

5-2015

Activity-Rest And Skin Temperature Circadian Rhythms And Sleep Patterns In Community-Dwelling Women

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ACTIVITY-REST AND SKIN TEMPERATURE CIRCADIAN RHYTHMS AND
SLEEP PATTERNS IN COMMUNITY-DWELLING WOMEN

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN NURSING

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
SCHOOL OF NURSING

BY

KRISTINA L. LEYDEN, MSN, FNP, APRN, BC

MAY, 2015

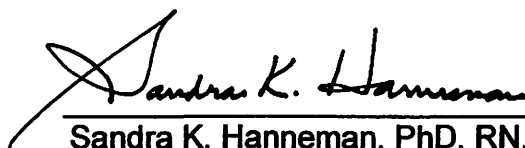
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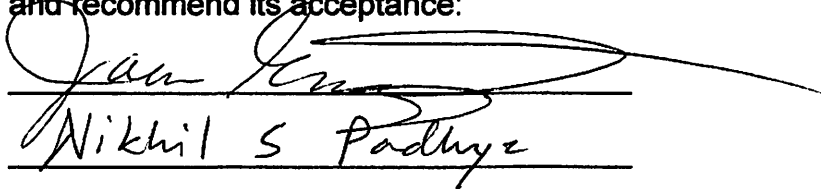
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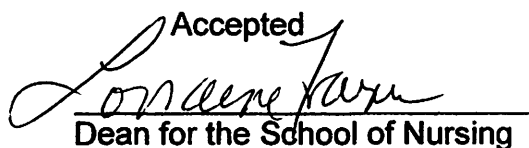
To the Dean for the School of Nursing:

I am submitting a dissertation written by Kristina Leyden and entitled "Activity-Rest and Skin Temperature Circadian Rhythms and Sleep Patterns in Community-Dwelling Women." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.


Sandra K. Hanneman, PhD, RN, FAAN, Committee Chair

We have read this dissertation
and recommend its acceptance:


Nikhil S. Padhye

Accepted

Dean for the School of Nursing

Acknowledgements

With sincerest gratitude, I acknowledge Sandra K. Hanneman, PhD, RN, FAAN, as my mentor and for her support as chair of my dissertation committee. I wish to thank Nikhil Padhye, PhD, and Joan Engebretson, DrPH, AHN-BC, RN, for their expertise, guidance, and support. I heartfully thank my father, James and my late mother, Josephine, for their love, support, and always teaching me I can do anything I set my mind to. I wish to thank my sister Katrina N. Leyden, PhD, FNP-BC, for her love and support and for the shared journey. I thank my sisters Korine, Kathleen, and Karen, my brother Brett, and all my family and my dear friends who have encouraged and supported me.

I wish to dedicate this dissertation to my husband, Carlos R. Rivera, MD, and my wonderful children, Charlie, Kamilla, Colin, Christopher Liam, and Cassian “Cash.” Without their love and the love for them, this would not be possible.

Kristina L. Leyden

Activity-Rest and Skin Temperature Circadian Rhythms and

Sleep Patterns in Community-Dwelling Women

May 2015

Abstract

Purpose: The purpose of the study was to explore activity-rest and temperature circadian rhythms and sleep patterns in ambulatory women of reproductive, perimenopausal, and postmenopausal stages. Study aims were to (1) correlate the patterns of activity-rest with skin temperature and determine (2) lead-lag relation between activity-rest and circadian temperature rhythm, (3) stability of activity-rest patterns during work and non-work days, (4) duration of actigraphy sampling sufficient to reliably capture activity-rest patterns, and (5) sleep parameters in participating women across reproductive stages.

Design: Analysis of extant data sets.

Sample and Setting: Seven community-dwelling women, 27-to-54-years old

Methods: Participants wore an actigraph on the non-dominant wrist and a thermal sensor on the abdomen or under the breast for 13-52 consecutive days.

Data were fit to the 3-parameter cosinor model to test for a statistically significant circadian rhythm; acceptable goodness-of-fit was defined as $R^2 \geq .10$. Cosinor parameters from the activity-rest and temperature rhythms were correlated using the Spearman correlation coefficient to determine lead-lag relation. Stability of acrophase on work and non-work days was determined using the paired *t*-test.

The standard error of the mean was computed for individual participants and the

sample to determine minimum actigraphy monitoring duration to reliably assess activity-rest rhythms. Sleep parameters were scored by the Cole-Kripke method using Actiware™ software (Version 5.5, Mini Mitter).

Results: All participants had statistically significant activity-rest and skin temperature circadian rhythms ($p \leq 0.001$). Six of seven participants (86%) had a statistically significant correlation ($p \leq 0.05$) between activity-rest and temperature; three participants had a strong biologically meaningful ($R^2 \geq .10$) circadian rhythm for both activity-rest and temperature. A lead-lag relationship was estimated in 6 of the 7 participants (86%); one participant had a temperature rise before an increase in activity, indicating temperature led activity, and five participants had an activity rise before an increase in temperature, indicating activity led temperature. Differences in mesor, amplitude, and acrophase of the activity-rest rhythms between work and non-work days were not statistically significant in the majority of women. Weighted standard error of the mean decreased linearly as monitoring days increased after 3 days. Participants in the reproductive and menopausal stages experienced the most interrupted sleep, with a median of 22 awakenings during the sleep period. Participants in the perimenopausal stage averaged more sleep time, least number of awakenings during the sleep period, and least hours of wake after sleep onset than those in the reproductive or menopausal stage. The menopausal women slept the fewest number of hours a day (median, 4.6 hr).

Conclusions: Activity-rest and temperature circadian rhythms were correlated in the majority of participants. Lead-lag relationship between activity-rest and

temperature rhythms was inconsistent. Activity-rest rhythms were stable in work and non-work days in the majority of participants. A minimum of 4 monitoring days was needed to reliably determine activity-rest rhythms. In this small sample, sleep parameters differed by reproductive stage. The circadian rhythm findings are consistent with those from laboratory studies, but suggest that behaviors in the naturalistic setting may alter the lead-lag relationship between activity-rest and body temperature.

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Summary of Study

This dissertation is comprised of three main sections. The first section is the approved dissertation proposal. The second section is the manuscript with study results, “Activity-Rest and Skin Temperature Circadian Rhythms and Sleep Patterns in Community-Dwelling Women.” The third section includes the study approvals and the study protocol.

Extant actigraphy and skin temperature data (Sandra K. Hanneman, Principal Investigator) collected prospectively from seven ambulatory women, 27 to 57 years old and spanning the reproductive, perimenopausal, and postmenopausal stages, were analyzed to describe activity-rest and temperature circadian rhythms and sleep patterns. Participants wore an actigraph on the non-dominant wrist and a temperature sensor on the abdomen or under the breast for 13-52 consecutive days (Hanneman & Padhye, 2005).

The primary aim of this study was to correlate activity-rest and skin temperature circadian rhythms throughout the monitoring period. The hypothesis was that women with a strong circadian activity-rest rhythm would have a strong circadian temperature rhythm, indicating entrainment of the circadian pacemaker to a 24-hour day. Four secondary aims were to determine:

- (a) lead-lag relation between activity-rest and circadian temperature rhythm
- (b) stability of activity-rest patterns during work and non-work days,
- (c) duration of actigraphy sampling sufficient to reliably determine activity-rest patterns, and

(d) sleep parameters across the reproductive stages.

Hypotheses for secondary aims were: (a) activity-rest rhythm leads temperature rhythm, (b) activity-rest patterns are stable during work and non-work days, (c) 7 days of actigraphy sampling is sufficient to reliably determine activity-rest patterns, and (d) sleep parameters vary by reproductive stage.

The study varied from the one proposed in three ways. Data sets from nine women were to be analyzed. However, due to technical problems with actigraphy in one participant and no actigraphy data in another participant, the sample size was reduced to seven women. Because the activity-rest and temperature data were abnormally distributed and the sample size was small, the Spearman correlation coefficient was used instead of the Pearson Product-Moment correlation coefficient. Finally, the plan to use the intra-class correlation coefficient to determine the duration of actigraphy sampling was unsuccessful and, therefore, replaced with the weighted standard error of the mean.

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OCTOBER 14, 2013

Activity-Rest Patterns in Community-Dwelling Women

Specific Aims

The endogenous circadian pacemaker, located in the suprachiasmatic nuclei, synchronizes physiologic, biochemical, and behavioral rhythms to a 24-hour period (Aschoff, 1965; Czeisler & Khalsa, 2000; Moore & Eichler, 1972; Reinberg, Ashkenazi, & Smolensky, 2007). Core body temperature, plasma cortisol, and plasma melatonin serve as reliable markers of circadian pacemaker function (Klerman, Gershengom, Duffy, & Kronauer, 2002), and these rhythm markers are dependent on the activity-rest pattern to help align circadian rhythms (Scheer, Hilton, Mantzoros, & Shea, 2009; Touitou, Coste, Dispersyn, & Pain, 2010).

Analysis of actigraphy and temperature data from a previous study of skin temperature circadian rhythm (Hanneman & Padhye, 2005) is proposed. Participants included 12 community-dwelling women of reproductive, perimenopausal, or menopausal ages. Eight actigraphy data sets, including sleep parameters, from seven of the participants were collected, but not analyzed, to determine if the women were synchronized to a 24-hour rhythm by the activity-rest cycle during the collection of skin temperature data, which spanned several weeks. Descriptors of the participants available for analysis are in Table 1.

Activity-rest patterns are affected by a number of factors, including: light-dark cycles, social cues, food timing, and hormonal fluctuations (Kelly, 2006; Owens & Matthews, 1998; Pardini & Kaeffer, 2006; Patkai, Johansson, & Post, 1974; Wittmann, Dinich, Merrow, & Roenneberg, 2006). When these factors vary

throughout the week, the stability of both the activity-rest and temperature circadian rhythms is affected (Taillard, Philip, & Bioulac, 1999; Wittmann, et al., 2006). Activity rhythms are concurrent with temperature rhythms in many species (Aschoff, 1979), and such external synchronizers as activity are needed to keep the endogenous circadian pacemaker regulated in humans (Mills, Minors, & Waterhouse, 1978; Minors & Waterhouse, 1989; Refinetti & Menaker, 1992). Activity-rest pattern variation can cause circadian misalignment, defined as failure of external synchronizers to entrain the endogenous circadian pacemaker to the 24-hour day (Scheer, et al., 2009; Touitou, et al., 2010).

Table 1
Characteristics of the Study Participants

Participant	Classification	Age	BMI ^a	Ethnicity	Medications/Hot Flashes
1	Reproductive	29	20.5	Caucasian	Oral contraceptives discontinued 2 weeks prior to study
2	Reproductive	27	32.9	Caucasian	Oral contraceptives
3	Perimenopausal	54	24.5	Caucasian	Hot flashes
4	Perimenopausal	51	35.5	Caucasian	Hot flashes
5	Perimenopausal	53	20.8	Caucasian	Lipid lowering, diuretic, antithrombotic, antacid
6	Menopausal	52	37.1	Caucasian	Angiotensin receptor blocker, glucose lowering, diuretic, lipid lowering, antithrombotic, beta-blocker/hot flashes
7	Menopausal	54	32.3	African American	Thyroid supplement, lipid lowering, biophosphonate/hot flashes

Note. Participants, N=7

^aBMI, body mass index

Actigraphy is a convenient and objective approach for measuring activity-rest circadian and sleep patterns over time in natural environments. Several days of monitoring is recommended to capture activity-rest patterns in healthy men and women (Padhye & Hanneman, 2007; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001) and 30 days of monitoring should be collected in women when considering menstrual cycle effects on circadian rhythm (Padhye & Hanneman).

The proposed study will focus on the activity-rest rhythm as a synchronizer of circadian temperature rhythm in women. The primary aim is to correlate the activity-rest and temperature circadian rhythms throughout the monitoring period. The hypothesis is that women with a strong circadian activity-rest rhythm will have a strong circadian temperature rhythm, indicating entrainment of the circadian pacemaker to a 24-hour day. Four secondary aims are to determine:

- (a) lead-lag relation between activity-rest and circadian temperature rhythm
- (b) stability of activity-rest patterns during work and non-work days,
- (c) duration of actigraphy sampling sufficient to reliably determine activity-rest patterns, and
- (d) sleep parameters.

The hypotheses for secondary aims were: (a) activity-rest rhythm leads the circadian temperature rhythm, (b) activity-rest patterns are stable during work and non-work days, (c) 7 days of actigraphy sampling is sufficient to reliably

determine activity-rest patterns, and (d) sleep parameters vary by reproductive stage.

Research Strategy

SIGNIFICANCE

Circadian Misalignment

The two primary external synchronizers of the endogenous circadian pacemaker are the light-dark and the activity-rest cycles (Touitou, et al., 2010). The activity-rest rhythm can be disrupted by such day-to-day variations as shift work or transmeridian travel, and sustained disruptions are associated with adverse health consequences (Knutsson, 2003; LaDou, 1982; Scheer, et al., 2009; Touitou, et al., 2010). Potential consequences of misaligned rhythms include obesity, cardiovascular disease, diabetes, epilepsy (Scheer, et al., 2009; Winget & LaDou, 1978), breast and colorectal cancer (Schernhammer, et al., 2001; Schernhammer, et al., 2003), hypertension, osteoporosis, and gastrointestinal problems (Foley, Ancoli-Israel, Britz, & Walsh, 2004). In addition, risk of miscarriage, low birth weight, and preterm birth in pregnant women are higher (Knutsson, 2003) with activity-rest rhythm misalignment. Cognitive impairment, such as impaired attention, memory, social and interpersonal functioning, and communication (Rosekind, et al., 2010) also have been reported with activity-rest rhythm misalignment.

Circadian misalignment is associated with higher healthcare costs, lost productivity, and decreased quality of life (Bolge, Balkrishnan, Kannan, Seal, & Drake, 2010; Rosekind, et al., 2010). Women with activity-rest rhythm

misalignment due to female cyclical hormonal changes have decreased productivity in the workplace (Heinemann, Minh, Filonenko, & Uhl-Hochgraber, 2010; Mishell, 2005). The annual economic impact of circadian misalignment has been estimated at \$54 million (Rosekind, et al., 2010).

Circadian Body Temperature and Activity-Rest Rhythms

Body temperature is lowest during sleep (Czeisler & Khalsa, 2000; Mills, et al., 1978); thus, the nadirs of the circadian temperature and activity-rest rhythms are temporally aligned in healthy people. Sleep efficiency is highest during the temperature nadir (Dijk & Czeisler, 1995). An unstable activity-rest rhythm may be explained by hormone fluctuations in women (Owens & Matthews, 1998; Patkai, et al., 1974). The activity-rest rhythm differences found in women are most prominent during the menstrual cycle with the shortest rest periods during ovulation and the longest, but most disrupted, during the premenstrual phase (Patkai, et al., 1974).

Binkley (1992) reported circadian activity-rest rhythms across the menstrual cycle in women studied over 1 year. Findings included: onset of activity was latest near ovulation; activity cessation, reported activity per 5 minutes, and alpha (duration of activity or width of the curve) decreased during the follicular phase; and activity onset and cessation, alpha, and acrophase were delayed by 0.7 hours during the weekend. Ito et al. (1993) studied rectal temperature in seven healthy, 18-to-19-year-old women, measured every 3 days for 5 weeks. The researchers concluded that the lowest temperatures for the 5-week data series were during the menstruation and follicular phases and the

highest during the luteal phase. Women have better sleep patterns during the menstruation phase of the menstrual cycle as reflected by decreased sleep onset latency (Driver, Dijk, Werth, Biedermann, & Borbely, 1996; Shinohara, et al., 2000) and sleep interruptions (Driver, et al., 1996).

The proposed study is expected to offer insights as to temperature and activity-rest patterns across the reproductive stages and work and non-work days. The knowledge gained may help target temporally where different interventions could be tried to improve activity-rest rhythms with the goal of keeping circadian rhythms aligned, thereby increasing work productivity and decreasing health problems.

No literature was found documenting lead-lag relation between activity-rest and temperature; however, Refinetti and Menaker (1992) suggested markers of the circadian pacemaker stray from their usual pattern when an external factor, such as activity-rest, is absent or modified from its usual state. Because body temperature is dependent on activity-rest patterns to help align circadian rhythm (Scheer, et al., 2009; Touitou, et al., 2010), it is reasonable to expect a correlation between temperature and activity-rest rhythms.

In this study, the investigator will correlate the skin temperature and activity-rest rhythm parameters. It is hypothesized that activity-rest leads the temperature rhythm as suggested by Refinetti & Menaker (1992), especially given that both are needed for circadian pacemaker synchronization (Mills, et al., 1978; Minors & Waterhouse, 1989; Refinetti & Menaker, 1992), and sleep

efficiency has been reported to peak during the temperature nadir (Dijk & Czeisler, 1995).

In the parent study, all women had a statistically significant circadian temperature rhythm, and 5 of the 9 (56%) women had a strong rhythm ($R^2 \geq .10$). Mesor (midline-estimating statistic of rhythm) was higher and amplitude lower during the luteal phase of the menstrual cycle in the menstruating women (Hanneman & Padhye, unpublished data). The hypothesis of the proposed study is that women with a strong circadian activity-rest rhythm will have a strong circadian temperature rhythm, and women with a weak circadian activity-rest rhythm ($R^2 < .10$) will have a weak temperature rhythm. Theoretically, if the temperature rhythm is susceptible to the influence of activity-rest rhythm, an abnormal or unstable activity-rest rhythm will be associated with an attenuated circadian temperature rhythm.

Skin Temperature vs. Core Body Temperature

Core body temperature has long been recognized as a marker of the circadian pacemaker (Kelly, 2006; Klerman, et al., 2002). Core body temperature generally has been measured by rectal probe (Kattapong, Fogg, & Eastman, 1995) and is independent of blood flow (Thomas, Burr, Wang, Lentz, & Shaver, 2004) or ambient temperature (Tsujimoto, Yamada, Shimoda, Hanada, & Takahashi, 1990). Not only is skin temperature influenced by these factors, but temperature varies between distal and proximal sites (Krauchi & Wirz-Justice, 1994). Krauchi and Wirz-Justice compared rectal and skin temperature in men and concluded that temperature measured at proximal skin sites (infraclavicular,

thigh, and forehead) was phase advanced by 25-180 minutes, whereas temperature measured at distal skin sites (hands and feet) had an acrophase opposite to that of core body temperature.

In the parent study, Hanneman and Padhye (unpublished data) used breast and abdominal proximal skin temperature, with temperature sensors applied as done by Krauchi & Wirz-Justice (1994), to detect circadian temperature rhythm. They reported mesor and amplitude of skin temperature comparable to values from core body temperature monitoring by others; however, acrophase was delayed by 3 to 4 hours for skin temperature when compared with core body temperature. Hanneman and Padhye suggested that either the breast or abdominal skin site can capture circadian temperature rhythm mesor and amplitude and recommended further studies on the measurement of acrophase with a larger sample size to evaluate acrophase findings with differing hormones across the reproductive cycles. Their skin temperature findings include decreased amplitude during the luteal phase of the menstrual cycle similar to the core body temperature measured by Nakayama, et al. (1992). Furthermore, their findings support those of Krauchi and Wirz-Justice, showing differences between core and skin temperature rhythms. Krauchi and Wirz-Justice reported a 2-hour phase advance in temperature minima when compared to rectal core temperature. However, in comparing the two studies, proximal temperature minima were reported by one-way analysis of variance (ANOVA) at 1-hour intervals in Krauchi and Wirz-Justice (1994), not cosinor model core temperature parameters with sampling rates of ≤ 6 min as in the Hanneman and Padhye

study. It is difficult to fully compare these two studies because the temperature parameters were not analyzed in the same way. The 1-hour intervals yield a significant variation. Furthermore, differences between the acrophase advance found in men (Krauchi & Wirz-Justice, 1994) and acrophase delay in women could be attributed to hormonal influences.

Although core body temperature acrophase has been reported as 15:00-16:00 in women between 19 and 36 years of age and between 39 and 56 years of age (Thomas, et al., 2004), and older women (aged 69 ± 7 years) have a 1.25 hour phase advance (Campbell, Gillin, Kripke, Erickson, & Clopton, 1989), skin temperature acrophase is not well understood. Comparison of acrophases of activity-rest and skin temperature rhythms from the parent study will need to take into account the suggested boundaries of existing skin temperature acrophase using the assumption of a 2-to-4-hour lag when comparing or discussing core body temperature in relation to activity-rest rhythms during the 24-hour cycle (Hanneman & Padhye, 2005; Krauchi & Wirz-Justice, 1994). The investigator will explore the lead-lag relationship between temperature and activity-rest to better understand the relation.

Stability of Activity-rest Rhythms

Persons adhering to a strict school or work schedule do not necessarily adhere to the same schedule on their days off, and may alter their activity-rest pattern on non-work days to catch up on sleep or revert to their preferred activity-rest rhythm (Taillard, et al., 1999; Taillard, Philip, Coste, Sagaspe, & Bioulac, 2003). Taillard et al. (1999) examined sleep pattern preference and habits on

work and non-work days in 617 healthy men and women, between 17- and 80-years of age, using questionnaires. The group with evening-hour preference, compared with the groups with morning-hour or no preference, reported needing more sleep, going to bed later on work days, and using non-work days to sleep more. A negative correlation ($p = -0.414$, $P < 0.005$) was found between work and non-work day sleep time; the more sleep lost during work days, the more sleep accrued during non-work days. Dinges, et al. (1997) examined 16 healthy young adults after restricting their sleep for 7 consecutive nights. They found that participants needed 2 full nights of sleep to recover following sleep restriction. The present study sample is community-dwelling women who adhered to a diurnal activity pattern during data collection, and this investigator will explore in the proposed study the expected work day and non-work day differences in activity-rest patterns.

Actigraphy Monitoring Duration

The need for participants to wear an actigraph continuously over long data collection periods may be tedious and burdensome. A 1-day monitoring period with actigraphy was sufficient in men and women to document wake after sleep onset, total sleep time, and sleep efficiency, but not sleep onset latency, when compared with polysomnography (Lichstein, et al., 2006). A 2-day monitoring period in women and infants provided adequate reliability (Thomas & Burr, 2008), suggesting that a 2-day monitoring period is sufficient to capture activity-rest patterns using actigraphy. A 7-day monitoring period in healthy men and women (20-85 years of age) demonstrated adequate validity estimates in measuring

activity-rest patterns compared with the gold standard of polysomnography (Pollak, et al., 2001). A monitoring period of at least 30 days should be used when considering hormonal influences, such as the menstrual cycle, on circadian rhythm (Padhye & Hanneman, 2007). The wide range of actigraphy monitoring days (7-63 days) in the study database offers the opportunity to compare within subject reliability estimates of activity and rest to determine sampling sufficiency.

Sleep

Age and gender differences have been demonstrated in sleep patterns. Circadian rhythm and sleep-wake pattern differences across age groups may be attributed to the aging suprachiasmatic nuclei in the older population; these nuclei decrease in size and volume with age (Swaab, Fliers, & Partiman, 1985). Increased sleep latency and number of arousals during sleep have been found in older adults, as compared with young adults (Czeisler, et al., 1992; Weitzman, Moline, Czeisler, & Zimmerman, 1982). Yoon, Kripke, and Young (2003) reported increased wake after sleep onset and sleep latency and decreased total sleep time and sleep efficiency in older adults compared with younger ones.

Sleep patterns were examined in 2 groups of healthy men and women in a controlled facility (Weitzman, et al., 1982). Groups included young participants, between 23- and 30-years of age, and older participants, between 53- and 70-years of age. Participants were examined in 2 conditions: (a) investigator controlled light and meal entrainment based on participants' daily routines logged prior to the study; and, (b) under free-running conditions (participant in control of turning lights on and off and meal times). In both the entrained and free-running

conditions, the older adults demonstrated increased sleep latency and number of arousals during sleep compared with the younger participants. Similar results were demonstrated in 21 elderly participants, 65- to 85-years of age, when activity-rest rhythms were examined in a controlled laboratory setting (Czeisler, et al., 1992). Frequent arousals led to poor sleep efficiency and promoted daily napping (Czeisler, et al., 1992; Weitzman, et al., 1982).

Sleep patterns were examined by polysomnography in 4 groups of healthy women in a controlled setting for 24 hours (Lukacs, Chilimigras, Cannon, Dormire, & Reame, 2004). The groups were separated into 14 women, 20 to 30 years of age; 15 women, 40 to 50 years of age; 12 women, 40 to 50 years old and taking estrogen; and 10 women, aged 40-50 years and menopausal. The 40-to-50-year-old women in both groups had reduced sleep efficiency and longer wake time, compared with the 20-to-30-year-old women.

Increased sleep latency, decreased sleep efficiency, decreased total sleep time and increased wake time have been found in women (Jean-Louis, Mendlowicz, Von Gizycki, Zizi, & Nunes, 1999; Lehnkering & Siegmund, 2007; Mongrain, Carrier, & Dumont, 2005). Trouble falling asleep, trouble sleeping, waking at night, and waking earlier were found in women across the different reproductive stages (Owens & Matthews, 1998). Trouble sleeping, waking at night, and waking up earlier were most often reported by post menopausal women taking hormone replacement therapy (HRT) when compared with pre-, peri-, and postmenopausal women without HRT. Trouble falling asleep, objectively estimated by sleep onset latency, was most often reported by

postmenopausal women without HRT when compared to pre-, peri-, and postmenopausal women with HRT. Because there is known activity-rest rhythm variance in women during the menstrual cycle and only sparse literature exists comparing activity-rest patterns across the reproductive, perimenopausal, and menopausal states (Leyden, 2011; Owens & Matthews, 1998; Patkai, et al., 1974), one of the proposed aims of this study will further knowledge of sleep parameters in women across the reproductive stages.

Actigraphy Analysis

Actigraphy is a reliable method to analyze sleep, rest, and activity levels (Ancoli-Israel, Martin, Kripke, Marler, & Klauber, 2002; Gironda, Lloyd, Clark, & Walker, 2007; Van Someren, 2000). Parameters used to analyze the levels are shown in Table 2. Analytical approaches include single, 5-parameter, and nonparametric cosinor analysis. Single-cosinor analysis is the most commonly used, but has a disadvantage in that activity-rest data do not completely follow a cosine curve (Ancoli-Israel, et al., 2002; Martin, Marler, Shochat, & Ancoli-Israel, 2000). Single-cosinor analysis was used in the parent study for circadian temperature rhythm analysis (Hanneman & Padhye, unpublished data), and its use in the proposed study would allow easy comparison of all cosinor parameters. The advantage of using a 5-parameter cosinor model is estimation of a square wave, which is more typical of activity-rest data (Ancoli-Israel, et al., 2003); a disadvantage is the inability to compare all cosinor parameters. Non-parametric analysis has the advantage of handling data that are abnormally distributed (Gogenur, Bisgaard, Burgdorf, Van Someren, & Rosenberg, 2009;

Rosner, 2006). Nonparametric analysis may be more sensitive to the typical wave of the activity-rest data, whereas the cosinor model may overestimate the acrophase and nadir (Dowling, et al., 2005); however, some power is lost with the nonparametric approach (Rosner, 2006).

Table 2

Activity, Rest, and Sleep Parameter Definitions

Parameter	Acronym	Definition
Activity Count		Minimum, maximum and median movement captured by actigraph
Acrophase		Clock time at which peak activity count occurs
Amplitude		Distance of the fitted cosine curve between mesor and peak value
Mesor		Rhythm-adjusted mean
Nadir		Trough or minimum value
Sleep Efficiency	SE	Total sleep time compared to time spent in bed
Sleep Onset Latency	SOL	Time it takes to fall asleep after lying down
Subjective Sleep	SS	Self-reported total sleep time obtained through daily log
Total Sleep Time	TST	Total sleep time during 24 hours
Wake After Sleep Onset		More than one minute of wakefulness after sleep onset
Wake Time	WT	Time spent awake including sleep interruptions

Summary

Collectively, the cited studies have demonstrated that circadian misalignment is associated with altered health or presence of disease. Because activity-rest and core body temperature rhythms are coupled, disrupted activity-rest rhythm may lead to disruption of circadian temperature rhythm. The stability of activity-rest rhythm may be affected by individual preferences and individuals may change their sleep schedules depending on social demands or work

schedules. Compared with young adults, older adults have increased sleep latency, increased number of night arousals, decreased sleep efficiency, and increased wake times.

In the proposed study, the activity-rest circadian rhythm and sleep patterns of ambulatory women living in their natural environment will be analyzed to explore the hypothesis that women with a strong activity-rest rhythm have a strong circadian temperature rhythm, indicating entrainment of the circadian pacemaker to a 24-hour day. Activity-rest and skin temperature data sets also will be used to determine lead-lag relation between activity-rest and circadian skin temperature rhythms, stability of activity-rest patterns during work and non-work days, the duration of actigraphy sampling sufficient to reliably determine activity-rest patterns, and sleep parameters in the 3 groups of women.

APPROACH

Activity-rest circadian rhythm and sleep patterns will be analyzed from time-series actigraphy data that were collected prospectively from ambulatory women of reproductive, perimenopausal, and postmenopausal ages. The Institutional Review Board of the University of Texas Health Science Center at Houston approved the study (Appendix A) and all participants provided informed consent.

Sample and Setting

Nine women wore an actigraph; however, due to technical problems with actigraphy in 1 participant, actigraphy data will be analyzed in 8 women. The women were between 19 and 55 years of age during data collection: 3 women in

the reproductive age range (19-29 years old); 3 perimenopausal (51-55 years old), and 2 women in menopause (52 and 54 years old). The women were recruited by convenience through word of mouth in the surrounding medical center community without bias for race or ethnicity. Participants had intact uterus and ovaries, no known gynecological abnormalities, and reported a diurnal activity and nighttime sleep social routine and no travel outside a 1-hour time zone change during the observation time. Data were collected from July 2002 through July 2004. Participants completed daily logs with menses onset (as appropriate), bedtimes, wake times, exercise, medications, alcohol/drug/caffeine use, and times of actigraph removal and application.

Instruments

Activity-rest was measured with the Actiwatch Score (Mini Mitter Company Inc.) actigraphy monitor. This monitor is 29 X 37 X 12 mm and weighs 22 grams with the wristband. The actigraph measures activity counts using an omnidirectional accelerometer that senses degree and speed of motion and elicits an electrical current to varying magnitudes of movement (Gironda, et al., 2007). It is sensitive to 0.01 g change in movement, and collects data in 3 modes: zero-crossing (ZCM), time above threshold (TAT), and proportional integral mode (PIM).

Construct validity has been estimated by comparing scores obtained with the Actiwatch Score to those obtained with the VICON Motion Analysis System ($r = .88$) (Gironda, et al., 2007) and for Actiwatch with polysomnography ($r = .8, .9$) for total sleep time, sleep efficiency, wake after sleep onset, and the number of

awakenings (Lichstein, et al., 2006). Test-retest reliability was $r = .9$ in adult women (Torrence & Hanneman, 2003) and $r = .9$ in women across 3 reproductive stages (Leyden & Hanneman, 2010).

Concurrent validity of a daily log has been estimated by comparing a 3-day log of activity with accelerometer readings ($r = .69$, females) (Machado-Rodrigues, et al., 2012). It has also been estimated by comparing 24-hour log of activity with physical activity levels ($r = .64$, $p = .018$) and by comparing accelerometer readings with physical activity levels ($r = .91$, $p < .001$) (Bharathi, et al., 2007), and sleep reports with actigraphy for total sleep time ($r = .64$, $p < .01$) and sleep efficiency ($r = -.55$, $p < .01$) (Landis, et al., 2003).

Data Collection

The participants wore the actigraph on the non-dominant wrist for the 7 to 63 days of monitoring. Actigraphy epochs were 1 minute, and data points vary from 10,080-90,720 per woman. Data collection and download were programmed with Actiware™ software (Version 3.2, Mini Mitter) by connecting a reader to a computer.

Data Analysis

All data will be analyzed using the PIM mode. The PIM mode better estimates movement intensity, daytime activity (Berger, et al., 2008), movement acceleration, and amplitude than the other modes (Ancoli-Israel, et al., 2003). The PIM mode was found to be most reliable in older community-dwelling women for movement acceleration and amplitude and determining wake from sleep periods (Blackwell, et al., 2008). It was also found to be most correlated with

polysomnography in community-dwelling men overall and especially with sleep onset latency estimation and total sleep time (Blackwell, Ancoli-Israel, Redline, & Stone, 2011). Sleep and wake episodes will be estimated by the software and compared with the daily logs. The log time stamp will be used if discrepancies between software estimated sleep and wake episodes and log are greater than 15 minutes; notation of this adjustment will be reported. A 15-minute criterion is recommended to distinguish between estimation of and actual sleep (Hauri & Olmstead, 1983). Furthermore, The Actiware™ software (Version 5.5, Mini Mitter) used for this analysis defines sleep onset latency as the first 20-minute instance when the actigraph begins recording data. Utilizing the recommended 15-minute criterion will further help distinguish between estimated and actual sleep. Activity counts will be reported as minimum value, maximum value, and mean (\pm SD) or median (\pm IQR); median will be used if the data are not normally distributed (Rosner, 2006). The procedures for data management and analysis are outlined in Appendix B. Alpha will be .05 unless otherwise specified.

Aim1: Correlation of circadian temperature rhythm with activity-rest pattern

Skin temperature data sets will be retrieved from the parent study.

Temperature data sets in the previous study (Hanneman & Padhye, unpublished data) were analyzed using the average waveform approach (Padhye & Hanneman, 2007). In the proposed study, the activity-rest and temperature data sets will be sectioned by 7 days to include 5 work days and 2 non-work days. The data sets will be fit to the 3-parameter 24-hour cosinor model to test for a statistically significant circadian rhythm, defined as $p \leq .001$ because of auto-

correlation in the time series, with the zero amplitude test (Nelson, Tong, Lee, & Halberg, 1979). R^2 will be evaluated for goodness-of-fit to the cosinor model (Padhye & Hanneman, 2007; Rosner, 2006), with acceptable goodness-of-fit defined as $R^2 \geq .10$; the higher the R^2 , the stronger the rhythm (Pallant, 2001). The amplitude, acrophase, and mesor from the activity-rest and temperature cosinor models will be correlated using the Pearson correlation coefficient.

Aim 2: Lead-lag relation between circadian activity-rest and skin temperature rhythms

The differences between the activity-rest and temperature acrophases retrieved from the 3-parameter, 24-hour cosinor model analyses will be computed to yield an estimate of lead or lag time using a one-sample t -test. A log transformation will be completed and a cross-correlation function will be completed if linearity is satisfied. A lead-lag relation will be determined if the differences between the means are other than zero. Advantages of using the 3-parameter, 24-hour cosinor model to derive acrophase include no effect from missing values and independence from needing linearity between activity-rest and temperature variables (Nikhil S. Padhye, personal communication, November 8, 2012).

Aim 3: Stability of activity-rest patterns during work and non-work days

The work-day acrophase will be compared with the non-workday acrophase using the paired t -test to determine statistically significant difference between the 2 acrophases for individual participants and for the complete group.

Aim 4: Duration of actigraphy sampling

The intraclass correlation coefficient (ICC) will be computed for amplitude, mesor, and acrophase of the first 2 days of activity-rest data for individual participants and the complete group. Then the ICC will be computed for the first 3 days, first 4 days, and so on until the ICC is $\geq .75$. An ICC > 0.75 is considered to indicate excellent reproducibility (Rosner, 2006).

Aim 5: Sleep parameters

Sleep parameters will be scored by the Cole-Kripke method (Cole et al., 1992) using Actiware™ software (Version 5.5, Mini Mitter). The parameters of SOL, SE, TST, WT, and SS will be reported.

Limitations

Skin temperature measurement offers feasibility advantages over rectal temperature measurement and may enhance compliance when participants are monitored longitudinally in a community setting; female participants have dropped out of research studies because of repeated rectal insertions (Dzarr, Kamal, & Baba, 2009). However, the use of skin temperature presents a challenge for comparing findings with extant ones that were determined from core body temperature. Although mesor and amplitude are comparable with those obtained from core body temperature (Hanneman & Padhye, unpublished data), comparison of skin temperature acrophase findings may be difficult because the extant literature exists for core body temperature. Inferences for core body temperature cannot be made, as acrophase findings differ between skin and core body temperature.

Although 10,080 to 90,720 activity-count epochs per woman increases the precision of the analyses, the small sample size is a limitation. The women were not restricted by bedtimes, wake times, activity, medication, alcohol, or caffeine use. Use of certain medications, such as sleep aids (Lemmer, 2007) and alcohol after 8 pm can suppress melatonin (Rupp, Acebo, & Carskadon, 2007), and an excess of 300 mg of caffeine per day and after 8 pm can interfere with the natural circadian rhythms that enhance sleep (Carrier, et al., 2007). The health of the women was not specifically assessed by physical examination or laboratory testing, but the women documented illness and medications and were able to execute their student and/or occupational role(s).

Protection of Human Subjects

The proposed study is an analysis of extant data and was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston. There is only minimal risk to human subjects with the proposed study: potential for breach of confidentiality. To reduce that risk, participants' data were de-identified by investigators of the parent study prior to transfer to this investigator. No names or other personal identifiers are associated with the data sets.

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Appendix A
Study Approval



The Committee for the
Protection of Human Subjects

April 5, 2001

Sandra K. Hanneman, Ph.D., RN
Center for Nursing Research
School of Nursing

Dear Dr. Hanneman:

We are in receipt of your request for approval for your summer research students to conduct a research study with themselves as subjects. It is our understanding that the study involves the placing of a thermistor probe to their skin and the carrying of a small data logger. The consent form you have developed is appropriate and you have adequately addressed the confidentiality issues. We are therefore pleased to extend administrative approval for you to proceed.

Thank you for keeping us informed.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Paula Knudson".

Paula Knudson, CIP
Executive Coordinator

Appendix B
Protection of Human Subjects



Center for Nursing Research
Sandra K. Hanneman, RN, PhD, FAAN
Associate Dean for Research and Evaluation

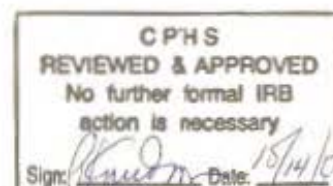
Memo

To: Paula Knudson
Committee for the Protection of Human Subjects

From: Sandra K. Hanneman, PhD, RN, FAAN
Associate Dean for Research

Re: Age-related Differences in Female Circadian Temperature Rhythms

Date: October 14, 2002



Attached please find copies of previous communications regarding the study entitled "Age-related Differences in Female Circadian Temperature Rhythms." We have been monitoring skin temperature in the summer science students assigned to my lab and in myself. My circadian temperature rhythm patterns changed when I entered the perimenopause, raising a question about circadian temperature rhythm (CTR) instability in women during periods of hormone fluctuation.

I recently presented the preliminary findings to the Board members of PARTNERS, the community support group for the School of Nursing. Four members of the board asked if they could participate in the study. Thus, we would like to explore further in a small sample of older women if the CTR findings hold for the perimenopausal period. We would like to extend study participation to the PARTNERS volunteers. However, it's possible that some of these women may be menopausal and/or post-menopausal. Because we need perimenopausal women to verify my data and for comparison with our young women (the summer science students), we would like to recruit additional women if needed from the community by word of mouth to assure a minimum of 4 perimenopausal data sets.

If the data in other perimenopausal women are similar to my data, we will submit a protocol to CPHS and to NIH for a full pilot study that compares CTR in premenopausal, perimenopausal, and postmenopausal women. Prior to doing so, we need "proof of concept" that CTR does indeed vary across hormone-related transitions in women.

I am enclosing a consent form for the older women and the daily log. Please advise if we may collect data on 4 older women. Let me know if you need further information or clarification. Thank you for your assistance.

Enclosures: Approval request materials (04/02/01)
Administrative approval materials (04/05/01)
Older woman consent form
Daily log page

May, 2015

Susan G. Kornstein, MD
Virginia Commonwealth University
School of Medicine
P.O. Box 980319
Richmond, VA 23298-0319

Dear Dr. Kornstein,

Please find enclosed the manuscript entitled "Activity-Rest and Skin Temperature Circadian Rhythms and Sleep Patterns in Community-Dwelling Women" for consideration of publication in the *Journal of Women's Health*. I explored activity-rest and temperature circadian rhythms and sleep patterns in ambulatory women of reproductive, perimenopausal, and postmenopausal stages and describe the findings. Your journal is the only journal to which I have submitted this manuscript. Please consider the abstract, 18-page narrative, references, 11 tables, and 3 figures. There are no conflicts of interest in relation to this work.

Please let me know if you need any further information to facilitate the review.

Sincerely,

Kristina Leyden, MSN, RN, FNP-BC
PhD student
University of Texas Health Sciences Center at Houston
Center for Nursing Research
6901 Bertner Avenue, Room 594
Houston, TX 77030

Running head: ACTIVITY-REST PATTERNS

Activity-Rest and Skin Temperature Circadian Rhythms and
Sleep Patterns in Community-Dwelling Women

Kristina L. Leyden, MSN, RN, PhD Student

University of Texas Health Science Center at Houston School of Nursing

Abstract

Purpose: Explore activity-rest and temperature circadian rhythms and sleep patterns in ambulatory women of reproductive, perimenopausal, and postmenopausal stages.

Methods: Seven community-dwelling women wore an actigraph and thermal sensor for 13 – 52 consecutive days. Data were fit to the cosinor model to test for statistically significant rhythms. Cosinor parameters from activity-rest and temperature rhythms were correlated to determine lead-lag relation. Work/non-work day acrophase stability was determined using the paired *t*-test. The standard error of the mean (SEM) was computed to determine actigraphy monitoring duration variance. Sleep parameters were scored using Actiware™ software.

Results: All participants had significant activity-rest and skin temperature circadian rhythms ($p \leq 0.001$); six (86%) had a significant correlation ($p \leq 0.05$) between activity-rest and temperature. Inconsistent lead-lag relationships were estimated in 6 participants (86%). Differences in activity-rest rhythms between work/non-work days were not statistically significant in 86% of the women. Four days of actigraphy monitoring yielded variance of 33 minutes. Reproductive and menopausal stage participants experienced the most interrupted sleep. Perimenopausal participants averaged more sleep time, fewer night awakenings, and least hours of wake after sleep onset. Menopausal participants slept the least number of hours a day.

Conclusions: The circadian rhythm findings were consistent with those from laboratory studies, but suggest that behaviors in the naturalistic setting may alter the lead-lag relationship between activity-rest and body temperature. In general, activity-rest patterns were stable between work and non-work days. Four days of actigraphy monitoring provided evidence of adequate reproducibility of data. Sleep parameters varied across reproductive stages.

Introduction

The activity-rest rhythm helps align biological and behavioral rhythms to the 24-hr day (Baron & Reid, 2014; Touitou, Coste, Dispersyn, & Pain, 2010). Activity-rest rhythms are coupled with such markers of the circadian pacemaker (i.e., biologic clock) as circadian temperature rhythm (Aschoff, 1979); the activity period corresponds with peak body temperature and the rest period with the temperature nadir. Variations in activity-rest patterns, as occur with shift work or transmeridian travel, can lead to circadian misalignment, defined as failure of external synchronizers to entrain the endogenous circadian pacemaker, located in the suprachiasmatic nuclei, to the 24-hr day.

Sustained circadian misalignment is associated with adverse health consequences (Knutsson, 2003; LaDou, 1982; Scheer, et al., 2009; Touitou, et al., 2010), higher healthcare costs, lost productivity, and decreased quality of life (Bolge, et al., 2010; Rosekind, et al., 2010). Potential health consequences of misaligned rhythms include obesity; cardiovascular disease; diabetes; epilepsy (Scheer, et al., 2009; Winget & LaDou, 1978); breast and colorectal cancer (Schernhammer, et al., 2001; Schernhammer, et al., 2003); hypertension; osteoporosis; gastrointestinal disorders (Foley, et al., 2004); and such cognitive changes as impaired attention, memory, and social and interpersonal functioning (Rosekind, et al., 2010). Furthermore, risk for miscarriage, low birth weight, and preterm birth in pregnant women have been reported with activity-rest rhythm misalignment (Knutsson, 2003). Women with circadian misalignment from cyclical hormonal changes have been shown to have decreased productivity in

the workplace (Heinemann, et al., 2010; Mishell, 2005). The annual economic impact in the United States of circadian misalignment has been estimated at \$54 million (Rosekind, et al., 2010).

Temporal alignment of activity-rest and temperature circadian rhythms has been demonstrated, with both activity and body temperature lowest during sleep (Czeisler & Khalsa, 2000; Mills, et al., 1978), and sleep efficiency is highest during the temperature nadir (Dijk & Czeisler, 1995). However, these studies were conducted in controlled laboratory settings. Others have found unstable activity-rest rhythms in women in the natural setting (Owens & Matthews, 1998; Patkai, et al., 1974).

In terms of coupling of rhythms, research with human and animal subjects (Refinetti & Menaker, 1992) suggests that activity leads temperature (i.e., a rise in activity level comes before a rise in temperature). Demonstration of this “lead-lag” relation in community-dwelling women may justify activity-rest interventions to prevent adverse consequences of disrupted activity-rest rhythms and, consequently, circadian misalignment. Research on activity-rest and body temperature rhythms in women largely has been conducted across the menstrual cycle phases with women in the reproductive stage (Baker et.al., 2001; Lee, 1988; Nakayama, et al. 1992). Little is known about activity-rest and temperature rhythms in perimenopausal and postmenopausal women. Women in these latter stages often are plagued by nocturnal hot flashes that disrupt sleep. The peripheral vasodilation and heat loss that occurs with hot flashes (Freedman,

2014) may affect the body temperature rhythm as well as the activity-rest rhythm given that hot flashes can occur throughout the 24-hr day.

Activity-rest patterns may differ between work and non-work days: individuals may retire and awaken later on non-work days either to recover sleep lost during the work week or follow a preferred activity-rest pattern based on chronotype, or preference for morning versus evening activity (Taillard, et al. 1999). Taillard and colleagues (1999, 2003) found a negative correlation ($p = -0.414$, $P < 0.005$) between work and non-work day sleep time; the more sleep lost during work days, the more sleep accrued during non-work days. The extent to which unstable activity-rest patterns within the week contribute to circadian misalignment has not been fully considered, and may be particularly relevant for working women.

Activity-rest patterns commonly are assessed with actigraphy (Sadeh, et al. 1995). Capture of work and non-work day patterns requires longitudinal data. Although others have provided evidence of duration of actigraphy sampling to obtain reliable data, the evidence is highly variable, ranging from 2 (Thomas & Burr, 2008) to 30 days (Padhye & Hanneman, 2007), depending on the purpose of the study. The activity-rest datasets used for the present study varied in length; thus, reliability of data was of interest.

In this exploratory pilot study, activity-rest and skin temperature circadian rhythms and sleep patterns of ambulatory women living in their natural environment were analyzed to inform future hypotheses of circadian misalignment in women across the reproductive stages. The aims of the study

were to: (1) assess the strength of the correlation between activity-rest and temperature circadian rhythms; (2) determine lead-lag relation (change in one variable precedes change in another) between activity-rest and skin temperature circadian rhythms; (3) determine stability of activity-rest patterns during work and non-work days; (4) estimate duration of actigraphy sampling needed for reliable data; and (5) describe sleep parameters of women in the reproductive, perimenopausal, and postmenopausal stages. The study findings lay a beginning foundation for future research that may ultimately lead to interventions that improve activity-rest rhythms, and subsequently circadian alignment, in community-dwelling women, thereby decreasing health problems, health care costs, and lost productivity.

Materials and Methods

Analysis of de-identified extant data was approved by the Institutional Review Board of the University of Texas Health Science Center at Houston. Activity-rest and temperature circadian rhythms and sleep patterns were analyzed from time-series actigraphy and skin temperature data that were collected prospectively from ambulatory women of reproductive, perimenopausal, and postmenopausal ages. Actigraphy is a reliable method to analyze activity, rest, and sleep parameters (Ancoli-Israel, et al., 2002; Gironde, et al., 2007; Van Someren, 2000), for which the definitions as used in this study are in Table 1. The cosinor model was used for analysis of circadian rhythms.

Sample and Setting

Actigraphy and temperature data from seven community-dwelling women were analyzed. The women were between 27 and 54 years of age at the time of data collection: two women in the reproductive age range (27 and 29 years old); three perimenopausal (51-55 years old), and two in menopause (52 and 54 years old). The women were recruited by convenience through word of mouth in the surrounding medical center community without bias for race or ethnicity. All participants had intact uterus and ovaries, no known gynecological abnormalities, and reported a diurnal activity and nighttime sleep social routine and no travel outside a 1-hour time zone change during the observation time. Data were collected from March 2002 through July 2004.

Data Collection

The participants wore an actigraph (Actiwatch Score, Mini Mitter Company Inc.) on the non-dominant wrist for 13 to 52 consecutive days of monitoring. Actigraphy epochs were 1 minute, resulting in time series lengths that varied from 10,080 to 90,720 measurements per woman. Data collection and download were programmed with Actiware™ software (Version 3.2, Mini Mitter). Participants completed daily logs with menses onset (as appropriate), bedtimes, wake times, exercise, medications, alcohol/drug/caffeine use, and times of actigraph removal and application.

Data Management and Analysis

Actigraphy data were analyzed using the proportional integration mode (PIM) because the PIM estimates for movement intensity, daytime activity

(Berger, et al., 2008), movement acceleration, and amplitude have better estimates of reliability and validity than the time above threshold or zero-crossing modes (Ancoli-Israel, et al., 2003; Blackwell, et al., 2008; Blackwell, et al., 2011). Sleep and wake episodes were estimated by the Actiware software and compared with the daily logs.

The first aim was to assess the strength of the correlation between activity-rest and temperature circadian rhythms. Actigraphy and skin temperature data sets were retrieved from the parent study. The distributions of the data were assessed by skewness and kurtosis statistics and histograms. The full-data sets were subjected to the 3-parameter, 24-hour cosinor model and tested for a statistically significant circadian rhythm with the zero amplitude test. Alpha was set at 0.001 because autocorrelated residuals tend to underestimate the p-value (Nelson, et al., 1979). R^2 was evaluated for goodness-of-fit (Rosner, 2006) of the data to the cosinor model, with acceptable goodness-of-fit defined as $R^2 \geq .10$. Activity counts and temperature for full data sets were aggregated for consistent time intervals and correlated using the Spearman correlation coefficient (r_s).

The second aim was to determine the lead-lag relation between activity-rest and skin temperature circadian rhythms. Hourly activity counts and temperature values were correlated for lags ranging from -8 to 8 hours. The lead lag relationship was determined by the largest absolute value of the r_s coefficient falling outside the 59-minute time period.

The third aim was to determine stability of activity-rest patterns during work and non-work days. The activity-rest data sets were sectioned weekly by

the first noted work days in succession and the first non-work days in succession. Work days were a minimum of 2 and a maximum of 5; non-work days were a minimum of 2 and a maximum of 3. The average acrophase, mesor (midline-estimating statistic of rhythm), and amplitude for the work-day sections was compared with the average respective parameter in the non-work day sections using the paired *t*-test to determine statistically significant differences in the parameters for individual participants and the group.

The fourth aim was to estimate duration of actigraphy sampling needed for reliable data. Using the daily acrophase for each participant, the acrophase standard error of the mean (SEM) was computed for the various lengths of data for individual participants and the group to estimate duration of monitoring needed for reliable data. The monitoring day when the weighted SEM, in minutes, decreased linearly in each subsequent day over all data sets determined the acceptable length of monitoring for reproducible, longitudinal actigraphy data.

The fifth aim was to describe sleep parameters. The sleep parameters of sleep onset latency (SOL), sleep efficiency (SE), total sleep time (TST), wake time (WT), and subjective sleep (SS) were scored by the Cole-Kripke method (Cole et al., 1992) and computed by Actiware™ software (Version 5.5, Mini Mitter). Definitions of these parameters are in Table 1.

Results

Characteristics of the participants are shown in Table 2. Four of the seven participants were obese, defined as having a body mass index (BMI) greater than 30 (National Institutes of Health, 2000).

Descriptive statistics for activity counts and temperature values during wake and rest periods are shown in Tables 3 and 4, respectively. Activity counts and skin temperature are reported as minimum and maximum values with a group range of 30-344 activity counts and temperature values of 35.3-37.0°C. These statistics are separated into two tables to compare activity with temperature and rest with temperature. Activity count and temperature data approximated a normal distribution with a cubic root transformation. Descriptive statistics for sleep parameters by participant and for the group are shown in Table 5.

Participant daily log completion rates are shown in Table 6; all but one participant's log were available. The participants kept a log from 33-62 days, and compliance with daily log completion varied from 70% to 100%. Although all participants noted wake and bed times, there was variation in detail, types of activity, and oral intake; perimenopausal and menopausal women noted when they had hot flashes.

All activity-rest and body temperature data sets met the criterion for a statistically significant circadian rhythm ($p \leq .001$); mean (\pm SD) activity-rest and temperature cosinor parameters of the transformed data for the sample are presented in Table 7. The activity-rest cosinor parameters are: mesor, 4 ± 1

activity counts/minute; amplitude, 2 ± 0 movements/minute; and acrophase $14:59 \pm 1:30$, which varied from 12:29 to 17:22 across participants. Data from all participants (100%) met the criterion for a strong activity-rest rhythm ($R^2 \geq .10$). The mean (\pm SD) temperature cosinor parameters of the transformed data for the sample are mesor, $3.29 \pm 0.02^\circ\text{C}$; amplitude, $0.01 \pm 0.01^\circ\text{C}$; and acrophase, $19:09 \pm 4:19$, which varied from 13:50 to 00:27 across participants. Three of the seven participants (43%) met the criterion for a strong rhythm ($R^2 \geq .10$): participant 4 in the perimenopausal stage and participants 6 and 7 in the menopausal stage. Activity-rest and temperature data are plotted in Figure 1 to show examples of strong and weak circadian rhythms in two perimenopausal women; participant 4 (Figure 1A and 1B) had strong rhythms and participant 5 (Figure 1C and 1D) had weak rhythms.

Aim 1: Correlation of activity-rest and temperature circadian rhythms. The Spearman correlation between individual activity-rest and temperature rhythms was statistically significant ($p \leq 0.05$) in 86% of the women, without regard to reproductive stage: four were positively correlated and three were negatively correlated. Three participants (4, 6, and 7) had biologically meaningful ($R^2 \geq .10$) circadian rhythms for both activity-rest and temperature (Table 7).

Aim 2: Lead-lag relationship between activity-rest and temperature. A significant lead-lag relationship between activity and temperature acrophases was found in 6 of 7 participants (86%), with r_s varying from 0.21- 0.58 at variable lags (highlighted in Table 8). Temperature rise before an increase in activity was

indicated by a significant correlation ($r_s = 0.21$) at a negative lag in participant 1. Activity rise before an increase in temperature was indicated by a significant correlation at zero or positive lag in participants 2, 3, 4, 6 and 7 ($r_s = 0.22, 0.24, 0.58, 0.28$, and 0.42 , respectively). Data from participants 1, 4, and 6 had the strongest correlations within the 2- to 4-hour lag allotment for the boundaries of skin temperature acrophase, compared with core body temperature acrophase suggested in the extant literature (Hanneman & Padhye, 2005; Kräuchi & Wirz-Justice, 1994).

Aim 3: Stability of activity-rest patterns during work and non-work days. The activity-rest rhythm characteristics for work and non-work days are shown in Table 9. All but one participant (5) had strong biologically meaningful ($R^2 \geq .10$) circadian rhythm for activity-rest in all data sets. In general, the acrophase was phase-delayed (occurred later) in non-work days. Only participant 4 had a statistically significant difference in acrophase ($p = .05$) between work and non-work days, although the differences in participants 1 and 3 approached significance ($p = .06$ and $.07$, respectively).

Aim 4: Duration of actigraphy sampling. The duration of actigraphy monitoring varied across participants from 13 to 52 days, with a maximum of 10 sequential days across participants to evaluate variance. Individual participant SEM for acrophase varied from 24 to 164 minutes. The standard errors were weighted for duration of monitoring and a group SEM computed by day. As shown in Table 10, the weighted SEM decreased with each additional monitoring day; monitoring for only 1 day had an estimated variance of 123 minutes,

whereas monitoring for 10 days decreased the variability estimate to 33 minutes. Thus, in this small sample, a minimum of 4 days of monitoring was needed to produce the most reliable actigraphy data for the purposes of the present study.

Aim 5: Sleep parameters. Participants in the perimenopausal stage averaged more sleep time and had longer SOL, albeit a marginal difference in the latter, than participants in the reproductive or menopausal stage (Table 5). Number of awakenings during the sleep period and hours of WASO were less in the perimenopausal women. The menopausal participants had the least amount of sleep time. Participant 6 had a median sleep time of 3.9 hours; her data are shown in Figures 2 and 3. Figure 2 illustrates the first 12 days of data showing calculated times for rest and sleep and the next 12 days of data showing where the majority of rest periods were calculated as rest, not sleep, throughout the night. Although she consistently marked sleep time from 2200-2300 and wake time of 0400-0600 in the daily log, the software scored markedly shorter intervals as sleep (Figure 2) on several days from July 19 onward and no sleep time for 6 days of the last week of monitoring. Her average sleep time increases to 3.9 hours if the days with no calculated sleep intervals are eliminated. Days 7/19 and 7/21 show very few sleep intervals. Days 7/23-8/6 show marked rest periods with virtually no sleep time. Figure 3 illustrates a magnified view of recorded rest and sleep intervals; two days (7/16 and 7/19) were selected to illustrate how the software estimated rest and sleep; Figure 3D shows increased magnitude of movement during the reported sleep intervals.

Discussion

This study appears to be the first to explore the relation between activity-rest and temperature circadian rhythms in women of three reproductive stages and estimate: lead-lag relation between activity-rest and temperature circadian rhythms, stability of activity-rest patterns during work and non-work days, and sleep parameters. It was hypothesized that women with a strong activity-rest rhythm have a strong circadian temperature rhythm, indicating entrainment of the circadian pacemaker to a 24-hour day. Overall, 86% of the participants exhibited a statistically significant correlation between activity-rest and temperature circadian rhythms; however, there was one negatively correlated relationship in each of the reproductive stages. Only three participants (one perimenopausal and two postmenopausal) had biologically meaningful rhythms for activity-rest and temperature; all three were obese and reported hot flashes. Hot flashes are thought to be caused by peripheral vasodilation, excessive sweating, and a heightened response to heat dispersion (Freedman, 2014), which would be expected to interrupt sleep and therefore disrupt circadian rhythms. Weak rhythms for activity-rest and temperature in the reproductive-stage participants may be attributed to instability of temperature rhythms due to hormonal fluctuations (Baker & Driver, 2007; Kelly, 2006). Furthermore, these women were taking oral contraceptives, which have been shown to modify temperature and sleep rhythms (Baker & Driver, 2007; Reinberg, et al., 2007).

Because both are needed for circadian pacemaker synchronization (Mills, et al., 1978; Minors & Waterhouse, 1989; Refinetti & Menaker, 1992) and sleep

efficiency peaks during the temperature nadir (Dijk & Czeisler, 1995), it was hypothesized that activity-rest leads the temperature rhythm as suggested by Refinetti & Menaker. An estimated lead-lag relationship was found in the majority of participants, with activity leading temperature in five and temperature leading activity in one. Temperature was elevated prior to activity in one reproductive-stage participant whose log entries noted exercise late in the evening on some days; it is not clear if that behavior explains the negative lead-lag relationship. She is the only participant that had a higher maximum activity count during the rest period than during the wake time period. Furthermore, this woman discontinued oral contraceptive use 2 weeks prior to monitoring. Perhaps a washout period from oral contraceptives prior to monitoring is needed as menses after cessation of oral contraceptives can be delayed by up to 6 months (Huggins & Cullins, 1990) and stability of the menstrual cycle return may impact the relationship of activity and temperature. A negative lead-lag relationship (i.e., temperature leads activity) is consistent with an earlier temperature nadir in women on oral contraceptives (Kattapong, et al., 1995). The reasons for inconsistencies in the direction of the relationship of the activity-rest and circadian temperature rhythms and the lead-lag relationship are unclear, but may relate to the measurement of skin temperature instead of core body temperature. Previous hypotheses about coupling of activity-rest and temperature rhythms (Refinetti & Menaker, 1992) assumed core body temperature, and less is known about the circadian behavior of skin temperature.

All but one participant exhibited stability in activity-rest patterns between work and non-work days. According to Taillard and colleagues (1999, 2003), persons adhering to a strict school or work schedule do not necessarily adhere to the same schedule on their days off, and may alter their activity-rest pattern on non-work days to catch up on sleep or revert to their preferred activity-rest rhythm. Dinges et al. (1997) examined 16 healthy young adults after restricting their sleep for 7 consecutive nights; the participants needed 2 full nights of sleep to recover following sleep restriction. Although the differences were not significant in the present study, the clear majority of data sets showed a later acrophase on non-work days than on work days, which is consistent with previous research. In the present study, community-dwelling women who adhered to a diurnal activity pattern did not change substantially their activity-rest pattern between work and non-work days. The findings may reflect the small sample size and monitoring in the naturalistic setting, and chronotype (i.e., morning or evening preference) was not assessed. Future research examining activity-rest rhythms in participants across reproductive stages would benefit from assessment of chronotype to determine if stability of work and non-work day activity-rest patterns depends on congruence between work hours and innate morning vs. evening activity preference.

A minimum of 4 consecutive monitoring days was estimated to reliably determine activity-rest rhythms for these longitudinal datasets. Literature recommendations for the duration of monitoring vary. A 1-day monitoring period with actigraphy was sufficient in men and women to document wake after sleep

onset, total sleep time, and sleep efficiency, but not SOL, when compared with polysomnography (Lichstein, et al., 2006). Others found a 2-day actigraphy monitoring period in women and infants provided adequate reliability estimates (Thomas & Burr, 2008). A 7-day monitoring period in healthy men and women (20-85 years of age) demonstrated adequate validity estimates in measuring activity-rest patterns compared with the gold standard of polysomnography (Pollak, et al., 2001). Others (Padhye & Hanneman, 2007) suggested a monitoring period of at least 30 days should be used when considering hormonal influences, such as the menstrual cycle, on circadian rhythms. The wide range of actigraphy monitoring days in the present study offered the opportunity to compare within-subject reliability estimates of activity and rest to determine sampling sufficiency. There were unstable variance estimates in the first 3 days of actigraphy monitoring in this sample; 4 days of monitoring produced a linear decrease in variance. Nonetheless, the individual data suggest the number of monitoring data needed for reproducible data varies by individual. Individual variability may be age-related as the reproductive stage women in this small sample required longer periods of actigraphy monitoring to achieve the lowest SEM. The method used in this study reported days with varying shifts from the mean, which allows the researcher to decide allowable variance and the number of minutes that are acceptable for a given study.

Sleep patterns varied among the women. Participants in the reproductive and menopausal stages experienced the most interrupted sleep, women in the perimenopausal stage experienced a longer SOL, and those in the menopausal

stage experienced the least amount of sleep. Others reported differences in sleep latency, wake time, sleep efficiency, and total sleep time in women across different reproductive stages (Jean-Louis, et al., 1999; Lehnkering & Siegmund, 2007; Mongrain, et al., 2005; Owens & Matthews, 1998), with differences in postmenopausal women on hormone replacement therapy (HRT). The small number of participants in each reproductive stage in the present study makes it difficult to determine individual versus reproductive stage variation, but the findings are consistent with the extant literature.

In this small sample, SOL was longer in the perimenopausal and menopausal women, the latter being consistent with previous reports, which included participants on HRT with and without hot flashes (Owens & Matthews, 1998). Hot flashes, experienced by four of the five perimenopausal and menopausal women in the present study, may have contributed to delayed sleep onset. Consistent with a previous study (Lukacs, et al., 2004), sleep time was decreased in menopausal women, who also had greater WASO compared with the reproductive-aged and perimenopausal women.

Sleep interruptions have been reported in perimenopausal (Kravitz, et al., 2005) and menopausal (Antonijevic, Stalla, & Steiger, 2000; Lukacs, et al., 2004) women. In the present study, the number of awakenings was highly variable, with one participant in each reproductive stage showing a large number of awakenings. Other researchers suggested sleep interruptions may be due to co-morbidities such as elevated blood pressure and higher hip-to-waist ratio (Owens & Matthews, 1998). Only one woman in the present study was taking

antihypertensive medication, her BMI was 37.1, and she had the fewest number of awakenings of all subjects.

It is unclear why participant 6 had such a short sleep time in the latter part of study participation. She was hypertensive and diabetic. Although her log provided no indication as to whether or not her diabetes was controlled, uncontrolled diabetes can cause hot flashes and frequent urination. Also, several of the medications she was taking have such side effects as difficulty sleeping, muscle aches/cramps, and frequent urination. It is unclear if other factors, such as being on-call for her administrative position, restless leg syndrome, or undiagnosed/untreated obstructive sleep apnea were a cause of her poor sleep. Because of the erratic sleep intervals, it is surprising that participant 6 had strong biologically meaningful rhythms for activity-rest and temperature. Perhaps other behavioral routines are more important than quantity or quality of sleep for synchronizing biological rhythms, as suggested by Pardini and Kaeffer (2006).

Four of the seven participants were obese, and obesity can impact the activity-rest pattern (Patel et al., 2014) through reduced activity and sleep (e.g., obstructive sleep apnea). Nonetheless, three of the four obese participants in the present study had strong circadian rhythms in activity-rest and temperature. Obesity did not impact median wake activity, as obese participants had higher median wake activity counts than non-obese participants. Further studies with larger sample sizes are needed to confirm an association between obesity and activity-rest pattern.

Study Limitations

The small sample size was the major limitation of this exploratory study. Although 10,080 to 90,720 activity-count epochs per woman increased the precision of the analyses, heterogeneity was a limitation. The women differed in race, BMI, type of work, medications, and co-morbidities. The women were not restricted by bedtimes, wake times, activity, medication, alcohol, or caffeine use in order to reflect community-dwelling women; consequently, the usual controls over variables imposed in laboratory studies were not operable.

The health of the women was not assessed by physical examination or laboratory testing, but the women documented illness and medications and were able to execute their student and/or occupational roles. The participants' co-morbidities and potential side effects from medications may have had an impact on the results.

Conclusions and Implications

Despite the study limitations, the findings of this study contribute to the science of women's health by exploring activity-rest and temperature circadian rhythms across the reproductive stages. There was a statistically significant correlation between activity-rest and circadian temperature rhythm in the majority of participants, and lead-lag relationship between activity-rest and temperature rhythms was consistent with theoretical expectation in the majority of participants. Activity-rest rhythms were not significantly different between work and non-work days for the majority of women. A minimum of 4 monitoring days was sufficient to reliably determine activity-rest rhythms in longitudinal data of

community-dwelling women. Sleep parameters varied by individual participant rather than by reproductive-stage grouping, with the exception of sleep time; participants in the menopausal stage experienced the least amount of sleep.

Further research is needed with community-dwelling women who are more homogeneous than the sample in this pilot study with respect to chronic health status, BMI, and menstrual cycle phases (in reproductive-stage women) to understand relations among activity-rest, body temperature, sleep pattern, and behavioral routine in the naturalistic setting; the research should capture chronotype of individual participants. Future findings could be used to educate women regarding optimal activity-rest behaviors to lessen risk for co-morbidities and loss of productivity from circadian misalignment.

Acknowledgements

The author thanks Sandra K. Hanneman, PhD, RN, FAAN; Nikhil S. Padhye, PhD; and Joan Engebretson, DrPH, AHN-BC, RN, who served on the author's dissertation committee. The author also thanks Philips Respironics/MiniMitter for use of Actiware Software™ analysis software.

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Table 1

Activity, Rest, and Sleep Parameter Definitions

Parameter	Acronym	Definition
Activity Count		Minimum, maximum, and median movement captured by actigraph
Acrophase		Clock time at which peak activity count occurs
Amplitude		Distance of the fitted cosine curve between mesor and peak value
Mesor		Rhythm-adjusted mean
Nadir		Trough or minimum value
Sleep Efficiency	SE	Total sleep time compared to time spent in bed
Sleep Onset Latency	SOL	Time it takes to fall asleep after lying down
Subjective Sleep	SS	Reported total sleep time obtained through daily log
Total Sleep Time	TST	Total sleep time during 24 hours
Wake After Sleep Onset		More than 1 minute of wakefulness after sleep onset
Wake Time	WT	Time spent awake including sleep interruptions

Table 2
Characteristics of the Study Participants

Participant	Classification	Age	BMI ^a	Ethnicity	Monitoring	Medications/Hot Flashes
					Period ^b	
1	Reproductive	29	20.5	Caucasian	31	Oral contraceptives discontinued 2 weeks prior to study
2	Reproductive	27	32.9	Caucasian	52	
3	Perimenopausal	54	24.5	Caucasian	13	Hot flashes
4	Perimenopausal	51	35.5	Caucasian	32	Hot flashes
5	Perimenopausal	53	20.8	Caucasian	23	Lipid lowering, diuretic, antithrombotic, antacid
6	Menopausal	52	37.1	Caucasian	20	Angiotensin receptor blocker, glucose lowering, diuretic, lipid lowering, antithrombotic, beta-blocker/hot flashes
7	Menopausal	54	32.3	African American	18	Thyroid supplement, lipid lowering, biophosphonate/hot flashes

Note. Participants, N=7

^aBMI = body mass index

^bMonitoring Period In days

Table 3

Minimum, Maximum, and Median Activity Counts for Wake and Rest Times

Participant	Wake Time	Wake Activity Counts			Rest Time	Rest Activity Counts		
		Max ^a	Median	IQR ^b		Max ^a	Median	IQR ^b
1	06:30-23:29	2446	154	18-392	23:30-06:29	2602	0	0-2
2	09:30-00:59	4865	339	66-584	01:00-09:29	3156	0	0-8
3	07:30-23:59	5139	112	24-274	00:00-07:29	2299	0	0-0
4	08:00-22:29	1923	121	30-297	22:30-07:59	1030	0	0-0
5	07:00-22:29	20090	69	7-207	22:30-06:59	1923	0	0-24
6	04:00-21:59	2727	157	43-344	22:00-03:59	1075	15	9-11
7	04:30-21:59	5638	203	45-432	22:00-04:29	1684	0	0-8
Median		2299	154	30-344		3796	2	1-11
IQR ^b		(2587- 5389)	(117- 180)			(1380- 2451)	(0-0)	

Note. Data sets, $N=7$. Minimum rest and wake activity counts were zero. Wake and rest times are averages across days of study participation.

^aMaximum count.

^bIQR = interquartile range.

Table 4
Minimum, Maximum, and Median Temperature for Wake and Rest Times

Participant	Wake Time	Wake Temperature				Rest Time	Rest Temperature			
		Min ^a	Max ^b	Median	IQR ^c		Min ^a	Max ^b	Median	IQR ^c
1	06:30-23:29	31.3	38.8	35.9	35.5-38.8	23:30-06:29	31.3	37.2	35.7	35.4-36.1
2	09:30-00:59	31.3	37.1	35.5	34.9-36.0	01:00-09:29	31.3	37.3	35.7	35.0-36.1
3	07:30-23:59	32.1	37.2	35.7	35.3-36.1	00:00-07:29	32.9	36.7	35.7	35.4-35.9
4	08:00-22:29	31.3	37.6	37.1	37.0-37.2	22:30-07:59	31.3	38.7	36.7	36.4-37.0
5	07:00-22:29	31.3	37.8	36.3	35.7-36.6	22:30-06:59	31.4	37.2	36.4	36.6-36.1
6	04:00-21:59	31.2	37.9	36.7	36.4-36.9	22:00-03:59	31.9	37.1	36.3	36.1-36.4
7	04:30-21:59	31.4	37.4	34.5	33.3-37.4	22:00-04:29	31.4	36.9	35.3	34.5-35.6
Median		31.3	37.2	35.7	35.4-37.0		31.3	37.5	35.8	35.4-36.1
IQR		(31.3-31.4)	(37.3-37.9)	(35.6-36.5)			(31.3-31.7)	(37.0-37.2)	(35.7-36.3)	

Note. Data sets, N=7. Wake and rest times are averages of all monitoring days.

^aMinimum temperature.

^bMaximum temperature.

^cIQR = interquartile range.

Table 5

Median Sleep Parameters

Participant	Sleep Time (hr) ^a	Sleep Latency (min) ^b	Number of Awakenings	Wake after sleep onset (hr)
1	6.4	21	17	0.5
2	7.0	13	27	1.0
3	6.6	14	16	0.5
4	7.0	78	17	0.5
5	7.3	37	25	0.8
6	3.9	58	15	0.8
7	5.3	15	30	1.3
Group Median	6.6	21	17	0.8
IQR ^c	(5.4-7)	(21-53)	(18-26)	(0.6-1.1)

Note. Data sets, $N=7$.

^aTotal amount of sleep time during night.

^bMinutes to start of first 20-minute sleep period.

^cIQR = interquartile range.

Table 6

Compliance with Log Completion

Participant	Log Available	Days Completed	Days (%) Marked Wake and Sleep	Days (%) Marked Alcohol/Drugs/Caffeine Use
1	Yes	33	23 (70)	22 (67)
2	Yes	62	53 (85)	58 (94)
3	No	N/A	N/A	N/A
4	Yes	36	30 (83)	36 (100)
5	Yes	34	34 (100)	34 (100)
6	Yes	33	27 (82)	33 (100)
7	Yes	34	34 (100)	34 (100)
Mean		39	34 (87)	35 (94)
SD		11	10 (12)	12 (13)

Note. Participants, $N=7$.

Table 7

Rhythm Characteristics of Activity and Temperature by Single Cosinor Analysis after Cubic Root Transformation of the Data

Participant	Activity				Temperature			
	Acrophase	Mesor	Amplitude	R^2^a	Acrophase	Mesor	Amplitude	R^2^a
1*	14:51	4	2	0.31	16:37	3.29	0.00	0.03
2*	17:22	5	3	0.33	0:27	3.28	0.00	0.01
3	15:23	4	2	0.39	15:34	3.30	0.01	0.05
4*	15:18	4	2	0.43	17:45	3.32	0.01	0.54
5*	15:33	4	2	0.18	0:40	3.30	0.00	0.01
6*	12:29	5	2	0.28	13:50	3.32	0.01	0.35
7*	13:58	5	2	0.34	21:12	3.25	0.03	0.22
Mean	14:59	4	2	0.32	19:09	3.29	0.01	0.17
SD	1:30	1	0	0.08	4:19	0.02	0.01	0.21

Note. Data sets, N=7. Statistically significant (p < .05) correlation between activity-rest and temperature circadian rhythms.

^aR² = Goodness of fit/strength of circadian rhythm

Table 8
Lead-lag Relationship between Acrophases of Activity-Rest and Temperature
Circadian Rhythms

lag	Reproductive		Perimenopausal				Postmenopausal							
	1	2	3	4	5	6	7							
	r_s	p	r_s	p	r_s	p	r_s	p						
-8	0.11	0.00	0.18	0.00	0.14	0.00	-0.13	0.00	0.32	0.00				
-7	0.14	0.00	0.19	0.00	0.16	0.01	-0.11	0.01	0.35	0.00				
-6	0.17	0.00	0.19	0.00	0.14	0.01	0.37	0.00	-0.07	0.10	0.33	0.00		
-5	0.19	0.00	0.16	0.00	0.11	0.05	0.45	0.00	-0.04	0.40	-0.02	0.69	0.28	0.00
-4	0.21	0.00	0.09	0.00	0.08	0.14	0.52	0.00	0.00	0.92	0.01	0.75	0.22	0.00
-3	0.21	0.00	0.06	0.06	0.00	0.96	0.52	0.00	0.04	0.38	0.06	0.16	0.12	0.00
-2	0.16	0.00	-0.01	0.82	-0.03	0.64	0.49	0.00	-0.01	0.84	0.09	0.04	-0.01	0.76
-1	0.11	0.00	-0.05	0.11	-0.01	0.88	0.41	0.00	-0.06	0.16	0.12	0.01	-0.10	0.00
0	0.07	0.04	-0.35	0.00	0.02	0.67	0.46	0.00	-0.31	0.00	0.28	0.00	-0.24	0.00
1	0.12	0.00	-0.18	0.00	-0.02	0.77	0.58	0.00	-0.13	0.00	0.22	0.00	-0.17	0.00
2	0.14	0.00	-0.01	0.74	-0.01	0.85	0.57	0.00	0.04	0.34	0.13	0.00	0.01	0.83
3	0.19	0.00	0.10	0.00	0.06	0.32	0.51	0.00	0.03	0.43	0.05	0.22	0.19	0.00
4	0.19	0.00	0.16	0.00	0.12	0.03	0.45	0.00	0.07	0.09	0.00	1.00	0.29	0.00
5	0.15	0.00	0.21	0.00	0.15	0.01	0.37	0.00	0.06	0.17	-0.06	0.17	0.36	0.00
6	0.08	0.02	0.22	0.00	0.20	0.00	0.26	0.00	0.08	0.07	-0.12	0.00	0.42	0.00
7	0.03	0.35	0.20	0.00	0.24	0.00	0.12	0.00	0.06	0.18	-0.17	0.00	0.41	0.00
8	0.01	0.77	0.19	0.00	0.15	0.01	-0.02	0.65	0.04	0.38	-0.21	0.00	0.37	0.00

Note. Data sets, $N=7$. r_s , Spearman rho correlation coefficient. Statistical significance $p < 0.05$.

Table 9

Rhythm Characteristics of Activity by Single Cosinor Analysis on Work and Non-work Days

Participant	Work					Non-work				
	Days	Acrophase	Mesor	Amplitude	R^{2a}	Days	Acrophase	Mesor	Amplitude	R^{2a}
1	5	14:38	4.52	2.50	0.38	3	15:46	3.95	3.05	0.46
	5	14:21	4.14	2.54	0.43	2	15:49	4.42	2.56	0.35
	5	12:45	4.17	1.59	0.15	2	13:59	3.68	2.59	0.35
2	2	12:16	4.55	2.65	0.46	3	18:26	4.40	2.69	0.34
	5	17:33	5.48	2.58	0.40	2	15:54	5.09	3.40	0.45
	5	17:09	5.47	3.30	0.51	2	16:39	4.63	2.63	0.38
	5	15:49	5.43	2.96	0.42	2	20:03	4.78	2.24	0.20
	5	19:01	5.24	3.40	0.51	2	18:10	4.91	2.83	0.29
	5	19:04	5.31	2.82	0.38	2	17:41	4.43	2.66	0.29
	5	16:57	4.91	2.76	0.36	2	18:15	5.13	2.41	0.27
	5	17:06	4.09	2.13	0.22	2	18:07	3.79	2.10	0.22
	4	16:48	4.78	2.61	0.36	2	18:21	5.20	3.11	0.49
	5	15:25	3.90	2.08	0.35	2	17:17	4.09	1.79	0.28
3	4	14:42	3.90	2.47	0.43	2	15:52	3.66	2.35	0.41
	5	15:02	3.95	2.58	0.47	2	17:32	3.79	2.50	0.51
4	5	15:36	3.79	2.76	0.52	2	15:41	1.75	1.41	0.24
	5	14:56	4.04	2.67	0.52	2	16:57	3.32	2.00	0.37
	5	14:58	3.88	2.52	0.44	2	15:51	3.61	1.94	0.31
5	5	15:08	3.43	1.79	0.30	2	13:58	3.50	2.68	0.44
	5	14:09	3.91	2.49	0.43	2	17:34	4.02	2.09	0.37
	5	18:12	4.19	0.70	0.04	2	14:43	3.61	2.04	0.37
6	5	11:50	4.84	1.77	0.32	2	13:17	4.12	1.33	0.21
	5	13:12	5.32	1.81	0.39	2	12:18	4.60	1.56	0.24
7	4	12:41	5.28	1.30	0.32	2	13:27	4.62	1.47	0.33
	5	12:30	5.22	2.46	0.45	2	14:17	4.25	2.22	0.36
	5	14:10	5.24	2.53	0.44	2	13:28	4.14	1.77	0.26
	5	13:12	5.13	2.09	0.30	2	16:01	4.60	2.01	0.27
	5	12:26	4.86	1.98	0.25	2	13:08	4.67	2.93	0.51

Note. Data sets, $N=7$. After cubic root transformation of the data

^aGoodness of fit/strength of circadian rhythm

Table 10

*Group Weighted Mean
Standard Error by Days
of Activity-Rest
Monitoring*

Days	Mean Std. Error ^a
1	123
2	97
3	100
4	79
5	63
6	61
7	55
8	46
9	42
10	33

Note. Data sets, $N=7$.

^aMean Standard Error in minutes.

Figure Legends

Figure 1. Comparison of Strong and Weak Cosinor Rhythms in Activity and Temperature. Strong temperature (A) and activity (B) rhythms (Participant 4). Weak temperature (C) and activity (D) rhythms (Participant 5).

Figure 2. Actigraphy Data (Participant 6) for Days 7/11/02 – 8/03/02. Days 7/11/02 – 07/22/02 with rest and sleep intervals (A). Days 7/23/02 – 8/03/02 with majority rest-only intervals (B). Dark blue, excluded times when logger off; aqua, sleep intervals; light aqua, rest intervals. Green circle indicates the only sleep time scored by the software in Figure 2.B.

Figure 3. Comparison of Days with Long and Short Sleep Time (Participant 6). Day 7/16/02 showing rest and sleep intervals (A). Day 7/16/02 magnified to show activity counts in detail (B). Day 7/19/02 showing rest and sleep intervals (C). Day 7/19/02 magnified to show activity counts in detail (D). Red to blue line indicates rest interval; blue to green line indicates sleep interval; green to purple line indicates return to rest interval.

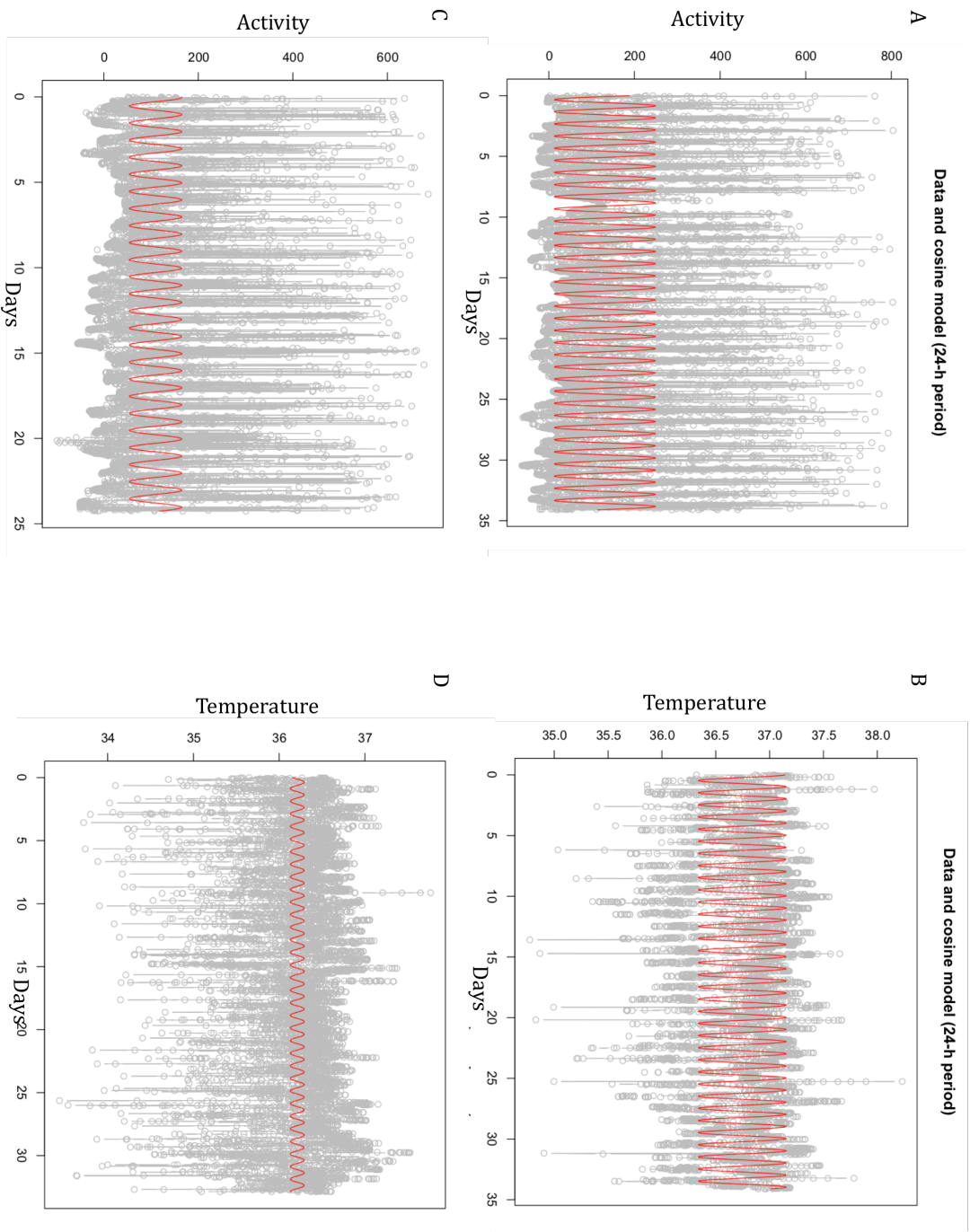


Figure 1.

A

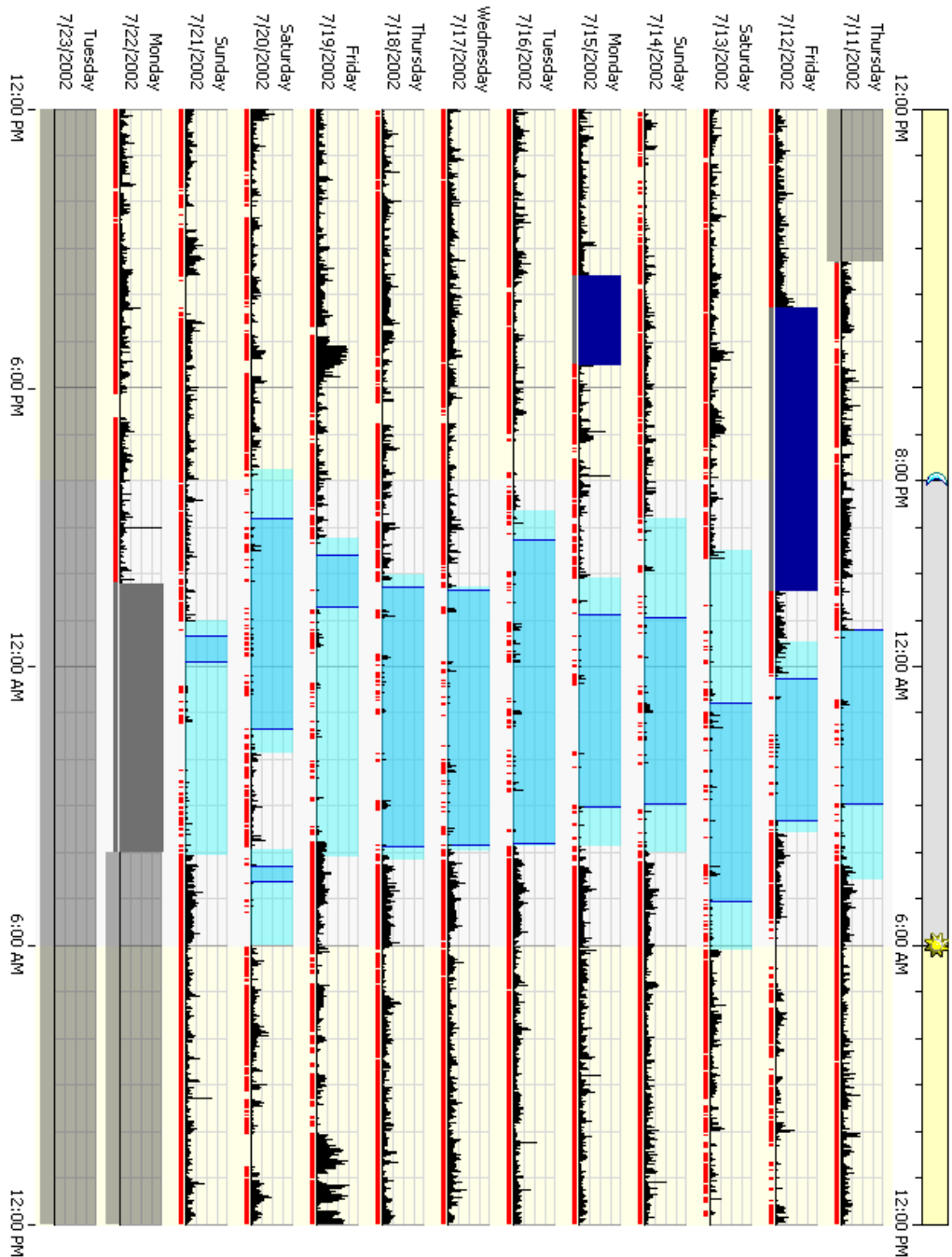
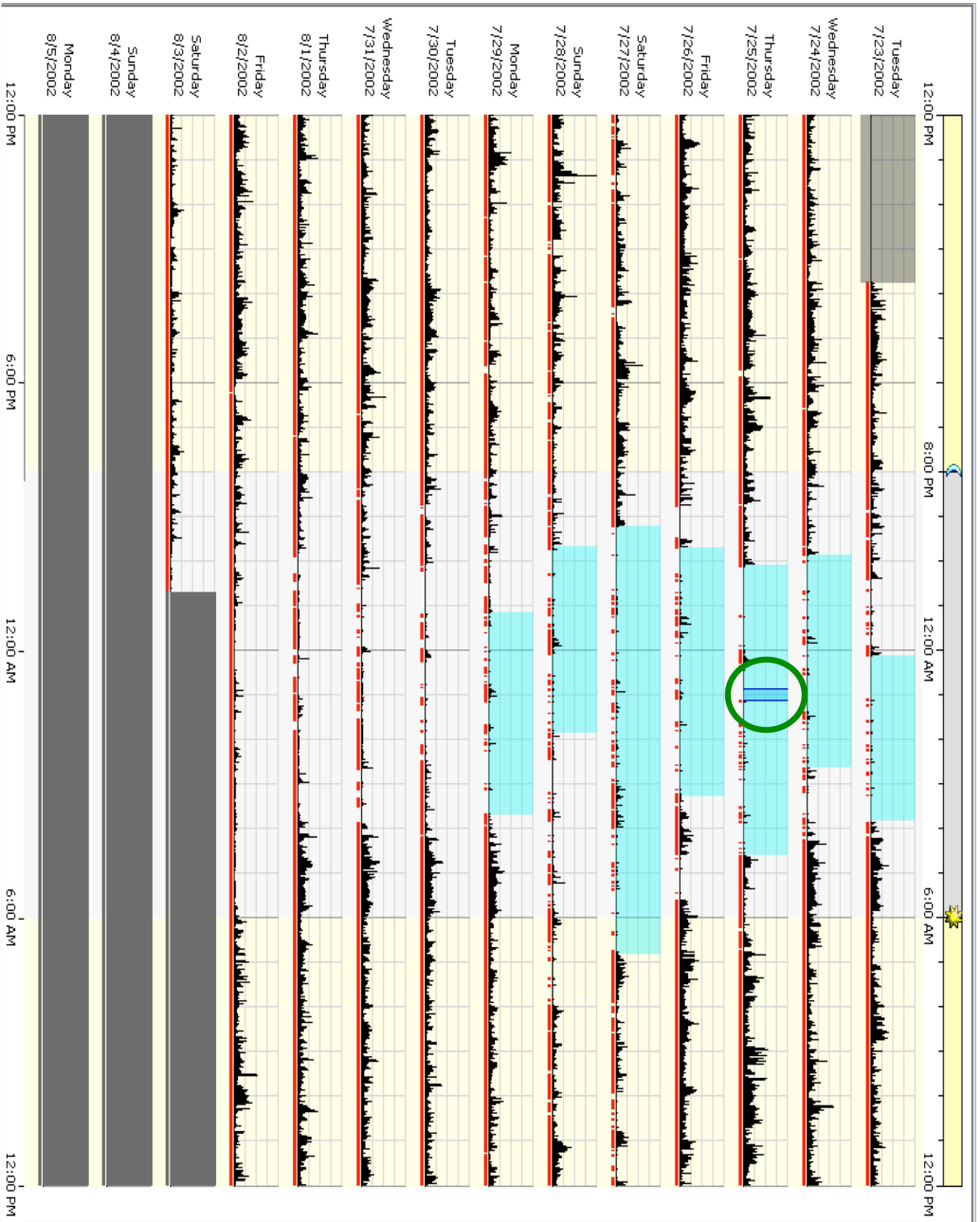


Figure 2.

B



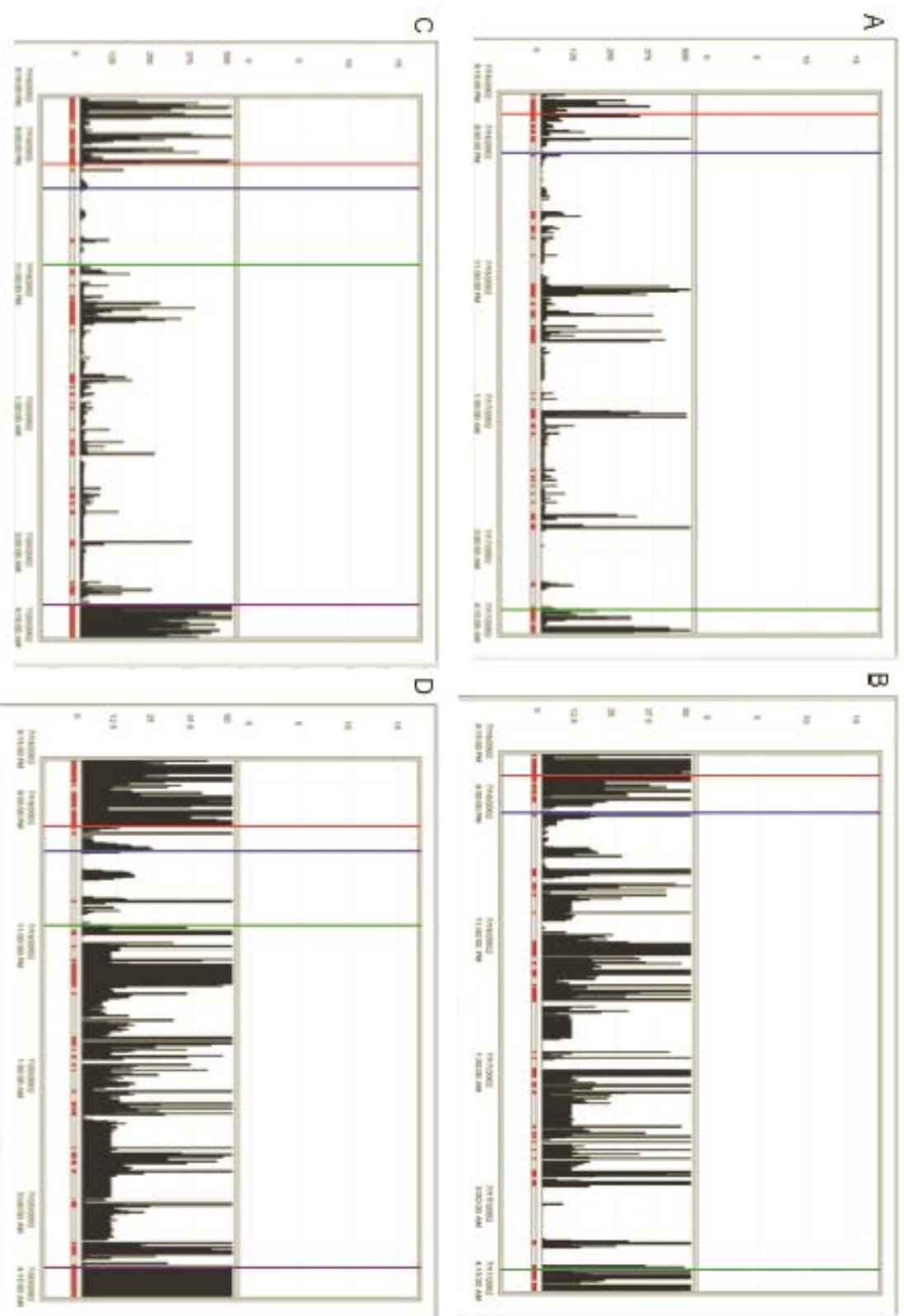


Figure 3.

Appendix A
Study Approvals



The Committee for the
Protection of Human Subjects

April 5, 2001

Sandra K. Hanneman, Ph.D., RN
Center for Nursing Research
School of Nursing

Dear Dr. Hanneman:

We are in receipt of your request for approval for your summer research students to conduct a research study with themselves as subjects. It is our understanding that the study involves the placing of a thermistor probe to their skin and the carrying of a small data logger. The consent form you have developed is appropriate and you have adequately addressed the confidentiality issues. We are therefore pleased to extend administrative approval for you to proceed.

Thank you for keeping us informed.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Paula Knudson".

Paula Knudson, CIP
Executive Coordinator

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Sandra.K.Hanneman@uth.tmc.edu
Located in the Texas Medical Center

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Center for Nursing Research
Sandra K. Hanneman, RN, PhD, FAAN
Associate Dean for Research and Evaluation

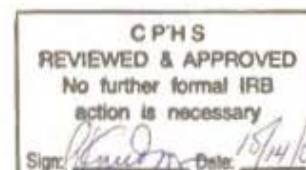
Memo

To: Paula Knudson
Committee for the Protection of Human Subjects

From: Sandra K. Hanneman, PhD, RN, FAAN
Associate Dean for Research

Re: Age-related Differences in Female Circadian Temperature Rhythms

Date: October 14, 2002



Attached please find copies of previous communications regarding the study entitled "Age-related Differences in Female Circadian Temperature Rhythms." We have been monitoring skin temperature in the summer science students assigned to my lab and in myself. My circadian temperature rhythm patterns changed when I entered the perimenopause, raising a question about circadian temperature rhythm (CTR) instability in women during periods of hormone fluctuation.

I recently presented the preliminary findings to the Board members of PARTNERS, the community support group for the School of Nursing. Four members of the board asked if they could participate in the study. Thus, we would like to explore further in a small sample of older women if the CTR findings hold for the perimenopausal period. We would like to extend study participation to the PARTNERS volunteers. However, it's possible that some of these women may be menopausal and/or post-menopausal. Because we need perimenopausal women to verify my data and for comparison with our young women (the summer science students), we would like to recruit additional women if needed from the community by word of mouth to assure a minimum of 4 perimenopausal data sets.

If the data in other perimenopausal women are similar to my data, we will submit a protocol to CPHS and to NIH for a full pilot study that compares CTR in premenopausal, perimenopausal, and postmenopausal women. Prior to doing so, we need "proof of concept" that CTR does indeed vary across hormone-related transitions in women.

I am enclosing a consent form for the older women and the daily log. Please advise if we may collect data on 4 older women. Let me know if you need further information or clarification. Thank you for your assistance.

Enclosures: Approval request materials (04/02/01)
Administrative approval materials (04/05/01)
Older woman consent form
Daily log page

Appendix B
Study Protocol

Activity-rest Patterns in Community Dwelling Women

Data Management and Analysis Study Protocol

Cleaning of Data

1. Open Subject 1's Excel activity-rest data file
2. Examine file for missing data, using Edit "find," first for empty cells
3. Assess congruence of time stamp by comparison with log. Record any differences between time and use log time for analysis if discrepancy > 15 minutes
4. Save as "Subject 1 cleaned AR data set"
5. Repeat steps 1 – 4 for all subjects
6. Repeat steps 1 – 5 for skin temperature data set, but save as "Subject 1 cleaned Temp data set"
7. Place all above data sets into one folder "Cleaned activity and temp data sets" (reference folder for cleaned data sets)

Alignment of activity-rest and temperature data sets

8. Open Subject 1's cleaned Excel activity-rest and skin temperature files
9. Open new Excel document
10. Review data columns for alignment of time
 - a. Check beginning time stamp
 - i. If match, continue to step "check end time stamp"
 - ii. If do not match:
 1. If AR data begins at earlier time: trim AR data to match temp data

2. If temp data begins at earlier time: trim temp data to match AR data
3. Record set and number of data points trimmed
- b. Check end time stamp
 - i. If match, continue to step “Save as “Subject 1 aligned full AR and temp data set”
 - ii. If do not match:
 1. If AR data exceeds temp data: trim AR data to match temp data
 2. If temp data exceeds AR data: trim temp data to match AR data
 3. Record set and number of data points trimmed
11. Save as “Subject 1 aligned full AR and temp data set”
12. Repeat above steps for all subjects
13. Place all above data sets into one folder “Aligned activity and temp data sets” (reference folder for aligned activity and temp data sets)

Trimming of activity-rest and temperature data to include sets of work days

14. Open “Subject 1 cleaned AR data set”
15. Compare log with data set and trim to work day data sets
16. Save as “Subject 1 work day (insert work dates of data set)”
17. Repeat steps 14 – 16 above for all work days and all subjects
18. Place in folder “Work days”

Trimming of activity-rest data to include sets of non-work days

19. Open "Subject 1 cleaned AR data set"
20. Compare log with data set and trim to non work day data sets
21. Save as "Subject 1 non-work day (insert non-work dates of data set)"
22. Repeat steps 19 – 21 for all non-work days and all subjects
23. Place in folder "Non-work days"

Trimming of activity-rest data to 24-hours

24. Open "Subject 1 cleaned AR data set"
25. Compare log with data set and trim to 24 hour data sets
26. Save as "Subject 1 work day (insert 24 date of data set)"
27. Repeat steps for each 24 hour day and for all subjects
28. Place in folder "daily acrophase"

Descriptive statistics

Activity-rest Data

Instructions modified from R scripts written by Nikhil Padhye, PhD

29. Open "Subject 1 cleaned AR data set"
30. Save as .cvs file and close
31. Open .cvs using text edit
32. Duplicate file
33. Save file
34. Copy file into users directory
35. Open R software
36. Code to retrieve file from directory:


```
filein <- "Subject 1 cleaned AR data set.txt"
```

37. Code to store data files:

```
fn0 <- substring(filein, 1, (nchar(filein)-4))
```

38. Code to choose data set to be analyzed:

```
data <- read.table(filein, sep=",")
```

39. Code to read data from file:

```
dt <- data[,1]
```

```
tm <- data[,2]
```

```
x <- data[,3]
```

```
dt[1:10]
```

40. Code to combine data and time for analysis:

```
dtm <- paste(as.character(dt), as.character(tm), sep=" ")
```

```
(use y for 2-digit year) dtm <- strptime(dtm, "%m/%d/%y %H:%M:%S")
```

```
(use y for 2-digit year without seconds) dtm <- strptime(dtm, "%m/%d/%y  
%H:%M")
```

```
(use Y for 4-digit year) dtm <- strptime(dtm, "%m/%d/%Y %H:%M:%S")
```

```
(use y for 4-digit year without seconds) dtm <- strptime(dtm, "%m/%d/%Y  
%H:%M")
```

41. Code to preserve initial time

```
dtm.0 <- dtm[1]
```

42. Code time into number for R understanding starting at zero:

```
ddtm <- difftime(dtm, dtm[1])
```

```
t <- as.numeric(ddtm, units="hours")
```

43. Code to determine median sampling interval and length of data collection:

```
cat("\n Median sampling interval: \n")
```

```
median(diff(dtm))
```

```
cat("\n Length of data collection (hours): ", max(t)-min(t), "\n")
```

44. Code to determine length of dataset

```
length(x)
```

45. Code to remove missing values

```
x.na <- is.na(x)
```

```
cat("Number of missing values discarded:", sum(x.na), "\n")
```

```
x <- x[!x.na]
```

```
t <- t[!x.na]
```

46. Code to save descriptive stats for original data

```
stats1 <- c(summary(x), sd(x), sqrt(var(x)/length(x)), length(x))
```

47. Code to display descriptive stats:

```
median(dt1)
```

```
mean(dt1)
```

```
pdf()
```

```
hist(x)
```

```
boxplot(x)
```

```
plot(t,x)
```

48. Save all data to designated folder

49. Repeat for all subjects

50. Visually inspect distribution from histogram for each subject

51. Describe the following parameters for subject

a. Minimum

b. Maximum

c. Median

- d. Interquartile range
- e. Skewness

Sleep Parameters

- 52. Open Actiware™ Software
- 53. File, Database, New, select Subject 1's AWD file
- 54. Find AWD file in the database viewer and double click
- 55. Double click on timeframe
- 56. Double click on New Analysis
- 57. Select "Ok"
- 58. Select "Ok" to have software estimate intervals
- 59. File, Print Clinician's report
- 60. Repeat for all subjects
- 61. Describe the following parameters for subject
 - f. Activity Count
 - g. Acrophase
 - h. Amplitude
 - i. Mesor
 - j. Nadir
- 62. Describe the following sleep parameters for subject
 - k. Sleep Efficiency
 - l. Sleep Onset Latency
 - m. Subjective Sleep
 - n. Total Sleep Time

o. Wake Time

Aim 1: Correlation of activity-rest and temperature circadian rhythms

Cosinor Model

63. Open R software

64. Code to retrieve file from directory:

```
filein <- "Subject 1 cleaned AR data set.txt"
```

65. Code to store data files:

```
fn0 <- substring(filein, 1, (nchar(filein)-4))
```

66. Code to choose data set to be analyzed:

```
data <- read.table(filein, sep=";")
```

67. Code to read data from file:

```
dt <- data[,1]
```

```
tm <- data[,2]
```

```
x <- data[,3]
```

```
dt[1:10]
```

68. Code to combine date and time for analysis:

```
dtm <- paste(as.character(dt), as.character(tm), sep=" ")
```

```
(use y for 2-digit year) dtm <- strptime(dtm, "%m/%d/%y %H:%M:%S")
```

```
(use y for 2-digit year without seconds) dtm <- strptime(dtm, "%m/%d/%y  
%H:%M")
```

```
(use Y for 4-digit year) dtm <- strptime(dtm, "%m/%d/%Y %H:%M:%S")
```

```
(use y for 4-digit year without seconds) dtm <- strptime(dtm, "%m/%d/%Y  
%H:%M")
```

69. Code to preserve initial time

```
dtm.0 <- dtm[1]
```

70. Code time into number for R understanding starting at zero:

```
ddtm <- difftime(dtm, dtm[1])
```

```
t <- as.numeric(ddtm, units="hours")
```

71. Code to determine median sampling interval and length of data collection:

```
cat("\n Median sampling interval: \n")
```

```
median(diff(dtm))
```

```
cat("\n Length of data collection (hours): ", max(t)-min(t), "\n")
```

72. Code to determine length of dataset

```
length(x)
```

73. Code to remove missing values

```
x.na <- is.na(x)
```

```
cat("Number of missing values discarded:", sum(x.na), "\n")
```

```
x <- x[!x.na]
```

```
t <- t[!x.na]
```

74. Code to save descriptive stats for original data

```
stats1 <- c(summary(x), sd(x), sqrt(var(x)/length(x)), length(x))
```

75. Code to check distribution and skewness

```
hist(x1)
```

```
skew(x1)
```

```
skew(x1[x1>0])
```

76. Code for transformation of variable

```
x1=x1^(1/3)
```

77. Code to check distribution and skewness of transformed variable

```
hist(x1)
skew(x1)
skew(x1[x1 > 0])
```

78. Code to plot the time series and plot marked outliers

```
dev.new()
plot(t1, x1, type='l', col=16, xlab="Time (h)")
title("Aggregated time series with far outliers marked, if any")
x.out <- outliers(x1, 3.0, 3.0)
points(t1[x.out], x1[x.out], col=2)
```

79. Code to save data set with outliers

```
dtm.agg <- dtm.0 + t1*3600
data.out <- data.frame(Time=dtm.agg, t=t1, x=x1, outlier=x.out)
zz <- file(paste(fn0, ".agg.csv", sep=""), "w")
write.table(data.out, sep="," , row.names=F, file=zz)
close(zz)
```

80. Code to save descriptive stats for original data for analysis of other variables

```
stats2 <- c(summary(x1), sd(x1), sqrt(var(x1)/length(x1)), length(x1))
```

81. Code to remove outliers

```
x1 <- x1[!x.out]
t1 <- t1[!x.out]
cat("Number of far outliers discarded after aggregation:", sum(x.out), "\n")
```

82. Code to save descriptive stats for original data for analysis of other variables

```
stats3 <- c(summary(x1), sd(x1), sqrt(var(x1)/length(x1)), length(x1))
```

83. Code to report and save set gaps

```

lgap <- 30/60 ## this is 30 minutes
dt1 <- c(0, diff(t1))
ngaps <- sum(dt1 > lgap)
cat('Gaps > ', lgap, ' h:\n')
listgaps <- cbind(t1[dt1 > lgap], 60*dt1[dt1 > lgap])
colnames(listgaps)=c("Timestamp.after.gap", "Gap duration (min)")
listgaps
zz <- file(paste(fn0, ".gaps.csv", sep=""), "w")
write.table(listgaps, sep=";", row.names=T, file=zz)
close(zz)

```

84. Code to interpolate on uniform time grid, create grid

```

deltat <- median(dt1)
t1u <- seq(from=t1[1], to=t1[length(t1)], by=deltat)
x1u <- approx(t1, x1, t1u, method='linear', rule=1)$y

```

85. Code to begin cosinor analysis section; estimata time period from nonlinear cosine model

```

period.est4 <- cosinor.nl.period(x1, t1, 24)
period.est <- c(24, period.est1, period.est2, period.est3, period.est4)

```

86. Code for storing results

```

ampmat <- matrix(NA, length(period.est), 12)

```

87. Code to compute cosine model on entire series and store in first row of ampmat

```

for (i in 1:length(period.est)) {
  if (!is.na(period.est[i])) {
    ampmat[i,1] <- period.est[i]
    ampmat[i,2:3] <- range(t1)
    ampmat[i,4:11] <- cosinor.AMPerr(x1, t1, period.est[i])
    ## compute zero-amp test
    ampmat[i,12] <- cosinor.zeroamp(x1, t1, period.est[i])
  }
}

```

88. Code to get clock time phases

```

ampmat[,7] <- clock.phase(dtm.0, ampmat[,7], 24, unit="h") #, limit24=F)
ampmat[,8] <- clock.phase(dtm.0, ampmat[,8], 24, unit="h") #, limit24=F)

```

89. Code to display cosinor model information; save cosinor model parameters in file

```
colnames(ampmat) <- c("Rhythm Period", "Start time", "End time", "Rsqr",
  "Amp", "Mes",
  "Acro", "Bathy", "Amp.SE", "Mes.SE", "Acro.SE",
  "p.zeroamp")
rownames(ampmat) <- c("24h", "Lomb1", "Lomb2", "ACF", "NLcos")
ampmat

zz <- file(paste(fn0, ".cosinor.csv", sep=""), "w")
write.table(ampmat, sep=";", row.names=T, file=zz)
close(zz)
```

90. Code to plot entire series and cosine model (with 24-h rhythm)

```
dev.new()
par(mfrow=c(1,1))
plot(t1/24, x1, type='b', col="grey", xlab='Days')
lines(t1/24, cosinor.fitted(x1, t1, 24), col="red")
title("Data and cosine model (24-h period)")
```

91. Highlight all displayed information in R workspace, edit, copy; open Word

Document, paste; save as “Cosinor analysis for subject 1” in
corresponding folder

92. Move all saved files for subject from Users directory to corresponding
folder

93. Repeat steps 63-92 for all subjects

94. Repeat steps 63-93 for all temperature data sets

95. Open new Excel document

96. Combine aggregated activity-rest and temperature data sets

97. Save as “Subject 1’s AR and Temp Correlation” .csv file and close

98. Repeat steps 95-97 for all subjects

99. Move .csv files into Users directory

100. Code to retrieve file, read data, attach data

```
filein = paste(path, "peri1cActCBT.csv", sep="/")
data = read.table(file=filein, header=T, sep="," , stringsAsFactors=F)
str(data)
attach(data)
```

101. Code to write graphics to PDF file

```
pdf(file=paste(path, "masking_plots.pdf", sep="/"))
```

102. Code to plot activity and temperature

```
plot(tcum, Act, type='n', xlab="Cumulative time", ylab="Activity")
#   xlim=c(0,24), xaxp=c(0,24,6))
for (i in unique(SubjectID)) {
  lines(tcum[SubjectID==i], Act[SubjectID==i], col=i)
}
legend("topleft", as.character(unique(SubjectID)), lty=1,
      col=unique(SubjectID), bty="n")
title("Activity time plot for each subject")

plot(tcum, CBT, type='n', xlab="Cumulative time",
      ylab="Temperature")
#   xlim=c(0,24), xaxp=c(0,24,6))
for (i in unique(SubjectID)) {
  lines(tcum[SubjectID==i], CBT[SubjectID==i], col=i)
}
legend("topleft", as.character(unique(SubjectID)), lty=1,
      col=unique(SubjectID), bty="n")
title("Temperature time plot for each subject")
```

103. Code to display scatterplots

```
scatterplotMatrix(~Act+CBT|SubjectID, data=data)
```

104. Code to compute correlations and store them

```
obj1 = vector(mode="list", length=3)
obj1 = list(cor.test(Act, CBT, method = "spearman"))

## Store all correlations computed until now
tab1 = data.frame(VarPair=sapply(obj1, function(x) c(x$data.name)))
tab1 = cbind(tab1, lag=c(0,0,0))
tab1 = cbind(tab1, t(sapply(obj1, function(x) c(x$estimate,
      'p-value' = x$p.value, x$statistic, x$parameter))))
tab1
```

105. Code to calculate correlation using Spearman Correlation Coefficient

```
ccf.spearman = function(x, y, max.lag){
  rho.minus=rep(0, max.lag)
  rho.plus=rep(0, max.lag)
  p.minus=rep(0, max.lag)
  p.plus=rep(0, max.lag)
  lag=seq(-max.lag, max.lag, by=1)
  for (i in 1:max.lag) {
    rho.minus[i]=cor(y[1:(length(y)-i)], x[(i+1):length(x)], method="s")
    rho.plus[i]=cor(x[1:(length(x)-i)], y[(i+1):length(y)], method="s")
    p.minus[i]=cor.test(y[1:(length(y)-i)], x[(i+1):length(x)],
method="s")$p.value
    p.plus[i]=cor.test(x[1:(length(x)-i)], y[(i+1):length(y)],
method="s")$p.value
  }
  rho = c(rho.minus, cor(x,y,method="s"), rho.plus)
  p = c(p.minus, cor.test(x,y,method="s")$p.value, p.plus)
  round(cbind(lag, rho, p),4)
}

ccf.mat = ccf.spearman(Act, CBT, 24)
plot(ccf.mat[,1], ccf.mat[,2], type="h", xlab="Lag", ylab="Rho")
ccf.mat
```

106. Code to compute mixed models of activity and temperature

```
cbtmod1 = lmer(CBT ~ Act + (1|SubjectID), na.action=na.omit)
summary(cbtmod1)
df1 <- sum(!is.na(CBT)&!is.na(Act)) -2
Vcov1 <- vcov(cbtmod1, useScale = FALSE)
betas1 <- fixef(cbtmod1)
se1 <- sqrt(diag(Vcov1))
zval1 <- betas1 / se1
pval1 <- 2 * pt(abs(zval1), df1, lower.tail = FALSE)
cbind(betas1, se1, zval1, pval1)

tab1 = cbind(tab1, betas, pvals)
tab1
```

107. Code to display scatterplot

108. `scatterplotMatrix(~dAct+dCBT|dSubjectID,`
`main=paste("Lag = ", lag))`

109. Code to compute correlations

```
obj2 = list(cor.test(dAct, dCBT, method = "spearman"))

tab2 = data.frame(VarPair=sapply(obj2, function(x) c(x$data.name)))
tab2 = cbind(tab2, lag=c(II,II,II))
tab2 = cbind(tab2, t(sapply(obj2, function(x) c(x$estimate,
      'p-value' = x$p.value, x$statistic, x$parameter))))
```

110. Code to compute mixed effects model and random slope model

```
if ((length(dSubjectID)/length(unique(dSubjectID))) >= 3) {
  cbtmod1 = lmer(dCBT ~ dAct + (1|dSubjectID), na.action=na.omit)

  df1 <- sum(!is.na(dCBT)&!is.na(dAct)) -2
  Vcov1 <- vcov(cbtmod1, useScale = FALSE)
  betas1 <- fixef(cbtmod1)
  se1 <- sqrt(diag(Vcov1))
  zval1 <- betas1 / se1
  pval1 <- 2 * pt(abs(zval1), df1, lower.tail = FALSE)

  ##cbind(betas1, se1, zval1, pval1)

}
else {
  betas = c(NA, NA)
  pvals = c(NA, NA)
}

tab2 = cbind(tab2, betas, pvals)

tab1 = rbind(tab1, tab2)

} ## end loop over lags

dev.off()
```

111. Code to write correlation table to output file

```
zz <- file(paste(path, "masking_cor.csv", sep="/"), "w")
write.table(tab1, sep="," , col.names=T, row.names=F, append=F,
  file=zz)
close(zz)
```


112. Move all saved files for subject from Users directory to corresponding folder
113. Repeat steps through 100-112 for all subjects

Aim 2: Lead-lag relation between circadian temperature and activity rest rhythm

114. After steps for correlation: Create differenced variables with allowance for various lags

```
lagvec = c(1,2,3,4,6,8,12) ## control lags by changing this vector
```

```
for (ll in lagvec) {
lag = ll ## set lag
igp = SubjectID*100 +1 +(tcum %/% lag) ## define time groups within
subject
```

115. Code to compute means on groups within subjects

```
mAct = tapply(Act, igp, mean, na.rm=T)
mCBT = tapply(CBT, igp, mean, na.rm=T)
mSubjectID = tapply(SubjectID, igp, mean, na.rm=T)
```

116. Code to initialize difference variables

```
dAct = rep(NA, length=length(mAct))
dCBT = rep(NA, length=length(mCBT))
dSubjectID = rep(NA, length=length(mSubjectID))
```

117. Code to compute differences per subject

```
for (i in unique(mSubjectID)) {
dAct[mSubjectID==i] = c(rep(NA, length=ll),
diff(mAct[mSubjectID==i],lag=ll))

dCBT[mSubjectID==i] = c(rep(NA, length=ll),
diff(mCBT[mSubjectID==i],lag=ll))
dSubjectID[mSubjectID==i] = c(NA, diff(mSubjectID[mSubjectID==i]))
}
i.na = which(is.na(dSubjectID))
dAct = dAct[-i.na]
dCBT = dCBT[-i.na]
dSubjectID = mSubjectID[-i.na]
```

118. Code to display Scatter plots of differenced variables

```
scatterplotMatrix(~dAct+dCBT|dSubjectID,
                  main=paste("Lag = ", lag))
```

Aim 3: Stability of activity-rest patterns during work and non-work days.

119. Open "Subject 1 work day (insert work dates of data set)"
120. Open "Subject 1 non-work day (insert non-work dates of data set)"
121. Copy acrophase of Subject 1 work day (1st set) and paste into L upper cell of new Excel spreadsheet
122. Copy acrophase of Subject 1 non-work day (1st set) and paste into cell to the right of L upper cell
123. Open Subject 1's next work dates
124. Copy acrophase and paste under previous acrophase
125. Open Subject 1's next non-work dates
126. Copy acrophase and paste under previous acrophase
127. Repeat until all work and non-work dates are entered in cells
128. Change all cells into number format
129. Save as "Subject 1 worknonwork.csv" file and close
130. Open .csv using text edit
131. Duplicate file
132. Save file as .txt
133. Copy file into users directory
134. Open R software
135. Code to retrieve file from directory:

```
testdata <- read.table("Subject 1 worknonwork.txt", sep=",")
```

136. Code to read data table and set columns

```
data <- testdata
x1 <- data[,1]
x2 <- data[,2]
```

137. Code to run paired t-test

```
t.test(x1,x2, alternative=c("less"), mu=0, paired=TRUE, conf.level =
0.95)
```

(results will immediately display)

138. Repeat for all subjects

Aim 4: Duration of actigraphy sampling

- 139. Open "Subject 1 work day (insert 24 date of data set)"
- 140. Complete steps 63-118 to retrieve 24-hour acrophase
- 141. Copy acrophases for each 24-hour acrophase and paste to new Excel document
- 142. Repeat for each subject and paste below previous acrophase in succession
- 143. Change all acrophase cells to number format
- 144. Insert column between subject number and acrophase
- 145. Fill number of days of monitoring
- 146. Save as "all daily acrophase.csv" file
- 147. Copy into Users directory
- 148. Open R software
- 149. Code to import, read, and attach data

```

zz = paste(path.in, "all daily acrophase.csv", sep="/")

data = read.csv(zz, header=TRUE, sep=",")
str(data)

attach(data)

```

150. Set columns

```

x = acrophase[subject==10]
d = days[subject==10]

```

151. Code to compute error margins for acrophase vs duration of data collection

```

is = unique(subject)
ns = length(is)
vararr = array(NA, dim=c(10, 7, ns)) ##1-10 days, 7 outputs, ns
subjects
for (i in 1:ns) {
  ## read subject data
  x = acrophase[subject==is[i]]
  d = days[subject==is[i]]
  ## process subject's data
  n = length(x)
  njmax = floor(n/5)
  #varmat = matrix(NA, nrow=njmax, ncol=6)
  for (nj in 1:njmax) {
    iagg = 1+ (seq(0,n-1) %/% nj)
    #cbind(seq(1,n), iagg)
    xagg = aggregate(x, list(iagg), mean)
    vararr[nj, 1, i] = nj
    vararr[nj, 2, i] = dim(xagg)[1]
    vararr[nj, 3, i] = sum((xagg[,2] - mean(x))^2)/dim(xagg)[1]
    vararr[nj, 4, i] = 24*60*sqrt(vararr[nj, 3, i])
    vararr[nj, 5, i] = 24*60*sd(xagg[,2])
    vararr[nj, 6, i] = vararr[nj, 4, i]*qt(0.975, df=dim(xagg)[1])
    vararr[nj, 7, i] = vararr[nj, 5, i]*qt(0.975, df=(dim(xagg)[1]-1))
  }
}
dimnames(vararr) = list(paste(1:10,"day",sep=""),
  c("Duration", "N", "Variance", "SEM-true (m)", "SEM (m)", "95%
CI-true (m)", "95% CI (m)"),
  paste("Subject",is,sep=""))

```

152. Code to display output for each subject

```
vararr
```

153. Code to compute median error bounds across subjects

```
var.median.mat = apply(vararr, c(1,2), median, na.rm=T)
cat("\n\n Median error bounds across subjects: \n")
print(round(var.median.mat,3))
```

154. Code to compute weighted mean error bounds across subjects

```
wtmean.mat = matrix(NA, nrow=10, ncol=2)
for (i in 1:10) {
  wtmean.mat[i,1] = i
  wtmean.mat[i,2] = weighted.mean(vararr[i,4,], vararr[i,2,],
na.rm=T)
}
colnames(wtmean.mat) = c("Duration", "Weighted mean std. error
(m)")
cat("\n Weighted mean error bounds across subjects: \n")
print(round(wtmean.mat,3))
```

155. Code to plot and save results

```
plot(wtmean.mat[,1], wtmean.mat[,2], type='n',
  ylim=c(30, 135), xlim=c(0,10), xaxp=c(1, 10, 9), yaxp=c(30,135,7),
  xlab='Duration of Data Collection (Days)',
  ylab='Std. Error of Mean Acrophase (m)')
lines(var.median.mat[,1], var.median.mat[,4], col="blue", type='b',
  pch=20)
lines(wtmean.mat[,1], wtmean.mat[,2], col="red", type='b')
abline(h=120, lty=2, col="plum")
abline(h=105, lty=2, col="plum")
abline(h=90, lty=2, col="plum")
abline(h=75, lty=2, col="plum")
abline(h=60, lty=2, col="plum")
abline(h=45, lty=2, col="plum")

legend("topright", pch=c(1,20), lty=c(1,1), col=c("red", "blue"),
  c("Weighted Mean Error", "Median Error"),
  bty="n", cex=1, horiz=F)

dev.print(device=png,
  file=paste(path.in, "SEM_vs_duration.png", sep="\\"),
  width=600, height=600)
```

dev.off()

Aim 5: Sleep Parameters

156. Open Actiware™ Software
157. Import Subject 1's .awi file
158. Select run
159. Print report
160. Record sleep parameters
161. Repeat steps 156-160 for each subject's .awi file
162. Repeat steps 156-161 for each subject
163. Compare each subjects bed time and get up time with written log
 - a. Use log stamp if discrepancy > 15 minutes
 - b. Enter statistics in spreadsheet

Interpretation of data

Aim 1: Correlation of activity-rest and temperature circadian rhythms

164. Entrainment of the circadian pacemaker to a 24-hr day will be indicated if both the activity-rest and temperature data are statistically and clinically significant, defined as $p < .001$, and $R^2 \geq .10$, respectively. If the Spearman correlation coefficient values are zero, there will be no determination that activity-rest and temperature are correlated.

Aim 2: Lead-lag relation between activity rest and circadian temperature rhythm

165. Only the activity-rest and temperature acrophase means/medians and standard deviations/IQR compared from one-sample t -test with a statistical significance, $p < .05$, was interpreted as statistically significant.

Once interpreted as statistically significant, the parameter with the earlier acrophase was interpreted as leading the other parameter.

Aim 3: Stability of activity-rest patterns during work and non-work days.

166. Results from the work and non-work day acrophase comparison, using the paired t-test to determine statistically significant difference between the two with $\alpha \leq .05$ was reported for all subjects and for the group.

Aim 4: Duration of actigraphy sampling

167. Lowest variance with monitored day was reported

Aim 5: Sleep parameters

168. Sleep parameters for women across the reproductive stages were reported

CURRICULUM VITAE
Kristina L. Leyden, PhD, RN, FNP-BC

EDUCATION:

University of Texas Health Science Center Houston, Texas	2015 (expected graduation)	PhD in progress	Nursing
University of Texas Medical Branch Galveston, Texas	1999	MS, FNP	Nursing
Washington State University Vancouver, Washington	1997	BS	Nursing
Clark College Vancouver, WA	1996	AAS	Nursing
Clark College Vancouver, WA	1994	AAS	

PROFESSIONAL POSITIONS:

The University of Saint Thomas School of Nursing Houston, Texas	Assistant Professor	2012-present
	Academic Affairs Policy Committee	2015-present
	Course Planning and Evaluation Task Force	2015-present
Mint Physician Staffing Houston, Texas	Family Nurse Practitioner	2010-present
TakeCare Health Systems Houston, Texas	Family Nurse Practitioner	2007-2012
Texas A&M Corpus Christi, Texas	Assistant Professor	2008-2009
University of Texas Medical Branch Galveston, Texas	Assistant Professor	2003-2008

Baylor College of Medicine Department of Clinical Systems Services Houston, Texas Consultant	2005-2006
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Baylor College of Medicine Department of Family Medicine Houston, Texas Family Nurse Practitioner Clinic Leadership Committee	2001-2005 2002-2005
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University of Texas Medical Branch Family Medicine Clinic Galveston, Texas Family Nurse Practitioner	2000-2001
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University of Texas Medical Branch General Medicine Galveston, Texas Nurse Clinician III	1998-2000
---	-----------

University of Texas Medical Branch Pathology Department Galveston, Texas Instructor	1999
--	------

Southwest Washington Medical Center Labor and Delivery; Float Pool Vancouver, Washington Staff Nurse	1997
---	------

PROFESSIONAL MEMBERSHIPS:

Sigma Theta Tau International Honor Society of Nursing	1998-present
--	--------------

PUBLICATIONS (Abstracts in Conference Proceedings):

From, A., Leyden, K. L., Thompson, J., & Tschirch, P. (2013). An Academic-Practice Partnership Innovation: Integrating Perioperative Nursing in a BSN Curriculum. Partnership Excellence in Nursing Education – Interprofessional Collaboration. Galveston, TX.

Leyden, K. L., Hanneman, S. K., McCarley, C. Padhye, N. S, & Smolesky, M. H. (2012). Activity-rest Circadian Rhythms in COPD. Council for the Advancement of Nursing Science. Washington, D.C.

Leyden, K. L., & Hanneman, S. K. (2010). Reproducibility of the actiwatch-score in women. 26th Conference of the International Society for Chronobiology. Vigo, Spain.

PRESENTATIONS:

Leyden, K. L. (2014). Perioperative nursing goes to college: Part 1 and 2. Association of perioperative Registered Nurses Surgical Expo. Chicago, IL.

Leyden, K. L., Hanneman, S. K., McCarley, C., Padhye N. S., & Smolensky, M. H. (2012). Activity-rest Circadian rhythms in COPD. Council for the Advancement of Nursing Science. Washington, DC.

Leyden, K. L. (2010). Reproducibility of the actiwatch-score in women. 26th Conference of the International Society for Chronobiology. Vigo, Spain.

Leyden, K. L. (2010). *Staff Education*. Recognizing illness in early childhood. St Jerome Early Childhood Center. Houston, TX.

Leyden, K. L. (2009). *Staff Education*. Recognizing allergic symptoms in the elementary school child. St. Jerome School. Houston, TX.

Leyden, K. L. (2002-2005). *Staff Education*. Topics include Asthma, COPD, pneumonia, diabetes mellitus, heart disease, and hypercholesterolemia. Baylor College of Medicine, Department of Family Medicine. Houston, TX.

Leyden, K. L. (2002-2005). *IV Therapy*. Baylor College of Medicine, Department of Family Medicine. Houston, TX.

Leyden, K. L. (2002-2005). *Standards & Expectations Certification Class*. Baylor College of Medicine, Department of Family Medicine. Houston, TX.

Leyden, K. L. (2002-2005). *Clinic Flow, Standards, and Expectations*. Baylor College of Medicine, Department of Family Medicine. Houston, TX.

Leyden, K. L. (2004). Conference developer and featured speaker: *Enhancing the Nurse Practitioner Image: Professional Issues with Professional Solutions*. Disney's Yacht Club Resort, Walt Disney World. FL.

Leyden, K. L. (2004). *Diabetes Management*. Diabetic Care Program Initiative. Baylor College of Medicine, Department of Family Medicine. Houston, TX.

PROJECTS:

Clinic-Based Staff Education
 Baylor College of Medicine
 Department of Family Medicine
 Houston, TX

Project Director

2002-2005

Cholesterol Care Program
 Baylor College of Medicine
 Department of Family Medicine
 Houston, TX

Project Director

2004-2005

Diabetic Care Program
 Baylor College of Medicine
 Department of Family Medicine
 Houston, TX

Project Director

2003-2004

CONFERENCES DEVELOPED AND PRESENTED

Crossroads Cultural Center, Program Coordinator
 Houston Baptist University
 University of St. Thomas Office of Academic Affairs, Houston, TX

Life Lessons from Dante's Divine Comedy, 2015

The Fine Art of Temptation: C.S. Lewis' Screwtape Letters, 2014

Crossroads Cultural Center, Program Coordinator
 University of Houston
 University of St. Thomas Office of Academic Affairs, Houston, TX

A Glimpse into the Unknown: The Wonder that Inspires Scientific
 Discovery, 2015

American Protestant Theology: Presentation of Msgr. Giussani's Book,
 2014

Face to Face with John Lienhard, 2013

Wounded by Beauty, 2013

The Mystery of Matter and the Hunt for the God Particle, 2013

Crossroads Cultural Center, Program Coordinator
 University of St. Thomas, Houston, TX

The Risk of Education: An Introduction to Reality In Its Totality, 2013

Three Chords and a Longing for the Truth, 2013

New York Encounter, Program Coordinator

Manhattan Center, New York, NY

Freedom, Risk, Responsibility: What Lies Behind a Corporate Success Story, 2013

Crossroads Cultural Center, Program Coordinator

Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, TX

Research: The Surprise of Discovery, 2012

Crossroads Cultural Center, Program Coordinator

University of St. Thomas, Houston, TX

Arab Spring, 2012

Crossroads Cultural Center, Program Coordinator

Rice University, Houston, TX

Van Gogh: Seduced by Beauty, 2011

Crossroads Cultural Center, Program Coordinator

University of St. Thomas, Houston, TX

Holy Happiness- Trio Napolincanto, 2011

The Earth: A Human Habitat, 2011

Science as an Adventure: A Conversation with Mauro Ferrari, 2011

Crossroads Cultural Center, Program Coordinator

University of Houston, Houston, TX

Natural Gas: Human Capital at Work, 2010

Crossroads Cultural Center, Program Coordinator

University of St. Thomas, Houston, TX

Gaudi's Sagrada Familia: Through the Sculptor's Eye, 2010

Crossroads Cultural Center, Program Coordinator

Texas Heart Institute at St. Luke's Episcopal Hospital, Houston, TX

Stem Cell Research: What Do We Know?, 2010

Crossroads Cultural Center, Program Coordinator
Rice University, Houston, TX

Knowledge is Infinite: The Mystery of Space, 2009

OTHER:

Crossroads for Kids, Co-Director
Leakey, TX

The Screwtape Letters, 2014

A Day in the Life, 2013

Crossroads for Kids, Director
Leakey, TX

Living Art, 2011

Crossroads for Kids, Co-Director
St. Maximillian Kolbe, Houston, TX

A Christmas Story: Waiting for Him, 2011

Crossroads for Kids, Co-Director
Houston, TX

The Show That Never Existed, 2010

St. Aquinas Homeschool Group, Assistant Director
University of St. Thomas
Houston, TX

Peter Rabbit's Stomach Ache – by Marianne Ivany, 2009

Crossroads for Kids, Developer
Houston, TX

Art Through History, 2008-2009

AWARDS AND RECOGNITION:

2013-2014	Nominated for the St. Thomas Aquinas Excellence in Teaching Award – University of Saint Thomas
2014	Nominated for Outstanding Nurse Educator for Nursing Celebration for Texas Nurses Association - District 9
1992	Young Women's Christian Association Community Service Award
1991-1993	National Honor Society Outstanding Service Award