

Rest Activity Rhythms and Their Association with Cardiorespiratory Fitness and Walking Energetics in Older Adults: Study of Muscle, Mobility, and Aging

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ABSTRACT

ERICKSON, M. L., T. L. BLACKWELL, R. E. GARCIA, T. MAU, P. M. CAWTHON, S. R. CUMMINGS, S. FARSIJANI, L. M. SPARKS, J. NOONE, N. W. GLYNN, A. B. NEWMAN, and K. A. ESSER. Rest Activity Rhythms and Their Association with Cardiorespiratory Fitness and Walking Energetics in Older Adults: Study of Muscle, Mobility, and Aging. *Med. Sci. Sports Exerc.*, Vol. 57, No. 9, pp. 1886–1896, 2025. **Purpose:** It is recognized that disruptions in circadian behavior, such as with shift work or jet lag, are associated with diminished health. This known relationship implies that people with stronger indices of circadian behavior will exhibit improved physiology. To address the association between rhythmic activity behavior and physiology, we proposed that metrics indicative of “more rhythmic” rest-activity patterns would be associated with better cardiorespiratory fitness and walking energetics in a cohort of older adults. **Methods:** Using baseline data from the Study of Muscle, Mobility and Aging ($N = 799$, age: 76 ± 5 yr, 58% female), we quantified metrics describing rhythmic aspects of rest-activity behavior (amplitude, robustness, time of peak activity, others) from continuous wrist-worn accelerometry. We used linear models to examine cross-sectional associations between rhythmic metrics with $\dot{V}O_{2peak}$ and walking energetics (cost-capacity ratio at slow and preferred walking speeds) adjusted for age, sex, race, height, health conditions, and other factors. **Results:** Metrics that reflect more rhythmic behavior were associated with $\dot{V}O_{2peak}$ (higher amplitude: Q1: 18.4 vs Q4: 22.0 mL·kg⁻¹·min⁻¹; P -trend < 0.001) higher pseudo- F statistic/robustness (Q1: 19.2 vs Q4: 21.3 mL·kg⁻¹·min⁻¹; P -trend < 0.001), and earlier time of peak activity (Q1 (earliest): 20.9 vs Q4 (latest): 19.2 mL·kg⁻¹·min⁻¹; P -trend < 0.001). Similar trends were observed with lower cost-capacity ratio at preferred and slow walking speeds (amplitude, pseudo- F statistic, acrophase: P -trend < 0.001 for all). **Conclusions:** More rhythmic activity behavior and earlier time of peak activity were associated with better cardiorespiratory fitness and walking energetics. These findings support the framework that rhythmic activity supports healthy physiology. Further investigations are warranted to determine if declines in rhythmicity of human behavior are predictive of disease. **Key Words:** AGING, FITNESS, CIRCADIAN RHYTHMS, WALKING ENERGETICS

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A fundamental role of the circadian system is to temporally align behavior and physiology to support health and resilience (1). This temporal integration requires alignment of a network of endogenous circadian clocks that exist in central and peripheral tissues (2,3). These molecular clock mechanisms regulate a daily program of cell and tissue physiology to support different demands over time of day, such as rest and active periods. Research over the last 10 yr has uncovered that changes in behavioral rhythms in situations such as shift work and jet lag lead to changes in health including altered blood pressure and circulating glucose levels (4). In some settings, disruption of circadian behaviors such as fasting/feeding cycles and sleep/wake cycles leads to overt pathophysiology (5,6). The “circadian disruption hypothesis” therefore posits that unpredictable (or arrhythmic) behaviors lead to pathophysiology by compromising the systemic homeostasis supported by cell/tissue circadian clock function and downstream physiology (1–3,7).

In light of the circadian disruption hypothesis, it is pertinent to better define whether physiological outcomes associate with parameters of human behavior. One of the more well-defined circadian behaviors is the rhythms of rest and activity that occur each day (8). For this study, we hypothesized that more rhythmic patterns of rest and activity behavior support healthy physiology with improved outcomes of physical performance; whereas diminished circadian parameters would be associated with poorer physiological functions. If this hypothesis is supported, this would suggest that observing highly rhythmic behavior—or *lack of* rhythmic behavior—in an organism gives insight into underlying physiological health.

One can measure rhythmic features of human activity behavior with wearable devices that continuously record times of rest and activity over several days (8). From these wearable data, numerous variables describing aspects of rhythmicity can be derived, such as amplitude (peak to trough height of a rhythm), acrophase (time of peak activity of the fitted curve), and robustness (defined by goodness of fit of activity to a modified cosine wave pattern over several days). To date, amplitude is the most consistent metric in this field that is linked with health status, in that a lower amplitude (e.g., weaker rhythm) is associated with aging and age-related chronic diseases (9). Links between rhythmic variables and fitness have not been empirically addressed, and we sought to fill this knowledge gap. Specifically, we aimed to determine if various parameters of rhythmic behavior are associated with aspects of better physical fitness. To address this question, we selected metrics of fitness that decline with age, including cardiorespiratory fitness and measures of walking energetics (10–13).

This current study is a continuation of our previous work reporting that lower rhythmic amplitude is associated with aging (9). Herein, we examined cross-sectional associations between rhythmic variables and cardiorespiratory fitness assessed during treadmill cardiopulmonary exercise testing (CPET), as well as measures of walking energetics calculated from CPET assessments, including cost-capacity ratio from slow and preferred walking speeds, and others. We used data from baseline assess-

ments in the Study of Muscle, Mobility and Aging (SOMMA) cohort. This cohort consisted of community-dwelling older adults ≥ 70 yr of age. We hypothesized that higher rhythmic amplitude would be positively associated with better cardiorespiratory fitness and walking energetics. We also aimed to determine how the other rhythmic variables were associated with cardiorespiratory fitness and walking energetics.

METHODS

Participant Cohort

This current study used baseline data collected (April 2019 to December 2021) as part of the SOMMA (<https://sommaonline.ucsf.edu>) at the University of Pittsburgh and Wake Forest University School of Medicine. Eligible participants were required to be 70 yr old and have the ability to walk one-quarter of a mile (walk speed ≥ 0.6 m·s⁻¹). They were also excluded if they had body mass index (BMI) ≥ 40 kg·m⁻², active malignancy or dementia, or any medical contraindication to biopsy or magnetic resonance (MR). A full description of the study design including enrollment is described elsewhere (14). Study visits for SOMMA included three to four separate clinic visits that were generally collected within 6 wk of each other. SOMMA was approved by the Western IRB-Copernicus Group (WCG) Institutional Review Board (WCGIRB, study number 20180764). All participants provided written informed consent.

Assessment of Outcomes

Assessment of cardiorespiratory fitness and walking energetics. CPET is considered the gold standard measure of fitness (15). A CPET protocol, using a modified Balke or manual protocol, was conducted on a treadmill to measure ventilatory gases, oxygen, and carbon dioxide during exercise (15). Staff conducting CPET went through formal, centralized training to standardize the testing process. Participants were screened for safety to perform either all 3 phases, or only phases 1 and 3 (subpeak). Phase 1 consisted of 5 min of walking at 0% grade at each participant's preferred walking speed that was based on gait speed during a 400-m walk test that occurred prior to CPET. Immediately after, phase 2 was performed, which consisted of the “peak” portion of the test, which used the modified Balke Protocol. Phase 2 started immediately after phase 1. The treadmill incline increased by 2.5% every 2 min, but the maximal incline was limited to 10% to avoid biomechanically awkward walking at steeper angles. After reaching a 10% incline, progressive exercise intensity relied on increasing treadmill speed by 0.5 mph (0.22 m·s⁻¹) every 2 min until the participant reached volitional fatigue (15). Participants were provided standard encouragement in order to reach a respiratory exchange ratio (RER) ≥ 1.05 and a Borg rating of perceived exertion ≥ 17 (range of scale, 6–20) (16). After a 20-min seated recovery period, phase 3 began with 5 min of walking at a slow speed of 0.67 m·s⁻¹ (1.5 mph) at 0% incline. Participants were generally provided with a time window of opportunity for CPET

scheduling that included 8:30 AM to 4:45 PM. The majority of the exams took place between 10:00 AM and 3:00 PM (93%).

Primary variables used in the current analysis included the following:

- a) $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), which was defined as the highest 30-s average of $\dot{V}O_2$ achieved during phase 2. A higher $\dot{V}O_{2peak}$ value reflects better cardiorespiratory fitness.
- b) Cost-capacity ratio (%), which was defined as the average $\dot{V}O_2$ from the last 3 min of the preferred walking speed phase of the CPET to $\dot{V}O_{2peak}$ ($100 \times \dot{V}O_2$ from preferred walking speed/ $\dot{V}O_{2peak}$). A higher value indicates that a larger proportion of one's maximum fitness capacity was used to walk at a preferred walking speed.
- c) Cost-capacity ratio (%), which was defined as the average $\dot{V}O_2$ from the last 3 min of the slow walking speed phase of the CPET to $\dot{V}O_{2peak}$ ($100 \times \dot{V}O_2$ from slow walking speed/ $\dot{V}O_{2peak}$). A higher value indicates that a larger proportion of one's maximum fitness capacity was used to walk at a minimal gait speed.

Secondary variables included the following:

- d) Energetic cost of walking per distance traveled (EC_w ; $\text{mL}\cdot\text{kg}^{-1}\cdot\text{m}^{-1}$) from preferred walking speed, which was defined as the average $\dot{V}O_2$ from the last 3 min of phase 1 divided by walking speed. A higher value indicates greater energetic cost needed to walk at their preferred speed.
- e) EC_w per distance traveled ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{m}^{-1}$) from slow walking speed, which was defined as the average $\dot{V}O_2$ from the last 3 min of phase 3 divided by walking speed. A higher value indicates greater energetic cost used at a minimal gait speed.
- f) Energy reserve ($\text{mL}\cdot\text{min}^{-1}$), which was defined as the delta of $\dot{V}O_{2peak}$ and $\dot{V}O_2$ from slow walking speed. A higher value indicates that more energy is available above that needed for minimal gait speed.

Assessment of Actigraphy Actigraph. Actigraphy data were collected using the ActiGraph GT9X (ActiGraph, Pensacola, FL), which has a three-axis accelerometer with a sampling rate of 80 Hz. The watch-like device was placed on a participant's nondominant wrist during the initial SOMMA clinic visit (on average, 2–4 wk prior to the CPET exam). The device gathered activity data continuously. Data were processed in 1-min epochs (activity, counts per minute). Data were scored using ActiGraph LLC's ActiLife Software. Participants were asked to wear the device continuously (24 h·d) for 7 d (17). Data from the first day of wear were excluded from these analyses, as the participants were required to do a number of physical performance tests during their clinic visit and the activity level may not be representative of their usual activity patterns. Sleep diaries were used to aid in setting intervals for when the participants were in bed asleep or trying to sleep. Nonwear time was determined by a combination of an off-wrist detector in the device, a nonwear algorithm, and review by an actigraphy data scorer (17,18). Nonwear times were set to missing. The Cole-Kripke sleep scoring algorithm was used to determine sleep from wake (19). Total sleep time during the in-bed interval and sleep efficiency (percent of time

during the in-bed interval spent sleeping) were averaged over all nights of wear, to obtain a more representative characterization of usual sleep patterns. Total activity count per 24-h day was averaged over all days to get an estimate of overall activity level.

Rest activity rhythmic variables. We calculated variables to quantify aspects of the rhythmic pattern using parametric and nonparametric approaches. The two approaches provide complementary information, which increases the analytical rigor. Brief descriptions of these variables (9,20,21) are presented hereinafter:

Parametric variables. Activity data were fit to a modified cosine wave pattern determined using a five-parameter extension to the traditional 24-h cosine curve to derive rhythmic summary variables (22).

- a) Amplitude, which is peak to nadir difference in activity (units of activity (counts per minute)). A higher value indicates higher rhythmic strength.
- b) Meso, which is the mean level of activity (units of activity (counts per minute)) determined by the midpoint between the rhythmic maximum and minimum. A higher value indicates higher rhythmic strength.
- c) Pseudo-*F* statistic, describes the goodness of fit of raw activity data to a modified cosine wave form over multiple days (e.g., consistent rhythmic peak and trough wave pattern). It can be conceptualized as rhythmic robustness in that a higher value indicates a stronger fit to a modified cosine wave form over multiple days (e.g., better aligns with a consistent rhythmic peak and trough wave pattern).
- d) Acrophase, which is the time of day (expressed as either time of day or portion of hours) at which peak activity of the fitted curve occurred. A higher value indicates a later time to peak.

Nonparametric variables.

- e) Interdaily stability (IS), which describes the day-to-day rhythmic stability ranging from 0 to 1
- f) Intradaily variability (IV), which describes the rhythmic fragmentation across 24 h ranging from 0 to 2
- g) M10, which is the average activity level of the most active consecutive 10-h period (counts per minute)
- h) L5, which is the average activity of the least active consecutive 5-h period (counts per minute)
- i) Relative amplitude (RA), which is the difference in activity between M10 and L5 in the average 24-h pattern, normalized by their sum. With the assumption that M10 is largely during the day and L5 occurs during the night, a higher value indicates relatively lower activity during the night and greater activity when awake. A lower value would suggest relatively more activity during the night versus day and potentially significant sleep disruption.

Time of day of CPET assessments. We calculated the difference of the time of day in which the CPET exam occurred and the participants' acrophase (time of peak activity of the modified cosine curve). Participants were then categorized into three groups based on CPET start time: 1) over an hour before acrophase, 2) within an hour of acrophase, and 3) over an hour after acrophase.

Assessment of Other Variables

Self-report data were collected on date of birth, sex, race, ethnicity, smoking status (none, past, current), alcohol use (drinks per week), and history of medical conditions. Daily caffeine intake was estimated from 2 nonconsecutive days of 24-h Food Recall (ASA24) developed by the National Cancer Institute (23). Self-reported medical conditions were used to calculate a multimorbidity index, using the modified Rochester Epidemiology Project multimorbidity scale (0–11), which included cancer (non-melanoma skin cancer excluded), chronic kidney disease or renal failure, atrial fibrillation, lung disease (i.e., chronic obstructive pulmonary disease, bronchitis, asthma, or emphysema), coronary heart disease (i.e., blocked artery or myocardial infarction), depressive symptoms (e.g., ≥ 10 score on the 10-item version of the Center of Epidemiologic Studies Depression scale), heart failure, dementia, diabetes, stroke, and aortic stenosis (24). Height (m) was measured by stadiometers and body weight (kg) by balance beam or digital scales, and BMI was calculated ($\text{kg}\cdot\text{m}^{-2}$). Perceived physical fatigability was measured with the Pittsburgh Fatigability Scale, a validated self-administered 10-item scale (25).

Statistical Analysis

Participant characteristics, rhythmic variables and CPET outcomes were summarized by means and standard deviations (SD) for continuous variables, and counts and percentages for categorical variables. Differences in these characteristics across quartiles of amplitude were analyzed using ANOVA or Kruskal–Wallis tests for continuous variables and χ^2 tests for homogeneity for categorical characteristics. To study correlations between rhythmic parameters, the Pearson correlation coefficients were represented as a heatmap. Associations of rhythmic variables and CPET outcomes ($\dot{V}\text{O}_{2\text{peak}}$, cost-capacity ratio at preferred and slow walking speed, energetic cost of walking at preferred and slow walking speed, and energy reserve) were examined with linear regression models. Rhythmic variables were expressed categorically in models as quartiles, calculated by rank ordering values of the variables and dividing the data into four equal groups. Results are presented as adjusted means and their 95% confidence intervals. Tests for a linear trend across categories were performed by including each characteristic (ordinal variable) as an independent variable in models. Models were adjusted for clinic site, sex, age, race, multimorbidity burden (or index scores as a continuous variable), smoking status, alcohol intake, caffeine intake, and height. The outcomes $\dot{V}\text{O}_{2\text{peak}}$, cost-capacity ratio, and energetic cost of walking were corrected for body weight, so adjustment for body weight was only included in the models for energy reserve. In sensitivity analyses, models were further adjusted for total activity (counts per minute), sleep efficiency (sleep fragmentation), and perceived physical fatigability to determine whether associations were independent of these parameters. As a secondary analysis, linear regression models with the rhythmic variables expressed as continuous predictors per SD increment were also performed. Results are presented as beta coefficients and their 95% confidence intervals. Statistical significance is considered at $P < 0.05$.

We explored differences in associations by sex by performing formal tests for interaction with sex and each rhythmic variable (as a continuous variable) with linear regression models that included clinic site, the rhythmic variable, sex, and a term for sex–rhythmic variable. Interaction terms were considered significant if $P < 0.10$.

Age attenuation was assessed by examining the percent of attenuation of the beta coefficient for age after adjustment for rhythmic variable for each outcome.

A series of models were performed to examine if there was a significant association of the difference of the timing of the CPET to the participants' acrophase with CPET outcomes ($\dot{V}\text{O}_{2\text{peak}}$, preferred walking speed and slow walking speed cost-capacity ratio, energetic cost of walking at preferred walking speed and slow walking speed, and energy reserve). First, we examined if the timing of CPET was related to acrophase, to estimate if either participants were randomly assigned test times or if there were patterns that might reflect the participants preferred timing for activity (indicated by congruence between test time and acrophase). Next, we examined models as described previously with each CPET measure as the outcome and quartile of test time, to determine if timing of the test was related to performance. We examined if the difference in test time and acrophase predicted CPET outcomes.

Last, although all analyses were prespecified, a Bonferroni correction was applied to all significant P values in the analysis to examine whether the associations observed held after correction for multiple comparisons.

All significance levels reported were two-sided, and all analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Participants

The analysis was conducted on a subset of participants ($N = 799$) from the SOMMA cohort (Fig. 1). Missing rest activity rhythm data derived from actigraphy ($N = 58$) were largely due to equipment issues. Almost all participants with rhythmic data also have data for one or more CPET outcomes. Most of those 32 participants who performed CPET but had no $\dot{V}\text{O}_{2\text{peak}}$ data were largely due to health concerns (Fig. 1). Regarding the analytical sample, the average age was 76.3 yr, 58% of the cohort was female, the average BMI was $27.6 \text{ kg}\cdot\text{m}^{-2}$, and the average SOMMA multimorbidity index (0–11) was 0.81. The average $\dot{V}\text{O}_{2\text{peak}}$ was $20.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and the average cost-capacity ratio for preferred walking speed was 63.4% and slow walking speed was 48.7% (Table 1). The average sleep duration was 6 h, 52 ± 61 min. The average acrophase (which is the timing of peak activity from the fitted rhythmic curve) was 2:17 PM. The median start time of the CPET test time was 12:35 PM, and the range was 8:36 AM–4:41 PM. Most participants (64.4%) had the start of their test time over 1 h before their acrophase, 26.4% had their test time within 1 h of their acrophase, and fewer (9.1%) had their test time over an hour after their acrophase (Table 1).

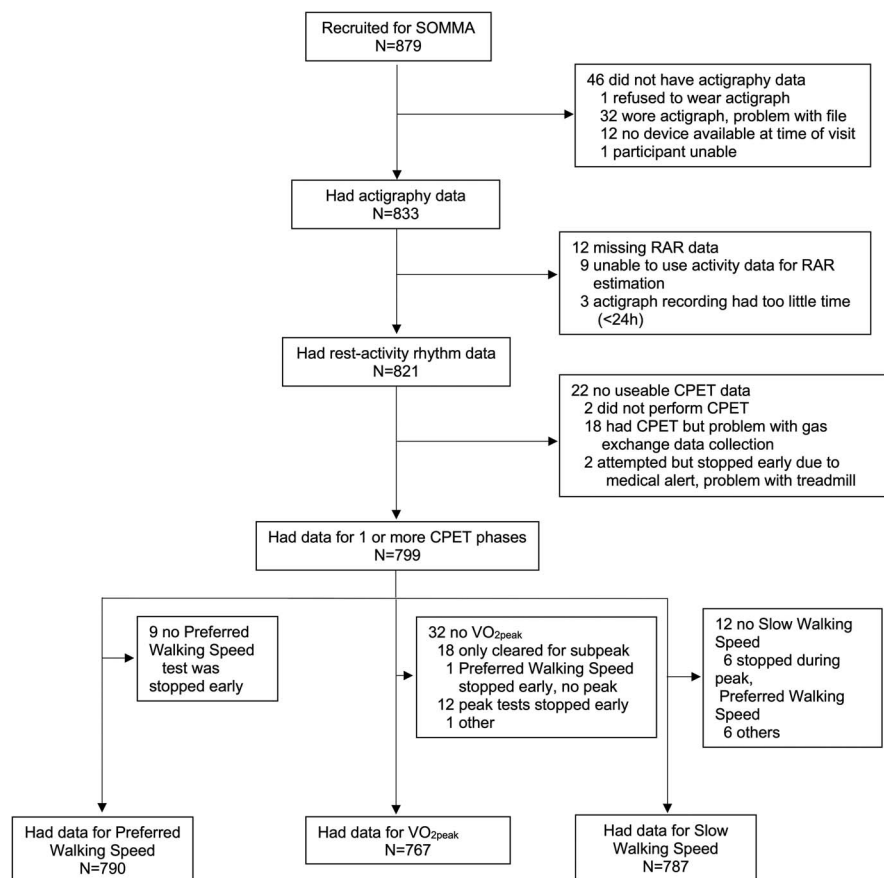


FIGURE 1—Flowchart of enrolled SOMMA participants with assessments and corresponding endpoints used in final analytical sample.

Associations between Rhythmic Metrics

The strength of correlations among acrophase versus other rhythmic variables, such as amplitude, is weak ($\text{abs}(\rho) \leq 0.33$; Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/MSS/D229>). This suggests that acrophase captures a distinct aspect of rhythmic behavior, likely related to timing of peak activity across the 24-h timescale. Correlations among rhythmic variables related to activity levels (amplitude, mesor, M10) are strong, suggesting that these variables provide complementary information.

Associations between Rhythmic Metrics and Cardiorespiratory Fitness

Parametric variables. Higher amplitude, higher mesor, and higher pseudo- F statistic were all positively associated with higher cardiorespiratory fitness (Fig. 2; Supplemental Tables 1A and 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>). These associations showed a graded increase in $\dot{V}O_{2\text{peak}}$ from smaller amplitude/less robust to higher amplitude/more robust (Q1–Q4, $P\text{-trend} < 0.001$). Acrophase represents the timing of peak activity within a 24-h day. The quartile breakdown by acrophase is Q1: 7:07 AM to <1:31 PM, Q2: 1:31 PM to <2:19 PM, Q3: 2:19 PM to <3:09 PM, and Q4: from 3:09 PM to 10:11 PM. We found that earlier acrophase was associated with higher $\dot{V}O_{2\text{peak}}$ (Fig. 2; Supplemental Tables 1A and 7A, Supplemental Digital Content,

<http://links.lww.com/MSS/D229>). These associations showed a graded decrease in $\dot{V}O_{2\text{peak}}$ from earlier timing to later timing of peak activity (Q1–Q4, $P\text{-trend} < 0.001$).

Nonparametric variables. Variables representing consistent patterns (higher IS, lower IV) as well as lower rhythmic trough (lower L5), higher rhythmic peak (higher M10), and higher delta between trough and peak (higher RA) were associated with higher $\dot{V}O_{2\text{peak}}$ (Fig. 3; Supplemental Tables 1B and 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

Associations between Rhythmic Metrics and Walking Energetics

Parametric variables

- Cost-capacity ratios: Higher amplitude, higher mesor, higher pseudo- F statistic, and earlier acrophase were associated with lower cost-capacity ratios at preferred and slow walking speeds ($P\text{-trend} < 0.001$; Fig. 2; Supplemental Tables 2A, 3A, 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).
- Energetic cost of walking: Higher amplitude and mesor were associated with lower energetic cost at preferred walking speeds; none were related to energetic cost at slow walking speed (Supplemental Tables 4A, 5A, 7A; Supplemental Digital Content, <http://links.lww.com/MSS/D229>).
- Energy reserve: Higher amplitude, higher mesor, higher pseudo- F statistic, and earlier acrophase were associated

TABLE 1. Participant characteristics: the SOMMA by quartile of amplitude.

Characteristic	All	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P ^a
	(N = 799)	500.83–<1574.97 (N = 199)	1574.97–<2035.75 (N = 200)	2035.75–<2564.77 (N = 200)	2564.77–15,614.10 (N = 200)	
Demographics and lifestyle						
Age (yr)	76.3 ± 5.0	77.9 ± 5.4	76.5 ± 5.1	76.0 ± 4.9	74.8 ± 4.0	<0.0001
Site						
Pittsburgh	388 (48.6)	94 (47.2)	100 (50.0)	92 (46.0)	102 (51.0)	0.73
Wake forest	411 (51.4)	105 (52.8)	100 (50.0)	108 (54.0)	98 (49.0)	
Sex						<0.0001
Male	339 (42.4)	112 (56.3)	88 (44.0)	65 (32.5)	74 (37.0)	
Female	460 (57.6)	87 (43.7)	112 (56.0)	135 (67.5)	126 (63.0)	
White race	688 (86.1)	171 (85.9)	163 (81.5)	175 (87.5)	179 (89.5)	0.12
BMI (kg·m ⁻²)	27.5 ± 4.6	28.4 ± 4.5	28.0 ± 4.5	27.0 ± 4.9	26.8 ± 4.2	0.00
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	0.00
SOMMA multimorbidity index (0–11) ^b	0.8 ± 0.9	1.0 ± 0.9	0.9 ± 1.0	0.7 ± 0.8	0.7 ± 0.8	0.00
Smoking status						0.461
Never	447 (56.3)	110 (55.6)	113 (57.1)	109 (55.1)	115 (57.5)	
Past	322 (40.6)	77 (38.9)	81 (40.9)	83 (41.9)	81 (40.5)	
Current	25 (3.1)	11 (5.6)	4 (2.0)	6 (3.0)	4 (2.0)	
Alcohol intake (drinks per week)	2.8 ± 4.5	2.0 ± 4.2	2.7 ± 4.4	2.4 ± 4.0	4.0 ± 5.2	0.00
Caffeine intake (mg·d ⁻¹)	145.2 ± 124.5	144.2 ± 123.1	135.7 ± 123.3	149.5 ± 137.6	151.2 ± 113.1	0.3231
Total activity counts over 24 h/100K	19.9 ± 5.8	13.9 ± 3.0	18.2 ± 3.0	22.2 ± 3.4	25.2 ± 5.8	<0.0001
Total sleep time (min)	412.3 ± 60.6	417.5 ± 66.7	413.4 ± 62.9	410.9 ± 56.6	407.4 ± 55.7	0.39
Sleep efficiency (%)	84.9 ± 6.3	85.3 ± 6.4	84.7 ± 6.4	84.5 ± 6.8	85.0 ± 5.6	0.58
Pittsburgh Physical Fatigability Score (range, 0–50)	15.5 ± 8.5	17.5 ± 8.4	16.9 ± 8.6	14.5 ± 8.1	13.2 ± 8.2	<0.0001
CPET parameters						
Preferred walking speed						
Energetic cost of walking (mL·kg ⁻¹ ·m walked ⁻¹)	0.20 ± 0.04	0.21 ± 0.05	0.20 ± 0.04	0.20 ± 0.04	0.20 ± 0.04	<0.0001
Treadmill speed (m·s ⁻¹)	1.05 ± 0.18	0.98 ± 0.17	1.03 ± 0.17	1.07 ± 0.18	1.11 ± 0.15	<0.0001
Cost-capacity ratio (%)	63.1 ± 12.5	68.1 ± 12.5	64.6 ± 11.7	60.9 ± 11.5	59.2 ± 12.2	<0.0001
Peak						
VO _{2peak} (mL·kg ⁻¹ ·min ⁻¹)	20.26 ± 4.86	18.27 ± 3.71	19.36 ± 4.16	20.87 ± 4.98	22.41 ± 5.37	<0.0001
Time of day peak test started (portions of hours)	12.3 ± 1.8	12.5 ± 1.8	12.4 ± 1.8	12.2 ± 1.8	12.1 ± 1.8	0.15
Time of day peak test started—acrophase (portions of hours)	–2.0 ± 2.3	–2.0 ± 2.4	–1.9 ± 2.3	–2.0 ± 2.0	–1.9 ± 2.5	0.89
Time of CPET test vs acrophase						
Test was over 1 h before acrophase	502 (64.4)	122 (63.5)	124 (64.2)	130 (65.7)	126 (64.3)	0.30
Test was within 1 h of acrophase	206 (26.4)	53 (27.6)	46 (23.8)	58 (29.3)	49 (25.0)	
Test was over 1 h after acrophase	71 (9.1)	17 (8.9)	23 (11.9)	10 (5.1)	21 (10.7)	
Slow walking speed						
Energetic cost of walking (mL·kg ⁻¹ ·m walked ⁻¹)	0.23 ± 0.04	0.24 ± 0.04	0.24 ± 0.04	0.23 ± 0.04	0.23 ± 0.04	0.16
Cost-capacity ratio (%)	48.7 ± 12.5	54.4 ± 12.2	50.6 ± 12.4	46.6 ± 11.5	43.5 ± 11.3	<0.0001
Energy reserve (mL·min ⁻¹)	817.5 ± 374.4	705.4 ± 331.8	764.2 ± 334.1	846.0 ± 387.5	946.4 ± 395.4	<0.0001
Rest activity rhythm parameters						
Amplitude (counts per minute)	2201.1 ± 1146.9	1229.4 ± 259.5	1797.3 ± 132.0	2290.6 ± 147.1	3482.4 ± 1549.9	<0.0001
Mesor (counts per minute)	1315.5 ± 621.6	864.0 ± 203.0	1121.4 ± 195.5	1353.9 ± 218.7	1920.6 ± 900.6	<0.0001
Acrophase (portions of hours)	14.3 ± 1.5	14.5 ± 1.6	14.4 ± 1.3	14.3 ± 1.3	14.0 ± 1.8	0.01
Pseudo-F statistic	675.5 ± 301.5	424.3 ± 161.1	606.8 ± 180.1	753.8 ± 224.0	915.8 ± 352.2	<0.0001
IV (range, 0–2)	0.89 ± 0.22	1.07 ± 0.21	0.90 ± 0.18	0.83 ± 0.17	0.76 ± 0.19	<0.0001
IS (range, 0–1)	0.58 ± 0.12	0.51 ± 0.12	0.56 ± 0.11	0.62 ± 0.10	0.64 ± 0.10	<0.0001
L5 (counts per minute)	151.0 ± 114.1	158.2 ± 114.5	153.0 ± 128.2	150.0 ± 119.8	142.8 ± 90.7	0.59
M10 (counts per minute)	2249.2 ± 660.0	1516.7 ± 309.0	2031.2 ± 275.6	2514.1 ± 301.4	2931.0 ± 602.5	<0.0001
Total 24-h periods the actigraph was worn	8.0 ± 0.8	8.2 ± 0.8	8.1 ± 0.8	7.9 ± 0.9	7.9 ± 0.7	0.00

Quartiles defined by amplitude parameter from rest activity rhythms.

^a P values for continuous variables are from an ANOVA for normally distributed data, and a Kruskal-Wallis test for skewed data. P values for categorical data are from a chi-square test for homogeneity.

^b Multimorbidity index includes cancer (excluding nonmelanoma skin cancer), atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, heart disease, congestive heart failure, dementia, depression, diabetes mellitus, stroke, and aortic stenosis.

L5, average activity of the 5 consecutive hours with least activity (counts per minute); M10, average activity of the 10 consecutive hours with most activity (counts per minute)

with higher values of energy reserve (Supplemental Tables 6A, 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

Nonparametric variables

A. Cost-capacity ratios: Variables representing consistent patterns (higher IS, lower UV) as well as lower rhythmic trough (lower L5), higher rhythmic peak (higher M10), and higher delta between trough and peak (higher RA) were associated with lower cost-capacity ratios at preferred and slow walking speed (Fig. 3; Supplemental Tables 2B, 3B, 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

B. Energetic costs: Some variables representing higher rhythmic trough (higher L5) and lower delta between trough and peak (lower RA) were associated with higher energetic cost of walking at preferred and slow walking speeds (Supplemental Tables 4B, 5B, 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

C. Energetic reserve: Variables representing lower rhythmic trough (L5), higher rhythmic peak (M10), and higher delta between trough and peak (higher RA) were associated with having more energy reserve (Supplemental Table 6B, 7A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

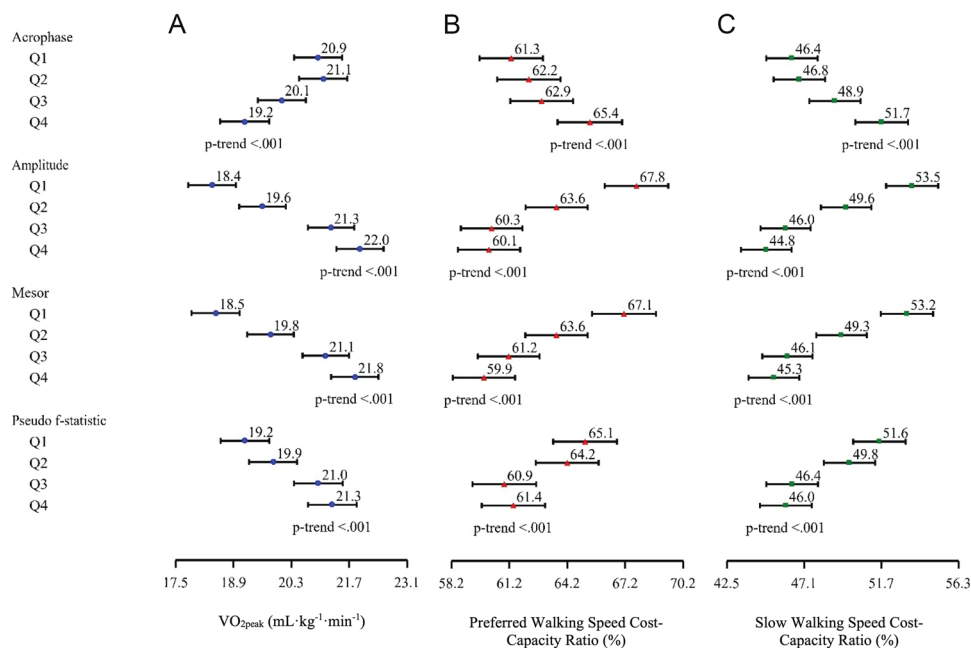


FIGURE 2—Multivariable-adjusted associations of parametric rest activity rhythm parameters by quartile with cardiorespiratory fitness outcomes from treadmill CPET, adjusted means (95% confidence intervals). A, $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹). B, Preferred walking speed cost-capacity ratio (%). C, Slow walking speed cost-capacity ratio (%). Models adjusted for clinic site, sex, age, race, multimorbidity burden, smoking status, alcohol intake, caffeine intake, and height. Quartile cutpoints are in Supplemental Tables 1A, 2A, and 3A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>.

Sex Interactions

Three associations between rhythmic variables and walking energetics were only significant among men: 1) pseudo-*F* sta-

tistic and cost-capacity ratio at preferred walking speed (Supplemental Table 2A, Supplemental Digital Content, <http://links.lww.com/MSS/D229>), and 2–3) pseudo-*F* statistic and

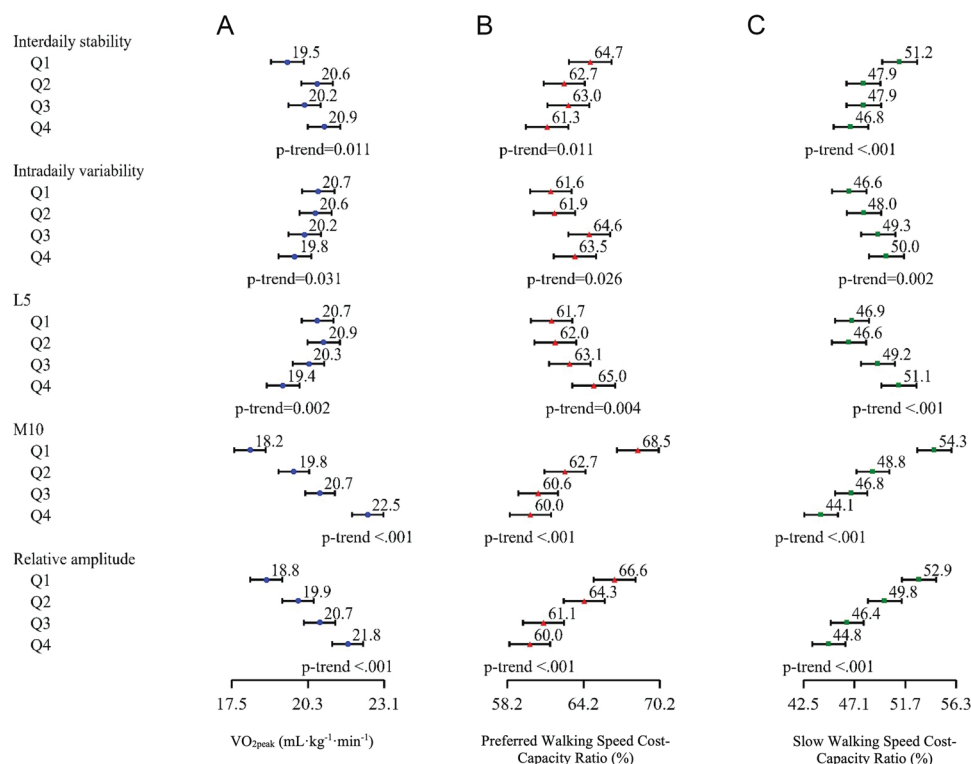


FIGURE 3—Multivariable-adjusted associations of nonparametric rest activity rhythm parameters by quartile with cardiorespiratory fitness outcomes from treadmill CPET, adjusted means (95% confidence intervals). A, $\dot{V}O_{2peak}$ (mL·kg⁻¹·min⁻¹). B, Preferred walking speed cost-capacity ratio (%). C, Slow walking speed cost-capacity ratio (%). Models adjusted for clinic site, sex, age, race, multimorbidity burden, smoking status, alcohol intake, caffeine intake, and height. Quartile cutpoints are in Supplemental Tables 1B, 2B, and 3B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>.

energetic cost at preferred and slow walking speed (Supplemental Tables 4A and 5A, 7B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

There was also a significant sex interaction with M10 and energetic cost at preferred walking speed; however, results were not significant for either sex after stratification (Supplemental Tables 5B, 7B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

Sensitivity Analyses

Further adjustment for sleep efficiency, which is a measure of sleep fragmentation, and perceived physical fatigability had very little effect on associations. Exceptions are the loss of statistical significance for the association of L5 and RA with energetic cost of walking at slow walking speed when further adjusting models for sleep efficiency, and loss of significance for the associations of IV with $\dot{V}O_{2peak}$ and mesor with energetic cost of walking at preferred walking speed after further adjustment for fatigability (Supplemental Tables 1A–6B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>). After further adjustment for total daily activity level (total counts per minute), the associations of pseudo-*F* statistic with $\dot{V}O_{2peak}$, cost-capacity ratio at both preferred and slow walking speeds, and energy reserve were no longer significant. Further adjustment for activity level also attenuated the associations of IS with $\dot{V}O_{2peak}$, cost-capacity ratio at both preferred and slow walking speeds, as well as the associations of mesor with $\dot{V}O_{2peak}$ and walking energetics at preferred walking speed (Supplemental Tables 1A–6B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

Additional Analysis

Beta coefficients for linear regression models are in Supplemental Tables 7A and 7B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>. Given the strong association of age with cardiorespiratory fitness (10), we were interested in how the rest activity rhythm variables may attenuate the association of age with cardiorespiratory fitness. Age alone was significantly associated with all outcomes examined. For example, each 5 yr of age was associated with lower $\dot{V}O_{2peak}$ (β (95% CI): -1.36 (-1.70 to -1.02) $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P < 0.001$; Supplemental Tables 8A, 8B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>). Amplitude had the largest attenuation of the association of age on all outcomes. The association of age with $\dot{V}O_{2peak}$ was attenuated to $\beta = 1.07$ $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with adjustment for amplitude (21% attenuation).

Bonferroni Corrections

We performed multivariable models for nine rest activity rhythm predictors and six outcomes. Adjusting the significance level of 0.05 with a Bonferroni correction would lead to a significance cutpoint of $P < 0.0009$ ($=0.05/54$). After applying this more-stringent cutpoint for significance, of the 40 associations with $P < 0.05$, 27 (68%) remained significant

($P < 0.0009$), with more robust associations with the parametric variables (amplitude, mesor, acrophase, pseudo-*F* statistic; Supplemental Tables 1A–6B, Supplemental Digital Content, <http://links.lww.com/MSS/D229>).

Time of Day of CPET Assessments

After multivariable adjustment, time of day of the CPET test was related to acrophase (P -trend = 0.04). Those in the later quartile of acrophase had start times of approximately 15 min later than the other three quartiles (adjusted means for start time Q1: 12:02 PM, Q2: 12:09 PM, Q3: 12:12 PM, Q4: 12:33 PM).

CPET start time was significantly related to cost-capacity ratio at slow walking speed (P -trend = 0.007) and energetic cost of walking at preferred walking speed (P -trend = 0.04), but not $\dot{V}O_{2peak}$ (P -trend = 0.12), cost-capacity ratio at preferred walking speed (P -trend = 0.24), energetic cost of walking at slow walking speed (P -trend = 0.10), or energy reserve (P -trend = 0.05).

There were no statistically significant associations between the difference in test times and acrophase with either measure of energetic cost of walking, the cost-capacity ratios, or energy reserve (P -trend ≥ 0.10). There was a significant association, however, with the difference in start time and acrophase with $\dot{V}O_{2peak}$ (P -trend = 0.04), with those tested over an hour before their acrophase having lower values of $\dot{V}O_{2peak}$, with higher $\dot{V}O_{2peak}$ seen among those tested within an hour of acrophase and those tested an hour after acrophase having even higher $\dot{V}O_{2peak}$ (Fig. 4). There was a significant sex interaction ($P = 0.09$) for this association. After stratification by sex, women had a significant association of the difference of their start time and acrophase to cardiorespiratory fitness ($\dot{V}O_{2peak}$ outcome P -trend = 0.02), although not statistically significant in men (P -trend = 0.48).

DISCUSSION

The primary finding of this study was that a higher rhythmic activity amplitude was positively associated with higher cardiorespiratory fitness (e.g., $\dot{V}O_{2peak}$ $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Of the nine rest activity rhythm variables examined, amplitude had the largest attenuation of the effect of age on the outcomes examined, and the significance was robust to corrections for multiple comparisons. To date, amplitude is one of the most common metrics used to describe a circadian rhythm, and it is thought to reflect a measure of circadian clock/rhythmic strength. Previous studies have reported that a lower amplitude is associated with higher age and age-related pathologies (26–36). These studies support the hypothesis that a person's pattern of rest activity rhythms are linked to indices of systemic health. The biological rationale is that weaker activity rhythms are a behavioral biomarker indicating diminished circadian clock alignment across tissues within the system. As noted by others, active disruption to circadian clock alignment is associated with pathophysiological outcomes including hypertension and glucose intolerance (37,38). In further support

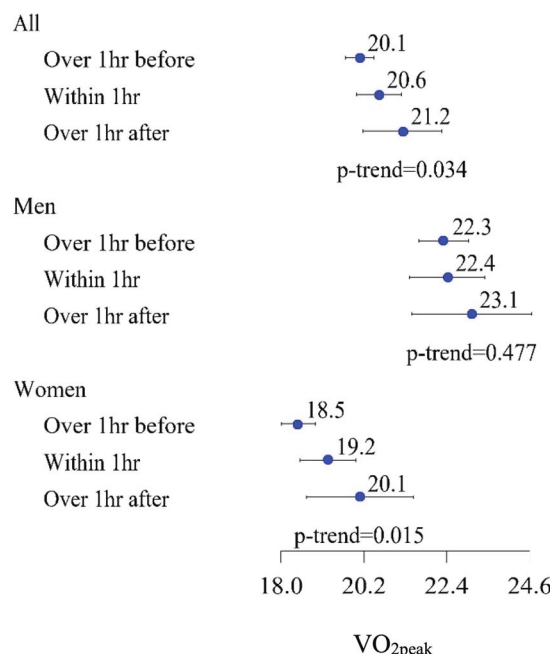


FIGURE 4—Multivariable-adjusted associations of the difference between treadmill CPET exam time of day versus acrophase by category with $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), adjusted means (95% confidence intervals). Models adjusted for clinic site, age, race, multimorbidity index, smoking status, alcohol intake, caffeine intake, and height.

of our hypothesis, we also found that rest and activity patterns that better aligned with peaks and troughs of a cosine wave shape over several days (e.g., assessed as goodness of fit to a modified cosine wave, or higher robustness) were associated with higher cardiorespiratory fitness, and nonparametric variables were also generally associated with higher cardiorespiratory fitness. Relations between rest activity rhythms and walking energetics largely paralleled those observed with cardiorespiratory fitness. We found that amplitude was associated with lower cost-capacity ratio at preferred walking speed and slow walking speed. In addition to amplitude, active patterns that followed an overall rhythmic shape (e.g., goodness of fit to a modified cosine wave or higher robustness) were associated with better walking energetics, and consistent trends were observed with nonparametric methods for quantifying rhythmic patterns.

Another finding of this study was that earlier acrophase (time of peak activity) was associated with higher cardiorespiratory fitness and better walking energetics. Somewhat similar to our finding, a previous study reported that activity during the morning hours was associated with lower cardiovascular disease incidence (39). Other studies categorized participants into groups based on time windows in which physical activity most often occurred, reporting that more afternoon/evening activity was associated with lower insulin resistance (40) and evening activity was associated with lower all-cause mortality (41). In our study, we measured acrophase, which quantifies the time of peak activity in a free-living setting. It may be reasonable to suspect that this variable gives insight into one's activity chronotype or inherent preference to be active during a particular time of day. Our analysis adds new evidence to the field of circadian behavior, reporting that an "early active" behavior phenotype is associated with higher cardiorespiratory fitness and better

walking energetics. Collectively, these studies suggest that time of day of activity is related to many health conditions.

We also found that the time of day in which the CPET exam occurred was not related to $\dot{V}O_{2peak}$. There is evidence supporting diurnal variations in aspects of exercise performance in generally younger adults (42). It may be that a larger range of exam times across the 24-h cycle is needed to detect diurnal variations in human $\dot{V}O_{2peak}$, whereas most exams occurred between 10 AM and 3 PM. Another novel finding of this study is that those in the latest acrophase quartile had start times approximately 15 min later than the other three quartiles. Participants were given a range of 8:30 AM to 4:45 PM to schedule their CPET. It is tempting to speculate that participants with the latest acrophase were self-selecting later times to align with their inherent preference of activity timing. We also found that among women, when times are analyzed relative to acrophase, there were associations with cardiorespiratory fitness. Specifically, start times that occurred within 1 h, or 1 h after, their acrophase were associated with higher $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). This finding is consistent with the hypothesis that peak exercise performance is better expressed when tested during times that are aligned with, or soon after, one's acrophase. This is the first study of which we are aware to examine associations between time of peak activity versus metrics of exercise testing. We note that SOMMA was not initially designed to address these questions, and additional work is needed to better understand how rest activity patterns in free-living settings are related to exercise performance.

$\dot{V}O_{2peak}$ is modifiable by physical activity levels (43). In the current study, the associations between rhythmic variables (amplitude and earliest acrophase) versus aspects of physical fitness ($\dot{V}O_{2peak}$ and cost-capacity ratio at preferred walking

speed and slow walking speed) remained significant after adjusting for physical activity levels (assessed as total counts per minute). Rest activity rhythms are linked to health status (26–32,34–36). Future interventional studies should determine whether changes in rest activity patterns (including timing of sleep, timing of rest, timing of volitional exercise) have impacts on health status that are distinct from changes in volume or intensity of exercise and improvements in sleep health. Consistent with the circadian disruption hypothesis, temporally predictable and consistent rhythmic patterns in behavior may also lead to beneficial downstream physiological effects. We posit that this occurs because the consolidation of known circadian clock timing cues, including light, time of feeding, and activity serve to support alignment of the cell and tissue endogenous molecular clocks across all central and peripheral tissues for metabolic and physiological health. Other fields have applied similar reasoning with success: intervening on the circadian timing of food intake positively impacts longevity in preclinical models (44). On the other hand, one might reason that in the setting of human aging, better cardiorespiratory fitness and walking energetics are phenotypic features that facilitate patterns of rest and activity to regularly occur.

Factors other than endogenous circadian rhythms contribute to rest activity patterns in humans in free living settings. Some factors may include social demands, lifestyle behaviors, and environmental stimuli. Our current analysis accounts for variables that represent health status, activity levels, caffeine intake, alcohol consumption, and smoking, as well as with some potential variation in associations by sex. Due to the cross-sectional nature of this analysis, it is not possible to determine if dampened rest active rhythms contribute to aging, or rather if other intrinsic aging processes contribute to dampened and disordered rest activity rhythms and other health effects. The analytical sample had relatively few participants from under-represented groups, limiting the generalizability of findings.

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CONCLUSIONS

In conclusion, several features of rhythmic variables are related to parameters of physical fitness in the setting of human aging. Higher amplitude, a rhythmic and repeatable (robust) shape, and an earlier time of peak activity of rest activity rhythms were associated with higher cardiorespiratory fitness and better walking energetics in a large cohort of healthy, community-dwelling older adults. We also report novel associations between time of peak activity in free-living settings with aspects of physical fitness. An “early active” behavior phenotype was associated with higher cardiorespiratory fitness and better walking energetics. In women, CPET times that occurred within 1 h, or after 1 h, of their acrophase were associated with higher cardiorespiratory fitness. Our findings are consistent with the circadian disruption hypothesis positing that temporally predictable and consistent behavior supports better physiological function and health. These associations are new evidence that extends the field of rest activity rhythms to exercise physiology. If intervening on “rhythmicity” of daily patterns of rest and activity translates to meaningful improvements in health status remains an interesting hypothesis for future investigation.

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