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Rest/Activity Rhythms and Mortality Rates in Older Men: MrOS Sleep Study

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Abstract

Background—An association between increased risk of mortality and disruptions in rest/activity circadian rhythms (RAR) has been shown among adults with dementia and with metastatic colorectal cancer. However the association among a more general population of older adults has not been studied.

Methods—Study population consisted of 2964 men aged 67 and older enrolled in the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. Rest/activity patterns were measured with wrist actigraphy. RAR parameters were computed and expressed as quintiles, and included acrophase (time of peak activity level), amplitude (peak-to-nadir difference), mesor (middle of the peak), pseudo F-value (overall circadian rhythmicity), beta (steepness) and alpha (peak-to-trough width).

Results—After adjustment for multiple potential confounders, men in the lowest quintile of pseudo F-value had a 57% higher mortality rate (Hazard ratio [HR]=1.57, 95%CI, 1.03–2.39) compared with men in the highest quintile. This association was even stronger with increased risk of cardiovascular disease-related mortality (CVD) (HR=2.32, 95%CI, 1.04–5.22). Additionally, men in the lowest quintile of acrophase had a 2.8-fold higher rate of CVD-related mortality (HR=2.84, 95%CI, 1.29–6.24). There was no evidence of independent associations with amplitude, mesor, alpha, beta and risk of mortality.

Conclusions—Older men with less robust RAR and earlier acrophase timing, have modestly higher all-cause and CVD-related mortality rates. Further research should examine potential biological mechanisms underlying this association.

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Keywords

rest/activity rhythms; circadian rhythms; mortality; elderly; sleep

Introduction

Disruptions in normal sleep patterns and sleep complaints are common among older adults, with as many as 57% reporting having at least one chronic sleep-related problem.(Foley DJ, Monjan AA et al.,1995) Several studies have also suggested that changes in circadian rhythms occur with advancing age. These changes include reduced amplitude, phase shifts (particularly an advancement of the rhythm), and a loss of robustness of the rhythm (weakening of rhythmic pattern) (Buysse DJ, Monk TH et al.,2005; Czeisler CA, Dumont M et al.,1992; Duffy JF, Zeitzer JM et al.,2002; Sakurai N and Sasaki M,1998; Weitzman ED, Moline ML et al.,1982; Yoon IY, Kripke DF et al.,2003)

It has been hypothesized that disruptions in these rhythms may occur in part, as a result of age-related deterioration of the SCN (Saper CB, Scammell TE et al.,2005) and could be a factor resulting in the high proportion of sleep complaints in the elderly (Czeisler CA, Dumont M et al.,1992). Although the exact health-related consequences of disrupted rest/activity rhythms are unknown, several potential biological mechanisms have been proposed. One such mechanism involves insufficient sleep caused by circadian disruption of the rest/activity cycle (Gehrman P, Marler M et al.,2004). Several prior studies have reported that loss of sleep in the elderly is associated with a variety of adverse health-related outcomes such as all-cause mortality (Foley DJ, Monjan AA et al.,1995), accidents, falls and poor health status (Ancoli-Israel S and Cooke JR,2005; Foley DJ, Monjan A et al.,1999).

Some studies have suggested that desynchronized or poor circadian activity rhythms may also be related to increased morbidity and mortality, particularly in demented nursing home patients (Gehrman P, Marler M et al.,2004) and patients with metastatic colorectal cancer (Mormont MC, Waterhouse J et al.,2000). However, the association between RAR parameters and mortality in a more general population of older adults is uncertain.

We hypothesized that disruptions in the timing of RAR as well as reductions in amplitude and model robustness would be associated with an increased risk of mortality in older, community-dwelling men. To test this hypothesis, we measured rest/activity rhythms among 2964 men aged 67 and older enrolled in the Outcomes of Sleep Disorders in Older Men (MrOS) study, and subsequently followed them for vital status and cause-specific mortality for an average of 3.5 years.

Methods

Participants

From March 2000 through April 2002, 5,995 men 65 years of age and older were recruited for participation in the baseline examination of the prospective Osteoporotic Fractures in Men (MrOS) study (Orwoll E, Blank JB et al.,2005) Men were recruited from population based listings in six areas of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California (Blank JB, Cawthon PM et al.,2005) As this was primarily a study of risk factors for osteoporosis and fractures, men with a history of bilateral hip replacement and men who were unable to walk without the assistance of another person were excluded.

From December 2003 through March 2005, subjects were invited to participate in an ancillary study to identify outcomes of sleep disorders in older men (Outcomes of Sleep Disorders in Older Men [MrOS sleep] study). In order to be eligible to attend the MrOS Sleep visit, men who were currently being treated for obstructive sleep apnea had to be willing and able to forgo sleeping with their equipment (CPAP, BiPAP, oxygen, mouthpiece) on the night of the PSG. However, in general, men who reported nightly use of any of these devices were excluded. Men who had an open tracheotomy were not eligible. Of the 5995 men enrolled in the overall MrOS study, 3135 (52% of overall cohort, 105% of recruitment goal) were enrolled in the MrOS sleep examination. Of the 2860 men not included in the MrOS Sleep examination, 1997 declined participation, 150 were not eligible, 344 died prior to the visit, 37 terminated their enrollment prior to the visit and 332 were not contacted because the recruitment goal had been achieved. Of the 3135 men who completed the MrOS Sleep Study, 3049 (97%) had technically adequate measures of rest/activity rhythms. Fifty-six men (2%) were excluded because they had less than three 24-hour periods of actigraphy data. Of the remaining 2993 men, 29 were excluded due to lack of follow-up data for vital status. Thus, 2964 (99% of MrOS sleep cohort) were included in this analysis. The Institutional Review Board (IRB) at each center approved the study protocol and written informed consent was obtained from all subjects. The study protocol was in accord with international ethical standards as recommended by the journal(Portaluppi F, Touitou Y et al., 2008).

Actigraphy

Rest-activity was measured using an octagonal sleep watch actigraph (Ambulatory Monitoring, Inc., Ardsley, NY), placed on the non-dominant wrist. Accelerometers within the actigraph measure movement several times per second and store the information digitally. Participants were instructed to wear the actigraph continuously for a minimum of five 24-hour periods (i.e., 120 consecutive hours), and were instructed to remove the actigraph only for bathing, or situations in which it might get submerged in water. In general, actigraphy is a valid measure of entrained sleep/wake rhythms (Ancoli-Israel S, Cole R et al.,2003).

Activity data were used to compute measures of RAR using the sigmoidally transformed cosine model, also referred to as the 5-parameter extended cosine model, with periods where the actigraph was removed deleted from the analysis (Marler MR, Gehrman P et al., 2006)This method involves fitting an antilogistic function to each individual's data by the non-linear least-squares method. This model has increased flexibility to model activity patterns that are more rectangular shaped, and has been generally accepted as more appropriate than the traditional cosine curve for modeling the rest/activity patterns.(Ancoli-Israel S, Cole R et al.,2003) The parameters obtained from the sigmoidally transformed cosine model were acrophase, amplitude, mesor, beta (β), alpha (α) and pseudo F-value. Acrophase is defined as the time of day of the maximum modeled value for activity (timing of peak activity), measured in portions of hours. Amplitude is the peak-to-nadir difference in the fitted curve, measured in activity counts/minute. Mesor (mesor=[minimum + amplitude]/2) approximates the middle of the fitted curve (average modeled activity level), measured in activity counts/minute. The beta statistic is a measure of steepness of the curve, in which larger values represent more square-shaped waves, which would suggest a more constant level of daytime activity. The alpha statistic is a measure of peak-to-trough width, in which small values would represent curves where the troughs are narrower than the peaks, suggesting greater a daytime to nighttime activity ratio. The pseudo F-value is a measure of model fit, with smaller values indicating a less robust rhythmic pattern in rest/activity and hence overall reduced circadian rhythmicity.

Mortality

After the MrOS Sleep visit, participants were contacted every 4 months and all reported deaths were confirmed with death certificates and additionally with medical records when available. Follow-up for vital status was 99% complete. Nineteen (0.6%) men terminated their enrollment in the study during the follow-up period and are censored in the analyses. The average follow-up time for the 2964 men in the cohort was 3.5 ± 0.6 years (for a total of 10,402 person-years). Cause-specific mortality, including deaths from cardiovascular disease and cancer, are based on the underlying cause of death as determined a Physician Adjudicator at the coordinating center.

Other Measures

All participants completed a questionnaire which included questions about medical history, specifically history of physician diagnosis of diabetes, Parkinson's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and cardiovascular disease including myocardial infarction, angina, stroke and congestive heart failure. Participants were also asked about their current health status, highest level of education attained, smoking status, caffeine and alcohol use. The Geriatric Depression Scale (GDS) was used to assess depressive symptoms, with a standardized cut-off of ≥6 used to indicate depression (Almeida OP and Almeida SA,1999; Sheikh J and Yesavage J.,1986). Functional status was measured with information on five Instrumental Activities of Daily Living (IADL) (Fitti JE and Kovar MG,1987; Pincus T, Summey JA et al.,1983) Cognitive function was assessed with the Teng Modified Mini-Mental State Exam (3MS) (Teng EL and Chui HC,1987). Self-reported physical activity was measured using the Physical Activity Scale for the Elderly (PASE) questionnaire(Washburn RA, Smith KW et al.,1993). Participants were asked to bring in all current medications used within the last 30 days, and a computerized medication coding dictionary was used to categorize the medications (Pahor M, Chrischilles EA et al.,1994) Body weight was measured with a standard balance beam or digital scale. Height was measured using a standard held-expiration technique with a wall-mounted stadiometer. Height and weight were used to calculate body mass index (kg/m^2).

Statistical Analysis

Characteristics of the analytical cohort of 2949 men were summarized by means and standard deviations (SD) for continuous variables, and counts and percentages for categorical variables. Summary statistics for each of the rest/activity rhythm parameters were calculated, by age group (≤69, 70–74, 75–79, and ≥80 years). Linear regression was used to calculate a p-for-trend.

RAR parameters were expressed in quintiles. Cox regression models were used to compare the adjusted relative hazard of mortality for each of the higher quintiles of amplitude, mesor, F-value and beta with the lowest quintile as the referent group. Tests for linear trend were also performed. Since both acrophase and alpha had a u-shaped association with mortality, the middle quintile of each was chosen as the referent group. All covariates listed in Table 1 were considered for inclusion in the multivariable models. Covariates were included in the multivariable model if they were related to any of the RAR parameters in univariate analyses and to mortality (independent of age) at $P \leq 0.10$ or if they were related to at least one RAR parameter or previous studies had reported an association with mortality. Older age was associated with an increased risk of mortality, and in order to reduce any residual confounding by age, both linear and quadratic age terms were included in multivariable models.

All models are adjusted for clinic site. The models presented include age and age^2 adjusted (base model), and a final multivariable adjusted model including age, age^2, race, alcohol

use, smoking status, caffeine use, education, self-reported health status, IADL impairments, cognitive impairment, depression and an ordinal variable (0,1 or ≥2) for number of medical conditions (cardiovascular disease, diabetes, chronic kidney disease, Parkinson's disease and chronic obstructive pulmonary disease). Use of antidepressants, benzodiazepines and non-benzodiazepine anxiolytic/hypnotics were weakly associated with mortality, independent of age, however, because of their strong association with RAR parameters, secondary analyses were performed additionally adjusting for use of these medications. To examine whether the association between RAR and increased risk of death became stronger among the oldest old, secondary analyses were performed stratifying participants by age (< 80 years vs ≥ 80 years) and testing for an interaction. We also examined the associations between RAR and cause-specific mortality (cardiovascular-related, cancer-related and other causes).

We repeated the analyses using continuous as well as log-transformed rest/activity rhythm parameters. Since the results from these sensitivity analyses were similar to those of the primary analyses, only the findings from the primary analyses are presented. All analyses were performed using SAS 9.1 (SAS Institute, Inc. Cary, N.C.).

Results

Baseline Characteristics

Of the 5995 men in the baseline MrOS cohort, 2964 men completed the MrOS Sleep visit and had technically adequate measures of RAR and complete vital status follow-up. Of the 3031 men who were not included in the cohort, 344 (9%) died prior to enrollment for the sleep visit. Compared with the 2687 men who were alive for the sleep visit, but did not have complete measures or were not enrolled for the sleep visit, upon entry into the study, men in the analytical cohort tended to be slightly younger, (73.0 vs. 73.9 years, $p<.001$), more educated (79% vs. 74% reporting having completed some college or beyond, $p<.001$), and were more likely to report good to excellent health status (89% vs. 85%, $p<.001$).

Characteristics of the 2964 men in this study are presented in Table 1. At the sleep examination, the average age for men in the cohort was 76 ± 6 years. They were primarily Caucasian (90%), and 87% reported their health as excellent or good. Also, 44% reported working for pay or volunteering within the previous 7 days, for an average of 13.7 ± 13.5 hours (range 1–80 hours).

In analyses examining characteristics of the cohort by quintiles of RAR parameters, reduced amplitude was associated with older age, poorer self-reported health status, living alone, greater number of IADL impairments, reduced caffeine consumption, higher body mass index, poorer cognitive function, higher rates of depression, lower alcohol consumption, greater number of medical conditions, greater use of antidepressants and benzodiazepines (results not shown). These results were generally consistent across the parameters of RAR with similar associations between these characteristics and lower pseudo F-value, and quintiles of acrophase.

Follow-up and Mortality

The average follow-up time for the 2964 men in the cohort was 3.5 ± 0.6 years. There were 233 (8.0%) recorded deaths in the cohort, of which 78 (34%) were attributed to cardiovascular disease, 75 (32%) were attributed to cancer, and 80 (34%) were attributed to other underlying causes which included pneumonia, Alzheimer's Disease, dementia, head injury, airway obstruction, and several less common causes.

Association between Rest/Activity Rhythms and Age

The mean for each RAR parameter by age group is presented in Table 2. Amplitude, mesor and pseudo F-value steadily declined with advancing age (p-trend<0.001), while mean beta values steadily increased with advancing age group (p-trend<0.001). There was no statistically significant evidence of a trend across advancing age groups for either mean acrophase (p-trend=0.481) or alpha (p-trend=0.426).

Rest/Activity Rhythms and Risk of All-Cause Mortality

There did not appear to be an independent association between most RAR and risk of all-cause mortality (Table 3). There was some evidence of an association between quintiles of amplitude and risk of all-cause mortality in age-adjusted models (data not shown), however, this association was attenuated and no longer statistically significant in multivariable adjusted models. Health and physical function covariates in multivariable-adjusted models had the greatest attenuating effect (IADL impairments, medical conditions, self-reported health status and cognitive impairment). Mesor, alpha and beta were not associated with risk of mortality in both age and multivariable adjusted models.

There was stronger evidence of an independent association between quintiles of pseudo F-value and increased risk of mortality in both age-adjusted (data not shown) and multivariable-adjusted models. In multivariable-adjusted models, men in the lowest quintile of pseudo F-value had a 57% increased mortality rate (HR=1.57, 95% CI 1.03–2.39) compared with men in the highest quintile.

Age (<80 vs. ≥80 years) appeared to be a modest effect modifier between beta and alpha and risk of mortality, with men <80 years of age having the highest risk of mortality for both quintiles of beta (p-interaction=0.053, p-trend for men<80=0.028) and alpha (p-interaction=0.377, p-trend for men <80=0.057). However, age was not significant for other RAR parameters in predicting increased risk of mortality (p-value>0.15 for all interaction terms).

Similarly, there was no evidence that increased risk of mortality for quintiles of acrophase, amplitude, mesor, pseudo F-value and alpha depended on level of physical activity (p≥0.20 for all interaction terms). However, there was some evidence that the association between quintiles of beta and risk of mortality was dependent on level of physical activity (p-interaction=0.065), with men who had higher levels of physical activity (PASE≥115.1) at greatest risk of mortality (p-trend=0.123). For example, men in the lowest quintile of beta had an 86% greater risk of mortality than men in the highest quintile (HR=1.86, 95%CI 1.03–3.37).

The association between RAR parameters and risk of all cause mortality were essentially unchanged after further adjustment for use of psychoactive medications. When use of antidepressants and use of benzodiazepines and use of non-benzodiazepine anxiolytic/hypnotics were added to the multivariable models, results were similar to the primary analyses (results not shown).

Rest/Activity Rhythms and Risk of Cause-Specific Mortality

In secondary analyses, the association between quintiles of RAR parameters and risk of cause-specific mortality (cardiovascular-related, cancer-related and other) were examined (Table 3). In general, the associations between RAR parameters and death tended to be somewhat stronger for CVD-related death than for either cancer or non-CVD non-cancer deaths. There was evidence of an association between quintiles of acrophase with risk of cardiovascular disease-related death (p-value=0.061). For example, men with the earliest

peak activity times (lowest quintile of acrophase) had a 2.8-fold increased risk of CVD-related death compared with that among men in the middle quintile (HR=2.84, 95%CI 1.29–6.24) in multivariable-adjusted models. There was no association between quintiles of acrophase and cancer-related or other-related risk of death. There was no association between quintiles of amplitude and quintiles of mesor with risk of CVD-related, cancer-related or other causes of mortality.

There was evidence of a moderate graded association between quintiles of pseudo F-value and risk of CVD-related (p-trend=0.006) and other causes (p-trend=0.024) of mortality. There was no evidence of an association between quintiles of beta and risk of cause-specific mortality, although the association between quintiles of beta and CVD-related mortality was borderline statistically significant (p-trend=0.077). There was some evidence of a U-shaped association between quintiles of alpha and risk of cancer-related mortality that was also borderline statistically significant (p-value=0.081). There also was some evidence of an association between quintiles of alpha and rate of CVD-related mortality (p-value=0.038), with men in the highest quintile of alpha having a slightly higher rate of CVD-related mortality, although this individual point estimate was not significant (HR=1.65, 95%CI 0.83–3.28).

Discussion

The results of this study suggest that among older, community-dwelling men there is not a consistent graded association across all of the RAR parameters and increased risk of death. There is however, some evidence that earlier peak activity times are moderately associated with increased risk of CVD-related mortality, independent of several potential confounders. Furthermore, there was evidence that lower pseudo F-values were moderately associated with an increased mortality rate, primarily driven by a higher CVD-related death rate. This suggests that decreased overall circadian rhythmicity (weaker rhythms), and perhaps earlier timing of peak activity are both independent predictors of CVD-related mortality. We did not find an independent association between amplitude, mesor, alpha and beta and mortality rate.

To our knowledge, no prior published study has evaluated the association between actigraphy measured RAR and mortality in a large sample of community-dwelling older men. However, preliminary findings presented by Dr. Tranah et. al. suggest that the relationship between RAR and mortality is consistent and stronger in older women(Tranah GJ, Blackwell T et al.,2008). The results of our study are in general agreement with those of a previous study examining the association between RAR and mortality in older people with dementia. In that study of 149 older adults with dementia (mean age 84.1 years), Gehrman et. al. found an association between greater deviations in acrophase timing and less steep rhythms (lower beta) and increased risk of all-cause mortality. Although we were unable to find an association between acrophase timing and risk of all-cause mortality in our cohort of older men, we did observe an association between early acrophase timing and increased risk of CVD-related mortality. We found a borderline significant association between reduced rhythm steepness and risk of CVD-related mortality that was not as strong as what Gehrman et. al had found. Contrary to our findings, the prior study did not find significant associations between pseudo F-value and risk of all-cause mortality, suggesting that overall circadian rhythmicity was not independently associated with risk of mortality in that cohort. The differences in results might be a function of the populations studied, as older individuals with dementia are generally less active and may have a different phase shaped relationship between RAR and risk of mortality than that of community dwelling older men (Gehrman P, Marler M et al.,2004). Likewise, the differences could be due to the low prevalence of men

with severely disrupted rhythms in this population, limiting our ability to fully observe the association between disrupted RARs and risk of mortality.

While it has been hypothesized that rhythm disruptions may occur as a result of age-related deterioration in the suprachiasmatic nucleus (SCN), the mediating roles of comorbidities and the effect they may have on the association between disrupted RAR and mortality is unclear. In our analysis we attempted to adjust for risk factors that might confound the relationship between RAR and mortality. Adjusting for age had the largest attenuating effect on the associations. Other prominent covariates included IADL impairments, cognitive impairment, depressive symptoms, medical conditions, alcohol use and self-reported health status.

Whether abnormal RAR play a causal role in deteriorating health resulting in higher mortality rates or are merely a marker of poor health is unknown. Future studies will need to examine the association between poor health, especially measurements of the degree of prevalent cardiovascular disease, and RAR.

This study has a number of strengths, including prospective design, large sample size, comprehensive set of measurements including validated measures of RAR parameters and completeness of follow-up. Furthermore, participants were not selected on the basis of sleep disturbances, medical conditions or vital status, and were enrolled from six clinical centers distributed throughout the United States.

This study was limited by its relatively short follow-up time period that averaged 3.5 years. Although the data suggest that there may be an association between RAR and risk of mortality within this time period, future research should examine this association in longer follow-up time periods. Also, since the cohort included only community-dwelling, primarily healthy, white men over the age of 67, these results may not apply to other populations and may underestimate the true association between disruptions in RAR and mortality in the general elderly population. Furthermore, RAR as measured by wrist actigraphy are subject to masking by voluntary behavior, and may not be as stable as melatonin or temperature rhythms as markers of SCN circadian output (Ancoli-Israel S, Cole R et al.,2003). Also, due to lack of power we were not able to explore the association between RAR and specific causes of death, such as accidents, suicides etc.

In summary, this study provides evidence that the timing and overall rhythmicity of RAR may have a modest association with risk of CVD-related mortality. These results emphasize the need for future research to focus on examining the physiologic and biologic changes underlying RAR and aging, as well as the mediating roles of co-morbid medical conditions and physical functioning to determine the influence of these factors on the association between RAR and mortality in older adults.

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Table 1

Baseline Characteristics of 2964 subjects

Characteristics	
Age,y, mean ± SD	76 ± 6
Caucasian*,†	2665 (90)
Education*,†	
Less than high school	157 (5)
High School	475 (16)
Some college or beyond	2332 (79)
Smoking status*	
Current smoker	58 (2)
Former smoker	1737 (59)
Never smoked	1168 (39)
Alcohol use*	
<1 drink/wk	1387 (47)
1–13 drinks/wk	1396 (47)
14+ drinks/week	167 (6)
Self-reported good or excellent health status*	2570 (87)
Living alone*,§	399 (14)
Work for pay or volunteer	1313 (44)
Caffeine use, mg/day, median (IQR) **	180 (36–368)
IADL impairments*	
None	2344 (79)
1–2	495 (17)
3+	124 (4)
BMI, kg/m^2, mean ± SD	27 ± 4
3MS Score, 0–100, median (IQR) **	94 (90–97)
Depressed (GDS≥6) *	193 (7)
Medical conditions*,‡	
0	1740 (59)
1	982 (33)
2+	241 (8)
Use of antidepressants*	229 (8)
Use of benzodiazepines*	133 (5)
Use of non-benzodiazepine anxiolytic/hypnotics*	59 (2)
PASE, mean ± SD	146 ± 71
Number of deaths*	233 (8)
CVD-related deaths	78 (34)
Cancer-related deaths	75 (32)
Other deaths	80 (34)

SD = Standard Deviation; IADL=Instrumental Activities of Daily Living; BMI=Body Mass Index; 3MS=Teng Modified Mini-Mental Examination Score; GDS=Geriatric Depression Scale; SD=Standard Deviation; CVD=Cardiovascular Disease; PASE=Physical Activity Scale for the Elderly;

[*] Unless otherwise stated, values represent number, with percentage in parentheses.

[†] Measurements obtained at baseline study visit an average of 3.2 years earlier

[‡] Medical conditions include physician diagnosis of diabetes, cardiovascular disease, Parkinson's disease, chronic kidney disease and chronic obstructive pulmonary disease.

[§] Measurement obtained at interim study visit an average of 1.4 years earlier.

[**] Continuous variables have a skewed distribution.

Table 2

Mean (95% CI) Rest/Activity Rhythm Parameters by Age Group

	Age Groups			
	<=69 (n=259)	**70–74 (n=1026)**	**75–79 (n=851)**	**80+ (n=828)**
Acrophase †	14.32 (14.18–14.47)	14.25 (14.18–14.33)	14.23 (14.15–14.31)	14.33 (14.25–14.42)
Amplitude*	3870 (3740–4000)	3794 (3728–3859)	3650 (3578–3722)	3257 (3184–3330)
Mesor*	2223 (2163–2284)	2227 (2196–2257)	2190 (2157–2224)	2058 (2024–2092)
F-value*	1151 (1090–1213)	1124 (1093–1155)	1058 (1024–1092)	930 (896–965)
Beta*	16.29 (8.56–24.02)	20.61 (16.7–24.49)	21.67 (17.41–25.93)	41.71 (37.39–46.03)
Alpha‡	−0.31 (−0.34, −0.27)	−0.29 (−0.31, −0.27)	−0.28 (−0.30, −0.26)	−0.29 (−0.31, −0.27)

CI refers to confidence interval

*P-trend<.001;

†P-trend=0.481;

‡P-trend=0.426

Table 3

Rest-Activity Rhythms and Risk of All-Cause and Cause-Specific Mortality

		HR* (95% CI)			
		All-Cause (N=2945)	**CVD (n= 78)**	**Cancer (n=75)**	**Other (n=80)**
Acrophase					
8.74–13.37	53 (9)	1.16 (0.77–1.74)	2.84 (1.29–6.24)	0.65 (0.32–1.32)	0.97 (0.47–2.01)
13.37–13.98	39 (7)	0.86 (0.56–1.33)	1.40 (0.58–3.40)	0.57 (0.28–1.16)	0.99 (0.48–2.05)
13.98–14.53	45 (8)	1.0	1.0	1.0	1.0
14.53–15.15	44 (7)	0.99 (0.65–1.50)	1.76 (0.76–4.07)	0.68 (0.34–1.36)	0.97 (0.47–2.03)
15.15–24.4	52 (9)	1.04 (0.69–1.57)	1.55 (0.67–3.60)	0.82 (0.42–1.61)	1.18 (0.59–2.35)
p-value		0.707	0.061	0.553	0.976
Amplitude					
<2732	84 (14)	1.25 (0.82–1.90)	1.27 (0.61–2.65)	1.23 (0.57–2.67)	1.24 (0.62–2.47)
2732–3316	39 (7)	0.77 (0.49–1.23)	0.92 (0.42–2.05)	0.85 (0.38–1.91)	0.60 (0.27–1.34)
3316–3780	44 (7)	0.98 (0.63–1.53)	0.95 (0.42–2.15)	1.30 (0.62–2.73)	0.78 (0.36–1.71)
3780–4362	30 (5)	0.75 (0.46–1.22)	0.57 (0.22–1.49)	1.22 (0.57–2.58)	0.47 (0.19–1.20)
≥4362	36 (6)	1.0	1.0	1.0	1.0
P-trend		0.187	0.226	0.963	0.244
Mesor					
<1790	69 (12)	1.04 (0.69–1.55)	0.80 (0.41–1.57)	0.98 (0.45–2.13)	1.23 (0.61–2.47)
1791–2030	47 (8)	0.90 (0.59–1.37)	0.65 (0.32–1.35)	1.07 (0.50–2.26)	1.05 (0.51–2.18)
2030–2235	38 (6)	0.79 (0.51–1.23)	0.56 (0.26–1.23)	1.22 (0.59–2.53)	0.64 (0.28–1.48)
2235–2500	36 (6)	0.71 (0.45–1.11)	0.56 (0.26–1.21)	1.17 (0.56–2.45)	0.41 (0.16–1.04)
≥2500	43 (7)	1.0	1.0	1.0	1.0
P-trend		0.394	0.841	0.854	0.057
Pseudo F-value					
<640	82 (14)	1.57 (1.03–2.39)	2.32 (1.04–5.22)	0.90 (0.42–1.90)	1.95 (0.94–4.05)
640–854	58 (10)	1.38 (0.89–2.12)	1.76 (0.76–4.10)	1.22 (0.62–2.42)	1.44 (0.67–3.08)
854–1093	28 (5)	0.73 (0.44–1.20)	1.19 (0.48–2.96)	0.66 (0.30–1.45)	0.45 (0.17–1.23)
1093–1416	31 (5)	0.88 (0.54–1.43)	0.86 (0.31–2.37)	0.80 (0.38–1.69)	1.07 (0.46–2.49)

		HR* (95% CI)			
		All-Cause (N=2945)	**CVD (n= 78)**	**Cancer (n=75)**	**Other (n=80)**
≥1416	34 (6)	1.0	1.0	1.0	1.0
Ptrend		0.003	0.006	0.755	0.024
Beta					
<4.4	52 (9)	1.39 (0.94–2.06)	1.82 (0.90–3.69)	1.06 (0.55–2.05)	1.49 (0.75–2.98)
4.4–6.8	37 (6)	1.06 (0.69–1.64)	1.58 (0.75–3.31)	0.43 (0.18–1.04)	1.53 (0.75–3.10)
6.8–12.0	44 (7)	1.19 (0.79–1.79)	1.46 (0.70–3.05)	0.86 (0.43–1.74)	1.46 (0.72–2.95)
12.0–26.2	41 (7)	0.93 (0.62–1.40)	1.23 (0.61–2.50)	0.86 (0.45–1.67)	0.76 (0.35–1.65)
≥26.2	59 (10)	1.0	1.0	1.0	1.0
P-trend		0.088	0.077	0.680	0.872
Alpha					
<−0.50	55 (9)	1.42 (0.93–2.18)	0.81 (0.36–1.83)	3.37 (1.51–7.52)	0.98 (0.48–2.01)
−0.50, −0.40	38 (6)	1.13 (0.71–1.79)	0.99 (0.44–2.25)	1.72 (0.71–4.16)	0.96 (0.46–2.03)
−0.40, −0.29	36 (6)	1.0	1.0	1.0	1.0
−0.29, −0.12	44 (7)	1.19 (0.76–1.86)	1.21 (0.57–2.56)	1.75 (0.72–4.26)	0.87 (0.41–1.84)
−0.12, 1.00	60 (10)	1.52 (1.00–2.31)	1.65 (0.83–3.28)	1.94 (0.82–4.59)	1.20 (0.61–2.37)
P-trend		0.661	0.038	0.081	0.655

*Adjusted for age, age^2, site, race, alcohol, caffeine use, self-reported health status, IADL impairments, cardiovascular disease, diabetes, cognitive impairment, depressive symptoms and self-reported kidney disease.