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Cross-sectional and Prospective Associations of Rest-Activity Rhythms With Body Mass Index in Older Men: A Novel Analysis Using Harmonic Hidden Markov Models

Brian Heckler[*], **Miryoung Lee**[†], **Katie Stone**[‡], **Cici Bauer**[*,1], **Qian Xiao**[§,2]

[*]Department of Biostatistics and Data Science, University of Texas Health Science Center at Houston School of Public Health, Houston, Texas,

[†]Department of Epidemiology, Human Genetics and Environmental Science, University of Texas Health Science Center at Houston School of Public Health, Brownsville, Texas,

[‡]California Pacific Medical Center Research Institute, San Francisco, California,

[§]Department of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center at Houston School of Public Health, Houston, Texas

Abstract

Growing evidence supports a role for rest-activity rhythms (RARs) in metabolic health. Epidemiological studies in adolescents and young adults showed that RAR characteristics consistent with weakened rhythmicity were associated with obesity. However, studies in older adults are lacking. The objective of this study was to examine the cross-sectional and prospective associations between RAR and obesity in older men using the Harmonic Hidden Markov Model (HHMM), a novel analytical approach with several advantages over conventional methods for characterizing RAR. The analysis included nearly 3,000 participants in the Osteoporotic Fractures in Men study with 5-day 24-h actigraphy data. The strength of RAR was measured by rhythmic index (RI), a scaled value between 0 and 1 with higher values indicating better RAR. Multiple linear and logistic regression adjusting for multiple confounders were performed to examine the RI in relation to body mass index (BMI) and obesity status at baseline and after ~3.5 years of follow-up. We showed that the HHMM can derive both meaningful visual profile and quantifier of RAR. A lower RI was associated with higher BMI and obesity at baseline, and an elevated likelihood for developing obesity over follow-up. Specifically, when compared with men in the highest quartile of RI, those in the lowest quartile on average had a higher BMI (β [95% confidence interval (CI)], 1.76 [1.39, 2.13]) and were more likely to be obese at baseline (odds ratio (OR) [95% CI], 2.63 [2.03, 3.43]). Moreover, among nonobese men at baseline, those in the lowest quartile of RI were

[1.] To whom all correspondence should be addressed: Cici Bauer, Department of Biostatistics and Data Science, University of Texas Health Science Center at Houston School of Public Health, 1200 Pressler St. Houston, TX 77030, USA; cici.x.bauer@uth.tmc.edu.
[2.] To whom all correspondence should be addressed: Qian Xiao, Department of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center at Houston School of Public Health, 1200 Pressler St., Houston, TX 77030, USA; qian.xiao@uth.tmc.edu.

CONFLICT OF INTEREST STATEMENT

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2.06 times (OR [95% CI], 2.06 [1.02, 4.27]) more likely to develop obesity over followup when compared with those in the highest quartile. In conclusion, our study demonstrated the utility of HHMM in characterizing RAR and showed that rhythmicity strength was associated with BMI and risk of obesity in older men.

Keywords

rest-activity rhythms; obesity; older adults; Hidden Markov Models; prospective cohort

The rest-activity rhythm (RAR) is generated and maintained by the internal circadian rhythm and influenced by environmental cues such as the 24-h light-dark cycle, social interactions, and daily schedules (Dibner et al., 2010). The increasing popularity of 24-h accelerometry in epidemiological studies has provided rich and complex data for characterizing the RAR and understanding its relationship to health outcomes. Several studies have linked weakened RAR with higher adiposity, particularly among school-aged children and adolescents (Garaulet et al., 2017; Qian et al., 2021; Quante et al., 2019). Aging may influence many aspects of the circadian organization of diurnal behaviors (Hood and Amir, 2017). Although research on RAR and obesity in older adults is limited, some have reported patterns similar to those observed in younger populations. For example, in two cross-sectional analyses, weakened rhythmic patterns, characterized by reduced regularity and increased fragmentation of the RAR, were associated with higher body mass index (BMI) in older men and women (Luik et al., 2013; Sohail et al., 2015). Together, these studies suggest that weakened RAR may play a role in obesity. However, relevant research in aging populations is still limited. In addition, to the best of our knowledge, no study has focused on the prospective relationship between RAR and obesity in older adults.

Currently, the two most popular methods for deriving RAR measures from accelerometry data are cosine-based parametric models (e.g., extended cosinor model) and nonparametric algorithms such as those used to calculate interdaily stability and intradaily variability (Marler et al., 2006; Van Someren et al., 1999). Although these methods have been widely applied in epidemiological studies that reported intriguing relationships between RAR and health outcomes, they both have important limitations. Parametric methods assume an average diurnal pattern, typically in a cosine or cosine-like shape, and may not be applicable to individuals whose activity patterns deviate from this waveform. Moreover, the rhythmic parameters derived from cosine-based models are dependent on the measuring device, wearing protocol, and study sample, which lacks comparability and generalizability across different populations and study designs (Terri Blackwell et al., 2011a). On the other hand, many nonparametric variables only capture limited aspects of the rhythm, such as day-to-day differences, and ignore the overall daily rhythmicity profile. Finally, these methods are often unable to handle missing data or extreme values.

Recently, the Hidden Markov Model /or/ Hidden Markov Models (HMMs) have gained substantial popularity in the analysis of actigraphy data. HMMs, a class of probabilistic time-series models, have been utilized across a wide range of applications from speech recognition to genome sequencing. For actigraphy data, HMMs have been used as an

unsupervised machine learning technique to identify and classify modes of movement such as standing, walking, and sitting (Peursum et al., 2004). More recently, to address the deficiencies of previous techniques and better classify transitions between periods of activity and rest, Huang et al. proposed a Harmonic Hidden Markov Model (HHMM). Based on the central role of circadian rhythms in influencing RAR, the transition probabilities of the dynamic Markov process can also be assumed to be influenced by a circadian oscillator, and the HHMM incorporates a 24-h harmonic oscillator into the dynamic Markov process to model various activity states (e.g., high, medium, and low activity) using actigraphy data (Huang et al., 2018). Huang and colleagues applied the HHMM to actigraphy data recorded during a period of 4–7 days among 46 healthy individuals and demonstrated that one could generate an individual-level 24-h rest-activity profile, from which a rhythmic index (RI) score of overall rhythmicity can be derived (Huang et al., 2018). They also showed that the HHMM could be applied to cancer patients to assess changes in rest-activity patterns over the course of chemotherapy. Compared with conventional approaches, the HHMM is flexible to accommodate different behavioral patterns in a diverse population and produce standardized measures of overall rhythmicity with better interpretability and comparability.

In this analysis, we employed the HHMM approach to assess the overall rhythmicity in older men from the Osteoporotic Fractures in Men (MrOS) Study and examined both the cross-sectional and prospective associations between RAR and indices of adiposity. We hypothesized that weakened overall rhythmicity, characterized by a lower RI, was positively associated with BMI and obesity. In addition, among nonobese older men, the overall rhythmicity, quantified by the RI, could be predictive of the risk of developing obesity in the future.

MATERIALS AND METHODS

Study Population

This analysis used data from the MrOS, a multicenter cohort study of risk factors for osteoporosis and other aging outcomes in older men (Blank et al., 2005; Orwoll et al., 2005). Between 2000 and 2002, MrOS enrolled 5994 community-dwelling, ambulatory men aged 65 years or older across 6 clinical centers in the United States. The Outcomes of Sleep Disorder in Older Men Study (MrOS Sleep study) was established as an ancillary study of MrOS and enrolled 3135 participants from the parent cohort between 2003 and 2005, which is considered the baseline time in this analysis (Blackwell et al., 2011b). The objective of the MrOS Sleep was to determine the relationships between sleep and health outcomes including cardiovascular disease (CVD), cognitive decline, and falls and fractures. Participants in the MrOS study, including those in the MrOS Sleep, were followed up at multiple clinical visits to obtain updated information on health and lifestyle factors. Both the original MrOS study and ancillary studies were approved by the institutional review boards at each of the participating field sites (University of Alabama at Birmingham; University of Minnesota; Stanford University; University of California, San Diego; Oregon Health and Science University; University of Pittsburgh), and written informed consent was obtained from study participants.

Measurement of RARs

At the baseline of the MrOS Sleep study, participants wore a sleep-watch-O (Ambulatory Monitoring, Inc.) actigraph on the nondominant wrist for a minimum of 5 consecutive 24-h periods, except when bathing or during water sports. The actigraph measures movement using a piezoelectric biomorphceramic cantilevered beam, which generates a voltage each time the actigraph is moved. These voltages are gathered continuously and stored in 1-min epochs. Activity data were collected using the proportional integration mode, which is optimized for effective sleep-wake inference (Blackwell et al., 2011a; Blackwell et al., 2008). For this analysis, the 1-minute activity count data were aggregated to 5-min epochs. We applied the HHMM approach in Huang et al. (2018) with 3 hidden activity states (inactive [IA], moderately active [MA], and highly active [HA]) and a pair of harmonic functions in the time-dependent transition probability matrix of the states. Technical details of the HHMM are presented in Description of Models (Section 2.1) in Supplementary Materials. The resulting probabilities for each state are then summarized into 24-h day profile plots (see Figure 1 for selected participant profiles). Our primary measure of the overall rhythmicity was the RI, which was calculated using the mathematical formula reported previously (Huang et al., 2018). We categorized RI into quartiles, with the highest quartile (i.e., Q4) having the strongest rhythmicity, and used it as the reference group. All analyses were performed in R using the package depmixS4 /or/ the depmixS4 package (Visser and Speekenbrink, 2010).

Measure of BMI and Obesity

Adiposity measures were derived using height and weight measured at baseline (2003–2005) and at follow-up visit (2007–2009). BMI was calculated as weight (kg)/height $(m)^2$. Obesity was defined as BMI ≥ 30 kg/m^2.

Covariates

Study participants reported sociodemographic characteristics of age, race (White/non-White), and education (less than high school, high school, some college, college, more than college). We additionally considered measures of health behaviors, including alcohol use (<1, 1–13, >13 drinks/week) and smoking status (no, past, or current smoker). We also included study site as a covariate (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; San Diego, CA).

Analytic Samples

Supplementary Figure 1 presents a flowchart describing the process for sample selection. Of the 5994 participants enrolled in the MrOS study, 3135 participated in the MrOS Sleep study. Of these, we excluded participants without valid actigraphy data or who had less than a complete day of activity recordings ($N = 88$) and those for whom the HHMM encountered model convergence issues ($N = 9$). For cross-sectional analysis, we excluded those with missing BMI at baseline ($N = 2$) and those who were underweight (BMI < 18.5, $N = 9$), leading to an analytic sample of 3027 participants (analytic sample I). For prospective analysis focusing on changes in BMI, we further excluded those who were missing BMI or were underweight at follow-up ($N = 507$), leading to an analytic sample of 2520 participants

(analytic sample II). Finally, for the analysis focusing on the risk of developing obesity over follow-up, we additionally excluded those who were obese at baseline (N = 509), leading to an analytic sample of 2011 participants (analytic sample III).

Statistical Analysis

For cross-sectional analysis, we examined quartiles of baseline RI in relation to baseline BMI (outcome variable, continuous) and baseline obesity (outcome variable, dichotomized). For prospective analysis, we examined quartiles of baseline RI in relation to *changes* in BMI between baseline and follow-up in the overall sample, and the risk of obesity at follow-up among those who were not obese at baseline. For continuous outcome variables, we used multiple linear regression to obtain the coefficient and associated 95% confidence intervals (CIs) of the explanatory variables. For dichotomous outcomes, we used multiple logistic regression and reported the odds ratios (ORs) and 95% CIs. For all analyses, we reported results from 2 models: Model I, the minimal model, was adjusted for age and study site. Model II, the full model, was additionally adjusted for other sociodemographic and lifestyle factors that may confound the associations between RI and BMI, including race, education, alcohol use, and smoking. To study the trend of the results, we modeled RI as continuous to calculate effect estimates per 0.1 unit change in RI and used the Wald test to derive p values.

RESULTS

We present participant characteristics by RI quartiles in Table 1. At baseline, participants were predominantly White (90%) with an average age of 76.3 years (SD = 5.5). About half (46%) of the cohort consumed less than 1 alcohol drink per week. More than half (59%) participants reported smoking in the past, but only 59 subjects reported being current smokers. Compared with those in the highest RI quartile (Q4), those in lower quartiles were slightly older and more likely to be non-White, have a lower education level, and report <1 drink/week.

Figure 1 presents rest-activity profiles generated by the HHMM for 3 selected participants, representing high, medium, and low RI. Each profile provided the estimated time-dependent probability of being in one of the three activity states (inactivity in light gray color, moderate activity in medium gray, and high activity in dark gray), across a 24-h period centered at midnight. Participant A (age = 69 years, BMI = 28.9 kg/m^2) had an RI of 0.92, presenting high rhythmicity. The rhythmicity profile of A was characterized by a period of high probability in the inactive state during the night (e.g., light gray areas) and clear transitions into and out of the inactivity state. During the night, the probability of transitioning out of the inactivity state into either of the active states was small (5%- 10%), suggesting restful sleep with few interruptions. The probability of being in the high activity state was high throughout the morning and gradually decreased in the afternoon and evening. Participant B (age = 71 years, BMI = 27.7 kg/m^2) had an RI of 0.66, representing medium rhythmicity. When compared with that of A, the profile of B exhibited a more gradual transition between the inactive and active periods during night. The profile also showed that this participant had a lower probability of the high activity state throughout the day when compared with A. Finally, Participant C (age = 72 years, BMI = 34.3 kg/m^2) presented a weak RI of 0.27. This

profile showed the lowest peak of the inactive state of all 3 profiles, with only 20%−50% probability of the inactive state throughout the night, suggesting interrupted nighttime sleep. Moreover, similar to Participant B, Participant C exhibited a low probability for the high activity state (<0.50) throughout the day.

At baseline, the average BMI was 27.2kg/m^2, with 20.5% participants being obese. In cross-sectional analysis, we found a consistent and statistically significant association between lower RI and higher BMI (Table 2) and odds of obesity (Table 3), and the results from the minimally adjusted and full models were largely similar. Specifically, results from the full model showed that, when compared with participants in the highest quartile of RI, those in the lowest quartile of RI on average had 1.76 kg/m^2 higher BMI (β [95% CI], 1.76 [1.39, 2.13], $p < .0001$), and the odds of being obese was more than 2 times higher compared with that at baseline (OR [95% CI], 2.63 [2.03, 3.43], $p < .0001$). When RI was examined as a continuous variable, each 0.1-unit increase in RI was associated with 0.42-unit lower BMI (full model, β [95% CI], −0.42 [−0.34, −0.51]) and a 19% reduction in the odds of being obese (OR [95% CI], 0.81 [0.76, 0.85], $p < 0.0001$).

In the prospective analysis, no statistically significant association was observed between baseline RI (in quartiles) and changes in BMI (continuous) over follow-up (Table 4). However, we observed an association between lower RI and a higher likelihood of developing obesity among those who were not obese at baseline (Table 5). Specifically, men in the lowest 2 quartiles of RI were more than twice as likely (OR [95% CI], 2.16 [1.06, 4.50], p value = 0.04 for Q1 and 2.61 [1.37, 5.22], 0.005 for Q2) to develop obesity when compared with those in the highest quartile.

DISCUSSION

In this study, we employed the novel HHMM approach to characterize RAR and studied the association between overall rhythmicity, BMI, and obesity in both cross-sectional and prospective analyses. We showed that the HHMM can derive both meaningful visual profiles and a useful quantifier of RAR. Moreover, we found that lower rhythmicity, as measured by a lower RI derived from the HHMM, was associated with higher BMI and obesity at baseline, and an elevated likelihood for developing obesity over ~3.5years of follow-up. Our study demonstrated the utility of HHMM in studying RAR in the older population, and the findings contribute to the growing literature supporting a role of RAR and circadian rhythms in metabolic health.

The cross-sectional association between weakened rhythmicity (i.e., lower RI) and higher BMI and obesity was largely consistent with findings from previous research. For example, in older adults participating in the Rotterdam Study, Luik et al. characterized RAR using multiple nonparametric metrics, including interdaily stability, intradaily variability, and relative amplitude (Luik et al., 2013). They reported that lower stability and higher fragmentation of RAR were both associated with higher BMI. Similarly, in the Rush Memory and Aging Project, a community-based study focusing on aging, a more stable rhythm was associated with 27% lower odds of being obese (Sohail et al., 2015). In addition, several studies conducted in younger populations (i.e., school-age children and teens)

also found similar associations between higher BMI and weakened RAR characteristics, including lower relative amplitude (Qian et al., 2021; Quante et al., 2019) and higher fragmentation (Garaulet et al., 2017). In a recent analysis of the National Health and Nutrition Examination Survey, we found a clear association between weakened RAR profiles as measured by extended cosine models and impaired metabolic health, and the results were consistent across different adult age groups (Xiao et al., 2022). Taken together, findings from these cross-sectional analyses support a link between weakened RAR, and the obesity and metabolic dysfunctions.

Temporal ambiguity between exposure and outcome in cross-sectional studies makes it challenging to determine the direction of the observed associations. However, there has been limited epidemiological investigations focusing on the prospective relationship between RAR and obesity, or metabolic health in general. One such example is our recent study on RAR and metabolic health in the MrOS, which reported a relationship between impaired RAR as characterized by extended cosine models and a higher risk of developing diabetes over the follow-up (Xiao et al., 2020). However, this analysis did not examine obesity as an outcome, and to the best of our knowledge, no other study has investigated the prospective relationship between RAR and obesity. Here, we reported an inverse relationship between lower overall rhythmicity and higher risk of developing obesity over follow-up, although weakened RAR was not significantly associated with average changes in BMI since baseline. The weaker association with changes in BMI as a continuous outcome may be explained by several factors: First, when focusing on risk of obesity as the outcome, we excluded participants who were obese at baseline, while such an exclusion was not performed in the analysis focusing on changes in BMI. It is possible that the relationship between RAR and weight change was weaker for those who were already obese at baseline. Second, the relationship between RAR and weight change may differ across different degrees of weight gain. Specifically, the relationship may be stronger for more extreme changes such as developing obesity, when compared with smaller weight gains. Future studies are required to understand how the relationship between RAR and weight gain may differ across different subpopulations and by different amount of weight gain. In summary, our findings support the hypothesis that weakened RAR can be predictive of the risk of developing obesity, a finding that warrant further investigation from future studies.

Older adults face unique challenges in the RAR (Hood and Amir, 2017). The process of aging is associated with a decline in circadian output and shift in circadian phase (Dijk and Duffy, 1999; Nakamura et al., 2011). Moreover, retirement may lead to major changes in daily schedule, and a diminishing physical function may reduce outdoor exposure to day-light. Light is a potent zeitgeber for circadian entrainment, and lower daytime light exposure may also contribute to the weakening of circadian rhythms and circadian-controlled behaviors such as the RAR. Individual components of the RAR, such as sleep and physical activity, have well-established impact on adiposity and metabolic health (Wu et al., 2014). Moreover, circadian rhythms play a central role in orchestrating human metabolism. Therefore, agerelated changes in circadian rhythms and RAR may be an important risk factor for obesity and metabolic health in the older population. Indeed, experimental research has shown that lab-induced circadian disruption in human subjects led to changes in metabolic function that may lead to metabolic dysregulation and obesity (Scheer et

al., 2009). Future studies should focus on evaluating the potentially beneficial effects of strategies aimed at improving circadian function and enhancing RAR in older population, such as timed light exposure, improved sleep hygiene, and well-designed exercise and meal schedules.

A unique contribution of our study is demonstrating the utility of the HHMM, a novel analytical approach for characterizing RAR using 24-h accelerometer data. HHMM, as an often-referenced machine learning approach, presents several advantages over existing methods. First, conventional parametric approaches such as the cosinor models make rigid assumptions of the temporal activity pattern and may not be good for characterizing activity patterns that deviate from the assumed patterns. In contrast, the HHMM relaxes the assumptions and are more flexible in handling populations and individuals with varied activity patterns. Second, the HHMM creates a series of hidden activity states that are based on each individual's activity patterns. Thus, the HHMM is also expected to be more robust and less influenced by the overall physical activity levels because each activity state (e.g., high or low) is not defined by predetermined population-level cutoffs. This allows for the construction of RI, a scaled and standardized metric that is less impacted by the absolute measures of physical activity volume and intensity. Thus, HHMM-derived metrics such as RI allow for direct comparisons of RAR patterns among studies using different models of accelerometer devices and/or wearing protocols, which would improve the generalizability of epidemiological studies. Finally, as shown by our study, the HHMM generates temporal profiles that offer nuanced visualization of individual RAR patterns that are challenging to capture with other methods. This, combined with model flexibility and the ability to derive standardized measures, makes HHMM well-suited for clinical applications, including chronotherapy and telemonitoring. There has been limited but growing applications of HHMM in such settings. For example, in a small sample of cancer patients, Huang et al. applied HHMM to show how chemotherapy can disrupt rhythms for an extended period after treatment ends (Huang et al., 2018). In a later study, they also showed that HHMM can be used to estimate circadian phase for personalizing treatment timing (Komarzynski et al., 2019). Finally, a study of nightshift workers demonstrated the utility of HHMM in the identification of circadian and sleep markers as surrogate indicators of health risks (Zhang et al., 2022). Taken together, these studies suggested potential for applying HHMM in various clinical settings.

In addition to aforementioned methodological advantages, our study also has several other strengths. First, we were able to assess both crosssectional and prospective relationships between RAR patterns and BMI outcomes, and findings from the prospective analysis help clarify the temporal relationship between exposure and outcomes, and support RAR as a predictor of obesity outcomes. Second, while most of the previous studies on RAR and weight outcomes focused on adolescents and younger adults, we conducted the analysis in a well-established cohort of older men. Thus, our results in this understudied population make a unique contribution to the growing field of research on the role of diurnal behaviors and circadian rhythms in metabolic health.

Our study also presented several limitations. First, our cohort only included men, and study participants were predominantly White and of relatively high socioeconomic status.

Therefore, the results may not be generalizable to women or disadvantaged populations. Second, we only included weight measured at 2 time points over ~3.5 years of follow-up and were not able to capture weight trajectories for a longer period of time. Moreover, although advantageous in many aspects, the HHMM also has its own limitations. For example, it requires investigators to specify the number of states. Most existing studies suggest that 3–4 states should be sufficient to capture the variation in the activity data, but also do not overly complicate the model fitting. How to select the number of states is a continuing discussion among the modelers, and approaches such as analyzing pseudo-residuals and using cross-validated likelihood have been suggested to improve the estimate for the number of states (Celeux and Durand, 2008; Zucchini and MacDonald, 2009). For this study, the choice of 3 different states is sufficient to accurately categorize the activity level while remaining parsimonious. In addition, although the use of 3 states allows for improved model fit accounting for individual-specific heterogeneity in the daily activity patterns, the RI is calculated based on the probability of the inactive state. Further technical improvement of the model can be made by incorporating the probability of all states in the calculation of RI. Finally, complex models such as HHMM may face convergence issues. To address this challenge, we tried different starting values when fitting the model, a method also suggested by previous studies (Huang et al., 2018). However, it is worth noting that convergence issue is not unique to HHMM and could occur in models using nonlinear optimization techniques (e.g., extended cosinor models) as well.

In conclusion, our study adds to the growing literature linking RARs with metabolic health and provides new evidence suggesting that weakened RAR is a risk factor for obesity. Moreover, we showed that the HHMM is a useful analytical tool with many advantages over conventional methods for examining rhythm features and quantifying measures of RARs in epidemiological studies with 24-h actigraphy measure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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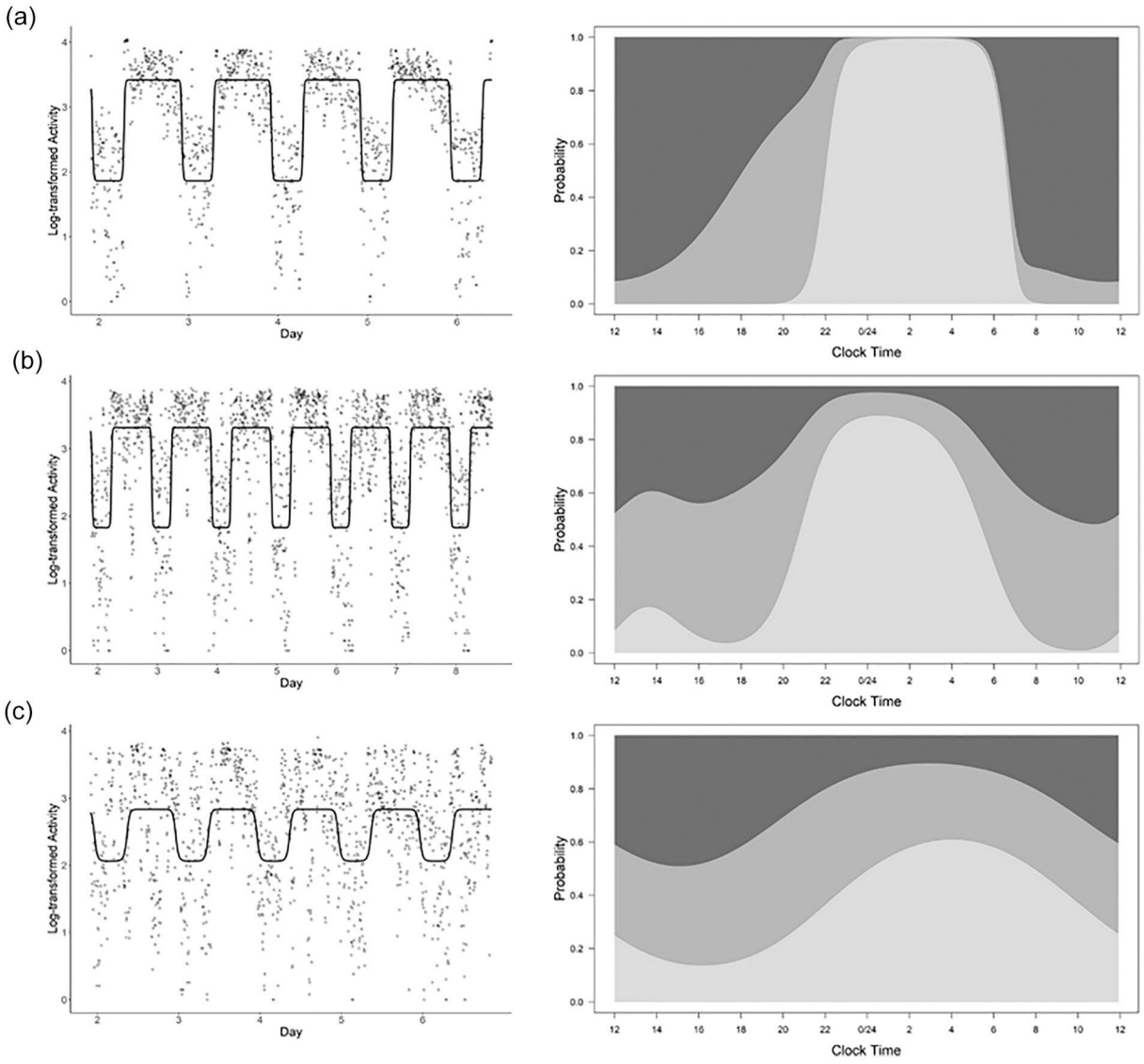

Figure 1.

Three selected individuals presenting different rest-activity profiles. The log-transformed raw activity data (black dots) and the fitted curve using an anti-logistic cosinor model (solid lines) are shown in the left panel. Figures on the right-hand panel are estimated 24-h rest-activity profiles (centered at midnight) obtained from the Harmonic Hidden Markov Model. Different colors represent the probability of each activity state (darkest gray: high activity state; medium gray: moderate activity state, and lightest gray: inactivity state). The selected subjects have estimated rest-activity profiles representing (a) high rhythmicity (RI = 0.92), (b) moderate rhythmicity (RI = 0.64), and (c) low rhythmicity (RI = 0.27). Abbreviation: RI = rhythmic index.

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Table 1.

Baseline (2003–2005) characteristics according to quartiles of rhythmic index (RI) in the MrOS Study (*N* = 3027).

	Q1	Q2	Q3	Q4	Overall
	(*N* = 757)	(*N* = 757)	(*N* = 756)	(*N* = 757)	(*N* = 3027)
RI, mean (SD)	0.48 (0.13)	0.67 (0.03)	0.76 (0.02)	0.85 (0.04)	0.69 (0.15)
Age (years), mean (SD)	77.5 (5.8)	76.9 (5.6)	75.9 (5.4)	75.1 (5.0)	76.3 (5.5)
Site, ***n*** (%)					
Birmingham, AL	124 (16)	127 (17)	113 (15)	131 (17)	495 (16)
Minneapolis, MN	133 (18)	142 (19)	127 (17)	126 (17)	528 (17)
Palo Alto, CA	106 (14)	107 (14)	124 (16)	160 (21)	497 (16)
Pittsburgh, PA	159 (21)	138 (18)	114 (15)	106 (14)	517 (17)
Portland, OR	102 (13)	120 (16)	137 (18)	95 (13)	454 (15)
San Diego, CA	133 (18)	123 (16)	141 (19)	139 (18)	536 (18)
Race, ***n*** (%)					
White	665 (88)	667 (88)	697 (92)	694 (92)	2723 (90)
Non-White	92 (12)	90 (12)	59 (8)	63 (8)	304 (10)
Education level, ***n*** (%)					
Less than high school	63 (8)	37 (5)	35 (5)	26 (3)	161 (5)
High school	132 (17)	133 (18)	116 (15)	103 (14)	484 (16)
Some college	159 (21)	174 (23)	182 (24)	164 (22)	679 (22)
College	136 (18)	129 (17)	146 (19)	148 (20)	559 (18)
More than college	267 (35)	284 (38)	277 (37)	316 (42)	1144 (38)
Alcohol use (drinks/week), ***n*** (%)					
1	395 (52)	380 (50)	321 (42)	311 (41)	1407 (46)
1–13	321 (42)	343 (45)	385 (51)	386 (51)	1435 (47)
≥14	40 (5)	31 (4)	45 (6)	55 (7)	171 (6)
Missing	1 (0.1)	3 (0.4)	5 (0.7)	5 (0.7)	14 (0.5)
Smoking status, ***n*** (%)					
Never	286 (38)	304 (40)	302 (40)	299 (39)	1191 (39)
Past	446 (59)	440 (58)	440 (58)	450 (59)	1776 (59)
Current	24 (3)	13 (2)	14 (2)	8 (1)	59 (2)

	Q1	Q2	Q3	Q4	Overall
	(*N* = 757)	(*N* = 757)	(*N* = 756)	(*N* = 757)	(*N* = 3027)
Missing	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)

Abbreviations: MrOS = The Osteoporotic Fractures in Men Study; RI = rhythmic index; SD = standard deviation.

Table 2.

Cross-sectional relationship[a] between baseline (2003–2005) RI and BMI in the MrOS Study.

	BMI (kg/m^2)				
		Model I		Model II	
RI	Mean (SD)[b]	β (95% CI)	*p* value	β (95% CI)	*p* value
Q1	28.1 (4.47)	1.76 (1.39, 2.13)	<0.001	1.79 (1.42, 2.17)	<0.001
Q2	27.2 (3.61)	0.75 (0.38, 1.12)	<0.001	0.78 (0.41, 1.15)	<0.001
Q3	27.0 (3.63)	0.58 (0.22, 0.95)	0.002	0.57 (0.20, 0.94)	0.002
Q4	26.5 (3.28)	Ref.		Ref.	
Continuous[a]	27.2 (3.81)	−0.41 (−0.33, −0.51)	<0.001	−0.42 (−0.34, −0.51)	<0.001

Abbreviations: BMI = body-mass index; CI = confidence interval; MrOS = The Osteoporotic Fractures in Men Study; RI = rhythmic index. The beta coefficients were obtained from fitting a linear regression model.

Model I: adjusted for age and site.

Model II: additionally adjusted for race, education, smoking status, and alcohol use.

[a]Expressed as beta coefficient obtained from multiple linear regression models, representing adjusted differences for each quartile of RI (Q1-Q3) when compared with the reference (Q4).

[b]Mean and SD were calculated based on participants in each quartile of the RI and β and 95% CI were calculated as per 0.1 increase in RI.

Table 3.

Cross-sectional relationship between baseline (2003–2005) RI and obesity in the MrOS Study.

		Obesity			
		Model I		Model II	
RI	***N* (%)**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Q1	222 (29.3)	2.63 (2.03, 3.43)	<0.001	2.63 (2.01 – 3.44)	<0.001
Q2	147 (19.4)	1.45 (1.10, 1.92)	0.01	1.44 (1.09 – 1.91)	0.01
Q3	138 (18.3)	1.32 (1.00, 1.75)	0.05	1.30 (0.99 – 1.73)	0.06
	113 (14.9)	Ref.		Ref.	
Continuous[a]	620 (20.5)	0.81 (0.76, 0.85)	<0.001	0.81 (0.76, 0.86)	<0.001

Abbreviations: CI = confidence interval; MrOS = The Osteoporotic Fractures in Men Study; OR = odds ratio; RI = rhythmic index. Model I: adjusted for age and site.

Model II: additionally adjusted for race, education, smoking status, and alcohol use.

[a] *N* and % were calculated based on participants in each quartile of the RI and OR and 95% CI were calculated as per 0.1 increase in RI.

Table 4.

Prospective relationship[a] between baseline (2003–2005) RI and changes in BMI between baseline and follow-up (2007–2009) in the MrOS Study.

		Changes in BMI (kg/m^2)			
		Model I		Model II	
RI	**Mean (SD)[b]**	**β (95% CI)**	***p* value**	**β (95% CI)**	***p* value**
Q1	−0.28 (1.64)	−0.15 (−0.31, 0.01)	0.07	−0.12 (−0.29 to 0.04)	0.15
Q2	−0.11 (1.35)	0.04 (−0.12, 0.20)	0.64	0.05 (−0.11, 0.21)	0.53
Q3	−0.15 (1.47)	−0.04 (−0.20, 0.11)	0.59	−0.03 (−0.19, 0.12)	0.68
Q4	−0.07 (1.15)	Ref.		Ref.	
Continuous[a]	−0.16 (1.45)	0.03 (−0.01, 0.07)	0.18	0.02 (−0.02, 0.06)	0.32

Abbreviations: BMI = body-mass index; CI = confidence interval; MrOS = The Osteoporotic Fractures in Men Study; RI = rhythm index. Model I: adjusted for baseline age and site.

Model II: additionally adjusted for race, education, smoking status, and alcohol use at baseline.

[a]Expressed as beta coefficient obtained from multiple linear regression models, representing adjusted differences for each quartile of RI (Q1-Q3) when compared with the reference (Q4).

[b]Mean and SD were calculated based on participants in each quartile of the RI and β and 95% CI were calculated as per 0.1 increase in RI.

Table 5.

Prospective relationship between baseline (2003–2005) RI and the risk of developing obesity at follow-up (2007–2009) among participants who were not obese at baseline in the MrOS Study.

		Obesity at follow-up			
		Model I		Model II	
RI	***N* (%)**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Q1	19 (4.7)	2.06 (1.02, 4.27)	0.05	2.16 (1.06, 4.50)	0.04
Q2	30 (5.9)	2.57 (1.36, 5.09)	0.005	2.61 (1.37, 5.22)	0.005
Q3	20 (3.8)	1.57 (0.79, 3.21)	0.21	1.54 (0.77–3.16)	0.23
Q4	14 (2.5)	Ref.		Ref.	
Continuous[a]	83 (4.1)	0.86 (0.75–0.99)	0.03	0.85 (0.74, 0.98)	0.02

Abbreviations: CI = confidence interval; MrOS = The Osteoporotic Fractures in Men Study; OR = odds ratio; RI = rhythm index. Model I: adjusted for baseline age and site.

Model II: additionally adjusted for race, education, smoking status, and alcohol use at baseline.

[a]*N* and % were calculated based on participants in each quartile of the RI and OR and 95% CI were calculated as per 0.1 increase in RI.