Published in final edited form as:
Chronobiol Int. 2011 April ; 28(3): 258–266. doi:10.3109/07420528.2011.553016.

Rest/Activity Rhythms and Cardiovascular Disease in Older Men

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Abstract

Prior studies have suggested an increased risk of CVD-related mortality in older adults with disturbed circadian rest/activity rhythms (RARs). The objective goal of this study was to examine the association between disrupted RARs and risk of cardiovascular disease (CVD) events in older men. A total of 2,968 men aged 67 yrs and older wore wrist actigraphs for 115±18 consecutive hours. RAR parameters were computed from wrist actigraphy data and expressed as quartiles (Q). CVD events consisted of a composite outcome of coronary heart disease (CHD), stroke, and peripheral vascular disease (PVD) events. Secondary analyses examined associations between RARs and individual components of the composite outcome (CHD, stroke, and PVD). There were 490 CVD events over an average of 4.0±1.2 yrs. Overall, reduced amplitude (HR = 1.31, 95%CI 1.01–1.71 for Q2 vs. Q4) and greater minimum (HR = 1.33, 95%CI 1.01–1.73 for Q4 vs. Q1) were associated with an increased risk of CVD events in multivariable-adjusted models. In secondary analyses, there was an independent association between reduced amplitude (HR = 1.36, 95%CI 1.00–1.86) and greater minimum activity counts (HR = 1.39, 95%CI 1.02–1.91) with increased risk of CHD events. Reduced F-value (HR = 2.88, 95%CI 1.41–5.87 for Q1 vs. Q4 and HR = 2.71, 95%CI 1.34–5.48 for Q2 vs. Q4) and later occurring acrophase of the RAR (HR = 1.65, 95%CI 1.04–2.63 for Q4 vs. Q2–3) were associated with an increased risk of PVD events. Results were similar in men without a history of CVD events. The findings revealed among older men, measures of decreased circadian activity rhythm robustness (reduced amplitude and greater minimum activity) were associated with an increased risk of CVD events, primarily through increased risk of CHD or stroke events, whereas measures of reduced circadian activity rhythm robustness were not associated with risk of CVD events overall, but were associated with an increased risk of PVD events. These results should be confirmed in other populations.

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Keywords

Rest/activity rhythm; Circadian rhythms; Sleep; Elderly; Cardiovascular disease

INTRODUCTION

Complaints of sleep disturbances are common in older adults, with up to 50% reporting symptoms of insomnia, such as complaints of sleep fragmentation and daytime sleepiness. It has also been reported that older adults may be prone to disturbed circadian rhythms, partly due to age-related deteriorations in the suprachiasmatic nucleus (Saper et al., 2005) and decline in melatonin levels, which may subsequently be associated with poor sleep efficacy (Karasek, 2004).

Wrist actigraphy often shows a very robust circadian pattern, and it has been shown to be a strong correlate of entrained endogenous circadian phase (Ancoli-Israel et al., 2003). Recent studies utilizing wrist actigraphy have suggested that disrupted circadian activity rhythms in older adults are associated with an increased risk of all-cause mortality (Gehrman et al., 2004; Paudel et al., 2010; Tranah et al., 2009), cardiovascular disease (CVD)-related mortality (Paudel et al., 2010; Tranah et al., 2009), stroke-related and cancer-related mortality (Mormont et al., 2000; Tranah et al., 2009). An experimental study by Scheer et al. (2009) reported that in younger adults, a forced desynchrony protocol had short-term effects on measures of metabolism, where subjects with a 12-h phase shift had decreased leptin levels, increased glucose, increased insulin, a misaligned cortisol rhythm, and increased mean arterial pressure. In general, previous studies are consistent in suggesting that disruptions of circadian activity rhythms are associated with adverse cardiovascular consequences, such as CVD and stroke-related mortality, as well as short-term consequences in metabolic measures.

While disrupted circadian activity rhythms and CVD events are both more common in the elderly, to our knowledge, no previous study has examined either the short-term or long-term associations between circadian activity rhythm variables and risk of CVD-related events in older adults. Therefore, to examine the longitudinal associations between circadian activity rhythm disruptions and CVD-related events in older adults, we measured circadian rest/activity rhythms using wrist actigraphy and assessed incident CVD events in a population of 2,968 older men enrolled in the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study who were followed prospectively for an average of 4 yrs.

MATERIALS AND METHODS

Subjects

From March 2000 through April 2002, 5,995 men who were aged 65 yrs and older were recruited for participation in the baseline examination of the prospective Osteoporotic Fractures in Men (MrOS) study (Orwoll et al., 2005). Men were recruited from population-based listings in six areas of the United States: Birmingham, Alabama; the Monongahela Valley near Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Palo Alto, California; San Diego, California; and Portland, Oregon (Blank et al., 2005). 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 (MrOS Sleep Study). Of the 3,135 men enrolled in the MrOS Sleep Study, 3,049 had technically adequate circadian

rest/activity rhythm (RAR) measures, meaning that participants had at least 24 h of data collection with <10% of daytime gaps (due to actigraph removal) and <2 h of nighttime gaps. Of those, we excluded 56 (2%) men with less than 72 h of data, and 25 (1%) men who had lack of follow-up data on CVD endpoints. Our final analytical cohort consisted of 2,968 men who had technically adequate measures of circadian RARs and CVD endpoints. The institutional review board 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 (Portaluppi et al., 2010).

Rest/Activity Rhythms (RARs)

RARs were measured using the Octagonal Sleep Watch actigraph (Ambulatory Monitoring, Inc., Ardsley, NY), a small device used to detect wrist movement and provide estimates of sleep/wake patterns. Actigraphy has been shown to be a valid measure of entrained sleep/wake patterns and RARs (Ancoli-Israel et al., 2003). Participants were instructed to wear the actigraph on the wrist of their non-dominant hand, continuously for a period of five consecutive 24-h periods, and were instructed to remove the actigraph only for bathing or other situations in which it might get submerged in water. The University of California at San Diego scoring algorithm was used for data collected in the digital integration mode (also known as the proportional integration mode [PIM]) (Jean-Louis et al., 2001) and time-above-threshold (TAT) mode, and the Cole-Kripke algorithm was used for data collected in the zero-crossing mode (ZCM) (Cole et al., 1992). Data collected in the PIM were used for analysis in this study. Raw actigraphy data were log-transformed for primary analyses, and a secondary analysis was performed using raw data in their original scale.

Actigraphy data were used to compute measures of RAR using the sigmoidally transformed cosine model, also referred to as the five-parameter extended cosine model, with periods when the actigraph was removed deleted from the analysis (Marler et al., 2006). This method involves fitting an antilogistic function to the log-transformed activity data by the non-linear least-squares method. The parameters obtained from the sigmoidally transformed cosine model were acrophase, amplitude, minimum, mesor, beta, alpha, and F-value. This method is typically favored over the traditional cosine analysis because it better characterizes the circadian activity rhythms of older adults, which tend to be less cosine and more rectangular shaped (Ancoli-Israel et al., 2003; Marler et al., 2006).

Acrophase is defined as the time of day in which the maximum modeled peak activity occurred, and is measured in portions of hours. The phase reference time was set to midnight, local time. Earlier acrophase times suggest a possible phase advance of the RAR whereas later occurring acrophase times suggest a possible phase delay. Amplitude is defined as the difference between the maximum modeled activity level and the minimum modeled activity level, and is measured in activity counts/min. Lower values suggest a dampened RAR. Mesor approximates the middle of the curve and is calculated as: Mesor = minimum + amplitude/2. It is also measured in activity counts/min. Alpha is a shape parameter which determines whether the peaks are wider than the troughs. Smaller values are the result of narrow troughs and wider peaks, suggesting more daytime activity, whereas larger values are the result of wide troughs and narrow peaks, suggesting more nighttime activity. Beta describes the steepness of the curve with large values suggesting waves which are more rectangular-shaped as opposed to cosine-shaped. Minimum is the lowest modeled activity, and is measured in activity counts/min. Large values may be indicative of greater nighttime activity. F-value is a measure of overall fit of the model to the raw activity data, with larger values suggesting a stronger circadian rhythm component in the data, and hence greater rhythmicity (Marler et al., 2006).

Cardiovascular disease (CVD) events

After the MrOS Sleep visit, participants were contacted every 4 mos, and all reported CVD-related events were confirmed with medical records by a central physician adjudicator. Incident CVD was defined as a composite outcome of incident coronary heart disease, stroke, and/or peripheral vascular disease. Coronary heart disease (CHD) was defined as definite or probable fatal or nonfatal events of: acute myocardial infarction (MI), ST elevation MI, Non-ST elevation MI, sudden CHD death (<1 h, non-traumatic), coronary artery bypass surgery, coronary revascularization procedures, and hospitalization for unstable angina, ischemic congestive heart failure, or other CHD events not meeting specific criteria for the above mentioned events. Incident cerebrovascular events were defined as definite or probable fatal or nonfatal stroke. Peripheral vascular disease (PVD) events were defined as definite or probable acute arterial occlusion, acute arterial rupture, acute arterial dissection, and vascular surgery.

Follow-up time for incident CVD events was the minimum number of days between the sleep visit and either the first event (fatal or nonfatal), death from other causes, or last contact.

Other Measures

All participants completed a questionnaire which included questions about their medical history, specifically physician diagnosis of diabetes, chronic obstructive pulmonary disease (COPD), emphysema, chronic kidney disease, and Parkinson's disease. Participants were also asked about other potential confounders of the RAR-CVD association, including current health status, highest level of education attained, smoking status, and current caffeine and alcohol use. The Geriatric Depression Scale (GDS) was used to assess depressive symptoms, with a standard cut-off of ≥6 used to indicate depression (Sheikh et al., 1986). Functional status was measured with information on five Instrumental Activities of Daily Living (IADL impairments) (Fitti et al., 1987; Pincus et al., 1983). Cognitive function was assessed with the 100 item Teng-Modified, Mini-Mental State Exam (3MS) (Teng et al., 1987). Participants were asked to bring in all current prescription and over-the-counter medications used within the last 30 days, and a computerized medication coding dictionary was used to categorize the medications (Pahor et al., 1994). Using this method, all prescription medications recorded by the clinics were stored in an electronic medications inventory database (San Francisco Coordinating Center, San Francisco, CA), and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA). Body weight was measured with a standard regularly calibrated balance beam or digital scale. Height was measured in participants without shoes, using a standard held-expiration technique with a wall-mounted stadiometer. Height and weight were used to calculate the body mass index (kg/m^2).

Prevalent or pre-existing physician-diagnosed, CHD, cerebrovascular disease, and PVD were assessed at the MrOS Sleep visit by self-report, since assessment of CVD-related events via medical records did not begin until after the sleep visit. Prevalent CHD was defined as history of physician diagnosis of heart attack, coronary or myocardial infarction, angina, congestive heart failure, and rheumatic heart disease. Prevalent cerebrovascular disease was defined as self-reported history of transient ischemic attack or stroke. Prevalent PVD was defined as history of intermittent claudication or pain in legs from blockage of the arteries, angioplasty of lower extremities, bypass procedure on arteries of legs, or medical or surgical procedures for blood vessels, or an ankle/brachial index (ABI) ratio <0.9 at the baseline examination conducted an average of 3.2 yrs earlier. Since the ABI was objectively measured at an earlier visit and was not based on self-report as compared with the other

components of the history of PVD definition, we performed analyses excluding this portion of the definition, and results were not substantially altered. Therefore, we present results that incorporate ABI <0.90 as a component of the history of PVD definition.

Statistical Analysis

Differences in characteristics of the analytical cohort of 2968 men, according to whether or not the primary CVD disease endpoint was reached, were assessed using t-tests for continuous variables, Kruskall-Wallis tests for skewed continuous variables, and X^2 tests for categorical variables. Crude incidence rates were calculated by dividing the number of events by person-years at risk.

Referent group selection for rhythm parameters was based on the pattern of the association between RAR parameters and risk of CVD events, since no standard clinically relevant cut-points currently exist. RAR parameters were expressed in quartiles (Q), with the higher quartiles of amplitude, mesor, F-value, and beta designated as the referent group, since they appeared to have a negative association with risk of CVD events. Since both acrophase and alpha had a u-shaped association with risk of CVD, the middle two quartiles of each were chosen as the referent group. Furthermore, since the minimum appeared to have a positive association with risk of CVD, the lowest quartile was selected as the referent group. Hazard ratios (HR) and 95% confidence intervals (95%CI) of incident CVD events across categories of RAR parameters were computed using Cox's proportional hazards regression. Tests for linear trend were performed when modeling quartiles of amplitude, mesor, F-value, and beta, whereas 2 df *p*-values were computed when modeling categories of acrophase and alpha. All covariates listed in Table 1 were considered for inclusion in multivariable models. Covariates were included in the multivariable model if they were related to any of the RAR parameters in univariate analyses and to incident CVD events (independent of age, clinic site, and race) at $p \leq .10$. Models included a base model, adjusted for age, clinic site, and race, and a multivariable-adjusted model that additionally adjusted for IADL impairments, smoking status, cognitive impairment, use of antidepressants, walking regularly for exercise, and history of CHD, stroke, and PVD. Since some of the covariates might also be on the causal pathway between RAR and incident CVD, multivariable-adjusted models were performed with and without inclusion of traditional CVD risk factors, including waist-to-hip ratio, systolic blood pressure, diabetes, antihypertensive medication use, total cholesterol, and HDL cholesterol.

Secondary analyses were performed examining the association between RAR parameters and risk of CHD, stroke, and PVD. In addition to adjusting for history of CVD in primary analyses, additional analyses were performed excluding men with a self-reported history of CHD, cerebrovascular events, and PVD. Finally, several sensitivity analyses were performed using non-log transformed actigraphy data, actigraphy data gathered in different modes (Time above threshold [TAT] and Zero Crossings Mode [ZCM]) and expressing rhythm parameters as continuous predictors, as well as adjusting for presence of sleep apnea among those who also underwent an overnight in-home polysomnography, and adjusting for total sleep time as measured by wrist actigraphy. We also performed analyses restricting the cohort to men with model fitting values (r-squared) that were above the median. Additionally, we also performed analyses using non-log transformed raw actigraphy data. For comparability across studies, the quartile cut points for non-log transformed actigraphy data were 2,908; 3,548 and 4,201counts/min for amplitude, and 1,854; 2,135 and 2,427 counts/min for mesor. Although we noticed a substantial difference in scale across the different actigraphy modes (ZCM, PIM and TAT), results from the aforementioned secondary and sensitivity analyses were essentially unchanged and remained statistically significant. Therefore, only results from our primary analyses are presented.

All analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the Study Population

A total of 3,051 participants in the MrOS Sleep Study had measurements of wrist actigraphy. Of those, 2,968 (99.2%) had complete follow-up information for CVD endpoints. Compared with the 154 men who attended the sleep visit but were not included in the analytical cohort, men in the analytical cohort were in general younger (76 vs. 78 yrs of age), had fewer IADL impairments (4% vs. 7% having 3 or more IADL impairments), had earlier acrophase times (i.e., peak activity times 14:42 vs. 15:01 h), lower amplitudes (14.7 vs. 15.01 counts/min), greater mesor (2.6 vs. 2.5 counts/min), greater F-values (1632 vs. 751), and lower betas (29 vs. 114) (data not shown).

Characteristics of the overall cohort of 2,968 men by incident CVD status are presented in Table 1. Participants wore the wrist actigraphs for an average of 4.68 ± 0.76 days (mean ± SD). The average age of the study participants was 76.3 ± 5.5 yrs (range 67–96 yrs). Men in the cohort were primarily Caucasian (90%), well educated, with 81% reporting having attended some college or beyond, and relatively healthy, with 87% reporting their health as being excellent or very good. Compared with men who did not have an incident CVD event, men who experienced an event during study follow-up were more likely to be older (77.4 vs. 76.1 yrs), report poorer health status (80% vs. 88% reporting excellent or very good health status), report more antidepressant use (11% vs. 7%), have more IADL impairments (9% vs. 3% reporting ≥3), and a history of CHD (58% vs. 33%), cerebrovascular disease (18% vs. 9%), and PVD (17% vs. 8%), and were more likely to have a higher BMI (27.6 vs. 27.1) and be less educated (73% vs. 80% reporting attending some college or beyond).

Men who experienced a CVD event during follow-up also had a significantly lower mean amplitude (1.48 vs. 1.56 counts/min), lower F-value (1338 vs. 1564), higher minimum (1.91 vs. 1.82 counts/min), and higher mesor (2.65 vs. 2.61) than men who did not experience an event. The two groups did not differ on mean alpha, beta, or acrophase (Table 1).

A total of 490 incident CVD events were recorded over the study follow-up period which averaged a mean ± SD of 4.00 ± 1.22 yrs, for a total of 11,870 person-years of follow-up. The number of events and corresponding incidence rates/1,000 person-years for each of the CVD outcomes are presented in Table 2. CHD had the greatest incidence (29.2/1000 person-years) in the cohort, and this was largely driven by coronary artery revascularization procedures (n = 156).

Rest/activity Rhythms (RARs) and Risk of Incident CVD Events

After adjustment for age group, clinic site, and race, greater risk of incident CVD events was associated with reduced amplitude (HR = 1.46, 95%CI 1.12–1.90 for Q1 vs. Q4; HR = 1.37, 95%CI 1.05–1.78 for Q2 vs. Q4) (*p* trend<.001), reduced F-value (HR = 1.48, 95%CI 1.14–1.92 for Q1 vs. Q4; HR = 1.39, 95%CI 1.07–1.80 for Q2 vs. Q4) (*p*-trend<.001), greater alpha (HR = 1.24, 95%CI 1.01–1.53 for Q4 vs. Q2–3) (*p* value = .106), and greater minimum (nadir) (HR = 1.32, 95%CI 1.01–1.72 for Q3 vs. Q1; HR = 1.49, 95%CI 1.14–1.94 for Q4 vs. Q1) (*p*-trend = .004)(data not shown).

In models further adjusting for IADL impairments, smoking status, cognitive function, use of antidepressants, walking for exercise, and history of CVD, stroke, and PVD, there was an association between reduced amplitude and greater risk of incident CVD events (*p*-trend = .036), with the greatest risk among men in Q2 compared with men in Q4 (HR = 1.31, 95%CI 1.01–1.71) (Table 3). Greater minimum was also associated with increased risk of incident

CVD events (*p*-trend = .040), with the greatest risk among men in the highest quartile (HR = 1.33, 95%CI 1.0–1.73) compared with men in the lowest quartile. Though tests for linear trend were not statistically significant (*p*-trend = .06), there was some evidence that reduced mesor (lower mean 24-h activity) was associated with a 24% risk reduction in incident CVD events for men in the lowest quartile compared with the highest quartile (HR = 0.76, 95%CI 0.58–0.98), and a 22% risk reduction for men in Q3 vs. Q4 (HR = 0.78, 95%CI 0.61–0.99) (Table 3).

Rest/activity Rhythms (RARs) and Risk of Incident CHD, Stroke, and Incident PVD Events

In multivariable-adjusted models, there was an association between quartiles of minimum activity level and risk of incident CHD (*p*-trend = .027), with the greatest risk among men in the highest quartile compared with the lowest quartile (HR = 1.39, 95%CI 1.02–1.91 for Q4 vs. Q1) (Table 3). Furthermore, there also was an association between reduced amplitude (*p*-trend = .040) and increased risk of incident CHD events, although comparisons between individual quartiles with the referent group (quartile 4) were not statistically significant.

There was evidence of linear trend across quartiles of mesor and risk of incident CHD events (*p*-trend = .024), with men in the lowest quartile having a 32% reduced risk of incident CHD events than men in the highest quartile (HR = 0.68, 95%CI 0.50–0.92) and men in Q3 having a 34% reduced risk of incident CHD events compared with Q4 (HR = 0.66, 95%CI 0.50–0.89). There was no association between categories of acrophase, alpha, and quartiles of F-value and beta with risk of incident CHD events.

Men in the lowest quartile of beta had a 78% increased risk of incident stroke compared with men in the highest quartile in multivariable adjusted models (HR = 1.78, 95%CI 1.01–3.14), although tests for linear trend across quartiles of beta were not statistically significant (*p*-trend = .083). Quartiles of amplitude, mesor, F-value, and minimum as well as categories of acrophase and alpha were not associated with increased risk of incident stroke.

Having a later occurring timing of peak activity (later acrophase) was associated with a 65% increased risk of PVD (HR = 1.65, 95%CI 1.04–2.63, *p*-value comparing Q4 with Q 2–3 = .036) in multivariable-adjusted models. Similarly, reduced circadian rhythmicity (lower F-value) was also associated with an increased risk of PVD events (*p*-trend = .009) in fully adjusted models, with the greatest risk among men in the lower two quartiles compared with the highest quartile (HR = 2.88, 95%CI 1.41–5.87 for Q1 vs. Q4, HR = 2.71, 95%CI 1.34–5.48 for Q2 vs. Q4) (*p*-trend = .007). Categories of alpha as well as quartiles of amplitude, mesor, beta, and minimum were not associated with an increased risk of PVD events.

Additional Analyses

Additional analyses excluding men who reported having a history of CHD, cerebrovascular disease, and PVD were similar to the primary analyses in that results remained statistically significant (data not shown). Our analyses used the five-parameter extended cosinor model, which had a better fit to the raw actigraphy data for 96% of men in the cohort than the traditional cosine model. The mean (SD) r-squared values for model fit for the five-parameter extended cosine model in our cohort were 0.37(0.10), and ranged from 0.006 to 0.73. To examine the effect that low model fit may be having on our estimates, we performed analyses restricting our cohort to men with model fit statistics that were above the median, and results were unchanged (data not shown).

DISCUSSION

We found that lower amplitude and higher minimum activity counts were significantly and independently associated with increased risk of incident CVD events and CHD events, and

shortened periods of daytime activity (lower beta) were independently associated with an increased risk of incident stroke; these associations were mild in magnitude. In addition, after adjustment for multiple potential confounders, reduced circadian rhythmicity (F-value) and delayed timing (acrophase) were moderately associated with increased risk of PVD events.

To our knowledge, this is the first study to examine the association between RAR parameters and risk of CVD in community-dwelling older men. These findings are generally consistent with previous studies that have reported an association between disrupted RARs and risk of CVD-related mortality in observational cohorts of older men and women. A prior analysis of a cohort of 3,027 older women enrolled in the Study of Osteoporotic Fractures (SOF) reported several associations between disrupted RAR and CVD-related mortality, including a 2.6-fold increased risk of stroke-related mortality among women with delayed peak activity times, a 2.3-fold increased risk of atherosclerotic-related mortality among women with reduced F-values, a 1.8-fold increased risk among women with reduced amplitude, and a 1.6-fold increased risk among women with reduced mesor. It also found a 2.8-fold greater risk of CHD-related mortality among women with reduced mesor (Tranah et al., 2009). Similarly, in an analysis using the MrOS Sleep cohort, we found a similar 2.3-fold increased risk of CVD-related mortality among men with reduced F-value and a 2.8-fold increased risk among men with delayed acrophase (Paudel et al., 2010). It is important to note that our earlier study was limited to mortality outcomes, and did not assess the risks associated with both fatal and nonfatal CVD events.

In contrast to earlier findings from studies examining the association between RAR parameters and death due to CVD, including CHD death and stroke death(Paudel et al., 2010; Tranah et al., 2009), we did not observe independent associations between delayed acrophase and risk of stroke or CHD events or an independent association between reduced F-value and risk of CHD events. We also ascertained incident PVD outcomes which, to our knowledge, have not been examined in prior studies of RAR parameters and CVD outcomes. However, taken in their entirety, the results of all three studies suggest that there is an increased risk of fatal and non-fatal CVD-related outcomes in older men and women with disrupted RAR's.

Although the biological mechanisms underlying the associations between disrupted RARs and increased risk of CVD are unknown, the results of this study suggest that the associations are independent of age, race, IADL impairments, smoking status, cognitive function, use of antidepressants, walking for exercise, and history of CVD, stroke, and PVD. While it is generally perceived that circadian rhythm disruptions precede CVD-related events, it is plausible that prevalent CVD disease, and/or other conditions such as diabetes, worsen circadian rhythm disruptions due to their debilitating impact on sleep/wake activity. It is also possible that circadian rhythms and conditions such as diabetes share common etiologies. We performed secondary analyses excluding men who reported having had prevalent CVD disease, and results remained statistically significant. We also adjusted for traditional CVD risk factors, such as diabetes, blood pressure, total cholesterol, and HDL cholesterol, and while the results from these analyses remained statistically significant, we did not present them to avoid over adjustment for factors that might be in the causal pathway.

A U-shaped association between levels of alpha and risk of CVD was observed in this study, although associations did not reach statistical significance. We chose the middle two quartiles of alpha as the referent group based on the observed U-shaped pattern and our prior hypotheses that extreme high values of alpha (greater nighttime vs. daytime activity that may possibly arise from a variety of factors, such as fragmented sleep, daytime inactivity,

etc.) as well as extreme low values of alpha (suggesting more daytime activity, and possibly due to insufficient rest at night), may be associated with an increased risk of CVD events. It is important to note, however, the associations between alpha and sleep duration and/or quality have not been addressed in prior research, although additional analyses adjusting for sleep duration in our cohort did not alter our results.

While a low F-value is interpreted as reduced circadian rhythmicity, it may also be indicative of circadian activity patterns that were not modeled well by the statistical approach we used. In our sample, application of the five-parameter extended cosine model explained 37% of the variation in the raw activity data (mean r-squared + SD = 0.37 + 0.11), and had a better fit to the data than the traditional cosine model, for 96% of men in the cohort. Further research is needed to determine whether alternate modeling approaches might provide improved characterization of circadian activity rhythms across population groups.

Although this study had several strengths, such as large sample size, completeness of follow-up, and use of validated measures, there were several limitations. This analysis was limited by its relatively short follow-up time of 4 yrs. The study population consisted of relatively healthy, primarily white, men over the age of 67; so, these results may not apply to other populations. Finally, RAR as measured by wrist actigraphy may be subject to masking and may be less stable than other measures of rhythms, such as melatonin or temperature (Ancoli-Israel et al., 2003). Also, we observed a couple of unexpected results, such as inconsistent trends across quartiles of amplitude, and a cardio-protective effect of lower mesor values. We feel that these spurious findings may be due to an effect of multiple comparisons, since we have several predictors and outcomes being examined in this study. Finally, several prior studies have suggested that there is a circadian component in the timing of CVD and stroke events, with a higher frequency of CVD-related events and stroke events occurring in the early morning hours (Muller et al., 1989). We did not record time of day in which CVD-related events occurred and are therefore unable to assess this in our analysis.

Conclusion

In summary, this study suggests that older men with reduced daytime/increased nighttime activity, as identified using the most appropriate statistical modeling approach we are aware of, have an increased risk of CVD-related events, which appears to be largely driven by an increased risk of CHD and stroke events. This study also suggests that older men with less robust circadian rest/activity rhythms and/or phase delays have an increased risk of PVD-related events. The biological mechanisms whereby the rest/activity rhythms of men increase their risk of CVD events require additional research, and results need to be confirmed in other populations.

Acknowledgments

The National Heart, Lung and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study "Outcomes of Sleep Disorders in Older Men" under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, R01 HL070839 and NIA AG08415. This work was also supported with resources and the use of facilities at the Minneapolis VA Medical Center.

The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

Sponsor's Role: The funding institutes had no role in the design, methods, subject recruitment, data collections, analysis and preparation of paper, or in the decision to submit the manuscript for publication.

We thank the study staff at each site and all the men who participated in MrOS Sleep.

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Table 1

Baseline characteristics of 2968 men according to CVD event status

	CVD Event (N=490)	No CVD event (2478)	*P*-value
Age group (yrs),%			<.001
64–69	5	9	
70–74	29	36	
75–79	31	28	
80+	34	26	
Caucasian,%*	92	89	.059
Education,%*			.002
Less than high school	7	5	
High School	21	15	
Some college or beyond	73	80	
Smoking status,%			.064
Current smoker	2	2	
Former smoker	63	58	
Never smoked	35	40	
Alcohol use,%			.569
<1 drink/wk	49	47	
1–13 drinks/wk	47	48	
14+ drinks/wk	5	6	
Self-reported good or excellent health status,%	80	88	<.001
Living alone,%†	15	13	.311
Caffeine use, mg/day, median (IQR)‡	172 (36–356)	180 (36–368)	.927
IADL impairments,%			<.001
None	71	81	
1–2	20	16	
3+	9	3	
BMI, kg/m^2, mean ± SD	27.6 ± 4.1	27.1 ± 3.8	.014
Waist-to-hip ratio, mean ± SD	0.974 ± 0.061	0.967 ± 0.063	.013
3MS Score, 0–100, median (IQR)‡	94 (89–97)	94 (91–97)	.002
Depressed (GDS665 ≥ 6),%	8	6	.145
Use of antidepressants,%	11	7	.002
Use of benzodiazepines,%	6	4	.182
Use of non-benzodiazepine anxiolytic/hypnotics,%	2	2	.928
Walks regularly for exercise,%	45	47	.311
Diabetic,%	20	12	<.001
Systolic Blood Pressure mmHg, mean ± SD	129 ± 18	126 ± 16	<.001
Use of Hypotensive agents,%	7	4	.008
Total Cholesterol, mg/dl, mean ± SD*	189 ± 34	195 ± 34	<.001

	CVD Event (N=490)	No CVD event (2478)	*P*-value
HDL, mg/dl, median (IQR)*‡	45 (37–53)	47 (40–57)	<.001
COPD/emphysema,%	22	16	.056
Parkinsons disease,%	11	17	.380
Apnea Hypopnea Index, median (IQR)‡	7.0 (3.5–12.9)	6.3 (2.9–12.7)	.118
History of CVD,%	58	33	<.001
History of TIA or Stroke,%	18	9	<.001
History of PVD,%	17	8	<.001
Acrophase, mean ± SD	14:43 ± 1:27	14:42 ± 1:06	.660
Amplitude, mean ± SD	1.48 ± 0.67	1.56 ± 0.55	.004
Mesor, mean ± SD	2.65 ± 0.25	2.61 ± 0.26	.001
F-value, median (IQR)‡	1338 (872–1950)	1564 (1028–2162)	<.001
Alpha, mean ± SD	−0.43 ± 0.24	−0.45 ± 0.20	.066
Beta, median (IQR)‡	13.6 (7.7–27.9)	13.8 (7.8–27.0)	.808
Minimum, mean ± SD	1.91 ± 0.51	1.82 ± 0.50	<.001

SD = Standard Deviation; IQR = Interquartile range; IADL = Instrumental Activities of Daily Living; BMI = Body Mass Index; 3MS = Teng-Modified Mini-Mental Examination Score; GDS = Geriatric Depression Scale; CVD = Cardiovascular Disease; TIA = Transient Ischemic Attack; PVD = Peripheral Vascular Disease.

*Measurements obtained at baseline study visit an average of 3.2 yrs earlier.

†Measurement obtained at interim study visit an average of 1.4 yrs earlier.

‡Kruskall-wallis test used to calculate *p*-value.

Table 2

Frequency of cardiovascular disease (CVD) events

Endpoint	Number of events	Incidence rate*
CVD†	**490**	**41.3**
Coronary Heart Disease (CHD)	**356**	**29.2**
Acute myocardial infarction	17	1.4
ST elevation MI	24	2.0
Non-ST elevation MI	77	6.3
Sudden CHD death (<1 h, non-traumatic)	26	2.1
Coronary artery bypass surgery	66	5.4
Coronary revascularization procedures	156	12.8
Hospitalization for unstable angina	90	7.4
Ischemic congestive heart failure	51	4.2
Other CHD event	47	3.8
Stroke	**86**	**6.7**
Peripheral vascular disease (PVD)	**101**	**7.9**
Acute arterial occlusion	11	0.9
Acute arterial rupture	4	0.3
Acute arterial dissection	2	0.2
Vascular surgery	92	7.2
Number of CVD events‡		
0	2478	
1	440	
2	47	
3	3	

*Crude (per 1000 person-years)

†Cardiovascular Disease (CVD) comprised of composite outcomes coronary heart disease (CHD), stroke, and peripheral vascular disease (PVD).

‡Numbers presented are number of events, not number of subjects with event. By definition, men in this study who had an event may meet the criteria for more than one CVD event.

Table 3

Rest/activity rhythms (RARs) and risk of incident CVD, coronary heart disease, stroke, and peripheral vascular disease events

		Hazard Ratios (HRs) and 95% confidence intervals			
	Range of values	**CVD*†**	**Coronary Heart Disease†**	**Stroke†**	**Peripheral Vascular Disease‡**
Acrophase					
Q 1	≤14.06 h	1.18 (0.95–1.46)	1.04 (0.80–1.34)	1.27 (0.78–2.06)	1.32 (0.80–2.17)
Q 2–3	14.07–15.33 h	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q 4	≥15.34 h	1.02 (0.81–1.27)	0.95 (0.73–1.24)	0.66 (0.36–1.19)	1.65 (1.04–2.63)
P-value§		.308	.849	.126	.107
Amplitude¶					
Q 1	≤1.18	1.24 (0.95–1.63)	1.30 (0.95–1.78)	0.85 (0.45–1.59)	1.52 (0.82–2.80)
Q 2	1.19–1.48	1.31 (1.01–1.71)	1.36 (1.00–1.86)	1.21 (0.68–2.16)	1.45 (0.79–2.64)
Q 3	1.49–1.83	1.02 (0.77–1.35)	1.05 (0.75–1.46)	0.70 (0.36–1.35)	1.30 (0.69–2.47)
Q 4	≥1.84	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
p-trend		.036	.040	.934	.180
Mesor#					
Q 1	≤2.45	0.76 (0.58–0.98)	0.68 (0.50–0.92)	0.98 (0.55–1.75)	0.94 (0.51–1.72)
Q 2	2.46–2.63	0.86 (0.67–1.09)	0.78 (0.59–1.03)	0.85 (0.46–1.54)	1.15 (0.65–2.03)
Q 3	2.64–2.79	0.78 (0.61–0.99)	0.66 (0.50–0.89)	0.73 (0.40–1.34)	1.41 (0.84–2.38)
Q 4	≥2.80	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
p-trend		.061	.024	.958	.722
F-value					
Q 1	≤994	1.15 (0.88–1.50)	0.99 (0.72–1.35)	0.87 (0.45–1.67)	2.88 (1.41–5.87)
Q 2	995–1524	1.23 (0.95–1.61)	1.14 (0.84–1.55)	1.14 (0.62–2.09)	2.71 (1.34–5.48)
Q 3	1525–2135	0.89 (0.67–1.18)	0.81 (0.59–1.13)	0.97 (0.52–1.83)	2.04 (0.98–4.22)
Q 4	≥2136	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
p-trend		.094	.580	.804	.009
Alpha					
Q 1	<−0.55	1.05 (0.84–1.31)	0.93 (0.72–1.22)	0.79 (0.45–1.38)	1.44 (0.89–2.32)
Q 2–3	−0.55—0.37	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)

	Range of values	Hazard Ratios (HRs) and 95% confidence intervals			
		CVD*†	Coronary Heart Disease†	Stroke†	Peripheral Vascular Disease‡
Q 4	>−0.37	1.17 (0.95–1.45)	1.09 (0.85–1.40)	1.11 (0.68–1.82)	1.32 (0.82–2.13)
p-value§		.329	.576	.539	.273
Beta					
Q 1	<7.77	1.08 (0.84–1.40)	1.06 (0.78–1.43)	1.78 (1.01–3.14)	1.14 (0.65–2.01)
Q 2	0.77–13.77	1.07 (0.83–1.38)	1.18 (0.88–1.58)	0.85 (0.44–1.66)	1.25 (0.71–2.18)
Q 3	13.78–27.04	1.02 (0.79–1.32)	1.05 (0.78–1.41)	1.09 (0.59–2.03)	0.96 (0.54–1.73)
Q 4	>27.04	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
p-trend		.503	.549	.083	.478
Minimum					
Q 1	≤1.55	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Q 2	1.56–1.88	1.17 (0.89–1.53)	1.14 (0.82–1.58)	1.21 (0.66–2.22)	1.16 (0.62–2.18)
Q 3	1.89–2.17	1.24 (0.94–1.62)	1.30 (0.94–1.78)	1.04 (0.56–1.95)	1.45 (0.80–2.61)
Q 4	≥2.18	1.33 (1.01–1.73)	1.39 (1.02–1.91)	0.98 (0.51–1.86)	1.33 (0.72–2.43)
p-trend		.040	.027	.809	.292

CI = confidence interval.

N = 2962 in multivariable-adjusted models.

*CVD is a composite of Coronary Heart Disease, Stroke, and Peripheral Vascular Disease Events.

†Model adjusted for age groups, clinic site, race/ethnicity, IADL impairments, smoking status, cognitive impairment, use of antidepressants, walking for exercise, and history of CVD, PVD, and stroke.

‡Model adjusted for age groups, clinic site, race/ethnicity, IADL impairments, smoking status, cognitive impairment, use of antidepressants, walking for exercise, and history of PVD.

§*p*-value presented is from a 4 df test.

¶Amplitude = Maximum modeled activity value – minimum modeled activity value in units of counts/min

#Mesor = minimum + amplitude/2 in units of counts/min