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Actigraphy-Derived Daily Rest–Activity Patterns and Body Mass Index in Community-Dwelling Adults

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Study Objectives: To examine associations between 24-hour rest–activity patterns and body mass index (BMI) among community-dwelling US adults. Rest–activity patterns provide a field method to study exposures related to circadian rhythms.

Methods: Adults (*N* = 578) wore an actigraph on their nondominant wrist for 7 days. Intradaily variability and interdaily stability (IS), M10 (most active 10-hours), L5 (least active 5-hours), and relative amplitude (RA) were derived using nonparametric rhythm analysis. Mesor, acrophase, and amplitude were calculated from log-transformed count data using the parametric cosinor approach.

Results: Participants were 80% female and mean (standard deviation) age was 52 (15) years. Participants with higher BMI had lower values for magnitude, RA, IS, total sleep time (TST), and sleep efficiency. In multivariable analyses, less robust 24-hour rest–activity patterns as represented by lower RA were consistently associated with higher BMI: comparing the bottom quintile (least robust) to the top quintile (most robust 24-hour rest–activity pattern) of RA, BMI was 3-kg/m^2 higher (p = .02). Associations were similar in magnitude to an hour less of TST (1-kg/m^2 higher BMI) or a 10% decrease in sleep efficiency (2-kg/m^2 higher BMI), and independent of age, sex, race, education, and the duration of rest and/or activity.

Conclusions: Lower RA, reflecting both higher night activity and lower daytime activity, was associated with higher BMI. Independent of the duration of rest or activity during the day or night, 24-hour rest, and activity patterns from actigraphy provide aggregated measures of activity that associate with BMI in community-dwelling adults.

Keywords: rest–activity patterns, actigraphy, body mass index.

Statement of Significance

Twenty-four-hour rest–activity indices from actigraphy provide a field method to study patterns that reflect sleep–wake, physical activity, and circadian exposures. In a cross-sectional study of community-dwelling adults, we found lower relative amplitude was associated with higher body mass index (BMI) independent of the duration of rest or activity. Our research suggests aggregate measures of the robustness of rest–activity patterns associate with health outcomes (eg, BMI). However, prospective studies are needed to determine the directionality of the associations, the rest–activity measures that most strongly associate with BMI, and their relation to circadian rhythms.

INTRODUCTION

Worldwide, 39% of adults were overweight in 2014 and obesity prevalence doubled between 1980 and 2014.[1] In the context of this global epidemic, identifying modifiable risk factors for high body mass index (BMI) is of urgent public health importance. Various aspects of sleep timing, duration, and quality, as well as circadian rhythmicity, have emerged as novel prevention targets.[2,3] In modern society, with artificial light and demanding schedules at work and at home, the timing and duration of sleep and physical activity can become irregular and misaligned with the 24-hour light-dark cycle.[4,5] This has consequences for health because the circadian system directs the sleep–wake cycle as well as metabolic processes,[6] as evidenced by the high risk of obesity and related chronic diseases among shift workers.[4,7–9] Further, short-term studies that force dramatic circadian misalignment in the laboratory setting observe impaired metabolism in animals and humans.[10–13] Milder misalignment (eg, early or late work hours) is widespread in the general population and may be associated with a higher BMI,[14] but is less often studied.

To understand how daily patterns (reflecting physical activity, sleep–wake, and circadian influences) associate with BMI at the population level, methods of data collection and analysis that are practical for large numbers of participants in community settings must be applied. Commonly used to estimate physical activity and total sleep time (TST) in epidemiologic studies, the objectivity and low-participant burden of actigraphy also makes it useful to derive reliable estimates of 24-hour rest–activity patterns related to circadian phase. This is done through the use of rhythmometric methods that parametrically model the periodicity of the rest–activity pattern (cosinor model[15]) or that use nonparametric models for quantifying the stability of the rest–activity pattern.[16] Few studies examine actigraphy-derived diurnal rest–activity patterns, but those that do reveal evidence for an association between higher BMI and more fragmented or flattened rest–activity patterns,[17,18] higher

intradaily variability (IV),[18] lower amplitude (indicating lower daytime and higher nighttime activity),[19] and greater variability in bedtimes.[20] However, this research has often been conducted in adolescents[21] or in small samples from clinical populations such as diabetics, cancer survivors, or adults with affective disorders.[18–20,22–25] This study is one of the first to examine whether 24-hour rest–activity patterns are associated with BMI in a population-based sample of US adults with appropriate adjustment for demographic factors like age, race/ethnicity, and education. Understanding which parameters of rest–activity patterns associate with BMI can generate hypotheses as to mechanisms and help target interventions. Here, we examine whether 24-hour rest–activity patterns are associated with BMI in a sample of US adults. Secondarily, we examine whether associations between the robustness of rest–activity patterns and BMI are statistically independent of (or modified by) total physical activity and/or TST.

METHODS

Participants

As described in detail elsewhere,[26] we used data from 3 studies in which participants wore an actigraph on their nondominant wrist for 1-week (N = 578 adults). Descriptive characteristics for each study are shown in Supplementary Tables S2–3. The first study, "xTREC" (2012–2013), enrolled women throughout the US aged 21–75 years old with BMI 21–39.9 kg/m^2, who were able to move about unassisted (N = 329).[27] The second study (2015–2016), "Impact of Nocturnal Zeitgebers on Energy in TREC" (INZEIT), enrolled adults aged 21–60 years living in/near Philadelphia, PA, San Diego, CA, and St. Louis, MO (N = 120). Participants were eligible if they did not have an illness requiring bed rest, nor a sleep or mobility disorder. Shift workers and those who planned to travel across time zones during the actigraphy monitoring period were excluded, as were pregnant or breastfeeding women. The third study, "iWatch," (2014–2015), included adults living in/near San Diego, CA (N = 129). Participants had to be able to move about unassisted, speak English, and not be in the second or third trimester of a pregnancy if female. The participants in all 3 studies provided informed consent. Institutional Review Boards approved all study protocols.

Actigraphy Protocol and Sleep Variables

Participants were instructed to wear an ActiGraph GT3X+ device (ActiGraph, Pensacola, FL) on their nondominant wrist for 24 hours per day (except when bathing or swimming) for 1 week. Via paper diary or mobile application, participants reported any time they removed their actigraph, and logged the times they went to bed and woke each night and morning, respectively. At the end of the wear period, data were downloaded using ActiLife software (version 6.7 [or later], ActiGraph, Pensacola, FL). All data files were visually screened for sufficient wear time and then processed for analysis. To be included, participants had to provide at least 4 days of recordings with >10 hours (600 minutes) recorded during wake time on each day and no more than 1 hour of nonvalid signal during sleep. Finally, all valid days of recording were averaged to produce the rhythms. Season of measurement was defined as a 4 level variable based on the first day of valid actigraphy recording as "Spring" March 1st–May 31st, "Summer" June 1st–August 31st, "Autumn" September 1st–November 30th, or "Winter" December 1st–February 28th.

Sleep Variables

For each day, we manually identified a main rest interval as the primary sleep period based on logs and observation of a sharp decrease/increase in activity. We defined time in bed using nighttime rest epochs and then applied the Cole–Kripke algorithm to estimate TST (hours per night) from actigraphy data.[28] We defined sleep efficiency as the proportion of the rest period scored as sleep.

The Cole–Kripke scoring algorithm in ActiLife software was originally validated in adults wearing a Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) and not the ActiGraph GT3X. After performing a side-by-side test using both devices worn together, Actigraph™ adjusted the epoch data by scaling the count values by 100, and setting scaled values over 300 to 300 so that the algorithm was compatible with the ActiGraph GT3X+.[29] Our group validated the GT3X+ device against overnight polysomnography and found the intraclass correlation for TST between the GT3X+ with the adjusted Cole–Kripke algorithm was 0.81 in adults.[29]

Rest–activity exposures derived from actigraphy have been defined in prior publications.[30,31] We review their derivation below, and describe their derivation and interpretation in laymen's terms in Supplementary Table 1.

Parametric Cosinor Variables

We transformed the actigraphy count data (1 sample per minute) using a natural log function. We then fit a single-component cosine curve representing a 24-hour period to the count data, using regression analysis in Matlab (The Mathworks, Inc., Natick, MA)/Octave. The regression model can be described as: $Y(t) = M + A\cos\left(\frac{2\pi t}{T} + \phi\right) + e(t)$, where T is the period of the cosinusoid (set to equal 24 hours), M is the Midline Estimated Statistic Of Rhythm (MESOR, which represents the mean activity count of the fitted 24-hour pattern), ϕ is the acrophase (the time of peak activity), and A is the amplitude (also called magnitude, representing the difference between the model fit peak value and the MESOR). We derived the parameters M, ϕ, and A by minimizing the residual sum of squares between the data and the model-estimated values.[32]

This approach (Cornellissen and colleagues)[32] is equivalent to that originally proposed (Naitoh and colleagues)[15] in that it searches for the cosinor curve that best fits the experimental data (represented by its baseline value, extent of predicted variation from the mean, and time of maximum activity) employing the least-squares method. Building upon Naitoh and colleagues, the Cornelissen approach describes the regression model for a single component directly in terms of its parameters (named MESOR, amplitude and phase): $Y(t) = M + A\cos(2\pi t/T + \phi) + e(t)$, where the period T is known and equal to 24 hours. Then, using trigonometric angle sum identity, the model is rewritten as $(t) = M + \beta x + \gamma z + (t)$, where $\beta = A\cos\phi$, $\gamma = -A\sin\phi$, $x = \cos(2\pi t/T)$, $z = \sin(2\pi t/T)$. The residual sum of squares between the measurements Y_i and the corresponding values obtained with the model is minimized obtaining (M, β, γ) and consequently (M, A, ϕ). The approach also allows

the computation of a confidence region for the rest–activity parameters.

Nonparametric Variables

As daily rest–activity patterns do not perfectly follow the sinusoidal waveform assumed by the cosinor parametric method, we also considered nonparametric alternatives to investigate 24-hour rest–activity patterns. We calculated the following nonparametric features using actigraph count data (1 sample per minute): (1) the intradaily variability (IV); (2) the interdaily stability (IS); (3) the time occurrence and corresponding activity counts of the most active 10 hour period (M10) and of the least active 5 hour period (L5); and (4) the relative amplitude (RA).[30] We give the formulae for calculating IV, IS, and RA in Supplementary Table 1. Different approaches have been used in literature for the calculation of M10 and L5 (averaging 10 highest and 5 lowest hourly means, respectively,[33] using the most active 10-hour period and least active 5-hour period of the average daily profile,[30] using a moving window in 1 hour steps across each day,[34] or a moving window in 1-minute steps[35]). In our study, we computed the average daily profile on a minute basis, and then filtered it with a moving window bi-directionally to obtain zero-phase output. M10 was chosen as the maximum of the profile filtered with a 10-hour window and L5 as the minimum of the profile filtered with a 5-hour window. The Matlab/Octave code used for the extraction of the parametric and nonparametric features has been made publicly available on the National Sleep Research Resource[36] website (https://sleepdata.org/community/tools/acticircadian).

The IV provides an estimate of the fragmentation of the 24-hour rest–activity pattern (IV ≃ 0 for a perfect sine wave, IV ≃ 2 for Gaussian noise). For example, higher IVs could be observed among individuals who often nap during the daytime and are more frequently awake during the night. The IS provides an estimate of how closely the 24-hour rest–activity pattern follows the 24-hour light–dark cycle (IS ≃ 0 for Gaussian noise, IS ≃ 1 for perfect stability). As such, higher IS could indicate good synchronization to light and other environmental cues that regulate the biological clock, assuming the participant was awake during the light cycle and asleep during the dark cycle. The M10 reflects the mean number of active minutes/hour during the 10 hours with the highest activity; thus, a higher M10 represents a more active wake period. The M10 midpoint provides an indication of whether a person is most active earlier or later in the day. In contrast, the L5 reflects the mean number of active minutes/hour during the 5 hours with the lowest activity; thus, a lower L5 indicates more restful sleep. Furthermore, the time of day when L5 occurs (L5 midpoint) provides an indication of whether a person goes to bed earlier or later in the day. Finally, the RA is the difference between M10 and L5 in the average 24-hour pattern, normalized by their sum; higher RAs therefore indicate a more robust 24-hour rest–activity pattern, reflecting both higher activity when awake and relatively lower activity during the night.

Demographics

We measured demographic factors by questionnaire and during screening phone calls. Age, sex (female or male), race (black, white or Asian/Other), education level (<college or ≥college degree), marital status (never married/living without partner or married/living with partner), and household income (<$50 000 or ≥$50 000) were all self-reported.

Body Mass Index

In xTREC, participants self-reported height and weight, from which we calculated BMI as weight in kilograms divided by height in meters squared (kg/m^2). In INZEIT and iWatch, research assistants weighed participants using calibrated scales and measured heights using wall-mounted stadiometers. We categorized participants as underweight (<18.5 kg/m^2), normal-weight (18.5–<25 kg/m^2), overweight (25–<30 kg/m^2), and class I or II obese (30–<35 kg/m^2 and ≥35 kg/m^2, respectively).

Statistical Analyses

We present the characteristics of the full study population, and for each study separately. To facilitate comparison of the strength of the associations of different measures of rest–activity with BMI, we examined associations between 1 standard deviation unit (SD) increases in each rest–activity parameters and BMI using linear regression models. To determine if associations differed by study, we tested product terms of the rest–activity patterns and study. We did not observe evidence of any such statistical interactions; we therefore combined the datasets to test for associations with BMI. All models were adjusted sequentially for age and sex, then for study (INZEIT, xTREC, or iWatch), and finally for race and education. In sensitivity analyses, we adjusted for season of measurement, a potential confounder due to its relationship both with rest–activity patterns and BMI. To examine if the influence of timing and stability of rest–activity patterns was independent of , or varied by, duration of TST and activity, we adjusted for TST and total activity counts in multivariable models. Subsequently, we tested multiplicative interactions through product terms of TST, total activity counts, and sleep efficiency with each of the rest–activity variables. To examine relative differences in rest–activity parameters and possible nonlinear associations with BMI, we conducted categorical analyses using quintiles of the rest–activity patterns as our exposures. We completed the statistical analyses using SAS 9.4 (SAS Institute, Cary NC).

RESULTS

Demographic Characteristics

Tables 1 and 2 show the demographic characteristics of the sample. The mean age of participants was 52 (SD, 15) years. Participants were 80% female and 65% had a college degree or higher education. With respect to self-identified race, 75% of participants were white, 15% were black or African American, and 10% were Asian or other categories. One third of participants were overweight, a fifth had class I obesity, and 12% had class II obesity. While most characteristics did not differ significantly across BMI categories, participants with higher versus lower BMI were more likely to self-identify as black. The rest–activity characteristics of the population as a whole are described in detail elsewhere,[26] where it was found that older age, female sex, and white race were associated with greater regularity of rest–activity patterns.

Table 1—Participant characteristics, overall and by category of body mass index (categorical measures).

Characteristic	Class	Overall (n = 578)	Underweight <18.5 kg/m^2 (n = 5)	Normal weight 18.5–<25 kg/m^2 (n = 225)	Overweight 25–<30 kg/m^2 (n = 168)	Obese I 30–<35 kg/m^2 (n = 116)	Obese II/III ≥35 kg/m^2 (n = 64)	p
		N, percent						
Sex	Female	473, 82%	5, 100%	190, 84%	126, 75%	95, 82%	57, 89%	.06
	Male	105, 18%	0, 0%	35, 16%	42, 25%	21, 18%	7, 11%	
Race	White	435, 75%	4, 80%	184, 82%	129, 77%	84, 72%	34, 53%	<.0001
	Black	86, 15%	1, 20%	20, 9%	18, 11%	21, 18%	26, 41%	
	Asian/other	57, 10%	0, 0%	21, 9%	21, 13%	11, 10%	4, 6%	
Ethnicity	Non-Hispanic	545, 94%	5, 100%	218, 97%	154, 92%	108, 93%	60, 94%	.20
	Hispanic	33, 6%	0, 0%	7, 3%	14, 8%	8, 7%	4, 6%	
Education	Less than college	203, 35%	1, 20%	67, 30%	57, 34%	51, 44%	27, 42%	.07
	College graduate or above	375, 65%	4, 80%	158, 70%	111, 66%	65, 56%	37, 58%	
Income	Less than $50 000	189, 33%	2, 40%	70, 31%	50, 30%	38, 33%	29, 45%	.49
	At least $50 000	310, 54%	2, 40%	125, 56%	96, 57%	62, 53%	25, 39%	
	Not reported	79, 14%	1, 20%	30, 13%	22, 13%	16, 14%	10, 16%	
Marital Status	Not married or living without partner	259, 45%	1, 20%	97, 43%	77, 46%	49, 42%	35, 55%	.35
	Married or living with partner	319, 55%	4, 80%	128, 57%	91, 54%	67, 58%	29, 45%	

N, % are presented, p values based on chi-squared tests or Fisher exact test where applicable.

Rest–Activity Patterns and BMI

Many of the daily rest–activity parameters examined differed significantly across BMI categories (Table 2). Class I and II obese participants (versus normal-weight participants) had lower values for magnitude derived from the parametric cosinor method; lower values for amplitude and RA derived from the nonparametric model; and lower values for other measures including IS, TST, and sleep efficiency.

In multivariable analyses adjusting for age, sex, race, education, and study, we standardized rest–activity patterns to SD units for comparability (Tables 3 and 4). Higher RAs (more robust 24-hour rest–activity patterns, reflecting both lower activity during the night and higher physical activity when awake) were consistently and inversely associated with BMI: for example, a 1 SD increase in RA (a 0.11 increment change) was associated with −0.92 kg/m^2 (95% CI: −1.44, −0.40; p = .001) lower BMI (Table 3). This association was similar to 1 SD increases in more commonly examined parameters of sleep duration and quality in Table 4, such as TST (mean difference in BMI of −0.70 kg/m^2 [95% CI: −1.15, −0.24; p = .006] per SD or 58 additional minutes of sleep), and sleep efficiency (mean difference −1.09 kg/m^2 [95% CI: −1.60, −0.57; p < .0001] per SD or 7% increase in sleep efficiency).

In categorical analyses (Table 5), there was a mean difference in BMI of 2.65 kg/m^2 (95% CI: 1.02, 4.28; p = .002) comparing the bottom (least robust) to the top quintile (most robust 24-hour rest–activity pattern) of RA.

Results From Parametric and Nonparametric Methods for Similar Rest–Activity Parameters

Magnitude (as calculated by the cosinor model) and amplitude and RA (as calculated by the nonparametric approach) estimate similar characteristics of the rest–activity pattern and are highly correlated (Pearson's r = 0.78 between magnitude and amplitude, r = 0.75 between magnitude and RA); yet, amplitude and RA more strongly associated with BMI after adjusting for demographic characteristics and TST than did magnitude. By contrast, although acrophase (parametric) and L10 midpoint (nonparametric) are highly correlated (r = 0.87), only acrophase was associated with BMI in models that adjusted for demographic factors (Table 3).

Influence of TST

TST was correlated with RA (r = 0.60; Supplementary Table 4). Thus, we tested whether associations of rest–activity patterns (reflecting overall robustness of rest–activity patterns, including timing of behavior) were independent of TST. Adjustment for TST attenuated associations of 1 SD increases in RA with BMI. For example, the association of a 1 SD increase in RA with BMI attenuated from −0.92 (p = .001) to −0.73 kg/m^2 (p = .02) after TST adjustment (Table 3). Associations of acrophase with BMI became nonsignificant after adjustment for TST. Adjustment for total activity counts produced similar results (associations of RA with BMI attenuated slightly but remained statistically significant; Table 3).

Table 2—Participant characteristics, overall and by category of body mass index (continuous measures).

Characteristic	Overall (n = 578)	Underweight <18.5 kg/m^2 (n = 5)	Normal weight 18.5–<25 kg/m^2 (n = 225)	Overweight 25–<30 kg/m^2 (n = 168)	Obese I 30–<35 kg/m^2 (n = 116)	Obese II/III ≥35 kg/m^2 (n = 64)	p
	Mean (standard deviation), N						
Body mass index, kg/m^2	27.5 (6.0)	17.2 (0.9)	22.2 (1.7)	27.2 (1.4)	32.2 (1.3)	39.3 (4.9)	
Age	51.9 (14.9)	53.0 (14.3)	51.2 (15.8)	53.0 (15.6)	52.1 (12.3)	50.9 (14.4)	.79
Days	7.5 (1.3)	7.4 (1.3)	7.5 (1.4)	7.4 (1.3)	7.4 (1.2)	7.4 (1.4)	.91
Parametric cosinor							
Mesor, log counts	3.9 (0.5)	4.0 (0.3)	3.9 (0.5)	3.9 (0.4)	3.9 (0.5)	3.9 (0.4)	.96
Magnitude, log counts	2.6 (0.5)	2.7 (0.3)	2.7 (0.4)	2.7 (0.5)	2.6 (0.4)	2.4 (0.6)	.003
Acrophase, decimal hours	14.6 (1.3)	13.9 (1.9)	14.7 (1.3)	14.6 (1.2)	14.6 (1.2)	14.4 (1.6)	.34
Nonparametric							
Amplitude, log counts	7.0 (0.3)	7.1 (0.2)	7.0 (0.3)	6.9 (0.3)	6.9 (0.3)	6.8 (0.4)	.007
Relative amplitude	0.77 (0.11)	0.79 (0.07)	0.79 (0.10)	0.78 (0.10)	0.77 (0.09)	0.70 (0.15)	<.0001
Interdaily stability	0.49 (0.12)	0.47 (0.07)	0.48 (0.12)	0.49 (0.12)	0.52 (0.12)	0.45 (0.12)	.01
Intradaily variability	0.86 (0.24)	0.86 (0.32)	0.87 (0.25)	0.86 (0.23)	0.85 (0.24)	0.83 (0.23)	.77
L5 midpoint, decimal hours	2.7 (1.3)	2.3 (1.6)	2.8 (1.3)	2.7 (1.1)	2.7 (1.3)	2.5 (1.9)	.48
M10 midpoint, decimal hours	14.2 (1.6)	13.1 (2.2)	14.2 (1.6)	14.2 (1.6)	14.2 (1.5)	14.0 (1.9)	.43
Other actigraphy measures							
Total sleep time, minutes	414.1 (58.2)	425.7 (30.9)	419.5 (56.3)	422.3 (62.8)	404.8 (50.5)	389.5 (59.8)	.0005
Sleep efficiency, %	85.6 (7.1)	90.1 (2.1)	86.6 (7.2)	86.4 (5.8)	84.8 (6.7)	81.3 (9.1)	<.0001
Total activity, counts per minute	1348.1 (426.5)	1497.8 (431.4)	1375.8 (423.0)	1308.7 (368.9)	1375.7 (511.7)	1280.1 (428.9)	.34

Mean (SD) were presented, p values are based on ANOVA. ANOVA = analysis of variance; SD = standard deviation.

We further investigated whether TST, total activity, or sleep efficiency modified associations of RA with BMI and other rest–activity variables and found no evidence of statistical interaction.

Sensitivity analyses shown in Supplementary Table 5 account for season of measurement; adjustment for season did not substantively alter the results, eg, the association of a 1 SD increase in RA with BMI changed from −0.92 kg/m^2 (95% CI: −1.44, −0.40; p = .001) to −0.89, (−1.40, −0.374; p = .0007).

DISCUSSION

In a community sample of US adults, we found that less robust 24-hour rest–activity patterns were independently associated with higher BMI: for example, comparing the bottom quintile (least robust) to the top quintile (most robust 24-hour rest–activity pattern) of RA, BMI was 2.65 kg/m^2 higher (p = .02). When considered in terms of SD units, the strength and direction of this association was comparable to sleep efficiency and TST. Moreover, the association persisted after adjusting for TST and total activity counts. This suggests that the strength of the rest–activity pattern could influence energy balance independent of the duration of TST and activity, though we cannot determine the directionality of this association in our cross-sectional study.

The association of rest–activity patterns with metabolic outcomes in community-dwelling adults is an emerging area of research, and thus few studies are directly comparable. Our results are consistent with an increasing number of studies linking the strength and regularity of daily rest–activity patterns to disease outcomes, metabolic perturbations in adolescents[21] and older adults,[37] and mortality.[38] In animal studies, inducing obesity in young rats via a high-fat diet disrupts rest–activity patterns in a manner similar to aging, suggesting the relationship of rest–activity patterns to BMI could be bi-directional or mutually

Table 3—Continuous associations with body mass index per 1 standard deviation increase in rest–activity parameters (n = 578).

Exposures	Beta coefficient (95% confidence interval); p value				
	Model 0	Model 1	Model 2	Model 3	Model 4
Mesor	0.08 (−0.47, 0.63); p = .78	0.08 (−0.47, 0.64); p = .77	−0.06 (−0.59, 0.48); p = .84	−0.61 (−1.23, 0.01); p = .05	−0.04 (−0.80, 0.72); p = .92
Magnitude	−1.00 (−1.53, −0.46); p = .0003	−1 (−1.55, −0.46); p = .0003	−0.51 (−1.07, 0.05); p = .07	−0.35 (−0.92, 0.21); p = .22	−0.58 (−1.22, 0.07); p = .08
Acrophase	−0.40 (−0.89, 0.09); p = .11	−0.47 (−0.98, 0.05); p = .08	−0.50 (−1.00, −0.01); p = .05	−0.42 (−0.92, 0.08); p = .10	−0.53 (−1.07, 0.01); p = .05
Amplitude	−0.87 (−1.31, −0.43); p = .0001	−0.92 (−1.37, −0.46); P<.0001	−0.66 (−1.11, −0.21); p = .004	−0.73 (−1.18, −0.28); p = .002	−1.56 (−2.35, −0.77); p = .0001
Relative amplitude	−1.40 (−1.89, −0.92); p<.0001	−1.41 (−1.91, −0.92); p<.0001	−0.92 (−1.44, −0.40); p = .001	−0.73 (−1.33, −0.13); p = .02	−0.85 (−1.42, −0.28); p = .003
Interdaily stability	0.05 (−0.44, 0.53); p = .85	0.14 (−0.37, 0.66); p = .58	0.27 (−0.24, 0.77); p = .30	0.41 (−0.09, 0.92); p = .11	0.23 (−0.30, 0.77); p = .40
Intradaily variability	−0.28 (−0.78, 0.21); p = .26	−0.26 (−0.77, 0.24); p = .30	−0.17 (−0.66, 0.33); p = .51	−0.24 (−0.73, 0.25); p = .34	−0.38 (−0.93, 0.17); p = .18
L5 midpoint	−0.29 (−0.66, 0.08) p = .13	−0.31 (−0.7, 0.08) p = .12	−0.37 (−0.74, 0.00) p = .05	−0.30 (−0.67, 0.07) p = .12	−0.46 (−0.87, −0.05) p = .03
M10 midpoint	−0.20 (−0.70, 0.29); p = .42	−0.27 (−0.81, 0.26); p = .32	−0.24 (−0.76, 0.27); p = .36	−0.16 (−0.68, 0.36); p = .55	−0.29 (−0.86, 0.28); p = .32

(Model 0) Unadjusted. (Model 1) Adjusted for age, sex and study of origin. (Model 2) Model 1 + race and education. (Model 3) Model 2 + total sleep time. (Model 4) Model 2 + total activity counts.

Table 4—Continuous associations with body mass index per 1 standard deviation increase in total sleep time and sleep efficiency (n = 578).

Exposures	Beta coefficient (standard error), p value				
	Model 0	Model 1	Model 2	Model 3	Model 4
Total sleep time	−1.11 (−1.56, −0.65); p < .0001	−1.05 (−1.50, −0.59); p < .0001	−0.70 (−1.15, −0.24); p = .006		−0.64 (−1.21, −0.07); p = .03
Efficiency	−1.54 (−2.01, −1.07); p < .0001	−1.58 (−2.06, −1.09); p < .0001	−1.09 (−1.60, −0.57); p < .0001	−0.94 (−1.50, −0.39); p = .001	−0.94 (−1.51, −0.37); p = .001

(Model 0) Unadjusted. (Model 1) Adjusted for age, sex and study of origin. (Model 2) Model 1 + race and education. (Model 3) Model 2 + total sleep time. (Model 4), Model 2 + total activity counts.

reinforcing.[39,40] In humans, rest–activity measures (including a more flattened pattern measured as magnitude from cosinor, a higher fragmentation of rest–activity patterns determined by higher IV, and lower amplitude) each predicted less response to a weight loss intervention; in contrast, total activity rates did not predict weight loss.[22] RA derived from nonparametric analysis of rest–activity patterns has been examined extensively in the psychology literature, where it is positively correlated with cognitive functioning in schizophrenia[41] and inversely correlated with risk of relapse in bi-polar disorder.[42] Lower values of RA (indicating less robust rest–activity patterns) are found in seasonal affective disorder.[43] In the present study, not only did we observe that the inverse associations of RA with BMI were consistent across subgroups defined by TST and total activity, but associations persisted even after adjustment for TST or total activity. Combined with the existing literature on rest–activity and metabolism, this suggests that not only the duration of rest or activity, but also consolidated measures of the strength of the rest–activity pattern over the entire sleep–wake period are associated with BMI.

While we did not detect associations of BMI with IV, prior studies have found associations of greater fragmentation of rest–activity patterns (as measured by higher IV and lower amplitude) with higher BMI and metabolic dysfunction.[17,21,37,44] One reason for this could be that previous studies focused on clinical populations with chronic disease among whom high fragmentation of the sleep period is common and could underlie associations with IS and IV. In our relatively healthy population, RA may be a better indicator of the strength of rest–activity patterns than IS or IV.

While we observed that more robust RA was associated with lower BMI, we did not find a difference in BMI related to the

Table 5—Categorical association of quintiles of relative amplitude with body mass index (n = 578).

Exposure		Range	Model 1	Model 2	Model 3	Model 4
Relative amplitude	Quintile 1	0.21–0.69	4.21 (2.65, 5.78); $p \leq .0001$	2.65 (1.02, 4.28); $p = 0.002$	1.89 (−0.03, 3.80); $p = .05$	2.34 (0.56, 4.12); $p = .01$
	2	0.70–0.76	2.19 (0.65, 3.73); $p = .005$	1.40 (−0.13, 2.93); $p = .07$	0.84 (−0.86, 2.54); $p = .33$	1.19 (−0.47, 2.85); $p = .16$
	3	0.77–0.81	1.73 (0.19, 3.27); $p = .03$	1.43 (−0.08, 2.95); $p = .06$	1.09 (−0.48, 2.67); $p = .17$	1.34 (−0.28, 2.95); $p = .11$
	4	0.82–0.85	2.01 (0.46, 3.55); $p = .01$	1.76 (0.24, 3.27); $p = .02$	1.51 (−0.04, 3.06); $p = .06$	1.53 (−0.1, 3.16); $p = .07$
	5	0.86–0.94	Ref.	Ref.	Ref.	Ref.

(Model 1) Adjusted for age, sex and study of origin. (Model 2) Model 1 + race and education. (Model 3) Model 2 + total sleep time. (Model 4), Model 2 + total activity counts.

timing of behavior; this could be because while rest–activity patterns are related to circadian rhythms, they are a behavioral rather than physiological measure. The larger literature linking energy metabolism to the circadian clock suggests that the alignment of energetic behaviors (eating and activity) with other biological processes matters: misalignment of the timing of feeding and fasting and sleeping and waking (or rest and activity) results in weight gain and metabolic disturbance. Optimizing the timing of meals and physical activity for obesity prevention is an active area of research,[45] with some small studies suggesting early morning exercise in the fasted state improves insulin sensitivity and weight maintenance.[46] As an example of the profound metabolic impact of the timing of behavior, when mice are provided food only during the light hours (the wrong circadian timing for nocturnal animals), they gain greater fat mass than when fed equivalent calories at the correct circadian time.[47] In accordance with this, observational studies find that increasing years of shift work are associated with higher risk of metabolic disorders including obesity.[9] Outside of shift work, later sleep timing is associated with higher BMI, independent of TST.[48–50]

Recent studies have attempted to isolate the effects of circadian misalignment independent of sleep duration and found impaired glucose metabolism and alterations in appetite hormones independent of the timing and quality of sleep.[11,13,51] However, these experiments represent large changes in circadian alignment. Our study observed community-dwelling adults, among whom social jet lag and the demands of work and home responsibilities result in less dramatic shifts in circadian alignment. In this population, the strongest associations emerged from the composite measure of rest–activity described by RA; TST and sleep efficiency increased in a dose–response manner across increasing quintiles of RA (data not shown). The strong association of RA with lower BMI likely results from the cumulative benefits of longer TST, higher sleep efficiency, higher M10, and lower L5. This is reflected in the fact that associations attenuated slightly (though remained significant) after adjustment for TST and sleep efficiency.

This research has multiple strengths: first, our observation in a large, community-dwelling sample that RA is inversely associated with BMI supports the utility of actigraphy as a tool for large epidemiologic cohorts to measure exposures related to daily sleep–wake (rest–activity) patterns. Second, few studies have utilized both parametric and nonparametric methods of measuring rest–activity patterns. In this analysis, the nonparametric methods produced parameters (eg, RA) for which associations with BMI withstood multivariable adjustment, whereas the equivalent variables from the cosinor model (magnitude) did not. Missing data was minimal: 98% of participants had 6+ days of complete actigraphy recording; the mean (SD) number of days of wear was 7.5 (1.3), and the mean (SD) duration of wear per day was 23.4 (1.1) hours. Further, the 2 methods we employed to derive rest–activity patterns are robust to missing data (eg, the cosinor method interpolates the rhythm by fitting the curve, and the nonparametric method uses averages over hours, so unless an hour is completely missing it is included).[52] This suggests that nonparametric methods, which make fewer assumptions about the shape on the rest–activity patterns, may produce estimates of the amplitude of circadian oscillations (as captured by rest–activity patterns) that are more biologically relevant and more strongly associated with health outcomes such as BMI. Fortunately, free software available in R,[35] as well as in MatLab and Octave,[36] enables researchers to reproduce the calculations used to estimate the nonparametric parameters such as RA.

This research also has important limitations that require discussion: our cross-sectional design prevents us from determining the temporal order of the association between rest–activity patterns and higher BMI; indeed, this relationship could be bi-directional and it will be an important area of future research to explore whether changes in the strength of rest–activity patterns predict subsequent development of obesity or metabolic disturbance. Another limitation was the lack of objective measurement of sleep-disordered breathing. However, individuals with known, untreated sleep disorders were excluded from participation. While our study population was generally healthy, one site included breast cancer survivors: women were several years past diagnosis at the time of measurement, and previous studies found no systematic differences in their rest–activity characteristics versus the other study populations included here.[26] In order to harmonize across datasets, we used self-reported BMI rather than research measurement for half of the

study participants. However, bias in the BMI variable did not meaningfully influence the results: associations did not vary across cohorts that used objective and subjective methods to assess BMI (p interaction < 0.05). Another inconsistency across studies was that moderate–vigorous physical activity (MVPA) was collected through a mix of wrist and hip accelerometry; for this reason, we included total activity counts (entirely derived from wrist actigraphy) as a covariate in our analysis. Though higher MVPA was associated with lower BMI, adjustment for MVPA (a mix of wrist and hip accelerometry) made little difference in the association of RA with BMI. Finally, while actigraphy offers many advantages as a noninvasive technique, actigraphy-derived rest–activity patterns are not always congruous with sleep–wake cycles,[53] and, when used in uncontrolled environments, do not directly assess circadian rhythms. Nevertheless, previous research has found that more fragmented rest–activity characteristics correlated with a decrease in the amplitude of melatonin secretion,[18] suggesting that these are indeed related to relevant biological signs of chronodisruption.

In summary, these results suggest that, independent of total duration of activity or sleep, aggregated measures of the robustness of rest–activity patterns are associated with BMI in community-dwelling adults. RA could be considered as a potential target for obesity prevention, but further research is needed to determine the optimal means to increase RA; for example, in addition to increasing TST and sleep quality (to lower L5) and physical activity (to increase M10), should these behavioral changes be synchronized over each 24-hour period?

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SUPPLEMENTARY MATERIAL

Supplementary data are available at *SLEEP* online.

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DISCLOSURE STATEMENT

None declared.