8: Analysis of Covariance: Activity Trajectory Clusters

ANCOVA of Mean Activity Clusters

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
clusters	1	2.56	2.56	5.28	**0.0255**
age	1	0.70	0.70	1.44	0.2357
sex	1	0.54	0.54	1.11	0.2976
Residuals	53	25.67	0.48		

ANCOVA of SD Activity Clusters

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
clusters	1	0.22	0.22	0.42	0.5199
age	1	1.12	1.12	2.14	0.1491
sex	1	0.46	0.46	0.88	0.3538
Residuals	53	27.66	0.52		

ANCOVA of Relative Activity Clusters

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
clusters	1	0.15	0.15	0.28	0.5973
age	1	1.00	1.00	1.91	0.1727
sex	1	0.54	0.54	1.03	0.3142
Residuals	53	27.77	0.52		

ANCOVA of clusters assignments based on each activity measure against HRSD scores, including age and sex as covariates.

4.0 CONCLUSIONS

The overall goals of this study were two-fold. First, to expand upon the methodological framework presented in Shou et al. (2017)[6] by proposing three statistical measures intended to characterize the timing of activity patterns. Second, to expand upon previous research by Smagula et al. (2017) [10] by exploring how timing of changes in RAR influence subclinical depression symptom severity in dementia caregivers.

Global means of activity measures and plots of RAR for all subjects (Table 3.2, Figure 3.2) show a characteristic RAR pattern, in which there is a period of activity and a period of little to no activity, with minimal activity occurring 20 to 24 hours after waking. Results from Spearman correlations suggested that increases in mean and relative activity 20 to 24 hours after waking both significantly positively correlated with non-sleep HRSD scores (ρ = 0.37, P-value <0.01 and ρ = 0.35, P-value = 0.01, respectively). These univariate associations also held true in simple linear models (Table 3.3). These associations were also seen in multiple regression models (Tables 3.5 - 3.7), where mean activity and relative activity both positively associated with non-sleep HRSD scores, controlling for age and sex. These findings all suggest that increased activity very late in a patient's activity cycle, particularly after they have gone to sleep, is associated with increased depression severity.

These results corroborate findings in this same population by Smagula et al. 2017 [10]. Smagula et al. 2017 [10] found that time awake after sleep onset (WASO) was positively associated with non-sleep HRSD scores. Results of the current study not only support but also specify when during sleep an increase in activity is associated with depression. Up-mesor adjusted 'Person-Time', along with our proposed measures of timing, provided a clearer understanding of where in the subject's RAR this increase in activity during sleep is the most influential. In this case, we see that increased mean as well as relative activity

just before waking (i.e., 20 to 24 hours after waking) is associated with higher depression symptom severity in this population.

Spearman correlation analyses also identified significant negative association between relative activity and depression severity at 12 to 16 hours after waking (ρ = -0.42, P-value <0.01, Table 3.4), suggesting a potential protective effect of increased relative activity at this point in a patient's RAR. These results were not replicated in multiple regression models that controlled for age and sex, however (Table 3.7). Diagnostic plots of multivariate models (Figure 3.6) at this time point did not indicate violations of regression assumptions and assessing the quadratic terms did not indicate a non-linear relationship between relative activity at this time point and depression scores. Thus, it is likely that the association between relative activity 12 to 16 hours after waking is explain primarily by differences in age and sex.

Results of this analysis did not explicitly support nor contradict the results found in Shou et al. (2017)[6]. Shou et al. (2017)[6] did not find any association between Major Depressive Disorder (MDD) and activity at any time point. However, as mentioned in the introduction, Shou et al. (2017)[6] used unadjusted clock-time when creating time-bins, which did not account for subject-to-subject variability in RAR timing. This was an important distinction in the methodological approaches between the present study and Shou et al. (2017)[6], and may explain the emergence of an effect between depression scores and activity in the present findings. To confirm this, Spearman correlations were re-examined using objective clock-time (Appendix B Table B1). Upon re-analysis, no association between HRSD and activity was found. This suggested that, where possible, correcting for waking time may increase the ability to detect an effect in patients with depression. This is especially important when analyzing subclinical outcomes, as effect sizes in such samples may be small.

Overall, this study found that standard deviation of mean activity across days was not significantly associated with depression scores in this population. Shou et al. (2017)[6], using a similar measure of standard deviation across days, found that the presence of BPD I and BPDII, but not MDD, significantly associated with standard deviation across days at certain time points. Thus, results of the present study do not contradict the lack of association between standard deviation and MDD found in Shou et al. (2017)[6]. However,

the lack of significance in the present study may also be explained by two factors. First, the present study has a relatively small sample size compared to the Shou et al. (2017)[6], which has a sample size of 339. Second, it is likely that there was not as much variability across days in the present sample as in the Shou et al. (2017)[6] study. For example, the ages of participants in the Shou et al. (2017)[6] study ranged from 10 to 84, which may have contributed to the variability in standard deviation of activity across days. The range of ages in the present study is 62 to 89.

Trajectory analyses identified two latent RAR types (i.e. clusters) based on each of the three measures of activity. This suggests that in this population, there are two main types of activity patterns. In mean activity, we saw that cluster A had overall higher activity across almost all time points, except for 16 to 20 hours after waking. ANCOVA results suggested that these RAR types were significantly associated with depression score, with cluster A having a significantly higher depression score than cluster B. While we saw increased activity across all time points, considering the previous regression analyses of mean activity, it is likely that these significant associations can be attributed to increased activity 20 to 24 hours after waking.

Clusters defined based on standard deviation of activity showed that cluster B had overall higher standard deviation of activity than cluster A. These differences did not significantly associate with depression scores, however. Clusters defined based on relative activity showed that cluster A has a sharper decline in relative activity after 8 to 12 hours after waking and then a steep increase in relative activity at 20 to 24 hours after waking (Figure 3.7c). And while ANCOVA analyses based on trajectory analyses in these measures did not identify any significant relationships between cluster and subclinical depression severity, trajectory analyses indicate there may be latent differences in relative activity RARs. Non-significance of ANCOVA findings may be due to the unsupervised nature of k-means or limited power from a relatively small sample size.

In addition to the use of 'Person-Time', the present study also proposed the use of a relative measure of activity. There are two main advantages to using a relative activity measure. First, relative activity measures may help to reduce variance of measures of activity (Table 3.2). Second, relative activity measures also standardize activity across subjects.

Figure 4.1 illustrates how relative activity measures standardize activity in this way and how absolute mean activity alone may not explain differences in RARs across subjects. Relative activity measures enabled us to look more directly at the temporal shape and weight of activity across a subject's RAR. However, one disadvantage to relative measures of activity is that they lack a simple interpretation or parallel to clinical application.

In the broader context of intervention, the results of the present study suggest that targeting sleep-based interventions 20 to 24 hours after waking may reduce the risk of depression. Previous work has shown that increasing physical activity can reduce depression [12] and correlates with improved sleep quality [13]. Thus, targeting activity interventions during active periods may reduce subclinical symptoms of depression by simultaneously increasing activity during the day and reducing activity at night. Future research should identify time periods that are highly correlated with increased activity late in the RAR, so as to better target activity-based interventions. Additionally, future studies should specifically address the efficacy of intervention based approaches that address the relative timing of activity in this population.

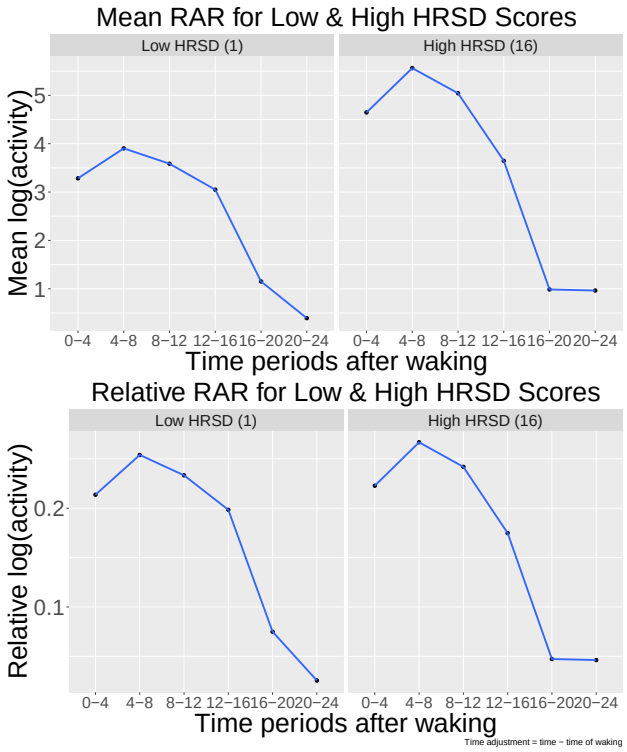


Figure 4.1: Example of Mean vs. Relative Activity.

Mean and Relative Activity RARs are highlighted for two subjects, one with a low HRSD score and one with a high HRSD score.

4.1 LIMITATIONS & FUTURE WORK

Limitations of the study include a fairly small sample size of 57, most of which were female. The present analysis also does not account for the impacts of body mass index (BMI) or race on activity patterns. Additionally, clustering techniques in the present analyses are unsupervised in nature and may not necessarily reflect differences in depression severity. Finally, the present study is cross-sectional in nature and thus does not fully characterize the causal relationship between relationship between activity and and depression severity in this population. Future studies should seek to assess the relationship of activity patterns against longitudinally collected data on depression outcomes.

APPENDIX A

SUPPLEMENTAL ANALYSES: ADDITIONAL MODELS

Supplemental analyses include multivariate regression models testing quadratic terms for each activity measures and up-mesor as a covariate. Overall, quadratic models did not significantly improve model fit and quadratic terms were not significant in any model A1 - A3. Diagnostic plots of quadratic models also revealed larger patterns in residual plots, indicating worse fit. Thus, quadratic terms were not included in final analyses.

Multivariate regression models testing up-mesor as a covariate also showed no significant improvement in model fit and up-mesor terms were not significant A4-A6. Thus, up-mesor was not included as a covariate in analyses.

Table A1: Quadratic Regression Models: Mean Activity (mean act.) and $MeanActivity^2$ at each time point.

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	mean activity	2.98	0.23	0.294	0.019
		I(mean activity^2)	-0.30	0.25	–	–
		age	-0.01	0.60	–	–
		sex	0.24	0.35	–	–
2	(4,8]	mean activity	1.66	0.54	0.225	0.032
		I(mean activity^2)	-0.14	0.60	–	–
		age	-0.01	0.61	–	–
		sex	0.22	0.40	–	–
3	(8,12]	mean activity	2.55	0.25	0.248	0.028
		I(mean activity^2)	-0.25	0.29	–	–
		age	-0.00	0.78	–	–
		sex	0.28	0.28	–	–
4	(12,16]	mean activity	-0.72	0.58	0.489	-0.01
		I(mean activity^2)	0.09	0.59	–	–
		age	-0.01	0.43	–	–
		sex	0.24	0.38	–	–
5	(16,20]	mean activity	-0.32	0.67	0.374	0.006
		I(mean activity^2)	0.15	0.53	–	–
		age	-0.01	0.34	–	–
		sex	0.26	0.32	–	–
6	(20,24]	mean activity	-0.14	0.93	**0.014**	0.149
		I(mean activity^2)	0.54	0.48	–	–
		age	-0.01	0.65	–	–
		sex	0.48	0.06	–	–

Table A2: Quadratic Regression Models: Standard Deviation of Activity and $StandardDeviationofActivity^2$ at each time point.

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	sd activity	0.69	0.73	0.518	-0.013
		I(sd activity^2)	-0.41	0.72	–	–
		age	-0.01	0.49	–	–
		sex	0.29	0.30	–	–
2	(4,8]	sd activity	-2.17	0.24	0.315	0.015
		I(sd activity^2)	1.27	0.31	–	–
		age	-0.01	0.45	–	–
		sex	0.32	0.22	–	–
3	(8,12]	sd activity	-0.58	0.75	0.312	0.016
		I(sd activity^2)	0.06	0.96	–	–
		age	-0.01	0.45	–	–
		sex	0.30	0.25	–	–
4	(12,16]	sd activity	0.76	0.65	0.356	0.009
		I(sd activity^2)	-0.65	0.49	–	–
		age	-0.01	0.43	–	–
		sex	0.31	0.25	–	–
5	(16,20]	sd activity	-0.38	0.76	0.52	-0.013
		I(sd activity^2)	0.27	0.74	–	–
		age	-0.01	0.45	–	–
		sex	0.26	0.33	–	–
6	(20,24]	sd activity	0.16	0.91	0.536	-0.015
		I(sd activity^2)	-0.08	0.94	–	–
		age	-0.01	0.42	–	–
		sex	0.26	0.33	–	–

Table A3: Quadratic Regression Models: Relative Activity (and $RelativeActivity^2$ at each time point.

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	relative activity	-9.65	0.90	0.428	-0.002
		I(relative activity^2)	11.65	0.94	–	–
		age	-0.01	0.38	–	–
		sex	0.32	0.25	–	–
2	(4,8]	relative activity	-432.63	0.05	0.124	0.061
		I(relative activity^2)	888.32	0.05	–	–
		age	-0.02	0.29	–	–
		sex	0.19	0.48	–	–
3	(8,12]	relative activity	-21.02	0.81	0.529	-0.014
		I(relative activity^2)	45.66	0.81	–	–
		age	-0.01	0.41	–	–
		sex	0.26	0.32	–	–
4	(12,16]	relative activity	-29.54	0.56	0.212	0.035
		I(relative activity^2)	62.34	0.66	–	–
		age	-0.01	0.52	–	–
		sex	0.17	0.53	–	–
5	(16,20]	relative activity	-6.08	0.71	0.472	-0.007
		I(relative activity^2)	50.79	0.63	–	–
		age	-0.01	0.35	–	–
		sex	0.25	0.36	–	–
6	(20,24]	relative activity	-45.94	0.33	**0.009**	0.164
		I(relative activity^2)	698.51	0.15	–	–
		age	-0.01	0.61	–	–
		sex	0.46	0.07	–	–

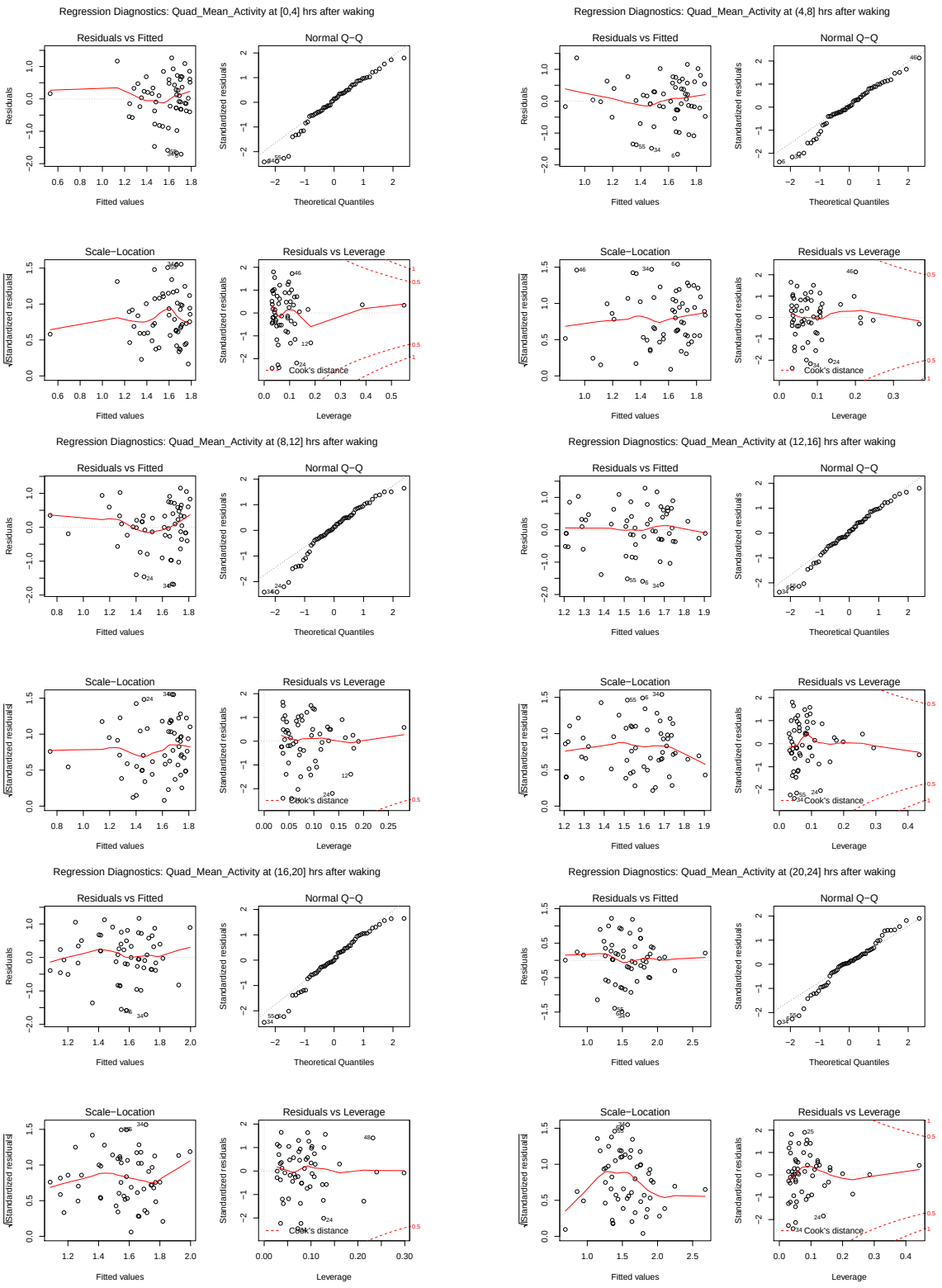


Figure A1: Diagnostic plots for Multiple Regression with Quadratic Terms: Mean Activity. All models include age and sex as covariates.

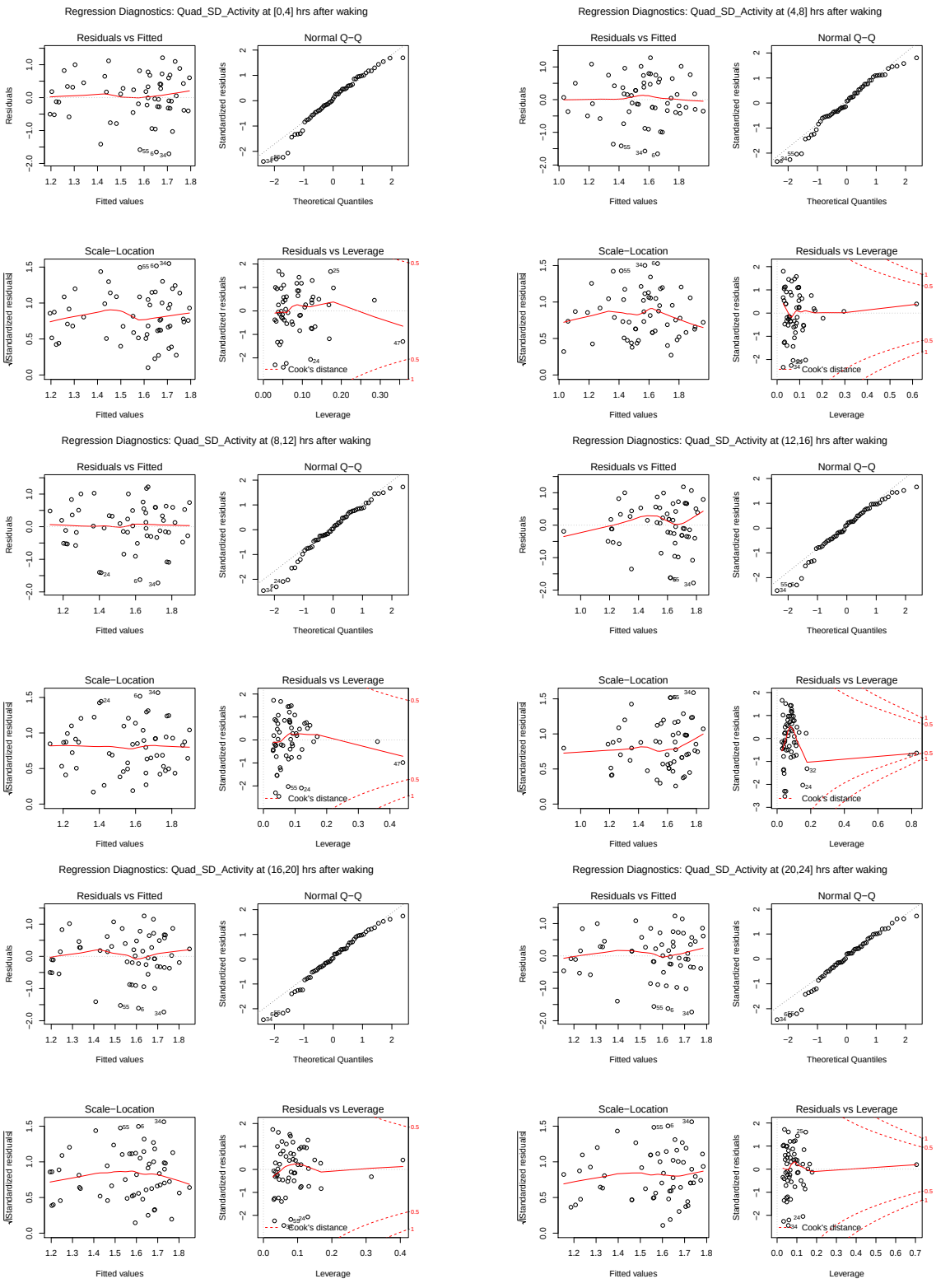


Figure A2: Diagnostic plots for Multiple Regression with Quadratic Terms: Standard Deviation of Activity.

All models include age and sex as covariates.

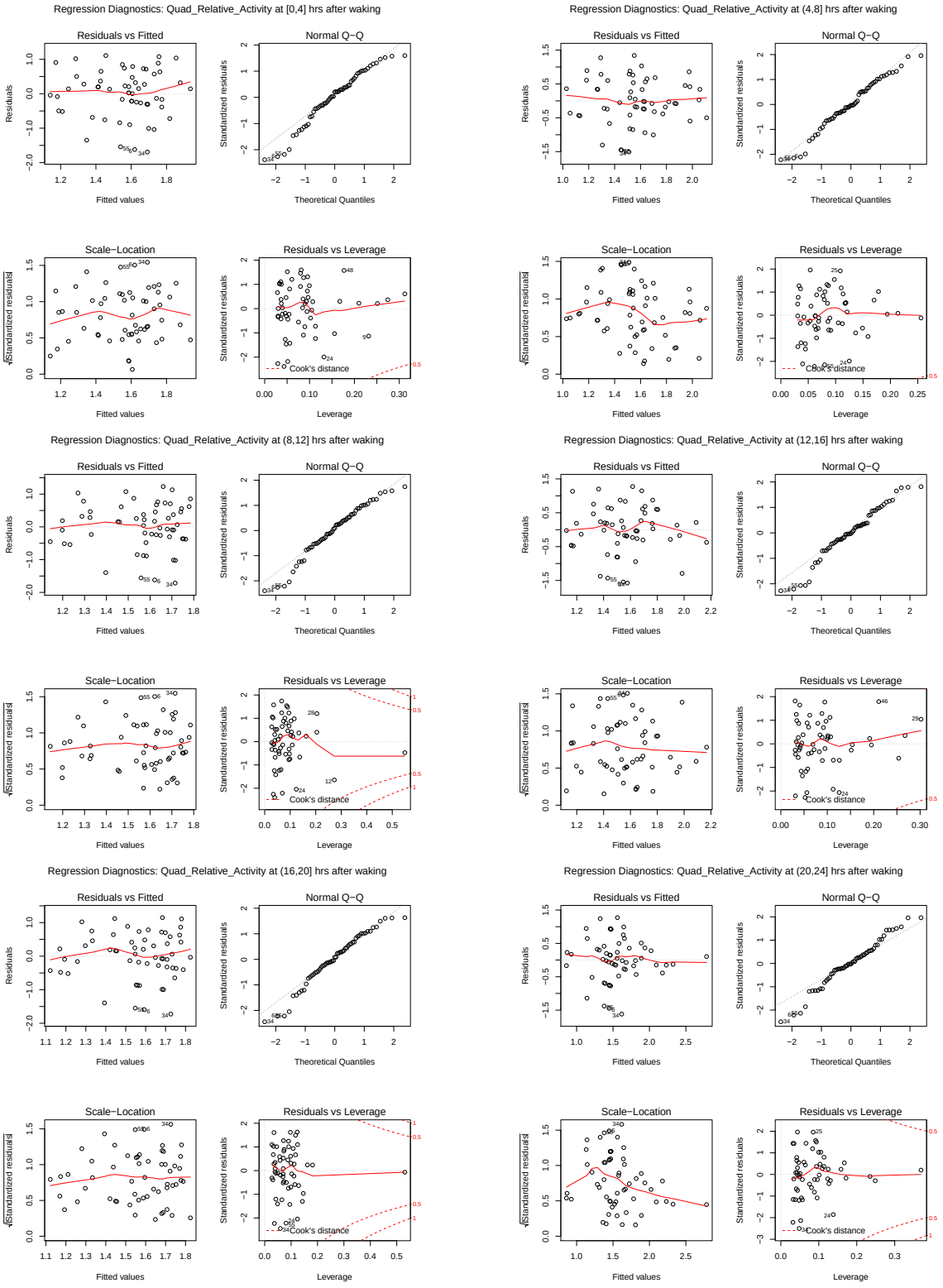


Figure A3: Diagnostic plots for Multiple Regression with Quadratic Terms: Relative Activity.

All models include age and sex as covariates.

Table A4: Multiple Regression Models: Mean Activity and Up-Mesor at each time point.

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	mean activity	0.15	0.46	0.452	-0.005
		up-mesor	-0.03	0.79	–	–
		age	-0.01	0.53	–	–
		sex	0.26	0.33	–	–
2	(4,8]	mean activity	0.27	0.13	0.242	0.029
		up-mesor	-0.03	0.77	–	–
		age	-0.01	0.56	–	–
		sex	0.25	0.35	–	–
3	(8,12]	mean activity	0.18	0.28	0.362	0.008
		up-mesor	-0.03	0.75	–	–
		age	-0.01	0.64	–	–
		sex	0.30	0.26	–	–
4	(12,16]	mean activity	-0.02	0.89	0.535	-0.015
		up-mesor	-0.01	0.92	–	–
		age	-0.01	0.41	–	–
		sex	0.26	0.35	–	–
5	(16,20]	mean activity	0.16	0.38	0.418	0
		up-mesor	0.03	0.77	–	–
		age	-0.01	0.36	–	–
		sex	0.27	0.31	–	–
6	(20,24]	mean activity	0.97	0.00	0.016	0.144
		up-mesor	-0.04	0.67	–	–
		age	-0.00	0.74	–	–
		sex	0.50	0.06	–	–

Table A5: Multiple Regression Models: Standard Deviation of Activity (sd activity) and Up-Mesor at each time point.

1	[0,4]	sd activity	-0.01	0.98	0.539	-0.015
		up-mesor	-0.01	0.95	–	–
		age	-0.01	0.41	–	–
		sex	0.26	0.33	–	–
2	(4,8]	sd activity	-0.33	0.46	0.452	-0.005
		up-mesor	-0.01	0.94	–	–
		age	-0.01	0.39	–	–
		sex	0.28	0.29	–	–
3	(8,12]	sd activity	-0.50	0.20	0.309	0.016
		up-mesor	-0.02	0.86	–	–
		age	-0.01	0.45	–	–
		sex	0.31	0.24	–	–
4	(12,16]	sd activity	-0.36	0.37	0.416	0
		up-mesor	0.02	0.88	–	–
		age	-0.01	0.35	–	–
		sex	0.30	0.26	–	–
5	(16,20]	sd activity	0.02	0.95	0.538	-0.015
		up-mesor	-0.01	0.96	–	–
		age	-0.01	0.42	–	–
		sex	0.26	0.32	–	–
6	(20,24]	sd activity	0.06	0.88	0.535	-0.015
		up-mesor	-0.01	0.91	–	–
		age	-0.01	0.42	–	–
		sex	0.26	0.33	–	–

Table A6: Multiple Regression Models: Relative Activity and Up-Mesor at each time point.

Model	Time	Terms	β Estimates	β P-value	Model P-value	Adj. R^2
1	[0,4]	relative activity	-4.73	0.39	0.421	-0.001
		tLeft	0.02	0.82	–	–
		age	-0.01	0.38	–	–
		sex	0.31	0.25	–	–
2	(4,8]	relative activity	2.16	0.76	0.523	-0.014
		tLeft	-0.01	0.89	–	–
		age	-0.01	0.41	–	–
		sex	0.24	0.40	–	–
3	(8,12]	relative activity	-0.22	0.97	0.538	-0.015
		tLeft	-0.01	0.96	–	–
		age	-0.01	0.42	–	–
		sex	0.26	0.33	–	–
4	(12,16]	relative activity	-8.77	0.09	0.187	0.041
		tLeft	-0.08	0.47	–	–
		age	-0.01	0.55	–	–
		sex	0.17	0.51	–	–
5	(16,20]	relative activity	1.69	0.67	0.508	-0.012
		tLeft	0.01	0.91	–	–
		age	-0.01	0.37	–	–
		sex	0.26	0.32	–	–
6	(20,24]	relative activity	22.57	0.00	0.02	0.135
		tLeft	-0.05	0.56	–	–
		age	-0.01	0.68	–	–
		sex	0.48	0.06	–	–

APPENDIX B

SUPPLEMENTAL ANALYSES: CLOCK TIME

Supplemental analyses below summarize the Spearman Correlation Coefficients found using clock-time as a means of dividing time into 4 hour bins, instead of wake-up-time adjusted "Person-Time". There are no significant associations between activity and HRSD score across all time points.

Table B1: Spearman Correlations: Clock Time.

Time Period	ρ Mean vs. HRSD	P-value	ρ SD vs. HRSD	P-value	ρ Relative vs. HRSD	P-value
[0,4]	0.12	0.39	0.04	0.79	0.08	0.56
(4,8]	0.01	0.93	0.00	0.98	-0.00	0.97
(8,12]	0.21	0.11	0.10	0.48	0.02	0.90
(12,16]	0.21	0.12	0.05	0.72	0.15	0.26
(16,20]	0.22	0.09	-0.19	0.15	0.11	0.40
(20,24]	-0.09	0.51	0.08	0.56	-0.22	0.10

Spearman correlation estimates and corresponding p-values for each activity measure at each time point, based on clock-time, against non-sleep log(HRSD+1) score.

APPENDIX C

R CODE

```
##################################
# PACKAGES & GLOBAL SETTINGS #
##################################
require(knitr) # for knitting mardown
require(tidyr) # package for separating out columns easily and
    reshaping dataframes (eg, rehsape())
require(plyr) # to use ddply for group means
require(ggplot2) # for plots
require(pander) # for making tables
require(dplyr) # for regression by groups
require(dotwhisker) # for covariate plots (eg, dwplot())
require(broom) # for tidying up linear model outputs (eg, tidy(),
    augment(), glance())
require(Hmisc) # for creating correlation matrices
require(lubridate) # For doing clock-time to Person-Time conversion
library(kableExtra) # for tables in functions
library(kml) # for trajectory analysis
library(xtable) # for latex tables

# R Markdown Global Settings
opts_chunk$set(tidy.opts=list(width.cutoff=80),tidy=TRUE)
opts_knit$set(root.dir = "/Users/jessgraves/Dropbox/BIOSTATS/Spring
    2018/Thesis/data/processed NPAR/") # set working directory
panderOptions("table.style", "simple")

# Global code Label Settings
time.labels <- c("[0,4]" = "0-4", "(4,8]" = "4-8", "(8,12]" = "8-12", "
    (12,16]" = "12-16", "(16,20]" = "16-20", "(20,24]" = "20 - 24") #
    creating label for time bins
p.labels = c("0-4", "4-8", "8-12", "12-16", "16-20", "20-24")
```

```
b.breaks = c("[0,4]" , "(4,8]" , "(8,12]" , "(12,16]", "(16,20]" ,"
    (20,24]")

##############################
# LOADING IN ALL DATASETS #
##############################
file_names = as.list(dir(pattern="*.csv")) # getting list file names
myfiles = lapply(file_names, read.delim, sep="," , header=F) # reading
    in file names as list

# Getting IDs from file names
get_file_id <- function(var_file_name) { unlist(strsplit(var_file_name,
     split="_", fixed=TRUE))[1] } # function to extract first character
    set before _ in file name and the [1] indicates that it's before the
     first "_"

    # SAVE IDs
    ids = lapply(file_names, get_file_id) # apply function

### READ IN TLEFT DATA #####
# tleft is equivalent to up-mesor
tleft.full = read.csv("/Users/jessgraves/Dropbox/BIOSTATS/Spring 2018/
    Thesis/data/TIME_HRSD.csv")
tleft = tleft.full[which(tleft.full$id %in% unlist(ids)),] # only
    samples that we have activity data for

### READ IN DEMOGRAPHIC DATA #####
demo.full = read.csv("/Users/jessgraves/Dropbox/BIOSTATS/Spring 2018/
    Thesis/data/TIME_HRSD_AGE_SEX.csv", header=T)
    demo = demo.full[c("id", "ageconsent", "SEX")][which(demo.full$id %
        in% unlist(ids)),] # only samples that we have activity data for
    colnames(demo)[c(2,3)] <- c("age", "sex")

#### READING INDIVIDUAL ACTIVITY DATASETS AS LIST OF DATAFRAMES ####
dfs <- vector(mode="list", length=length(myfiles)) # create a vector of
    lists

for (i in seq_along(myfiles)) {
    dfs[[i]] = as.data.frame(myfiles[i])    # save each as a dataframe
    dfs[[i]]$id = ids[i] # assigning ID to column mame
    dfs[[i]] <- separate(data=dfs[[i]], col=V1, into=c("date", "time"),
        sep=" ") # separating out date and time into 2 columns
    dfs[[i]]$time <- as.POSIXct(dfs[[i]]$time, format="%H:%M:%S")

    names(dfs[[i]])[names(dfs[[i]]) == 'V2'] <- 'raw.act' # renaming V2
        to activity
    dfs[[i]]$act = log(dfs[[i]]$raw.act+1) # Log(activity + 1)
```

```r

    dfs[[i]]$time.hrs <- hour(dfs[[i]]$time) + minute(dfs[[i]]$time)/60
        + second(dfs[[i]]$time)/3600 # needs library(lubridate)
    dfs[[i]]$tleft = tleft$tLeft[which(tleft$id==dfs[[i]]$id[i])] #
       importing tleft data and matching with ids

    dfs[[i]]$time.adj = dfs[[i]]$time.hrs - dfs[[i]]$tleft # creating
       Person-Time
    dfs[[i]]$time.adj[(dfs[[i]]$time.adj < 0) & !is.na(dfs[[i]]$time.
       adj)] = dfs[[i]]$time.adj[(dfs[[i]]$time.adj < 0) & !is.na(dfs[[
       i]]$time.adj)] + 24

    dfs[[i]]$clock.time = cut(dfs[[i]]$time.hrs, seq(0,24,4), include.
       lowest=TRUE) # CREATES 4-HR TIME BINS
    dfs[[i]]$person.time = cut(dfs[[i]]$time.adj, seq(0,24,4), include.
       lowest=TRUE) # adjusted time cut by 4 hours
}

# Example dataset
head(dfs[[1]])
tail(dfs[[1]])


############################
# CHECKING MISSING DATA #
############################

# Function to extract column names with missing data
    nacols <- function(x){
      y <- sapply(x, function(xx)any(is.na(xx)))
      names(y[y])
    }

# Loop to check all dataframes for missing data
# Prints out list of column names if data is missing
   for (i in seq_along(dfs)) {
       print(nacols(dfs[[i]]))
       print(dfs[[i]][1,4])
   }

############################
# READ IN HRSD DATA #
############################
hrsd.full = read.csv("/Users/jessgraves/Dropbox/BIOSTATS/Spring 2018/
   Thesis/data/depression_data.csv", header=T)
hrsd = hrsd.full[which(hrsd.full$id %in% unlist(ids)),] # only samples
   that we have activity data for
```

```
99
100     hrsd$HRSD_log = log(hrsd$HRS17NOSLP_T1+1) # log transform
101     hrsd = hrsd[, !names(hrsd) == "HRS17TOT_T1"] # remove full scale
102
103 # Summary Stats & Distribution of HRSD
104 # calculating median and mean for non-sleep hrsd items
105 mean.hrsd = mean(hrsd$HRS17NOSLP_T1)
106 median.hrsd = median(hrsd$HRS17NOSLP_T1)
107 mean.median=rbind(mean.hrsd, median.hrsd)
108     colnames(mean.median) <- "Value"
109     rownames(mean.median) <- c("Mean", "Median")
110 n.subs.median = length(hrsd$id[hrsd$HRS17NOSLP_T1 == median(hrsd$
    HRS17NOSLP_T1)])
111 n.subs.mean = length(hrsd$id[hrsd$HRS17NOSLP_T1 == mean(hrsd$HRS17NOSLP
    _T1)])
112     n.subs = rbind(n.subs.mean, n.subs.median)
113         colnames(n.subs) <- "No. Subs"
114
115 # table of mean and median
116 pander(cbind(mean.median, n.subs), caption="Table: HRSD Mean, Median,
    number of subjects who lie on mean and median", split.table = Inf)
117
118 # Histogram and qqplot of HRSD with no sleep items
119 qplot(hrsd$HRS17NOSLP_T1, geom="histogram", binwidth=2, main="
    Distribution of HRSD (no sleep) scores", xlab="HRSD Scores") + theme
    (plot.title = element_text(hjust = 0.5))
120 qqnorm(hrsd$HRS17NOSLP_T1);qqline(hrsd$HRS17NOSLP_T1, col=2)
121
122 # Histogram and qqplot Log(HRSD) no sleep items
123 qplot(hrsd$HRSD_log, geom="histogram", binwidth=.5 , main="Distribution
    of log(HRSD) (no sleep) scores", xlab="HRSD Scores") + theme(plot.
    title = element_text(hjust = 0.5))
124 qqnorm(hrsd$HRSD_log);qqline(hrsd$HRSD_log, col=2)
125
126 # Shapiro Wilk Test of Log(HRSD)
127 shapiro.test(hrsd$HRSD_log)
128
129 ###################################
130 # CALCULATING ACTIVITY MEASURES #
131 ###################################
132 # CALCULATING MEANS BY DAY AND TIME PERIOD (Person-Time)
133 day.means.person.time <- vector("list", length(dfs))
134
135 for (i in seq_along(dfs)) {
136     day.means.person.time[[i]] <- ddply(dfs[[i]], c("date", "person.
        time"), plyr::summarise,
137                 N    = sum(!is.na(act)),
```

```
138                     mean.activity = mean(act, na.rm=T),
139                     sd    = sd(act, na.rm=T))
140
141             day.means.person.time[[i]]$id <- ids[i] # assign id in
                    column
142             day.means.person.time[[i]] <- na.omit(day.means.person.time
                    [[i]]) # removes final row of NA observations
143     }
144
145 # CALCULATING THE MEAN AND STANDARD DEVIATION BY TIME PERIOD (across
        all days)
146 period.means.person.time <-vector("list", length(day.means.person.time)
    )
147 for (i in seq_along(day.means.person.time)) {
148     period.means.person.time[[i]] <- ddply(day.means.person.time[[i]],
          "person.time", plyr::summarise,
149                         N = sum(!is.na(mean.activity)),
150                         mean.periods = mean(mean.activity, na.rm=T),
151                         sd.periods = sd(mean.activity, na.rm=T),
152                         quant.25 = quantile(mean.activity, 0.25), #
                              calculating 25th percentile of data
153                         quant.75 = quantile(mean.activity, 0.75)) #
                              calculating 75th percentile of data
154     period.means.person.time[[i]]$id <- ids[i] # assign id in column
155 }
156
157 # Combine Means and Standard Deviation into one dataset
158 alldata.person.time <- do.call(rbind, period.means.person.time)
159     alldata.person.time$person.time <- unlist(alldata.person.time$
          person.time)
160     alldata.person.time$id <- as.factor(unlist(alldata.person.time$id))
161     alldata.person.time$mean.periods<-as.numeric(alldata.person.time$
          mean.periods)
162
163 # CALCULATING THE RELATIVE ACTIVITY MEASURES
164 # find sum of mean activity for each subject
165     sum.mean.activity = ddply(alldata.person.time, .(id), plyr::
          summarise,
166             sum.activity = sum(mean.periods))
167
168     # merge sum of mean activity per subject with alldata.person.time
          dataset
169     alldata.person.time <- merge(alldata.person.time, sum.mean.activity
          , by="id")
170
171     # create relative activity measure
```

```
172         alldata.person.time$relative.activity = alldata.person.time$
              mean.periods/alldata.person.time$sum.activity
173
174 print(alldata.person.time[1:15,])
175
176 ####################################
177 # PLOT RARs: ALL SUBJECTS #
178 ####################################
179     # Calculating 25th and 75th quantiles based on mean activity and
          standard deviation
180       combined = ddply(alldata.person.time, "person.time", plyr::
            summarise,
181               N = sum(!is.na(mean.periods)),
182               quant.25 = quantile(mean.periods, 0.25),    # 25th Quantile
                    around Mean Activity
183               quant.75 = quantile(mean.periods, 0.75),    # 75th Quantile
                    around Mean Activity
184               quant.sd.25 = quantile(sd.periods, 0.25),    # 25th
                  Quantile around SD Activity
185               quant.sd.75 = quantile(sd.periods, 0.75),    # 75th
                  Quantile around SD Activity
186               sd = sd(mean.periods),                       # SD of Mean
                  Activity
187               quant.rel.25 = quantile(relative.activity, 0.25),    # 25th
                    Quantile around Relative Activity
188               quant.rel.75 = quantile(relative.activity,0.75))    # 75th
                  Quantile around Relative Activity
189
190     # PLOT OF MEAN ACTIVITY
191     ggplot(alldata.person.time, aes(x=person.time, y=mean.periods)) +
          geom_point() + stat_summary(fun.y=mean, geom="line", aes(group
          =1), color="blue") + geom_line(data=combined, aes(x=person.time,
           y=quant.25, group=1, colour="blue", alpha=0.5), show.legend=F)
          + geom_line(data=combined, aes(x=person.time, y=quant.75, group
          =1, colour="blue", alpha=0.5), show.legend=F) + scale_y_
          continuous("Mean Log(activity)") + ggtitle("Mean Log(activity),
          25th & 75th percentiles, all subjects") + theme(plot.title =
          element_text(hjust = 0.5), axis.text.x = element_text(angle =
          60, hjust = 1)) + scale_x_discrete("Time periods after waking",
          labels = p.labels) + labs(caption="Time adjustment = time - time
           of waking")
192
193     # PLOT OF SD ACTIVITY
194     ggplot(alldata.person.time, aes(x=person.time, y=sd.periods)) +
          geom_point() + stat_summary(fun.y=mean, geom="line", aes(group
          =1), color="blue") + geom_line(data=combined, aes(x=person.time,
           y=quant.sd.25, group=1, colour="blue", alpha=0.5), show.legend=
```

```
        F) + geom_line(data=combined, aes(x=person.time, y=quant.sd.75,
        group=1, colour="blue", alpha=0.5), show.legend=F) + scale_y_
        continuous("Standard Deviation of Log(activity)") + ggtitle("
        Standard Deviation of Log(activity), 25th & 75th percentiles,
        all subjects") + theme(plot.title = element_text(hjust = 0.5),
        axis.text.x = element_text(angle = 60, hjust = 1)) + scale_x_
        discrete("Time periods after waking", labels = p.labels) + labs
        (caption="Time adjustment = time - time of waking")

    # PLOT OF RELATIVE ACTIVITY
    ggplot(alldata.person.time, aes(x=person.time, y=relative.activity)
        ) + geom_point() + stat_summary(fun.y = mean, geom="line", aes(
        group=1), color="blue") + geom_line(data=combined, aes(x=person.
        time, y=quant.rel.25, group=1, colour="blue", alpha=0.5), show.
        legend=F) + geom_line(data=combined, aes(x=person.time, y=quant.
        rel.75, group=1, colour="blue", alpha=0.5), show.legend=F) +
        scale_y_continuous("Relative Log(activity)") + ggtitle("Relative
         Log(activity), 25th & 75th percentiles, all subjects") + theme(
        plot.title = element_text(hjust = 0.5), axis.text.x = element_
        text(angle = 60, hjust = 1)) + scale_x_discrete("Time periods
        after waking", labels = p.labels) + labs(caption="Time
        adjustment = time - time of waking")

###################################
# GLOBAL MEANS (SDs) OF RAR MEASURES
###################################
global.means.person.time = ddply(alldata.person.time, .(person.time),
    plyr::summarise,
                                 mean.mean.act = mean(mean.periods),
                                 sd.mean.act = sd(mean.periods),
                                 mean.sd.act = mean(sd.periods),
                                 sd.sd.act = sd(sd.periods),
                                 mean.rel.act = mean(relative.activity)
                                     ,
                                 sd.rel.act = sd(relative.activity))

global.means.person.time

###################################
# MERGE ACTIVITY, HRSD, DEMOGRAPHIC #
###################################
# Merge depression data, activity data, and demographic data
alldata.person.time.hrsd <- merge(alldata.person.time, hrsd, by="id")
alldata.person.time.hrsd <- merge(alldata.person.time.hrsd, tleft, by="
    id") # adding in tleft data
alldata.person.time.hrsd <- merge(alldata.person.time.hrsd, demo, by="
    id") # adding in demographic data
```

```
alldata.person.time.hrsd$id <- as.factor(alldata.person.time.hrsd$id)
head(alldata.person.time.hrsd)

#####################################
# SCATTER PLOTS #
#####################################
#Scatter plots of Log(HRSD) vs Mean, SD and Relative Log(Activity) at each time point:
ggplot(alldata.person.time.hrsd, aes(x=mean.periods, y=HRSD_log)) + geom_point()  + geom_smooth(method="lm", se=TRUE, fullrange=FALSE, level=0.95) + facet_wrap(~person.time, labeller=labeller(person.time = time.labels)) + ggtitle("Log(HRSD) (No Sleep) vs Mean Log(activity) in each time period") + theme(plot.title = element_text(hjust = 0.5), axis.text.x = element_text(angle = 60, hjust = 1)) + scale_x_continuous("Mean Log(activity) for each time period after waking") + scale_y_continuous("Log(HRSD) score (no sleep)") + labs(caption="Time adjustment = time - time of waking")

ggplot(alldata.person.time.hrsd, aes(x=sd.periods, y=HRSD_log)) + geom_point() + geom_smooth(method="lm", se=TRUE, fullrange=FALSE, level=0.95) + facet_wrap(~person.time, labeller=labeller(person.time = time.labels)) + ggtitle("Log(HRSD) (No Sleep) vs SD Log(activity) in each time period") + theme(plot.title = element_text(hjust = 0.5), axis.text.x = element_text(angle = 60, hjust = 1)) + scale_x_continuous("Standard Deviation of Log(activity) for each time period after waking") + scale_y_continuous("Log(HRSD) score (no sleep)") + labs(caption="Time adjustment = time - time of waking")

ggplot(alldata.person.time.hrsd, aes(x=relative.activity, y=HRSD_log)) + geom_smooth(method="lm", se=TRUE, fullrange=FALSE, level=0.95) + geom_point() + facet_wrap(~person.time, labeller=labeller(person.time = time.labels)) + ggtitle("Log(HRSD) (No Sleep) vs Relative Log(activity) in each time period") + theme(plot.title = element_text(hjust = 0.5), axis.text.x = element_text(angle = 60, hjust = 1)) + scale_x_continuous("Relative Log(activity) for each time period after waking") + scale_y_continuous("Log(HRSD) score (no sleep)") + labs(caption="Time adjustment = time - time of waking")

# PAIRWISE T-tests of Activity Patterns
# Mean Activity
pander(pairwise.t.test(alldata.person.time$mean.periods, alldata.person.time$person.time, pool.sd = F, p.adjust.method = "bonf")$p.value)
# Sd Activity
pander(pairwise.t.test(alldata.person.time$sd.periods, alldata.person.time$person.time, pool.sd = F, p.adjust.method = "bonf")$p.value)
# Relative Activity
```

```r
pander(pairwise.t.test(alldata.person.time$relative.activity, alldata.person.time$person.time, pool.sd = F, p.adjust.method = "bonf")$p.value)


#####################################
# SPEARMAN CORRELATIONS #
#####################################
# User defined function to pass ddplyr correlation of two variables
corfun<-function(x, y) {
  corr=(cor.test(x, y,
                 alternative="two.sided", method="spearman", exact=F))
}

# Creating individual datasets for spearman correlations of mean, sd and relative activity
mean.hrsd.corr.person.time = as.data.frame(
    ddply(alldata.person.time.hrsd, .(person.time), plyr::summarise,
       correlation=corfun(mean.periods, HRSD_log)$estimate,
      p.value=corfun(mean.periods, HRSD_log)$p.value,
      statistic=corfun(mean.periods, HRSD_log)$statistic,
      alt=corfun(mean.periods, HRSD_log)$alternative
      ) )
    colnames(mean.hrsd.corr.person.time)[2] <- "Corr. Mean vs. HRSD"


sd.hrsd.corr.person.time = as.data.frame(
    ddply(alldata.person.time.hrsd, .(person.time), plyr::summarise,
       correlation=corfun(sd.periods, HRSD_log)$estimate,
      p.value=corfun(sd.periods, HRSD_log)$p.value,
      statistic=corfun(sd.periods, HRSD_log)$statistic,
      alt=corfun(sd.periods, HRSD_log)$alternative
      ) )
    colnames(sd.hrsd.corr.person.time)[2] <- "Corr. SD vs. HRSD"

relative.hrsd.corr.person.time = as.data.frame(
    ddply(alldata.person.time.hrsd, .(person.time), plyr::summarise,
       correlation=corfun(relative.activity, HRSD_log)$estimate,
      p.value=corfun(relative.activity, HRSD_log)$p.value,
      statistic=corfun(relative.activity, HRSD_log)$statistic,
      alt=corfun(relative.activity, HRSD_log)$alternative
      ) )
    colnames(relative.hrsd.corr.person.time)[2] <- "Corr. Relative vs. HRSD"

# Displaing spearman correlation results as table
```

```r
pander(cbind(mean.hrsd.corr.person.time[1:3], sd.hrsd.corr.person.time[2:3], relative.hrsd.corr.person.time[2:3]), caption="Correlation between log(HRSD) and Mean, SD, and Relative Log(Activity) within Time Periods (Person-Time)", split.table = Inf)

#####################################
# USER DEFINED FUNCTIONS:           #
# REGRESSION & DIAGNOISTIC PLOTS #
#####################################
# User defined regression function that allows for quick regression modeling for each activity measure at each time point.
# this function also outputs plots and tables of results
regression <- function(df, by_variable, formula, y_variable, model_name, time_type) {
  by_variable <- dplyr::enquo(by_variable)
  formula <- dplyr::enquo(formula)

  reg_untidy <- df %>%
  group_by(!! by_variable) %>%                                  # group data by time
  do(fits = lm(!! formula, data = .)) %>%                       # run model on each grp
  rename(model=!! by_variable)                                  # make model variable

  reg_tidy <- tidy(reg_untidy, fits)

  reg_coef_summary <- as.data.frame(reg_tidy[which(reg_tidy$term!="(Intercept)"),])

  reg_fit_stats <- data.frame(matrix(ncol = 3, nrow = 0))
  colnames(reg_fit_stats) <- c("model", "Model.Pvalue","adj.r.squared")
  for (i in 1:6){
    reg_fit_stats[i,1] <- as.character(reg_untidy$model[i])
    reg_fit_stats[i,2] <- round(glance(reg_untidy$fits[[i]])$p.value, 3)
    reg_fit_stats[i,3]<- round(glance(reg_untidy$fits[[i]])$adj.r.squared, 3)
  }

   reg_summary <- as.data.frame(merge(reg_coef_summary, reg_fit_stats, by="model", sort=F))

  if( length(reg_summary$model) > 6 & length(reg_summary$model) < 13){
```

```
309         reg_summary[,which(names(reg_summary) %in% c("Model.Pvalue", "
                adj.r.squared"))][seq(2,12,2),]="--"
310         #reg_summary[,which(names(reg_summary) =="model")][seq(2,12,2)
                ]="--"
311     }
312     if( length(reg_summary$model) >= 13 & length(reg_summary$model) <
            19){
313         reg_summary[,which(names(reg_summary) %in% c("Model.Pvalue", "
                adj.r.squared"))][seq(2,18,3),]="--"
314         reg_summary[,which(names(reg_summary) %in% c("Model.Pvalue", "
                adj.r.squared"))][seq(3,18,3),]="--"
315     }
316     if( length(reg_summary$model) >= 19){
317         reg_summary[,which(names(reg_summary) %in% c("Model.Pvalue", "
                adj.r.squared"))][seq(2,24,4),]="--"
318         reg_summary[,which(names(reg_summary) %in% c("Model.Pvalue", "
                adj.r.squared"))][seq(3,24,4),]="--"
319         reg_summary[,which(names(reg_summary) %in% c("Model.Pvalue", "
                adj.r.squared"))][seq(4,24,4),]="--"
320     }
321
322     table.html =  kable(reg_summary, format="html", caption=paste0("
            Model Summaries for ",  y_variable, " vs ", model_name, " at
            each time point ", time_type)) %>% kable_styling(bootstrap_
            options = "striped", full_width = F, position = "left")
323
324
325      table.tex = xtable::xtable(reg_summary, type="html", caption=
             paste0("Model Summaries for ",  y_variable, " vs ", model_name,
              " at each time point ", time_type)) # for outputting latex
             code
326
327     plot = dwplot(reg_tidy) + xlab("Coefficient estimate") + ylab("") +
328         labs(title=paste0("Predicting ", y_variable, " vs ", model_name
                , "\n by time period ", time_type)) +
329         geom_vline(xintercept = 0, colour = "grey60", linetype = 2) +
330         theme(plot.title=element_text(face="bold", hjust=0.5)) + scale_
                color_discrete(name=paste0(model_name, " Models:"),
331                  breaks=b.breaks,
332                  labels=p.labels) + guides(color = guide_legend(reverse =
                     TRUE))
333
334     objects <- list("fits" = reg_untidy, "coef_summary" = reg_coef_
            summary,  "model_summaries" = reg_summary, "html_table" = table.
            html, "latex_table" = table.tex, "beta_plot" = plot)
335 }
336
```

```r

# User defined diagnostic funciton that allows for outputting all diagnostic plots quickly
diagnostic_plots <- function(df, by_variable, formula, model_name){
    by_variable <- dplyr::enquo(by_variable)
    formula <- dplyr::enquo(formula)

    reg_untidy <- df %>%
    group_by(!! by_variable) %>%                    # group data by time
    do(fits = lm(!! formula, data = .)) %>%         # run model on each time group
    rename(model=!! by_variable)

    setwd("/Users/jessgraves/Dropbox/BIOSTATS/Spring 2018/Thesis/pittetd/images") # path to save files
    plots=c(1,2,3,4,5,6)
    for(i in 1:length(reg_untidy$model)){
       pdf(paste("diag", model_name, plots[i],".pdf",sep="")) # Automatically saves as PDF
        layout(mat=matrix(c(1,2,3,4),nrow=2,ncol=2,byrow=T))

        plot(reg_untidy$fits[[i]])
        mtext(paste0("Regression Diagnostics: ", model_name, " at ", reg_untidy$model[i], " hrs after waking"), line=-1.25, outer=TRUE)

        dev.off()
    }
}

#####################################
# MULTIPLE REGRESSION ANALYSES &
# DIAGNOSTIC PLOTS #
#####################################
# Univariate Regressions of each activity measure
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ mean.periods, "HRSD (no sleep)", "Mean Activity_univ", "Person-Time")$model_summaries
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.periods, "HRSD (no sleep)", "SD Activity_univ", "Person-Time")$model_summaries
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ relative.activity, "HRSD (no sleep)", "Relative Activity_univ", "Person-Time")$model_summaries

```

```
# Multiple Regressions of each activity measure with age and sex as covariates
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ mean.periods + age + sex, "HRSD (no sleep)", "Mean Activity", "Person-Time")$model_summaries
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.periods + age + sex, "HRSD (no sleep)", "SD Activity", "Person-Time")$model_summaries
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ relative.activity + age + sex, "HRSD (no sleep)", "Relative Activity", "Person-Time")$model_summaries

# Diagnostic Plots for above models
diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ mean.periods + age + sex, "Mean Activity (Person Time)")
diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.periods + age + sex, "SD Activity (Person Time)")
diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ relative.activity + age + sex, "Relative Activity (Person Time)")

# Multiple Regressions of quadratic models with age and sex as covariates
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ mean.periods + I(mean.periods^2) + age + sex, "HRSD (no sleep)","Quadratic Mean Activity", "Person-Time")$model_summaries
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.periods + I(sd.periods^2) + age + sex,"HRSD (no sleep)", "Quadratic SD Activity", "Person-Time")$model_summaries
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ relative.activity + I(relative.activity^2) + age + sex, "HRSD (no sleep)","Quadratic Relative Activity", "Person-Time")$model_summaries

# Diagnostic Plots for above models
diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ mean.periods + I(mean.periods^2) + age + sex, "Quadratic Mean Activity (Person Time)")
diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.periods+ I(sd.periods^2) + age + sex, "Quadratic SD Activity (Person Time)")
diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ relative.activity + I(relative.activity^2) + age + sex, "Quadratic Relative Activity (Person Time)")

# Multiple Regressions of controlling for up-mesor with age and sex as covariates
regression(alldata.person.time.hrsd, person.time, HRSD_log ~ mean.periods + tLeft + age + sex,"HRSD (no sleep)", "Mean Activity +
```

```
    tLeft", "Person-Time")$model_summaries
392 regression(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.periods
    + tLeft + age + sex, "HRSD (no sleep)","SD Activity + tLeft", "
    Person-Time")$model_summaries
393 regression(alldata.person.time.hrsd, person.time, HRSD_log ~ relative.
    activity + tLeft + age + sex, "HRSD (no sleep)","Relative Activity +
    tLeft", "Person-Time")$model_summaries
394
395 # Diagnostic Plots for above models
396 diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ mean
    .periods + tLeft + age + sex, "Mean Activity + tLeft (Person Time)")
397 diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~ sd.
    periods + tLeft + age + sex, "SD Activity + tLeft (Person Time)")
398 diagnostic_plots(alldata.person.time.hrsd, person.time, HRSD_log ~
    relative.activity + tLeft + age + sex, "Relative Activity + tLeft (
    Person Time)")
399
400 ######################################
401 # TRAJECTORY ANALYSIS
402 ######################################
403 # Prepping Data #
404   # Reshaping data into wide format
405   mean.wide.person.time <- spread(alldata.person.time.hrsd[,c(1,2,4,11)
        ], person.time, mean.periods)
406   sd.wide.person.time <- spread(alldata.person.time.hrsd[,c(1,2,5,11)],
        person.time, sd.periods)
407   rel.wide.person.time <- spread(alldata.person.time.hrsd[,c(1,2,9,11)
        ], person.time, relative.activity)
408     # renaming columns
409     colnames(mean.wide.person.time)[c(3:8)] <- c("mean.0_4", "mean.4_8"
          , "mean.8_12", "mean.12_16", "mean.16_20", "mean.20_24")
410     colnames(sd.wide.person.time)[c(3:8)] <-  c("sd.0_4", "sd.4_8", "sd
          .8_12", "sd.12_16", "sd.16_20", "sd.20_24")
411     colnames(rel.wide.person.time)[c(3:8)] <-  c("rel.0_4", "rel.4_8",
          "rel.8_12", "rel.12_16", "rel.16_20", "rel.20_24")
412
413   # Creating dataframes to use in trajectory analyses
414   mean.traj.pt.data = mean.wide.person.time[,-2]
415   sd.traj.pt.data = sd.wide.person.time[,-2]
416   rel.traj.pt.data = rel.wide.person.time[,-2]
417
418 #### Trajectory Analysis based on Mean Activity ####
419   test.mean=cld(mean.traj.pt.data) # converting into kml format
420   kml(test.mean, nbClusters=2:6) # running analysis for 2-6 clusters
421   X11(type = "Xlib")
422   try(choice(test.mean)) # plotting the mean of the selected clusters
        based on the analysis
```

```
423
424   # attaching clusters to dataset
425   mean.wide.person.time$clusters <- getClusters(test.mean, nbCluster=2)
426
427   # Summarizing HRSD mean and sd based on mean clusters
428   mean.clust.differences = ddply(mean.wide.person.time, .(clusters),
          summarise,
429           mean=mean(HRSD_log),
430           sd=sd(HRSD_log),
431           n=sum(!is.na(clusters)))
432
433   # Mean and Standard Deviation of Log(HRSD) based on cluster (mean
          activity)
434   pander(mean.clust.differences, caption="Mean and SD of HRSD Scores (
          log) based on clusters")
435
436   ### ANCOVA with age + sex ####
437   mean.wide.person.time.demo = merge(mean.wide.person.time, demo, by="
          id")
438
439   fit.ancova.kml.mean <- aov(HRSD_log ~ clusters + age + sex, data=mean
          .wide.person.time.demo)
440   summary(fit.ancova.kml.mean)
441
442   # Plotting the Mean Activity Trajectory based on Cluster #
443   # Put data in long format for ggplot
444   alldata.pt.mean.clusters=merge(alldata.person.time.hrsd, mean.wide.
          person.time[,c("id","clusters")], by="id")
445
446   ggplot(alldata.pt.mean.clusters, aes(x=person.time, y=mean.periods,
          group=clusters, color=clusters)) + stat_summary(fun.y = "mean",
          geom = "line", linetype = 1) + geom_point() + ggtitle("Mean log(
          activity) by Cluster") + theme(plot.title = element_text(hjust =
          0.5)) + labs(caption="Clusters defined based on Mean log(Activity)
          ") + ylab("Mean log(activity)") + xlab("Time Periods after waking"
          )
447
448 #### Trajectory Analysis based on SD Activity ####
449   test.sd=cld(sd.traj.pt.data) # converting into kml format
450   kml(test.sd, nbClusters=2:6) # running analysis for 2-6 clusters
451   X11(type = "Xlib")
452   try(choice(test.sd)) # plotting the mean of the selected clusters
          based on the analysis
453
454   # attaching clusters to dataset
455   sd.wide.person.time$clusters <- getClusters(test.sd, nbCluster=2)
456
```

```
457 # Summarizing HRSD mean and sd based on SD clusters
458 sd.clust.differences = ddply(sd.wide.person.time, .(clusters),
      summarise,
459       mean=mean(HRSD_log),
460       sd=sd(HRSD_log),
461       n=sum(!is.na(clusters)))
462
463 # Mean and Standard Deviation of Log(HRSD) based on cluster (SD
      activity)
464 pander(sd.clust.differences, caption="Mean and SD of HRSD Scores (log
      ) based on clusters")
465
466 ### ANCOVA with age + sex ####
467 sd.wide.person.time.demo = merge(sd.wide.person.time, demo, by="id")
468
469 fit.ancova.kml.sd <- aov(HRSD_log ~ clusters + age + sex, data=sd.
      wide.person.time.demo)
470 summary(fit.ancova.kml.sd)
471
472 # Plotting the Mean Activity Trajectory based on Cluster #
473 # Put data in long format for ggplot
474 alldata.pt.sd.clusters=merge(alldata.person.time.hrsd, sd.wide.person
      .time[,c("id","clusters")], by="id")
475 ggplot(alldata.pt.sd.clusters, aes(x=person.time, y=sd.periods, group
     =clusters, color=clusters)) + stat_summary(fun.y = "mean", geom =
      "line", linetype = 1) + geom_point() + ggtitle("SD log(activity)
      by Cluster") + theme(plot.title = element_text(hjust = 0.5)) +
     ylab("SD log(activity)") + xlab("Time Periods after waking") +
     labs(caption="Clusters defined based on SD log(activity)")
476
477 #### Trajectory Analysis based on Relative Activity ####
478 test.rel=cld(rel.traj.pt.data) # converting into kml format
479 kml(test.rel, nbClusters=2:6) # running analysis for 2-6 clusters
480 X11(type = "Xlib")
481 try(choice(test.rel)) # plotting the mean of the selected clusters
      based on the analysis
482
483 # attaching clusters to dataset
484 rel.wide.person.time$clusters <- getClusters(test.rel, nbCluster=2)
485
486 # Summarizing HRSD mean and sd based on relative clusters
487 rel.clust.differences = ddply(rel.wide.person.time, .(clusters),
      summarise,
488       mean=mean(HRSD_log),
489       sd=sd(HRSD_log),
490       n=sum(!is.na(clusters)))
491
```

```
  # Mean and Standard Deviation of Log(HRSD) based on cluster (Relative activity)
  pander(rel.clust.differences, caption="Mean and SD of HRSD Scores (log) based on clusters")

  ### ANCOVA with age + sex ####
  rel.wide.person.time.demo = merge(rel.wide.person.time, demo, by="id")

  fit.ancova.kml.rel <- aov(HRSD_log ~ clusters + age + sex, data=rel.wide.person.time.demo)
  summary(fit.ancova.kml.rel)

  # Plotting the Mean Activity Trajectory based on Cluster #
  # Put data in long format for ggplot
  alldata.pt.rel.clusters=merge(alldata.person.time.hrsd, rel.wide.person.time[,c("id","clusters")], by="id")
  ggplot(alldata.pt.rel.clusters, aes(x=person.time, y=relative.activity, group=clusters, color=clusters)) + stat_summary(fun.y = "mean", geom = "line", linetype = 1) + geom_point() + ggtitle("Relative log(activity) by Cluster") + theme(plot.title = element_text(hjust = 0.5)) + ylab("Relative log(activity)") + xlab("Time Periods after waking") + labs(caption="Clusters defined based on Relative log(activity)")


#######################################
# SUPPLEMENTARY ANALYSES: CLOCK TIME
#######################################
# Analyses to assess associations between activity at each time point against HRSD using clock time and not 'Person-Time'.
# CALCULATING MEANS BY DAY AND CLOCK TIME PERIOD
day.means.clock.time <- vector("list", length(dfs))

for (i in seq_along(dfs)) {
     day.means.clock.time[[i]] <- ddply(dfs[[i]], c("date", "clock.time"), plyr::summarise,
                    N    = sum(!is.na(act)),
                    mean.activity = mean(act, na.rm=T),
                    sd   = sd(act, na.rm=T))

            day.means.clock.time[[i]]$id <- ids[i] # assign id in column
            day.means.clock.time[[i]] <- na.omit(day.means.clock.time[[i]]) # removes final row of NA observations
            #day.means.clock.time[[i]]$time <- as.POSIXct(day.means.clock.time[[i]]$time, format = "%H:%M:%S") # convert
```

```
                time to POSIXct
523     }
524
525 # CALCULATING THE MEAN AND STANDARD DEVIATION BY TIME PERIOD (across
        all days)
526 period.means.clock.time <-vector("list", length(day.means.clock.time))
527 for (i in seq_along(day.means.clock.time)) {
528     period.means.clock.time[[i]] <- ddply(day.means.clock.time[[i]], "
            clock.time", plyr::summarise,
529                           N = sum(!is.na(mean.activity)),
530                           mean.periods = mean(mean.activity, na.rm=T),
531                           sd.periods = sd(mean.activity, na.rm=T),
532                           quant.25 = quantile(mean.activity, 0.25), #
                                calculating 25th percentile of data
533                           quant.75 = quantile(mean.activity, 0.75)) #
                                calculating 75th percentile of data
534     period.means.clock.time[[i]]$id <- ids[i] # assign id in column
535 }
536
537 # Combine Means and Standard Deviation into one dataset
538 alldata.clock.time <- do.call(rbind, period.means.clock.time)
539     alldata.clock.time$clock.time <- unlist(alldata.clock.time$clock.
            time)
540     alldata.clock.time$id<- as.factor(unlist(alldata.clock.time$id))
541     alldata.clock.time$mean.periods<-as.numeric(alldata.clock.time$mean
            .periods)
542
543 # CALCULATING THE RELATIVE ACTIVITY MEASURES
544 # find sum of mean activity for each subject
545     sum.mean.activity = ddply(alldata.clock.time, .(id), plyr::
            summarise, sum.activity = sum(mean.periods))
546
547     # merge sum of mean activity per subject with alldata.clock.time
            dataset
548     alldata.clock.time <- merge(alldata.clock.time, sum.mean.activity,
            by="id")
549
550     # create relative activity measure
551          alldata.clock.time$relative.activity = alldata.clock.time$mean.
                periods/alldata.clock.time$sum.activity
552
553 print(alldata.clock.time[1:15,])
554
555 ######################################
556 # MERGE ACTIVITY, HRSD, DEMOGRAPHIC #
557 ######################################
558    # Merge depression data with mean and standard deviation data
```

```
559   alldata.clock.time.hrsd <- merge(alldata.clock.time, hrsd, by="id")
560   alldata.clock.time.hrsd <- merge(alldata.clock.time.hrsd, tleft, by="
          id") # adding in tleft data
561   alldata.clock.time.hrsd<-merge(alldata.clock.time.hrsd, demo, by="id"
          ) #adding demoraphic data
562   alldata.clock.time.hrsd$id <- as.factor(alldata.clock.time.hrsd$id)
563   head(alldata.clock.time.hrsd)
564
565 ###################################
566 # SPEARMAN CORRELATIONS #
567 ###################################
568 # User defined function to pass ddplyr correlation of two variables
569 corfun<-function(x, y) {
570   corr=(cor.test(x, y,
571                  alternative="two.sided", method="spearman", exact=F))
572 }
573
574 # Creating individual datasets for spearman correlations of mean, sd
       and relative activity
575   mean.hrsd.corr.clock = as.data.frame(
576     ddply(alldata.clock.time.hrsd, .(clock.time), plyr::summarise,
            correlation=corfun(mean.periods, HRSD_log)$estimate,
577         p.value=corfun(mean.periods, HRSD_log)$p.value,
578         statistic=corfun(mean.periods, HRSD_log)$statistic,
579         alt=corfun(mean.periods, HRSD_log)$alternative
580         ) )
581     colnames(mean.hrsd.corr.clock)[2] <- "Corr. Mean vs. HRSD"
582
583 sd.hrsd.corr.clock = as.data.frame(
584     ddply(alldata.clock.time.hrsd, .(clock.time), plyr::summarise,
            correlation=corfun(sd.periods, HRSD_log)$estimate,
585         p.value=corfun(sd.periods, HRSD_log)$p.value,
586         statistic=corfun(sd.periods, HRSD_log)$statistic,
587         alt=corfun(sd.periods, HRSD_log)$alternative
588         ) )
589     colnames(sd.hrsd.corr.clock)[2] <- "Corr. SD vs. HRSD"
590
591 relative.hrsd.corr.clock = as.data.frame(
592     ddply(alldata.clock.time.hrsd, .(clock.time), plyr::summarise,
            correlation=corfun(relative.activity, HRSD_log)$estimate,
593         p.value=corfun(relative.activity, HRSD_log)$p.value,
594         statistic=corfun(relative.activity, HRSD_log)$statistic,
595         alt=corfun(relative.activity, HRSD_log)$alternative
596         ) )
597     colnames(relative.hrsd.corr.clock)[2] <- "Corr. Relative vs. HRSD"
598
```

```
599 pander(cbind(mean.hrsd.corr.clock[1:3], sd.hrsd.corr.clock[2:3],
      relative.hrsd.corr.clock[2:3]), caption="Correlation between log(
      HRSD) and Mean, SD, and Relative Log(Activity) within Time Periods (
      Clock time)", split.table = Inf)
```

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