Identifying Patterns of Free-Living Physical Activity that are Related to Perceived Physical Fatigability

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Previous accelerometry studies have shown that lower levels of physical activity (PA) are associated higher perceived physical fatigability, a modifiable risk factor which plays an important role along the disablement pathway. However, none have explored how the size, shape, timing and variability of the entire 24-hour rest-activity rhythm (RAR) is associated with fatigability. We examined cross-sectional associations of accelerometry-derived RARs with perceived physical fatigability (Pittsburgh Fatigability Scale (PFS, 0-50)) in a sample of 181 older adults (71.3 $\pm$ 6.7 years) from the Developmental Epidemiologic Cohort Study and the Mobility and Vitality Lifestyle Program. RAR features included parameter estimates from the anti-logistic extended cosine model, Intradaily Variability and Interdaily Stability, and 4-hour intervals of mean and standard deviation of PA across days. K-means clustering algorithm was applied to cosine model parameters to identify profiles of RAR features. Multivariate quantile and logistic regression were used to test the effects of each RAR feature and cluster on median PFS Physical scores and the odds of having greater perceived physical fatigability (PFS Physical score $\geq$ 15), adjusting for age, sex, race, BMI, and depression symptomology. Later rise times (up mesor) and timing of midpoint of activity (acrophase) were associated with higher PFS Physical scores (β=1.38, p=0.01; β=1.29, p = 0.01, respectively), later rise times were also associated with 46% increased odds of greater fatigability (OR=1.46, p=0.01). Those with higher physical fatigability showed an overall dampened activity profile, with lower levels of PA

between 4am and 8am significantly associated with higher PFS scores (β=-4.50, p=0.03). K-means clustering algorithm identified four RAR profiles: “Less Active/Robust”, “Earlier RAR”, “More Active/Robust” and “Later RAR”. Compared to “Earlier RAR” patterns, “Less Active/ Robust” and “Later RAR” patterns were associated with higher PFS Physical scores (β=6.14, p=0.01; β=3.53, p=0.01, respectively). Having either “Less Active/Robust” or “Later RAR” was associated with 2.26 times the odds of having greater fatigability (p=0.03). This study has public health significance because it is the first to identify classes of RARs which are associated with perceived physical fatigability, allowing future researchers and clinicians to develop interventions aimed at modifying RARs to prevent or delay functional decline.

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Preface

I would like to thank my committee members, Dr. Glynn, Dr. Boudreau, and Dr. Venditti for their guidance throughout this research project. I would like to extend special thanks and gratitude to Dr. Glynn for her constant support, invaluable insight, and encouragement over my years in the Graduate School of Public Health Epidemiology Department. I would also like to thank my family for always endless love and support.

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1.0 Introduction

The number of older adults in the United States is rapidly increasing. In 2017, there were 47.8 million adults aged 65 and older, making up 14.9% of the United States population, and this number is expected to double by 2060 (1). This steep increase in the aging population is likely to be met with a steep increase in health care costs associated with the health-care needs of older adults (2). It is well understood that health burden increases with age, as older adults are much more likely to suffer from reduced quality of life and multiple chronic conditions (3). In older adults, the effects of chronic conditions and overall health burden increases the likelihood of impaired mobility (4). In fact, in 2013, the Centers for Disease Control (CDC) estimated that 23% of women and 14% of men over the age of 65 were not able to walk 2-3 blocks (4). Impaired mobility such as the inability to walk is associated with a variety of health problems including depression, cardiovascular disease, cancer, risk of falls, and mortality (4–6). As our population continues to age, it is essential that public health officials and clinicians identify interventions which can enable older adults to retain independence, improve quality of life, and maintain (or even improve) health.

1.1 Fatigue, Fatigability, and Health in Older Adults

Fatigue is a commonly reported complaint among older adults and is an important risk factor for several health conditions. Fatigue can be defined as perceived experience of tiredness and exhaustion which interferes with usual or desired activities (7). The prevalence of fatigue in the general population varies wildly, with some estimating that 38% of community-dwelling

adults suffering from significant fatigue (8). However, the prevalence of fatigue increases dramatically with age, disease burden, and physical function. The estimated prevalence of fatigue in healthy older adults aged 70, 78, and 85 is 29%, 53%, and 68%, respectively (9).There are few studies that have explored gender and race/ethnic disparities of fatigue in older adults. One large cross-sectional study in younger-old adults (mean age of 65 years) found higher prevalence of fatigue in women (33%) compared to men (29%) and in minorities (48%) compared to white (28%) participants (10). Fatigue is important to study as it is highly prevalent in older adults and is thought to explain age-associated decline in physical activity (11), physical function (9), and mortality (12).

Fatigue can be thought of as a global measure of energy level and tiredness. Fatigability, on the other hand, is defined as an individual's perception of fatigue within the context of a defined activity of a specified intensity and duration (7, 13). The distinction between fatigue and fatigability is important as less physically active individuals may attenuate their exertion levels in order to maintain more tolerable effort (i.e. self-pacing) (7). Thus, fatigability is a whole-body measure of exercise tolerance, as it standardizes fatigue across activity levels by anchoring self-perceived fatigue to a specific duration and intensity of activity. The prevalence of grater perceived physical fatigability increases with age, with increased prevalence in women over men, ranging from 24.6% in 60-90 year old men and 94.3% in women aged 90 years and older (14).

Physical fatigability has become an increasingly popular area of research and numerous studies have shown that physical fatigability is associated with a variety of health outcomes, suggesting that it may lie along the disablement pathway. A study in the Baltimore Longitudinal Study of Aging (BLSA) found that those with higher fatigability were 13-19% more likely to

have meaningful functional decline (15). Additionally, a second study in this same sample found that physical fatigability was associated with reduced gait speed, chair stand pace, and reported walking ability (16). Other studies have shown that physical fatigability is associated with decreased gait speed (17, 18), an important predictor of disability and mortality (19, 20). In addition to these measures of physical function, higher physical fatigability has also been associated with other indicators of health status, such as: suboptimal thyroid hormone levels, chronic low-grade inflammation, subclinical peripheral artery disease and greater cardiovascular disease burden (21). Physical fatigability, therefore, may be an important marker for identifying older adults at risk of decline.

1.1.1 Measurements of Physical Fatigability

Measurements of physical fatigability fall into two broad categories: performance-based or perceived. Performance based physical fatigability involves completion of a physical or mental assessment, over the course of which the presence of performance deterioration is evaluated and is used to define fatigability (21–23). Examples of performance-based physical fatigability include performance deterioration during a fast-paced 400-meter walk ($\geq$6.5% difference in walking speed between lap 9 and 2). Benefits to performance-based fatigability measures are that they are not prone to self-report biases. However, there are several limitations to performance-based measures of fatigability. First, they may not capture fatigability in those with the lowest physical function, as the measurements often require completion of most if not all of the performance task. Second, variability in protocols, speeds, distances, and grades preclude comparability across studies. And finally, performance-based measures are often dichotomized, failing to capture the multidimensional and multifaceted nature of fatigability.

Perceived physical fatigability, on the other hand, involves an individual's self-reported perception of physical tiredness while completing specified tasks. It has been suggested that perceived fatigability is a more sensitive measure of whole-body tiredness over global measures of fatigue (7, 13). Two of the most commonly used perceived fatigability measures include the rating of perceived exertion (RPE) and the Pittsburgh Fatigability Scale (PFS). The RPE assesses fatigability using the Borg Scale after a participant has completed a 5-minute treadmill walk at a fixed speed (0.67 m/s) and grade (0%) where high scores indicate higher levels of perceived exertion. The RPE, similar to performance-based measures of fatigability, provides a direct physical assessment of fatigability. However, one limitation of this method is that it requires the equipment needed to run the task. The PFS is a self-report questionnaire in which participants are asked to "imagine" their fatigue across a variety of tasks of specified intensity (13). The PFS has recently been validated against performance-based measure of fatigability in older adults. The PFS may be ideal for community-based epidemiology studies, as it is a low-cost and easy-to-implement tool that does not requirement of special equipment. And more critically, it is able to evaluate fatigability status even in those who cannot complete the physical tasks.

1.2 Physical Activity and Rest-Activity Patterns in Older Adults

1.2.1 Physical Activity

The World Health Organization (WHO), the American College and Sports Medicine (ACSM), and the American Heart Association (AHA) have continued to emphasize the importance of physical activity, recommending that adults engage in at least 150 minutes of moderate-vigorous activity a week (24, 25). These recommendations have come forward as

numerous research studies have shown a wide-range of health benefits of physical activity, including its reduction on mortality (26). Specifically, physical inactivity is a risk factor for a variety of non-communicable chronic diseases, such as cardiovascular disease, diabetes mellitus, cancer, obesity, hypertension, bone and joint diseases, and depression (see Warburton et al. 2006 (26) for review).

Older adults in the US are the least physical active adults of any age group (27, 28), making them particularly vulnerable to the negative health impacts of physical inactivity. Most recent estimates by the Center for Disease Control (CDC) reveal that 28% of US adults > 50 years of age report no physical activity outside of work (29). Thus, older adults are particularly vulnerable to declines in health associated with reductions in physical activity. Physical inactivity is a particularly important risk factor as it is highly modifiable, making it a key target for public health interventions. Physical activity plays an important role in slowing the speed or preventing the onset of the disablement pathway associated with advancing age (30).

1.2.2 Rest-Activity Patterns

Circadian rhythms are approximately 24-hour endogenous cycles that help to regulate both biology and behavior (31). They are widespread and regulate most, if not all, of the major physiological systems in mammals (32). Perhaps the most salient of these circadian rhythms is the pattern of rest and activity, called the rest-activity rhythm (RAR). The RAR is the downstream behavioral manifestation of the alignment or misalignment of several circadian processes. However, RARs are not only influenced by the internal circadian systems, but are also driven by environmental and behavioral factors, such as sleep, food intake, and physical activity (32). Previous work has shown that disturbances in RARs are associated with increased

risk of sleep (33, 34) and mental health (35–38) disorders, as well as a variety of physical health outcomes, such as diabetes and coronary artery disease and overall mortality (31, 39–41).

Older adults are susceptible to age-related changes in RARs. These changes include: diminished melatonin and cortisol levels, hormones critical for dictating the strength of the RAR (42) and shifts in the timing of circadian patterns (43). These changes have dramatic impacts on sleep and RAR patterns in older adults. As reviewed in Van Someren 2000 (43), between 40-70% of older adults report that they suffer from chronic sleep disturbances, and only 20% of older adults do not report any sleep disturbances at all. These disturbances make older adults more susceptible to the negative physical health outcomes associated with dysregulated RARs. Studies utilizing the Osteoporotic Fractures in Men Study (MrOS) have shown that features of RARs in older men are associated with a variety of negative health outcomes. They found that irregular RARs are associated with increased risk for all-cause mortality and cardiovascular disease-related mortality (41), falls (44), and cognitive decline (45). Similar epidemiologic studies in older women in the Study of Osteoporotic Fractures showed that weakened RAR patterns were associated with increased mortality risk (40). Because RARs and physical activity may jointly influence each other, RARs should also be considered a key target for future intervention studies and may be a useful biomarker in identifying at-risk populations.

1.2.3 Physical Activity & Fatigability

The majority of the research looking at the associations between physical activity and fatigability show that declines in physical activity are associated with greater perceived fatigability, providing additional evidence that fatigability may lie along the disablement pathway. These associations have been seen in both performance-based as well as perceived

physical fatigability. Studies have been performed in the BLSA cohort, exploring the associations between physical activity and fatigability in older adults. Using objective measures of physical activity, one study found that total daily physical activity was 1.3% lower for every unit increase in physical fatigability based on perceived exertion (RPE) and that those with higher fatigability showed an overall dampened trajectory of activity than those with lower physical fatigability (46). A second study found that fragmented daily physical activity, as defined by increases in "Active-to-Sedentary Transition Probability", are associated higher physical fatigability and decreased physical performance. Individuals in the highest tertile of ASTP were more than two-times as likely to have high fatigability (RPE$\geq$10), have slower gait speeds, and reduced functional performance (47).

Many consider physical activity and fatigability to have a bidirectional relationship, where the effects of one influence the other, both contributing to decline in physical function—making it challenging to disentangle which should be the primary target of intervention. A recent study examined the bidirectional relationship of physical activity and perceived fatigability using the Long Life Family Study (LLFS) and found that physical activity attenuated the relationship between physical fatigability and gait speed by 39.5% in the offspring generation (48). Conversely, this study found that physical fatigability attenuated the relationship between physical activity and gait speed by 6.7% in the offspring generation. These results suggest that there is a mediating effect of physical activity on fatigability and gait speed, but not vice versa.

Previous work using free-living physical activity data (or RAR data) have focused on the associations between global levels or the magnitude of physical activity and how they associate with fatigability in older adults. These studies have shown that those with higher physical fatigability have overall decreased patterns across the entire day (46), however, few have studied

how other features, such as timing and variability, of physical activity over the entire rest-activity cycle may influence physical fatigability.

1.2.4 Measuring Free-Living Physical Activity & Rest-Activity Rhythms

There are several ways in which physical activity can be measured in older adults and fall into two broad categories: self-report and objective (or directly measured through wearable devices) physical activity.

Self-report questionnaires are often ideal for larger public health studies, as they are low cost, require minimal administration time and participant burden, and minimal staff training. However, they are prone to self-report and recall bias, and may not accurately characterize physical activity patterns in respondents with highly irregular or lower-intensity activity profiles (49). The Physical Activity Scale for the Elderly (PASE) and the Community Healthy Activities Model Program for Seniors (CHAMPS) are two of the more common self-report surveys used in studies of physical activity older adults. Recent work by Glynn et al 2020 reported that, when compared to objective measures of physical activity, the CHAMPS questionnaire outperformed the PASE questionnaire, particularly in participants who had lower physical function (50). The Pittsburgh Sleep Quality Index is a commonly used tool for evaluating sleep quality in older adults (51). Recent construct analysis revealed that self-reported sleep tools are valuable tools for measuring sleep quality, however but are not capable of capturing particular elements obtained from objective measures, suggesting that self-report tools alone do not paint the full picture of the circadian pattern (52).

Objective measures of physical activity include the use of wearable digital devices that quantify movement. As advancements in technology reduce the size of wearable devices, they

have become more commonly used in research settings and allow for a unique opportunity to monitor long-term free-living physical activity patterns. Objective measures of physical activity are less prone to response or recall biases, as self-report measures are, and allow us to measure global features of activity such as the fragmentation of activity, the frequency of particular activity events (e.g. walking bouts), as well as micro-features of activity, such as gait characteristics (Karas et al 2019 for review (53)). However, objective tools are more expensive, require more technological training, and often require advanced statistically techniques to model. Additionally, there is no standard approach to how to collect and analyze these data, making it difficult to compare across studies. One of the most commonly used objective tool used to measure the free-living activity and the RAR is actigraphy, or accelerometry. These devices use accelerometer-based movement estimates to reliably and objectively quantify sleep and activity patterns (54–56).

1.2.5 Physical Activity and Rest-Activity Rhythms as Modifiable Risk Factors

Physical activity is a highly modifiable risk factor, which has been shown to prevent or slow the onset of disability in older adults. The LIFE trial in older adults have shown that physical activity is a key intervention target for older adults and that physical activity interventions can reduce the risk of major and persistent mobility disability (30). Another study in the LIFE trial also showed that physical activity interventions may be more effective at preventing mobility disability in those who have higher baseline fatigue (57).

Similarly, rest-activity rhythms may also be potential targets for intervention, as pilot studies have shown that in older adults with Parkinson's Disease that Bright Light Therapy (BLT) reduced day time sleepiness (58, 59). Additionally, it is well understood that physical

activity plays a role in the rest-activity rhythms shape and rhythmicity, and a small pilot study found that a 3 month physical activity intervention reduced the fragmentation of the circadian rhythm in a sample of healthy older adults (60).

1.3 Analytic Methods for Objectively Measured Free-Living Rest-Activity Patterns

The raw data obtained from accelerometry data are often collected at very high sampling rates, often 30, 60, or 80 Hz. And while these data can be analyzed in their raw form, it is often computationally intensive and complications interpretation. Thus, accelerometry data are often aggregated, visualized, and analyzed within 1-, 30-, or 60- second epochs. The focus of this section will be in analytic methods for epoch-level accelerometry data. Common analytic methods for accelerometry fall into two main categories: parametric and nonparametric.

1.3.1 Parametric Methods

Parametric approaches model mean-level activity across all days of observation through transformed (or extended) cosine models (61).These models extend the number of parameters in the cosine model to more flexibly capture the characteristics of periodic rest and activity, such as allowing for a more square-like shape. There are several sigmoidal family transformations that can be performed to fit RAR data, however, the most commonly use is the “anti-logistic extended cosine model”. The parameters estimated from this provide interpretable estimates of the shape, size, and global variability of the RAR, as well as some elements of activity timing (estimated rise time). Most commonly, these estimated parameters are then tested for associations against an outcome of interest.

For example, for anti-logistic extended cosine model can be represented for each time-interval of observation as: $f(t;\theta) = m + amp * \{\beta[\cos\left(\left[\frac{t}{r} - \varphi\right]\frac{2\pi}{24}\right) - a]\}$ where t is time, r is the number of non-overlapping observation epochs within an hour, and is indexed by parameters $\theta = (m, amp, \alpha, \beta, \varphi)'$ (Figure 1). The five measures of interest from this model include: α, which quantifies the relative width of the activity period (higher α indicates more narrow active e period), β which describes the steepness of the transition between rest and active periods (higher β indicates steeper transitions or a more "square-like" curve), *mesor* = exp(m+amp/2) quantifies the middle of the height of the active period, and *amplitude* = exp(amp), provides an estimate of the overall magnitude or height of the activity pattern. Inverse functions of the mesor can also be used to the estimated rise and fall times of the activity pattern. And finally, the extended cosine model also allows us to estimate a global measure of model fit, or variability of activity around the estimated mean, using a 'pseudo-F' statistic. It is effectively a ratio of the residual sum of squares (RSS) and the mean squared error (MSE). Activity patterns that are more irregular will have lower pseudo-F statistics, indicating that there is weakened rhythmicity, or higher variability.

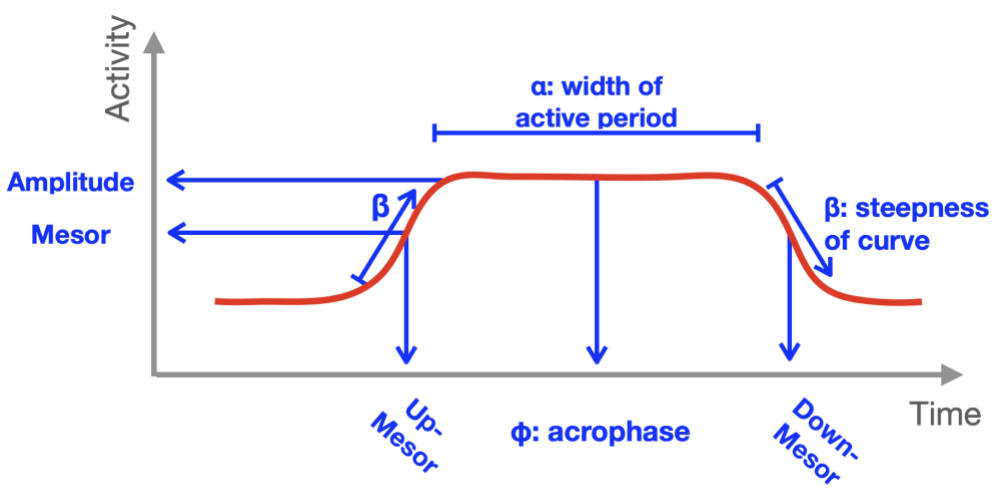

Figure 1 Example of parameters estimated from anti-logistic extended cosine model and how they impact the size and shape of the rest-activithy rhythm.

1.3.2 Nonparametric Methods

Nonparametric methods do not rely on an assumed model for that RAR pattern (e.g. a cosine shape), but are instead direct measures of variability around global and daily mean activity levels. The two most common nonparametric measure include the interdaily stability (IS) and the intradaily variability (IV) (62). IS provides a measure of the relative strength (or variability) of the RAR across days and can be written as: $IS = \frac{n\sum_{h=1}^{p}(\bar{x}_h - \bar{x})^2}{p\sum_{i=1}^{n}(x_i - \bar{x})^2}$, where n is the total number of observations, p is the number of observations per day, $\bar{x}_h$is the hourly means, and $\bar{x}$ is the global mean. IV, on the other can, can be written as $IV = \frac{n\sum_{i=2}^{n}(x_i - x_{i-1})^2}{(n-1)\sum_{i=1}^{n}(x_i - \bar{x})^2}$. While nonparametric methods are free from the limitations of an assumed model, they are unable to provide us with detailed understanding of the size, shape, or timing of the RAR.

1.3.3 Localized RAR Methods

Neither the parametric or nonparametric methods above retain information regarding the specific timing of RAR patterns or variability. Localized measures of RAR attempt to resolve this issue by calculating means and standard deviations of activity within pre-specified time-intervals (e.g. 00:00-04:00, 04:00-08:00, etc). These methods typically extract absolute mean activity, the mean of activity across days within a specific time interval, and the standard deviation of activity, which finds the variability of daily mean-level activity within specific time-intervals across days.

It is also important to note that the approximate timing of the onset of activity periods varies across individuals. This can create issues for researchers who are interested in comparing the daily distribution of activity across participant rather than the specific timing of activity with

respect to clock-time specifically. Graves 2018 (63) proposed the use of activity-onset adjusted "Person Time", to account for these participant-level differences. This adjustment allows for inter-participant comparisons of how activity changes standardized to the time the participant "gets going". "Person Time" is estimated by subtracting each participant's estimated rise time from the observed clock time and is interpreted as the number of hours after waking/rising.

1.4 Gaps in Knowledge

As stated previously, past work has shown that higher fatigability is associated with global decreases in objectively-measured physical activity patterns. Wanigatunga et al. 2018 (46) found that higher fatigability was associated with lower physical activity, particularly between the hours of 8:00am to 8:00pm. However, this study does not take into account for differences in person-specific rise times, also known as "Person Time" (Section 1.3.3), and therefore is not able to directly compare the trajectory of activity anchored from rise time. Additionally, these analyses did not explore how the degree of variability of activity may be associated with fatigability. The proposed study aims to expand on this by capturing both the mean and standard deviation of activity within 4-hour time bins in both clock and rise time adjusted "Person Time". Schrack et al. 2018 (47) also found that fragmentation of physical activity, or the Active-to-Sedentary Transition Probability (ASTP), was associated with higher fatigability. This study captured the importance of understanding the specific role of variability and fragmentation of activity on fatigability; however, it is limited in its ability to identify when in the activity cycle this fragmentation occurs, and on what scale (across versus within days).

Furthermore, to our knowledge, there are no extant studies which have utilized the traditional analytic methods of circadian science research, such as modelling the rest-activity rhythm using extended cosine modeling or nonparametric measures of variability. RAR analysis could provide specific insights as to which particular features of overall patterns of rest and activity, or combinations of features, are most strongly associated with higher physical fatigability.

1.5 Public Health Significance

As the number of older adults in the United States, and around the world, dramatically increases (4), it has become imperative that public health researchers identify risk factors and key intervention targets to maintain functional independence with age. Global fatigue is a commonly reported complaint among older adults and is an important marker of functional decline, overall health, and overall mortality (9, 12, 64–66). Perceived physical fatigability, or perceived fatigue within the context of a defined activity of specified intensity or duration (7), increases with age, such that roughly 25% of older adults aged 60-69 and approximately 82% at least 90 years of age report higher fatigability (14).

Previous work as shown that higher fatigability is associated with decreased and more fragmented activity patterns (47, 67). However, few studies have more closely explored how the shape, size, timing, and variability of the entire free-living rest-activity, or circadian rhythm, are associated with physical fatigability. It is thought that physical activity and fatigability play bidirectional roles on the disablement pathway, making them both important risk factors for functional decline, loss of mobility, and mortality. Older adults in the United States are the least

physical active of adults of any age group (27, 28) and as many as 70% of older adults report chronic sleep disturbances (43), making them particularly vulnerable to the negative effects of reduced physical activity and fragmented rest-activity rhythms.

Physical activity is a highly modifiable correlate of fatigability. Gaining a deeper understanding of precisely which features and patterns of activity are associated with fatigability will allow future researchers and clinicians to more effectively identify those at risk of higher fatigability and to develop interventions to aid in the prevention or delay of functional decline.

2.0 Objective

The objective of this study is to explore the relationship size, shape, timing, and variability of free-living accelerometry-derived rest-activity rhythms which may be associated with perceived physical fatigability, evaluated using the Pittsburgh Fatigability Scale (PFS), in older adults from the Developmental Epidemiology Cohort Study (DECOS) (68) and the Mobility Vitality and Lifestyle Program (MOVEUP) (69).

3.0 Methods

3.1 Study Samples

This study will leverage the data from two existing cohorts measuring physical activity in older adults (see below). Both studies were conducted in community-based samples of older adults without serious health conditions, and have obtained free-living rest-activity data using accelerometry.

3.1.1 Mobility and Vitality Lifestyle Program (MOVEUP)

The Mobility and Vitality Lifestyle Program (MOVEUP) was a non-randomized, pre-post, mixed methods intervention study that aimed to evaluate the feasibility and effectiveness of a four phase, 13-month healthy aging and behavioral weight management intervention program in community dwelling older adults (aged 60-75 years) who were obese or overweight (69). Inclusion criteria were based on age, body mass index (BMI) of 27-45 kg/m^2, ambulatory (with the use of a cane permitted), and cognitively intact. The primary outcome for the MOVEUP study was change in physical function at 13 months (post-intervention). Secondary outcomes included weight change, accelerometry-based and self-reported physical activity among other items. For these analyses, baseline data will be used.

3.1.2 Developmental Epidemiology Cohort Study (DECOS)

The Developmental Epidemiology Cohort Study (DECOS) is a cross-sectional study examining the impact of accelerometry wear location on the quantification of physical activity

and sedentary behaviors among healthy older adults (70-92 years) (68). The aim of this study was to identify the optimal tools to measure physical activity in older adults. Exclusion criteria for the study included any self-reported health contraindications to physical testing and the inability to perform basic walking tasks (e.g. a 400-meter walk). A total of 69 participants were enrolled in the study, 61 of which consented to accelerometry.

3.1.3 Assessment of Exposure, Outcome, Covariates

Assessment of Exposure: Free-living rest-activity rhythms were measured using accelerometry. Accelerometry data was only allocated to a subsample of participants in the MOVEUP sample (the first 11 sites, N = 127), due to budgetary limitations. Of the DECOS sample (n=69), 61 consented to accelerometry data collection. The Actigraph GT3x+ accelerometer was worn on the nondominant wrist for 7 consecutive days at baseline, 5 months, and again between 9 and 13 months. Participants were asked to wear the device at all times, except for showering, bathing, or swimming. The sampling rate for the Actigraph GT3x+ was set to 80Hz (80 observations per second). Only baseline accelerometry data from MOVEUP was used.

Assessment of the Outcome: Perceived physical fatigability was measured using the Pittsburgh Fatigability Scale (PFS) at baseline (and 5 months and 9 to 13 months in the MOVEUP sample). Baseline perceived physical fatigability scores were used for all participants who have completed usable accelerometry data at baseline. The PFS is a 10-item self-administered scale where participants are asked to rate the fatigue they expect or imagine that they would feel immediately after performing a task of specified intensity and duration (e.g. a "leisurely walk for 30 minutes"). Scores range from 0 to 5, no fatigue to extreme fatigue,

respectively. These self-reported items are then summed up to achieve a total PFS score, ranging from 0-50, with higher PFS scores indicating great perceived physical fatigability. Individuals are also asked to identify if they had performed the specific activity within the last month. A PFS score $\geq$ 15 has been established as a cut point indicating higher levels of physical fatigability (21, 70). Incomplete PFS scores were imputed based on the method described in Cooper et al. 2018 (71). If 1-3 items were missing, but the related question on if they performed the activity was completed, the value was imputed. In the MOVEUP, the number of imputed scores at baseline were 1; in DECOS sample four participants had imputed PFS scores.

Covariates: Age, sex, and race were determined by self-reported questionnaire. Anthropometrics included height, weight, and BMI. Height was measured to the nearest 0.25cm using a portable stadiometer; weight was measured using a calibrated digital scale, and height and weight were used to calculate BMI. Short Physical Performance Battery (SPPB) battery was used to evaluate lower extremity function, and included tests of gait speed, standing balance, and chair-stand tests. The total score from the SPPB will be used in analyses. Self-reported physical activity was evaluated using the CHAMPS questionnaire, estimating the total hours of physical activity within a week and the total hours of activities at least 2.5 METs and higher (i.e. moderate intensity). Depressive symptomatology was estimated using the Center of Epidemiologic Studies Depression Scale (CES-D). All covariates in MOVEUP were collected at baseline. See additional details on covariates used in DECOS sample in Lange-Maia et al 2015 (68).

3.2 Statistical Methods

3.2.1 Accelerometry Data Cleaning

Raw accelerometry data was extracted from each device and 80Hz data was converted into 60-second epoch counts using the ActiLife software. In order to capture complete days of accelerometry data, accelerometry data were truncated to start at first midnight and to end at the 6th midnight. Participants were then screened for non-wear time using a commonly-used algorithm used to detect wear time (72). Through this algorithm, non-wear time was defined as 90 consecutive minutes of zero counts, with an allowance of 2 minutes of nonzero counts provided that there were 30 minutes of consecutive zeros up and down stream. And a valid wear day was any day that consisted of at least 10 hours of wear time. And each participant must have at a minimum 3 valid days in order to be included in this sample.

3.2.2 Final Analytic Sample

Under accelerometry data cleaning criteria listed in Section 3.2.1, the DECOS sample has 57 participants with useable activity data, 54 of which have completed the PFS, and the MOVEUP sample has 127 participants with usable activity data and 127 who have completed the PFS, making a total analytic sample of 181.

3.2.3 Estimating Activity and RARs

Analytic methods described in 1.3 will be used to quantify the rest-activity rhythm in this sample. For the parametric approach, the anti-logistic extended cosine model (as described in Section 1.3.1) will be used to estimate the shape, size, rise times, and variability of each

participant's mean RAR. Parameters obtained will include α (width), amplitude, acrophase (φ), β (steepness), mesor, up mesor (also known as "estimated rise time"), and the "pseudo-F" statistic. Nonparametric measures IV and IS will also be estimated to capture overall variability of the activity cycle (Section 1.3.2), without the pitfalls of an assumed model.

Localized measures of timing and variability, mean and standard deviations of activity will be calculated within 4-hour time bins intervals. Analyses will be performed on both clock time and "Person Time". "Person Time" will be used in order to allow for direct comparison between the trajectories of activity adjusting for estimated rise time. Thus, there will be six time bins (00:00-04:00, 04:00-08:00, …, 20:00-24:00), each with a measure for the mean activity and standard deviation of activity. Rise time will be estimated using the up mesor estimated from the extended cosine model.

Parametric and localized measures will be performed using the R package RAR, and nonparametric measures will be obtained using the R package nparACT (73).

3.2.4 Outcome: Perceived Physical Fatigability

PFS Physical scores at baseline will be used as our outcome of interest and will be evaluated at both a continuous and a binary scale. Raw scores in the physical fatigability scale will be used as continuous data. Using the known cut point of 15, any participant with a physical PFS score $\geq$ 15 will be classified as having "higher" fatigability.

3.2.5 Analysis Plan

Descriptive analyses will be performed to identify any cohort characteristics that may differ based on our outcome of interest (higher versus lower perceived physical fatigability) to

identify any potential confounding variables and to characterize the sample. To test group differences, Pearson's Chi-squared tests will be performed for categorical variables and two-sample t-tests will be used for continuous variables when assumptions of normality hold (Kruskall-Wallis Test used if normality assumptions are not met).

As continuous PFS Physical scores are positively skewed, quantile regression models adjusting for both *a priori* and suspected confounders will be used to estimate the association between raw PFS Physical scores and individual cosine model parameters, IV, IS, mean and standard deviation of physical activity within time bins. Quantile regression is well-suited for non-normally distributed continuous variables (74,75) and is used to estimate quantiles (e.g. 25th, 50th (median), 75th percentiles) instead of the mean as is done in ordinary least squares (OLS) regression. Here the median is used to estimate the central tendency of PFS Physical scores. Multivariate logistic regression was also used to test the associations of each of the forementioned parameters against the odds of being in a higher or lower perceived physical fatigability (PFS Physical $\geq$ 15), adjusting for the same confounding variables.

K-means clustering algorithm was applied to the sample's extended-cosine RAR parameters to identify four clusters or classes of activity patterns using the R package stats. K-means is an unsupervised clustering approach, which partitions high-dimensional data into *k* groups such that the sum of the squares from points to the assigned cluster centers (means) is minimized. Cluster numbers were determined by using a variety of cluster-selection techniques, including: Ward's method, principal components analysis, evaluation of the within sum of squares at multiple cluster assignments, and visualization of cluster assignments along the first two dimensions of the data. Cluster assignments were subsequently tested to see if they were univariately associated with PFS Physical scores using Kruskall-Wallis tests, and if these

associations held after adjustment using multivariate quantile regression for raw PFS Physical scores and logistic regression for higher or lower fatigability status (PFS Physical score $\geq$15).

4.0 Results

Table 1 presents the characteristics of the entire cohort as well as the cohort stratified by fatigability status. This sample had a mean age of 71.3 years, was predominately female (79.0%), white (73.9%), educated (79.3% had at least high school education level), and obese (mean BMI = 32.3). When stratified by lower or higher fatigability (PFS Physical scores $\geq$ 15), we see that those in the higher fatigability category had worse SPPB scores (p=0.024), higher BMI (p<0.001), slower usual gait speeds (p<0.001), less self-reported physical activity (p=0.025), and worse depression symptomology (p<0.001). Univariate associations of higher fatigability status and RAR parameters show higher fatigability status was associated with later acrophase (i.e. time at which activity is at its midpoint, p=0.022) and up mesor (i.e. estimated rise time, p=0.005).

Table 2 shows the results of multivariate quantile (median) regression models where each RAR parameter was included as an individual predictor, adjusting for age, sex, race, BMI and CES-D score, of median PFS Physical score. Here we see that beta (p=0.04), acrophase (p=0.01), and up mesor (p=0.01) were all significantly positively associated with median PFS score. Such that increased steepness of the RAR curve (beta) and later timing (acrophase and up mesor) are associated with higher median PFS scores. Table 3 shows the results of multivariate logistic regression models where each RAR parameter was included as an individual predictor, adjusting for age, sex, race BMI, and CES-D score, of having a PFS Physical score $\geq$ 15. We see that later up mesor, or estimated rise time, is associated with 1.46 times the odds of having greater perceived physical fatigability (p=0.01).

Figure 1 shows the distribution of mean and standard deviation of physical activity across time stratified by higher and lower perceived physical fatigability. We see that those with higher fatigability have an overall dampened activity pattern compared to those with lower fatigability. They also show lower variability (standard deviation) of activity across all time points. Table 4 shows the results of multivariate quantile regression models for mean and standard deviation of activity are associated with PFS Physical scores across 4-hour time intervals on clock time and "Person Time" scales. These results show that lower levels of mean level activity between 4:00am and 8:00am are associated with higher PFS physical scores (β=-4.51, p=0.025), adjusting or age, sex, race, BMI, and CES-D score. Table 5 shows the multivariate logistic regression of mean and standard deviation of activity at 4-hour time intervals in both clock and "Person Time". Here we see, similarly, that higher levels of mean activity from 4:00am – 8:00am are associated 73% reduction in the odds of being in a higher fatigability category (OR = 0.27, p=0.007). We do not see any significant effects of standard deviation of activity, nor any significant effects when we use rise time adjusted "Person Time".

Diagnostics of k-means clustering algorithm on *k*=4 can be seen in Figure 2. The dendogram derived from using the Ward algorithm (based on Euclidean distances between scaled RAR parameters) provides strong evidence that at least three clusters should be selected. We can also see that a fourth branch allows for the emergence of an additional distinct class of RARs. Additionally, the within sum of squares ("the Elbow plot") estimated from alternative values of *k* are does not show a distinct "elbow", providing evidence that there is not a clear recommended number of clusters based on this selection technique. Additional diagnostic techniques, such as the "scree" plot generated from principal components analysis (PCA) showed that four clusters may be beneficial and may not result in over fitting (due to lack of

elbow), and its inclusion results in 91% of variance explained. We visualized how cluster assignments aligned with the first two principal components generated from PCA and saw that four clusters allows us to capture differences across these dimensions, while also retaining some nuance between them. For example, the “green” cluster is able to capture separations between the “red” and “purple” cluster, allowing for characterization of another cluster of RAR patterns. Four clusters was also confirmed to be the optimal cluster choice when using R package Mclust’s (76) Bayesian Information Criteria (BIC).

Figure 4 shows the mean RAR parameter estimates for each cluster assignment on a normalized scale (top panel). We see that Cluster 1 (“Less Active/Robust”) has higher alpha (or a narrow active period) and a higher beta (steeper transition from rest to active), but lower (earlier) timing, particularly towards the end of their RAR, and less rhythmicity/more variability (lower Pseudo-F statistic). Cluster 2 (“Earlier RAR”) is a fairly “average” RAR, with slightly earlier up mesor time. Cluster 3 (“More Active/Robust”) represents RAR patterns with higher magnitudes of activity (higher amplitude and higher mesor), and also stronger rhythmicity/less variability (higher Pseudo-F statistic). Cluster 4 (“Later RAR”) represents RAR patterns where timing is later in the day as up mesor, acrophase, and down mesor are all larger. The bottom panel of Figure 4 shows how distributions of PFS Physical scores differ by cluster assignment. Overall Kruskal-Wallis test shows that the distributions of PFS Physical scores differently significantly across these clusters ($p=0.006$). Pairwise two-sample Wilcoxon Rank Sum tests reveal that median PFS Physical scores in the Less Active/Robust RARs are statistically significantly higher than those in Clusters 2 and 3 ($p=0.04$, $p=0.04$, respectively), and that Cluster 4 has higher median PFS Physical scores than Clusters 2 and 3 ($p=0.009$ for both). Clusters 2 and 3 ($p=0.65$) and Clusters 1 and 4 ($p=0.45$) do not differ significantly in PFS Physical scores.

Quantile regression results show that being in Less Active/Robust and Late RARs (Clusters 4 and 1) were associated with 6.14 (p=0.05) and 3.53 (p=0.03) point higher PFS Physical scores compared to Earlier RAR patterns (Cluster 2, the referent group), respectively (Table 6, Model 1). A likelihood ratio test (LRT) comparing the model with cluster assignments versus without shows that cluster assignments significantly improve model fit (p=0.03) Additionally, having either Less Active/Robust or Late RAR patterns is associated with 3.71 point (p=0.01) higher PFS Physical score compared to having either an Earlier or More Active/Robust RAR (Table 6, Model 2). Logistic regression results (Table 7) show similar findings, such that individuals with Later RARs have 2.3 times higher odds of having greater perceived physical fatigability compared to those with Earlier RARs (Cluster 2, p=0.05). However, LRT indicate that all four cluster assignments do not significantly improve logistic model fit (p=0.13, Table 7, Model 1). We see that having either Less Active/Robust or Late RAR was associated with 2.3 times higher odds of having greater perceived fatigability compared to having an Earlier or More Active/Robust RARs (p=0.03, Table 7, Model 2).

5.0 Discussion

Results of this cross-sectional study of objectively-measured free-living physical activity in the DECOS and MOVE UP samples suggest that later and more variable rest-activity rhythms (RARs) are associated with greater perceived physical fatigability.

This study found that later activity patterns (i.e. those with later acrophases and up mesors) were associated with higher PFS Physical scores, with each hour later being associated with a 1.29 or 1.38 point increase in PFS Physical scores, respectively, and 46% increase in odds of having greater physical fatigability (PFS $\geq$ 15). These findings highlight the importance of timing and are consistent with other studies, which have shown that later peaks in activity (e.g. specifically later acrophase) are associated with increased risk of a variety of negative health outcomes (40,44,45) and negative cognitive outcomes (77) in samples of older adults.

We also identified that higher beta values (i.e. more square-like RARs, or steeper transitions from rest to activity), were associated with higher Physical PFS scores, however, this effect is quite small and difficult to interpret as the beta parameter is unitless. Few studies have found relationships between beta values and health in older adult samples. One study of the MrOS cohort found that lower beta values (less steep) were associated with higher risk of incident stroke (78). Another study of older adult caregivers found that lower beta values are also associated with depressions symptom severity (36). Both findings are in opposite direction of what we find here. The differences for these findings could be attributed to differences in cohorts (e.g. all male samples versus a largely female in the present study), or mechanistic differences. Smagula et al 2017 (36) found that the effect of beta on depression symptom severity of caregivers was strongly attenuated by the specific behaviors exhibited by those they cared for,

suggesting that the demands of caregiving may have been the predominate driver determining the beta of the RAR. It remains unclear exactly what role the beta parameter may play in determining risk for disease states and physical fatigability.

The present study also found that those with higher physical fatigability (PFS $\geq$ 15) had overall dampened levels of physical activity across all timepoints, with higher physical activity between 4am and 8am significantly associated with lower Physical PFS scores. These results are consistent with those found in Wanigatunga et al. (2018) (46), who found that BLSA participants with higher fatigability (based on the RPE scale) had an overall damped activity pattern compared to those with lower fatigability, and that these differences were most pronounced in the 8am-12pm interval. While they did not see significant differences in the 4am-8am time window, this could be attributed to differences between sample characteristics (the present cohort is older, more overweight, and has reduced physical function), differences in the ascertainment of physical fatigability (RPE versus PFS), or differences in rise times in these samples. For example, we speculate that differences in rise times (up mesor) may be the primary driver of the differences in mean levels of activity seen in the present study, as more highly fatigued participants may be delaying their rise time, resulting in dampened activity in their 4am-8am window. After adjusting for estimated rise time by using a rise time adjusted "Person Time", we still see that those with higher fatigability had lower activity levels, however, these results were not statistically significant. This further corroborates the notion that timing of activity within the 24-hour clock plays an important role in the relationship between physical activity and fatigability.

These results do not suggest an independent effect of variability of activity on perceived physical fatigability. We did not see a significant effect of the pseudo-F, IV, or IS measures of

total global variability of the RAR on perceived physical fatigability when tested independently. We also did not see a significant effect of standard deviation of activity within 4-hour time intervals on perceived physical fatigability (on either clock of "Person Time" scales). These results were not consistent with what we expected based on previous studies which found that lower pseudo-F statistic (or less robust/rhythmic RARs) were associated with negative health outcomes in older adults (40, 77). However, none of these studies specifically explored the relationship between variability of activity and perceived physical fatigability, making the present study is novel in this regard.

The majority of research surrounding the impacts of sleep and RARs on health have explored each characteristic or feature separately. However, more recently, researchers are interested in understanding sleep and RARs as a multidimensional construct, in which features co-occur or work together to create a healthy (or unhealthy) RAR (79). We attempted to capture the joint distribution of RAR features by using the k-means clustering algorithm on parameters estimated from the extended cosine model and identified four clusters of RARs: "Less Active/Less Robust" (patterns with shortened activity periods and lower pseudo-F statistics, Cluster 1), "Earlier RARs" (patterns with earlier rise times, Cluster 2), "More Active/More Robust" (patterns with higher amplitudes and higher pseudo-F statistics, Cluster 3), and "Later RARs" (patterns with later rise times and acrophases, Cluster 4).

Here we find that there are two potentially high-risk profiles of RARs which may be associated with higher levels of physical fatigability: Later RARs and Less Active/Less Robust RARs were both associated with higher PFS Physical score and higher odds of being in a higher physical fatigability category (PFS $\geq$ 15). Specifically, we found that being in the Less Active/Less Robust group was associated with a 6.1-point higher PFS Physical score compared

to being in the Earlier RAR group, and that being in the Later RAR group was associated with a 3.5-point higher PFS Physical score. We also saw that being in either group was associated with a 3.7-point higher PFS Physical score compared to being in the Earlier or More Active RAR group. There have been no known studies that have explored similar types of RAR "profiles" and how they relate to perceived physical fatigability. However, these results are in line with what we might expect based another study which used a similar clustering technique on RAR parameters and found that later and irregular RARs were associated with depression symptoms in a sample of adults (35).

As noted previously, we did not see an individual effect of variability of the RAR associated with physical fatigability, however, we see that participants in high-risk RAR clusters with less robust/more variable RARs are more likely to have higher PFS Physical scores. This finding suggests that the independent effect of variability alone may not be as important as its joint effect alongside other features of the RAR. Interestingly, individuals in the Less Active/Less Robust cluster also had steeper betas, earlier acrophases and earlier down mesors. Based on models which tested these parameters separately, we might have expected that these RAR patterns with earlier acrophases would be associated with lower perceived physical fatigability. However, instead, we see that the joint effect of earlier timing, reduced activity, and variability may be indicative of a high-risk RAR profile. Interestingly, individuals with this Less Active/Less Robust pattern had earlier acrophases but not earlier rise times (up mesor), suggesting that earlier rise times may specifically play an important role as a protective factor against higher physical fatigability. While we cannot know for certain without more information on sleep and activities, we might characterize those in the Less Active/Less Robust cluster as individuals who are highly fatigued, such that they compensate for their fatigue by delaying their

rise times, resulting in a steeper transition from rest to wake, shortened activity periods, and retiring to rest earlier in the day (earlier down mesors).

Limitations of the present study include the cross-sectional nature of the study, which precludes our ability to understand if changes in RARs may influence changes in perceived physical fatigability. However, previous studies have shown that physical activity interventions may stabilize rest activity rhythms in older adults (60), making it a physical activity a potential target for intervention to modify RARs. Future studies should explore how changes in RARs are associated with changes in perceived physical fatigability. While the present study was able to capture the overall variability of the RAR, the pseudo-F statistic is not able to capture the timing of variability throughout the week. For example, low pseudo-F (or low stability) could be attributed to a participant waking up regularly throughout the night, or a participant who has systematic differences in their waking times (e.g. early riser during weekdays versus late riser on the weekend). Future studies could investigate the use of the residual circadian spectrum to quantify frequency domains of variability (80). Additionally, there are limitations to the k-means clustering technique: it contains an implicit assumption of normality of the data (through the use of means over other statistics of central tendency), it does not account for covariances between variables making it challenging to classify correlated data, and it is an unsupervised technique. Future studies could explore the use of tree-based methods to classify RARs based on their association with perceived physical fatigability. The present sample is also small and fairly homogenous (largely white and female) and future studies should explore these relationships in larger, more diverse samples in order to determine the generalizability of these findings.

One major strength of this study is that it is novel in its application of classic circadian rhythm research (RAR parameters) techniques to understanding perceived physical fatigability.

It is also the first to utilize a clustering technique to identify RAR profiles associated with higher physical fatigability. Another strength of this study includes the use of objective accelerometry data, which limits the likelihood of self-report biases present in self-reported physical activity measures. The use of a community-based sample is also a strength of this study as these results may be more applicable to older adults out in the community.

Overall, the findings of this study suggest that delayed, dampened, and less robust rest-activity rhythms are associated with greater perceived physical fatigability in a community-based sample. This is the first study to investigate the role of RAR features on physical fatigability in older adults and highlights the role of the circadian rhythm as a key player in the relationship between physical activity and physical fatigability in older adults. This study has important public health implications as it specifically identifies patterns of activity that are associated with fatigability, providing evidence for future researchers and clinicians to focus intervention targets on timing, magnitude and variability of the rest-activity patterns so as to stem the downward spiral into disability.

Appendix Tables and Figures

Table 1 Characteristics of overall sample and straitified by perceived physical fatigability status.

	Total (N=181)*	Higher Fatigability (N=111)*	Lower Fatigability (N=70)*	p value
Age, years	71.3 ± 6.7	70.9 ± 6.5	72.1 ± 6.9	0.315[1]
	70.6 (66.1, 74.9)	70.6 (65.8, 74.0)	70.9 (66.7, 76.5)	
	60.5 - 91.0	60.5 - 91.0	60.7 - 89.0	
Sex, Female	143 (79.0%)	92 (82.9%)	51 (72.9%)	0.107[2]
Race, White	127 (70.2%)	82 (73.9%)	45 (64.3%)	0.170[2]
Education, High School +	140 (77.3%)	88 (79.3%)	52 (74.3%)	0.434[2]
Short Physical Performance Battery, 0-12	10.5 ± 1.8	10.3 ± 2.0	10.9 ± 1.5	0.024[1]
	11.0 (10.0, 12.0)	11.0 (10.0, 12.0)	11.5 (10.0, 12.0)	
	2.0 - 12.0	2.0 - 12.0	6.0 - 12.0	
Body mass index, kg/m^2	32.3 ± 6.0	33.6 ± 5.6	30.3 ± 6.1	< 0.001[1]
	32.1 (28.2, 36.0)	33.3 (30.1, 37.2)	30.1 (25.7, 34.5)	
	20.1 - 46.3	21.2 - 46.3	20.1 – 44.8	
Usual Gait Speed, m/s	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	< 0.001[1]
	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)	
	0.5 - 1.7	0.5 - 1.4	0.5 - 1.7	
Self-reported physical activity (CHAMPS[3]), MET-min/day	320.8 ± 251.7	292.7 ± 245.3	365.3 ± 257.0	0.025[1]
	256.1 (146.8, 421.1)	217.5 (128.3, 353.6)	287.9 (165.1, 520.7)	
	21.4 - 1311.4	26.8 - 1201.1	21.4 - 1311.4	
Depression symptomology (CES-D[4]), 0-30	6.9 ± 5.9	8.0 ± 6.1	5.0 ± 5.2	< 0.001[1]
	5.0 (3.0, 9.0)	6.0 (3.0, 12.0)	4.0 (3.0, 5.0)	
	0.0 - 31.0	0.0 - 27.0	0.0 - 31.0	
Rest-Activity Rhythm (RAR) Features				

Days of Activity Data	6.2 ± 0.7	6.1 ± 0.7	6.4 ± 0.5	0.001[1]
	6.0 (6.0, 7.0)	6.0 (6.0, 6.0)	6.0 (6.0, 7.0)	
	3.0 - 7.0	3.0 - 7.0	5.0 - 7.0	
Alpha	-0.3 ± 0.3	-0.3 ± 0.3	-0.4 ± 0.2	0.379[1]
	-0.4 (-0.5, -0.2)	-0.4 (-0.5, -0.2)	-0.4 (-0.5, -0.2)	
	-0.7 - 1.0	-0.7 - 1.0	-0.7 - 0.6	
Beta	22.2 ± 50.1	26.0 ± 58.1	16.4 ± 33.5	0.119[1]
	9.0 (4.6, 17.9)	10.1 (4.8, 20.4)	8.3 (4.4, 12.8)	
	1.7 - 530.9	1.7 - 530.9	1.8 - 243.1	
Acrophase	14.8 ± 1.3	14.9 ± 1.4	14.6 ± 1.1	0.022[1]
	14.9 (14.2, 15.7)	15.1 (14.4, 15.7)	14.6 (13.9, 15.3)	
	9.5 - 17.7	9.5 - 17.7	11.5 - 16.4	
Amplitude	5.9 ± 2.8	5.6 ± 2.7	6.4 ± 3.0	0.026[1]
	5.2 (4.2, 7.0)	4.9 (4.0, 6.8)	5.8 (4.5, 7.2)	
	1.6 - 17.5	2.0 - 17.2	1.6 - 17.5	
Mesor	2.8 ± 0.6	2.8 ± 0.6	2.9 ± 0.6	0.111[1]
	2.7 (2.4, 3.2)	2.7 (2.3, 3.0)	2.8 (2.6, 3.3)	
	1.6 - 5.2	1.7 - 5.2	1.6 - 4.5	
Up Mesor (hours)	7.5 ± 1.3	7.7 ± 1.3	7.2 ± 1.2	0.005[1]
	7.6 (6.7, 8.3)	7.7 (7.0, 8.4)	7.3 (6.4, 8.0)	
	3.2 - 11.4	4.0 - 11.4	3.2 - 9.8	
Down Mesor (hours)	22.0 ± 2.0	22.1 ± 2.3	22.0 ± 1.6	0.253[1]
	22.5 (21.2, 23.2)	22.5 (21.2, 23.4)	22.4 (20.8, 22.9)	
	11.3 - 25.4	11.3 - 25.4	15.8 - 25.1	
Pseudo-F Statistic	995.5 ± 479.6	962.8 ± 499.1	1047.4 ± 445.3	0.070[1]
	927.2 (683.7, 1182.7)	875.2 (610.8, 1112.0)	1005.7 (766.9, 1316.7)	
	79.0 - 2787.2	135.7 - 2787.2	79.0 - 2124.4	
Interdaily Stability	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.513[1]
	0.5 (0.5, 0.6)	0.5 (0.5, 0.6)	0.5 (0.4, 0.6)	
	0.1 - 0.8	0.2 - 0.8	0.1 - 0.8	
Intradaily Variability	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.926[1]
	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)	

	0.4 - 1.6	0.4 - 1.6	0.4 - 1.5

*Mean ± SD [N], % [N], Median (25th Percentile, 75th Percentile), Minimum – Maximum
1. Kruskall-Wallis rank sum test
2. Pearson's Chi-squared test
3. CHAMPS: Community Healthy Activities Model Program for Seniors
4. CES-D: Center of Epidemiologic Studies Depression Scale

Table 2 Individual effects of rest-activity rhythm parameters on median physical fatigability scores using multivariate quantile regression.

Parameter	β estimate	95% Confidence Interval	p value
Alpha	2.70	(-3.83, 9.23)	0.42
Beta	0.03	(0.01, 0.05)	0.04
Acrophase (hours)	1.29	(0.31, 2.27)	0.01
Amplitude	-0.09	(-0.58, 0.40)	0.74
Mesor	-0.50	(-3.05, 2.05)	0.70
Up Mesor (hours)	1.38	(0.40, 2.36)	0.01
Down Mesor (hours)	0.82	(-0.02, 1.66)	0.06
Pseudo-F Statistic	0.00	(0.00, 0.00)	0.82
Interdaily Stability	7.89	(-2.64, 18.42)	0.14
Intradaily Variability	0.32	(-5.70, 6.34)	0.92

* All models adjusted for age, sex, race, BMI, CES-D score

Table 3 Individual effects of rest-activity rhythm patterns on the odds of being in higher fatigability category (PFS $\geq$ 15) using multivariate logistic regression.

Parameter	Odds Ratio	95% Confidence Interval	p- value
Alpha	2.45	(0.63, 10.81)	0.21
Beta	1.01	(1.00, 1.02)	0.16
Acrophase (hours)	1.23	(0.95, 1.62)	0.12
Amplitude	0.95	(0.84, 1.07)	0.40
Mesor	0.90	(0.52, 1.58)	0.72
Up Mesor (hours)	1.46	(1.11, 1.96)	0.01
Down Mesor (hours)	1.02	(0.86, 1.21)	0.82
Pseudo-F Statistic	1.00	(1.00, 1.00)	0.84
Interdaily Stability	2.57	(0.14, 51.01)	0.53
Intradaily Variability	1.06	(0.24, 4.81)	0.94

* All models adjusted for age, sex, race, BMI, CES-D score

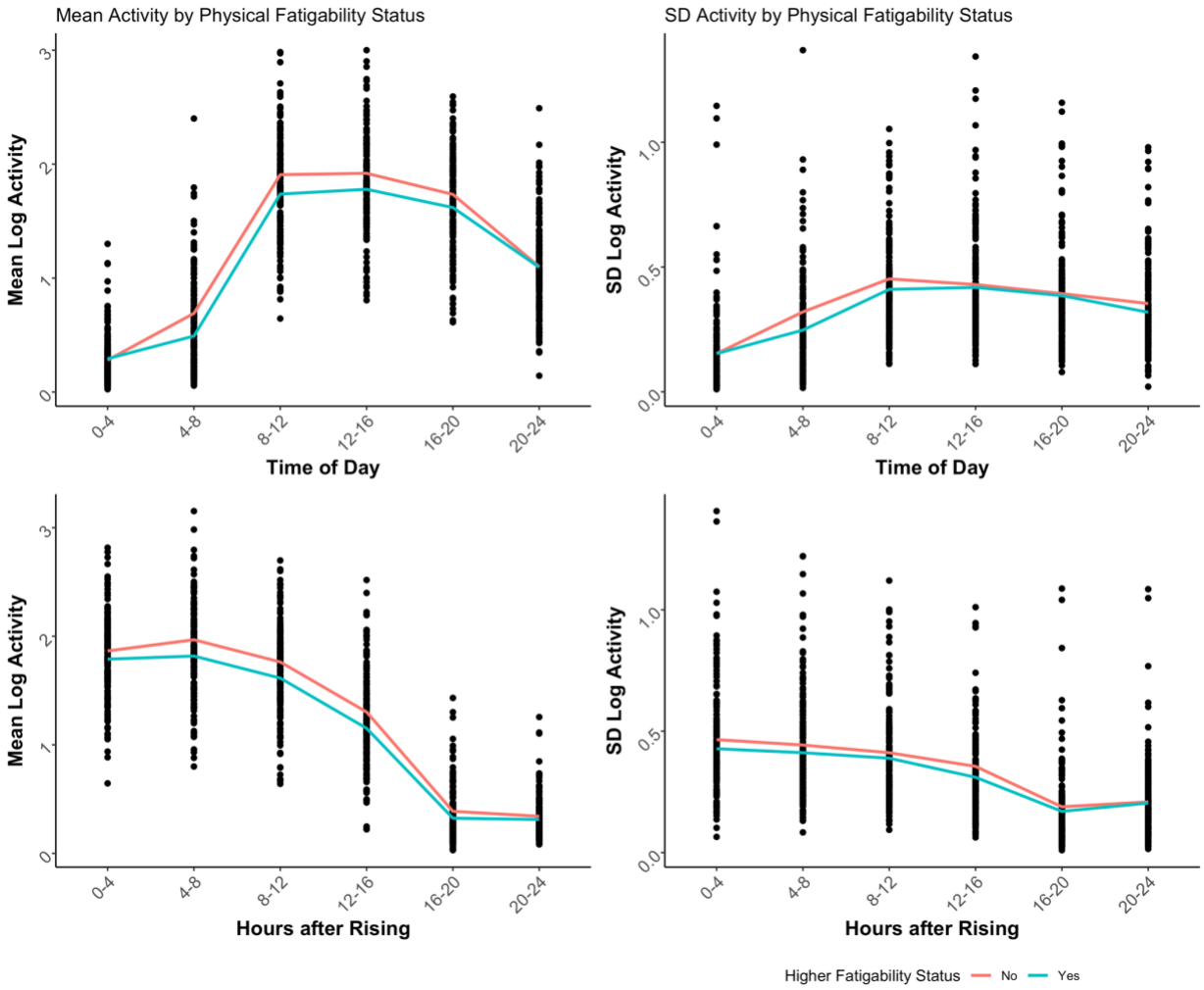

Figure 2 Mean and standard deviation (SD) of daily log activity counts stratified by fatigability status (PFS ≥ 15) at 4-hour time intervals on clock time and rise time adjusted "Person Time" scale.

Table 4 Multivariate quantile regression models of mean daily activity and standard deviation of daily activity across four-hour time intervlas of clock time and rise time adjusted "Person Time".

	Mean of Activity			Standard Deviation of Activity		
Clock Time	**β estimate**	**95% Confidence Interval**	**p value**	**β estimate**	**95% Confidence Interval**	**p value**
00:00-04:00	2.42	(-6.72, 11.56)	0.60	1.12	(-12.52, 14.76)	0.87
04:00-08:00	-4.50	(-8.39, -0.61)	0.03	-5.75	(-15.83, 4.33)	0.27
08:00-12:00	-3.05	(-6.98, 0.89)	0.13	-0.22	(-8.07, 7.64)	0.96
12:00-16:00	-1.96	(-5.83, 1.91)	0.32	-1.01	(-8.98, 6.95)	0.80
16:00-20:00	-1.53	(-5.82, 2.77)	0.49	-1.02	(-9.39, 7.35)	0.81
20:00-24:00	2.39	(-3.07, 7.84)	0.39	-7.42	(-16.64, 1.8)	0.12
Person Time+	**β estimate**	**95% Confidence Interval**	**p value**	**β estimate**	**95% Confidence Interval**	**p value**
00:00-04:00	-0.53	(-4.80, 3.75)	0.81	0.11	(-7.25, 7.47)	0.98
04:00-08:00	-2.09	(-5.57, 1.4)	0.24	-0.97	(-8.06, 6.12)	0.79
08:00-12:00	-2.07	(-6.29, 2.15)	0.34	-5.07	(-13.49, 3.34)	0.24
12:00-16:00	-2.10	(-5.79, 1.59)	0.27	-5.72	(-13.62, 2.18)	0.16
16:00-20:00	-2.56	(-9.76, 4.63)	0.49	-1.86	(-15.77, 12.05)	0.79
20:00-24:00	-3.07	(-11.81, 5.67)	0.49	4.48	(-4.97, 13.94)	0.35

All models adjusted for age, sex, race, BMI, CES-D score

+ Time is adjusted for average rise time (Person time = time - estimated up mesor), and is interpreted as "hours after estimated rise time"

Table 5 Multivariate logistic regression of mean daily activity and standard deviation of daily activity across four-hour time intervals of clock time and reise-time adjusted "Person Time".

	Mean of Activity			Standard Deviation of Activity		
Clock Time	**Odds Ratio**	**95% Confidence Interval**	**p value**	**Odds Ratio**	**95% Confidence Interval**	**p value**
00:00-04:00	1.03	(0.20, 5.17)	0.97	1.31	(0.18, 9.45)	0.78
04:00-08:00	0.27	(0.10, 0.68)	0.01	0.26	(0.04, 1.61)	0.14
08:00-12:00	0.49	(0.21, 1.07)	0.08	0.43	(0.08, 2.31)	0.32
12:00-16:00	0.49	(0.19, 1.27)	0.15	1.14	(0.24, 5.80)	0.88
16:00-20:00	0.70	(0.29, 1.68)	0.42	1.18	(0.22, 6.72)	0.85
20:00-24:00	1.21	(0.50, 2.92)	0.67	0.64	(0.09, 4.47)	0.65
Person Time[+]	**Odds Ratio**	**95% Confidence Interval**	**p value**	**Odds Ratio**	**95% Confidence Interval**	**p value**
00:00-04:00	0.68	(0.25, 1.81)	0.44	0.46	(0.10, 2.19)	0.32
04:00-08:00	0.44	(0.17, 1.10)	0.08	0.57	(0.12, 2.62)	0.47
08:00-12:00	0.51	(0.2, 1.25)	0.15	0.85	(0.16, 4.63)	0.85
12:00-16:00	0.56	(0.24, 1.27)	0.17	0.38	(0.05, 2.77)	0.35
16:00-20:00	0.35	(0.08, 1.47)	0.16	0.78	(0.08, 6.83)	0.82
20:00-24:00	0.57	(0.08, 3.47)	0.55	2.04	(0.23, 20.49)	0.53

[*]All models adjusted for age, sex, race, BMI, CES-D score

[+] Time is adjusted for average rise time (Person time = time - estimated up mesor), and is interpreted as "hours after estimated rise time"

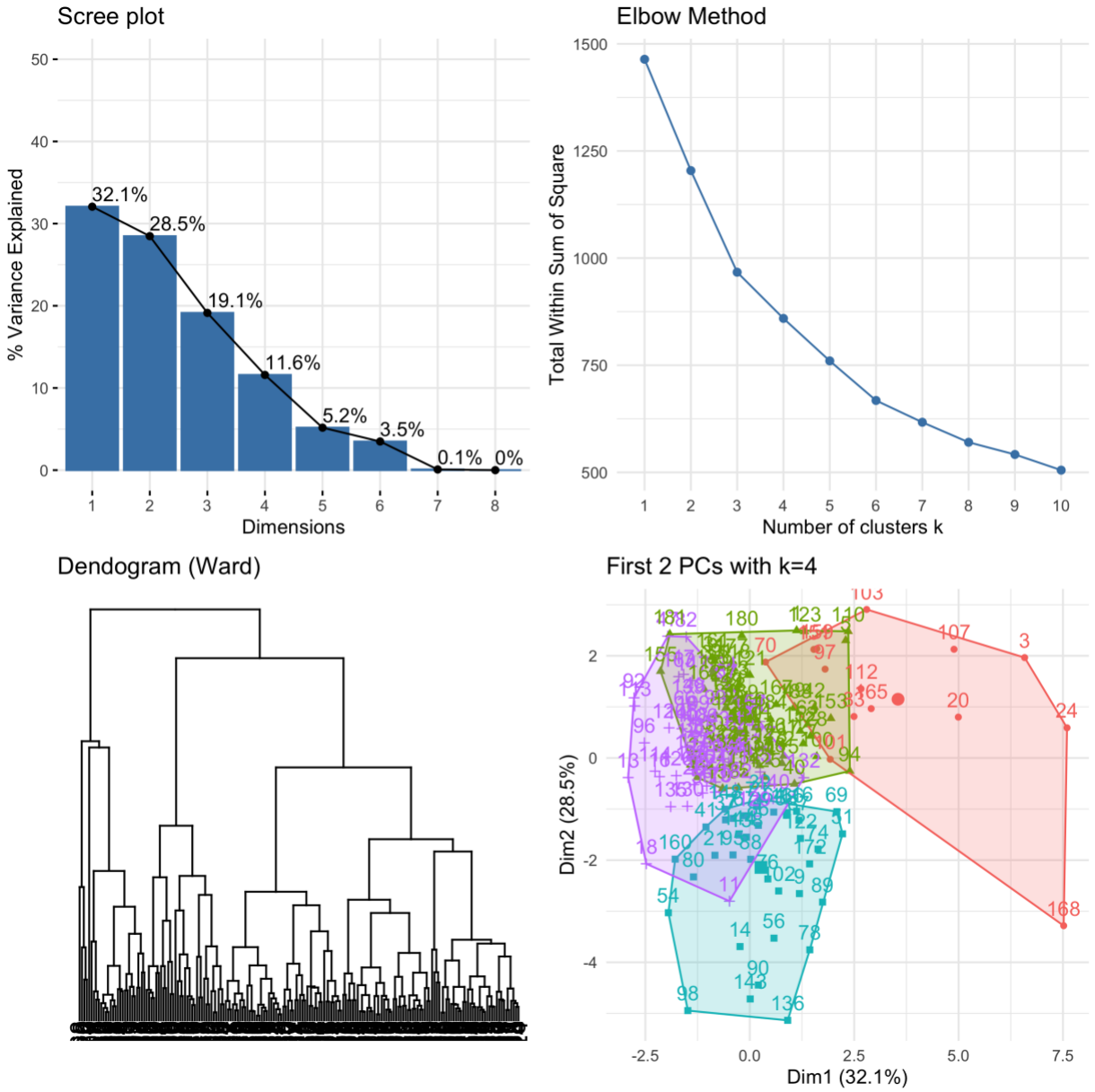

Figure 3 k-means clustering diagnostics for 4 clusters. Top left panel: percent of variance explained from principal components analysis (PCA); Top right panel: "Elbow method" of within sum of squares estimated by different cluster k assignments; Bottom left: Ward method dendogram; Bottom right: visulazation of first two dimension of PCA analysis with cluster assignments overlayed.

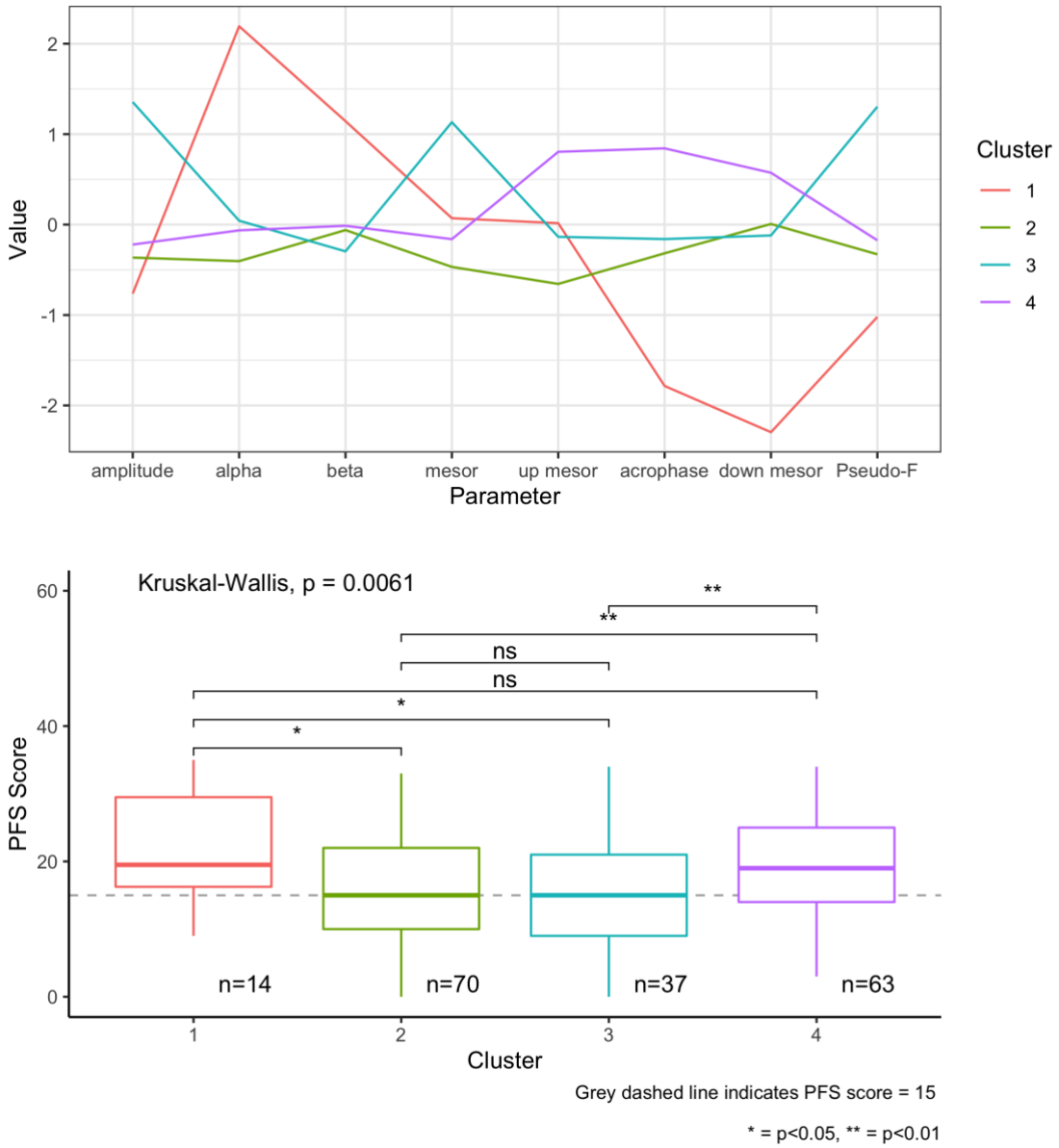

Figure 4 Top: Each k-means derived cluster's mean rest-activity rhythm (RAR) parameter estimates from the anti-logistic extended cosine model; Bottom: Differences in PFS score by cluster assignment. Overall differences tested with Kruskal-Wallis test, and pairwise differences tested with two-sample Wilcoxon Rank Sum. Cluster representations: Cluster 1 = "Less Active/Robust", Cluster 2 = "Earlier RAR", Cluster 3 ="More Active/Robust", Cluster 4 = "Later RAR".

Table 6 Multivariate quantile regression of effects of cluster assignments on median PFS scores.

	β Coefficient	95% Confidence Interval	p-value	LRT[+]
Model 1				
Cluster 3 vs. 2	0.45	(-2.78, 3.68)	0.79	0.03
Cluster 1 vs. 2	6.14	(-0.01, 12.29)	0.05	
Cluster 4 vs. 2	3.53	(0.30, 6.76)	0.03	
Model 2				
Cluster 1/4 vs. 2/3	3.71	(0.99, 6.43)	0.01	

[*]All models adjusted for age, sex, race, BMI, CES-D score
[+] LRT = likelihood ratio test for comparing model with cluster assignments versus model without
[1.] Cluster 1 = "Less Active/Robust", Cluster 2 = "Earlier RAR", Cluster 3 = "More Active/Robust", Cluster 4 = "Later RAR".

Table 7 Multivariate logistic regression of effects of cluster assignments on the odds of having higher fatigabiltiy status (PS ≥ 15).

	Odds Ratio	95% Confidence Interval	p-value	LRT[+]
Model 1				
Cluster 3 vs. 2	1.28	(0.51, 3.23)	0.60	0.13
Cluster 1 vs. 2	3.44	(0.80, 18.55)	0.12	
Cluster 4 vs. 2	2.32	(1.02, 5.42)	0.05	
Model 2				
Cluster 1/4 vs. 2/3	2.26	(1.11, 4.67)	0.03	

[*]All models adjusted for age, sex, race, BMI, CES-D score
[+] LRT = likelihood ratio test for comparing model with cluster assignments versus model without
[1.] Cluster 1 = "Less Active/Robust", Cluster 2 = "Earlier RAR", Cluster 3 = "More Active/Robust", Cluster 4 = "Later RAR"

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