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Authors

Xiao, Qian
Sampson, Joshua N
LaCroix, Andrea Z
et al.

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OXFORD

Original Article

Nonparametric Parameters of 24-Hour Rest–Activity Rhythms and Long-Term Cognitive Decline and Incident Cognitive Impairment in Older Men

Qian Xiao, PhD,[1,*] Joshua N. Sampson, PhD,[2] Andrea Z. LaCroix, PhD,[3] Aladdin H. Shadyab, PhD,[3] Jamie M. Zeitzer, PhD,[4,5] Sonia Ancoli-Israel, PhD,[6] Kristin Yaffe, MD,[7] Katie Stone, PhD,[8] and Osteoporotic Fractures in Men (MrOS) Study Group

[1]Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, USA. [2]Division of Cancer Epidemiology & Genetics, National Cancer Institute, Rockville, Maryland, USA. [3]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, USA. [4]Department of Psychiatry and Behavioral Sciences, Stanford University, California, USA. [5]Mental Illness Research Education and Clinical Center, VA Palo Alto Health Care System, California, USA. [6]Department of Psychiatry, Center for Circadian Biology, University of California, San Diego, La Jolla, USA. [7]Department of Psychiatry, Neurology, and Epidemiology and Biostatistics, University of California, San Francisco, USA. [8]Research Institute, California Pacific Medical Center, San Francisco, USA.

*Address correspondence to: Qian Xiao, PhD, Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, 1200 Pressler St., Houston, TX 77030, USA. E-mail: qian.xiao@uth.tmc.edu

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Abstract

Altered 24-hour rest–activity rhythms may be associated with cognitive impairment in older adults, but evidence from prospective studies is limited. Nonparametric methods were used to assess actigraphy-based activity patterns in 2 496 older men. Incident cognitive impairment was assessed 4 times over 12 years using the Modified Mini-Mental State Examination (3MS) and Trails B tests, self-reported medication use, and clinical diagnosis. The highest quartile (vs the lowest) of intradaily variability and the lowest quartiles (vs the highest) of interdaily stability and relative amplitude were associated with incident cognitive impairment (hazard ratio [95% confidence interval]: 1.82 [1.31–2.53], 1.36 [0.99–1.86], and 1.85 [1.33–2.56], respectively). A larger increase in intradaily variability over 7.5 years was associated with a greater subsequent decline in 3MS scores but not in Trails B performance. In conclusion, less stable and more variable rest–activity rhythms may represent early biomarkers of cognitive impairment in older men.

Keywords: Circadian rhythms, Cognitive impairment, Dementia, Older adults, Rest and activity

Dementia is a highly debilitating syndrome characterized by deterioration in various domains of cognitive functioning, such as memory, language, problem-solving, attention, and executive function (1). Risk factors for dementia include advanced age, low education, genetics, and various cardiometabolic conditions (2–6). On the other hand, multiple behaviors, including Mediterranean-type diet (7), physical activity (8), and cognitively stimulating activities, are associated with a lower likelihood of dementia (9). Despite the substantial progress made in this field, the etiology of dementia remains poorly understood, and there is a critical need to identify novel modifiable risk factors for disease prevention. Moreover, there is growing interest in using personal devices to develop biomarkers for risk prediction (10).

Altered sleep and circadian patterns may be associated with dementia (11). For example, longitudinal studies of older adults reported that various forms of sleep deficiency, including short or long sleep (12), excessive daytime sleepiness (13, 14), and lower sleep efficiency and longer sleep latency (15, 16), were associated with

cognitive decline and dementia. Although sleep deficiency may serve as an indicator of circadian dysfunction, sleep characteristics alone do not capture the complex 24-hour rest–activity patterns orchestrated by the circadian timing system.

A growing number of studies have used actigraphy data to examine 24-hour rest–activity characteristics in relation to cognitive outcomes in older adults. Of these, most were cross-sectional and only a handful studied the prospective association between rest–activity rhythms and cognitive outcomes (17). For example, analyses from 2 cohorts of older US men and women reported that a lower amplitude, altered activity timing, and reduced robustness of overall rhythmicity were associated with greater cognitive decline and risk of incident dementia (18–20). However, all of the previous studies measured rest and activity at a single time point, and no study has examined whether changes in rest–activity rhythms over time were associated with cognitive outcomes, which is critical to elucidating temporal relationships. Moreover, the follow-up duration of these studies was relatively short (3–5 years), and it is unclear to what extent rest–activity characteristics can predict long-term changes in cognitive outcomes. Finally, all of the studies used parametric algorithms (ie, cosine-based models) to derive rest–activity parameters (21). However, cosine-based models do not produce measures such as rhythm fragmentation and stability, 2 key rest–activity characteristics that have been consistently linked with dementia in cross-sectional studies (17). To the best of our knowledge, the only study that examined nonparametric rest–activity characteristics in relation to long-term (ie, up to 11 years of follow-up) cognitive outcomes is a recent analysis in the Rotterdam Study, which reported null associations but did not examine changes in rest–activity patterns (22). Therefore, there is a need to further investigate the prospective relationship between rest–activity rhythms and cognitive outcomes in older adults.

In the well-characterized Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep), we examined nonparametric rest–activity parameters, including rhythm variability and stability, in relation to incident cognitive impairment and changes in cognitive performance over 12 years of follow-up. In a subset of participants with repeated measures of rest–activity rhythms, we also examined if changes in rhythms over the first ~7.5 years in the follow-up predicted subsequent cognitive decline. We hypothesized that weakened baseline rhythmicity and greater decline in rhythmicity over time would be associated with incident cognitive impairment.

Method

Study Population

MrOS Sleep is an ancillary study of the parent Osteoporotic Fractures in Men Study (MrOS, https://mrosonline.ucsf.edu/), a multicenter cohort study of community-dwelling older men (23, 24). Participants were recruited from 6 clinical centers located in Birmingham, AL; Minneapolis, MN; Palo Alto, CA; the Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA. The main objective of MrOS Sleep was to investigate the role of sleep and rest–activity rhythms in a wide range of health outcomes in older adults (25). MrOS Sleep enrolled participants between 2003 and 2005 and collected information on sociodemographic characteristics, lifestyle behaviors, and disease history. Cognitive assessments were performed at baseline and 4 follow-up visits in 2005–2006, 2007–2009, 2009–2012, and 2014–2016. Actigraphy data were obtained both at baseline (Sleep Visit 1) and in a subsample of participants in the 2009–2012 visit (Sleep Visit 2). Both the MrOS and MrOS Sleep studies were approved by the Institutional Review Boards at all participating field sites, and written informed consent was obtained from each participant prior to enrollment.

Supplementary Figure 1 shows a flowchart for deriving analytic samples. Of the original 5 994 MrOS participants, 3 135 enrolled in MrOS Sleep. We excluded 146 participants with invalid actigraphy data and/or missing rest–activity parameters, 148 with missing or impaired cognitive performance at baseline (defined as using medication for Alzheimer's disease [AD] treatment and/or had a Modified Mini-Mental State [3MS] test score <80), and 121 with no follow-up visit. We also excluded cognitive impairment cases that occurred within 2 years after the baseline visit (n = 224) to minimize reverse causation. The study sample for the analysis focusing on baseline rest–activity rhythms included 2 496 men. For the analysis focusing on *changes* in rest–activity rhythms, we additionally excluded those who were not in Sleep Visit 2 (n = 1 536), had no measure of change in the rest–activity parameters intradaily variability (IV) and interdaily stability (IS; n = 17), developed cognitive impairment before Sleep Visit 2 (n = 106), or had no data on change in cognitive scores after Sleep Visit 2 (n = 265), resulting in a sample size of 572.

Rest–Activity Rhythm Characteristics

At baseline, MrOS participants wore a SleepWatch-O actigraph (Ambulatory Monitoring, Inc., Ardsley, NY) on the nondominant wrist for 5 consecutive 24-hour periods (4.8 ± 0.8). The orientation and sensitivity of the device were optimized for highly effective sleep-wake inference (26, 27). We derived nonparametric parameters of rest–activity rhythms using the method developed by Van Someren et al. (21). These parameters included (a) IV, defined as the ratio between the mean squares of the difference between all successive hours and the MS around the overall mean, with a higher value indicating more fragmented rest–activity rhythms; (b) IS, defined as the ratio between the variance of activity around the mean at each hour and the overall variance, with a lower value indicating less stable rhythmicity; (c) L5, defined as mean hourly activity during the 5 consecutive hours with the least activity; (d) M10, defined as mean hourly activity in the 10 consecutive hours with the highest activity; (e) midpoint in time of L5; (f) midpoint in time of M10; and (g) relative amplitude (RA), defined as (M10 – L5)/(M10 + L5), with a higher value indicating relatively higher activity during waking hours and lower activity when resting/sleeping.

At Sleep Visit 2, MrOS participants wore the Actiwatch 2 (Philips Respironics, Inc., Murrysville, PA) on the nondominant wrist for 5 consecutive 24-hour periods (4.7 ± 0.6). All the aforementioned rest–activity parameters were derived for this visit; however, due to differences in the measurement of activity amplitude by the 2 devices, not all parameters can be directly compared with baseline measures. As such, we focused on changes in IV and IS, as these 2 parameters are the main indicators of overall rhythmic patterns and are relative measures that do not dependent on the amplitude units of the 2 different devices.

Cognitive Outcomes

Cognitive performance was assessed using the 3MS and Trails B tests. The 3MS test is a brief, general cognitive battery including components for orientation, concentration, language, praxis, and immediate and delayed memory with scores ranging from 0 to 100, where higher scores indicate better global cognitive functioning (28). Trails B is a timed test of processing speed that measures attention,

sequencing, visual scanning, and executive function, where shorter time or lower scores represent better executive function (29). Study participants also reported medication use by bringing all prescription medications used within the past 30 days to the visit. Dementia medication use was categorized based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA) (30). Participants also reported if they had been diagnosed with dementia. Based on criteria published previously in MrOS (31), we defined cognitive impairment as having one or more of the following conditions in any follow-up visit: (a) a decline in 3MS scores of 1.5 *SD* or more since baseline; (b) use of medication for treating dementia; or (c) a self-reported physician diagnosis of dementia. In sensitivity analysis, we also used the latter 2 criteria alone to define dementia cases to assess the relationship between rest–activity rhythms and more severe cognitive outcomes. In addition, 3MS and Trails B scores were also analyzed as continuous outcomes to assess changes in cognitive performance over time.

Covariates

At baseline and at Sleep Visit 2, participants reported sociodemographic information, health behaviors, self-rated health status, and comorbidities. Depressive symptoms at baseline were determined using the Geriatric Depression Scale, with a score of ≥6 indicative of depression (32). Height and weight were measured at baseline, and body mass index (BMI, kg/m^2) was calculated as weight divided by height squared. Use of prescription sleep medication was classified using the IDIS medication coding dictionary. The dates of actigraphy data collection were used to classify the season. The Physical Activity Scale for the Elderly questionnaire was used to assess physical activity levels (33). From the actigraphy data, we also derived average total sleep time, sleep efficiency, and daytime napping duration using standard algorithms (15, 31).

Statistical Analysis

We derived quartiles for baseline IV, IS, RA, L5, M10, and changes in IV and IS. Because prior studies have reported U-shaped associations between acrophase and dementia (18), we examined the midpoints of M10 and L5 in 3-group categories (early, <mean – 1 *SD*; normal, mean ± 1 *SD*; and late, >mean + 1 *SD*). We chose the group hypothesized as having the lowest risk for cognitive impairment as the reference (Q1 for IV and changes in IV and L5; Q4 for IS, changes in IS, RA, and M10; and normal for a midpoint of L5 and M10). We evaluated the relationship between each rest–activity characteristic and the risk of cognitive impairment using Cox proportional hazards regression models and reported hazard ratios (HRs) and 95% confidence intervals (CIs). The follow-up time included the 4 discrete follow-up visits, with individuals censored at the time of the cognitive event or the date of the last visit, whichever came sooner.

We presented results from 3 models. Model 1 was the base model adjusted for age and 3MS scores at baseline. Model 2, which we consider as our main model, was additionally adjusted for potential confounders measured at baseline that could affect both rest–activity rhythms and cognitive outcomes, including season of actigraphy measurement, clinical site, race, education, BMI, smoking, alcohol use, coffee consumption, depression, hypertension, diabetes, cardiovascular disease, self-reported health, and use of sleep medication. Finally, in Model 3, which we consider as a sensitivity analysis, we additionally adjusted for physical activity, total sleep time, sleep efficiency, and daytime napping duration to assess whether the findings were robust against the individual components of the rest–activity cycle (ie, physical activity and sleep).

We evaluated the relationship between each rest–activity characteristic and the trajectories of the 3MS and Trails B test scores using mixed-effects linear regression models adjusting for the covariates in Model 2. Log transformation was performed on Trails B scores to improve the normality of the distribution, and the results were back-transformed to the original scale. The models included both linear and quadratic terms of follow-up time and an interaction term between rest–activity parameters and the linear term of follow-up time, because these terms were statistically significant ($p < .001$) in at least one model.

We used linear regression to evaluate if changes in rest–activity characteristics between the 2 Sleep visits (2003–2005, 2009–2012; mean duration between assessments = 7.5 years) were associated with subsequent changes in cognitive scores between the final 2 visits (2009–2012, 2014–2016; mean follow-up 4.1 years). Models 1 and 2 were adjusted for the same variables as described above, using information obtained in Sleep Visit 2 (except for education and race, which were only collected at baseline, and season, which included the season of data collection in both Sleep visits as 2 separate covariates). Model 3 was additionally adjusted for baseline IV and IS. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

We present baseline characteristics of the study population according to the quartiles of IV in Table 1. Those with higher IV (greater fragmentation of activity) were older and more educated. They also had lower coffee intake, higher alcohol consumption, higher BMI, lower levels of physical activity, shorter average total sleep time, poorer sleep efficiency, longer napping, worse self-rated health and a higher prevalence of CVD, hypertension, diabetes, depression, and sleep medication use.

Table 2 presents the association between rest–activity parameters and risk for developing cognitive impairment. Over an average follow-up of 6.8 ± 3.7 years, 354 (14.2%) men developed cognitive impairment. Higher IV, lower IS, and smaller RA were all associated with a higher risk of incident cognitive impairment and the associations persisted with slight attenuation after adjusting for multiple confounders (Model 2, p value for trend, .0001, .05, and .001, respectively). Specifically, when compared to those in the lowest quartile of IV, those in the highest quartile (greatest fragmentation) were 82% more likely to develop cognitive impairment over follow-up (HR [95% CI], 1.82 [1.31–2.53]). For IS and RA, when compared to the highest quartiles, the lowest quartiles (least regular, lowest amplitude) were associated with 36% and 83% higher risk, respectively (1.36 [0.99–1.86] for IS, and 1.83 [1.13–2.95] for RA). We also found an association between higher L5 (greater nighttime levels of activity) and elevated risk of cognitive impairment ($HR_{Q4\ vs\ Q1}$ [95% CI], 1.60 [1.17–2.18], p value for trend, .01), but no association for M10 (daytime activity levels) or the temporal midpoint of L5 and M10. Adjusting for sleep and physical activity variables overall led to similar findings (Model 3). Finally, results from using more severe cognitive outcomes (self-reported dementia diagnosis and use of dementia medication) are presented in Supplementary Table 1. A total of 153 (6.1%) participants developed dementia according to self-reported diagnosis or use of dementia medications. Overall, the results were largely similar to the results focusing on cognitive impairment using the original definition, but only the results for IV remained statistically significant with this new definition.

Table 1. Baseline (2003–2005) Characteristics by Quartiles of Intradaily Variability in the MrOS Sleep Study

	Intradaily Variability				
	Q1 (*N* = 624)	Q2 (*N* = 624)	Q3 (*N* = 624)	Q4 (*N* = 624)	*p**
Age, years, mean ± *SD*	74.5 ± 4.6	75.0 ± 4.9	76.1 ± 5.4	77.6 ± 5.5	<.0001
Education, college or higher, *N* (%)	328 (52.6)	364 (58.3)	361 (57.8)	393 (63.0)	.001
White, *N* (%)	576 (92.3)	562 (90.1)	564 (90.4)	575 (92.1)	.36
Nonsmoker, *N* (%)	234 (37.5)	236 (37.8)	255 (40.9)	264 (42.3)	.39
Alcohol intake, <1 drinks/week, *N* (%)	257 (41.4)	281 (45.2)	289 (46.5)	301 (48.3)	.03
Noncoffee drinker, *N* (%)	219 (35.1)	255 (40.9)	274 (43.9)	312 (50.0)	<.0001
Body mass index, kg/m^2, mean ± *SD*	27.0 ± 3.4	27.2 ± 3.9	27.3 ± 3.8	27.7 ± 4.2	.01
PASE physical activity score, mean ± *SD*	167.4 ± 70.9	157.9 ± 72.5	145.1 ± 65.0	123.3 ± 64.6	<.0001
Total sleep time, min, mean ± *SD*	400.7 ± 61.1	388.9 ± 66.2	382.5 ± 71.0	365.4 ± 85.1	<.0001
Sleep efficiency, %, mean ± *SD*	80.8 ± 8.8	79.1 ± 10.7	78.8 ± 11.2	75.5 ± 14.9	<.0001
Daily napping, min, mean ± *SD*	29.0 ± 32.1	40.6 ± 36.7	55.2 ± 41.9	87.6 ± 63.9	<.0001
Use of sleep medication, *N* (%)	30 (4.8)	28 (4.5)	42 (6.7)	50 (8.0)	.03
Self-rated health good/excellent, *N* (%)	562 (90.1)	557 (89.3)	551 (88.3)	511 (81.9)	<.0001
Disease history, *N* (%)					
Cardiovascular disease	193 (30.9)	208 (33.3)	207 (33.2)	272 (43.6)	<.0001
Hypertension	280 (44.9)	302 (48.4)	319 (51.1)	336 (53.8)	.01
Diabetes	71 (11.4)	93 (14.9)	79 (12.7)	102 (16.3)	.05
Depression	49 (7.9)	69 (11.1)	67 (10.7)	95 (15.2)	.001
Season of actigraphy data collection, *N* (%)					.05
Winter (December–February)	154 (24.7)	173 (27.7)	180 (28.8)	185 (29.6)	
Spring (March–May)	172 (27.6)	180 (28.8)	148 (23.7)	174 (27.9)	
Summer (June–August)	138 (22.1)	136 (21.8)	168 (26.9)	140 (22.4)	
Fall (September–November)	160 (25.6)	135 (21.6)	128 (20.5)	125 (20.0)	
3MS score (range 0–100), mean ± *SD*	93.9 ± 4.2	93.8 ± 4.3	93.6 ± 4.4	93.4 ± 4.6	.21
Trails B Score, seconds (range 0–300), mean ± *SD*	107.8 (42.9)	110.9 (44.2)	115.1 (47.7)	123.2 (54.8)	<.0001

Note: MrOS = Osteoporotic Fractures in Men Study; 3MS = Modified Mini-Mental State examination; PASE = Physical Activity for the Elderly; SD = standard deviation.

**p* values for categorical variables were derived from a chi-square test. *p* values for continuous variables were derived from analysis of variance for normally distributed variables or a Kruskal–Wallis test for skewed data.

The analysis examining trajectories of 3MS (Figure 1) and Trails B (Figure 2) scores produced results largely consistent with those for cognitive impairment. Relative to other quartiles, the highest quartile of IV and the lowest quartile of RA showed the steepest decline in 3MS scores (*p*-interaction with time of follow-up, .0003 for IV and .0002 for RA) and lower RA was also associated with a more rapid increase in Trails B scores (.001). In addition, we found that a lower M10 was associated with a greater decline in both tests (*p*-interaction, <.0001). In contrast, the differences among trajectories were less pronounced for IS, L5, and midpoints of L5 and M10.

Associations of changes in IV and IS with changes in cognitive scores are given in Table 3. On average, MrOS participants experienced an increase in IV (0.26 ± 0.23) and a decrease in IS (−0.11 ± 0.12) over the 7.5 ± 0.7 years between baseline and Sleep Visit 2, suggesting weakened rhythmicity as they aged. A larger increase in IV was associated with a greater decline in 3MS score after Sleep Visit 2 ($\beta_{Q4\ vs\ Q1}$ [95% CI], −1.46 [−2.60, −0.32], *p* for trend, 0.01), and adjusting for baseline level of IV had little impact on the results. No association was found between changes in IS and decline in 3MS or between changes in IV or IS and increases in Trails B test completion time.

Discussion

In a cohort of older men, we found that some, but not all, rest–activity rhythm characteristics were associated with risk of cognitive impairment and decline in cognitive function. In particular, greater rhythm fragmentation (IV) at baseline and a larger increase in fragmentation were associated with a higher risk of developing cognitive impairment and more rapid cognitive decline. Moreover, men with less rhythm stability (IS), lower difference between nighttime and daytime activity (RA), and higher levels of nighttime activity (L5) at baseline were more likely to develop cognitive impairment relative to men with more robust daily activity patterns. Overall, our results suggest that a weakened rest–activity profile may be a risk factor for poor cognitive outcomes and potentially serve as a biomarker of cognitive health in older men.

Our results on the association of RA, a nonparametric measure similar to cosinor amplitude, with cognitive decline support earlier analyses in the MrOS study that found that cosine-based measures of rest–activity rhythms were associated with greater decline in 3MS over up to 5.3 years of follow-up (20). In older women in the Study of Osteoporotic Fractures cohort, lower amplitude and weakened overall rhythmicity derived from extended cosine models at baseline were associated with a higher risk of developing dementia or mild cognitive impairment and decline in Trails B test performance over ~5 years (18, 19). Overall, our results are consistent with these earlier findings, with the added advantage of a longer follow-up period of 12.3 years. Moreover, while all studies excluded participants with evident cognitive impairment at baseline, the present study also excluded those who developed the condition within the first 2 years of follow-up to minimize reverse causation. Although we cannot exclude the possibility that preclinical impairment of cognition existed

Table 2. Associations Between Baseline (2003–2005) Rest–Activity Rhythm Parameters and Incidental Cognitive Impairment Over Follow-Up (2003–2016)

Rest–Activity Rhythm Parameters		Cognitive Impairment			
			HR (95% CI)		
Categories	Median (IQR)	*N* (%)	Model 1	Model 2	Model 3
Intradaily variability					
Q1	0.43 (0.39–0.46)	64 (10.3)	ref	ref	ref
Q2	0.56 (0.53–0.59)	83 (13.3)	1.33 (0.96–1.84)	1.29 (0.93–1.80)	1.27 (0.90–1.78)
Q3	0.68 (0.64–0.71)	100 (16.0)	1.57 (1.14–2.15)	1.59 (1.15–2.19)	1.55 (1.10–2.19)
Q4	0.85 (0.80–0.96)	106 (17.0)	1.86 (1.35–2.55)	1.82 (1.31–2.53)	1.67 (1.15–2.42)
p for trend			<.0001	.0001	.004
Interdaily stability					
Q1	0.63 (0.57–0.66)	92 (14.7)	1.39 (1.03–1.89)	1.36 (0.99–1.86)	1.15 (0.81–1.64)
Q2	0.72 (0.70–0.74)	94 (15.1)	1.22 (0.90–1.66)	1.20 (0.88–1.63)	1.06 (0.76–1.47)
Q3	0.78 (0.77–0.80)	92 (14.7)	1.11 (0.82–1.51)	1.10 (0.81–1.51)	1.06 (0.77–1.45)
Q4	0.84 (0.83–0.87)	75 (12.0)	ref	ref	ref
p for trend			.03	.05	.47
Relative amplitude*					
Q1	0.75 (0.68–0.78)	101 (16.2)	1.88 (1.37–2.58)	1.85 (1.33–2.56)	1.83 (1.13–2.95)
Q2	0.83 (0.81–0.84)	86 (13.8)	1.47 (1.07–2.03)	1.46 (1.05–2.02)	1.60 (1.07–2.39)
Q3	0.87 (0.86–0.88)	98 (15.7)	1.52 (1.11–2.08)	1.57 (1.14–2.16)	1.72 (1.21–2.44)
Q4	0.91 (0.90–0.93)	68 (10.9)	ref	ref	ref
p for trend			.0002	.001	.03
L5, activity count/min					
Q1	180.7 (151.1–207.0)	79 (12.7)	ref	ref	ref
Q2	271.2 (250.0–295.3)	91 (14.6)	1.19 (0.88–1.61)	1.20 (0.88–1.64)	1.30 (0.91–1.85)
Q3	369.5 (340.9–404.1)	87 (13.9)	1.10 (0.81–1.50)	1.09 (0.80–1.49)	1.27 (0.83–1.95)
Q4	546.9 (481.2–660.2)	96 (15.4)	1.58 (1.17–2.13)	1.60 (1.17–2.18)	1.63 (0.98–2.72)
p for trend			.01	.01	.09
L5 midpoint, HH:MM†					
Early	01:03 (00:34, 01:18)	57 (15.0)	1.27 (0.95–1.70)	1.27 (0.94–1.71)	1.24 (0.92–1.68)
Medium	02:53 (02:19, 03:30)	247 (14.3)	ref	ref	ref
Late	04:43 (04:29, 05:11)	49 (12.7)	0.98 (0.72–1.34)	0.92 (0.67–1.27)	0.89 (0.64–1.23)
M10, activity count/min					
Q1	3 059 (2 765–3 298)	108 (17.3)	1.42 (1.06–1.89)	1.28 (0.94–1.75)	1.18 (0.83–1.70)
Q2	3 759 (3 625–3 867)	83 (13.3)	1.04 (0.76–1.42)	0.98 (0.72–1.35)	0.94 (0.67–1.31)
Q3	4 234 (4 109–4 365)	79 (12.7)	1.01 (0.74 (1.37)	0.98 (0.72–1.34)	0.96 (0.69–1.32)
Q4	4 876 (4 683–5 204)	83 (13.3)	ref	ref	ref
p for trend			.02	.13	.42
M10 midpoint, HH:MM†					
Early	11:08 (10:40, 11:25)	48 (14.9)	1.09 (0.80–1.49)	1.06 (0.77–1.45)	0.99 (0.71–1.37)
Medium	13:06 (12:27, 13:51)	261 (14.3)	ref	ref	ref
Late	15:48 (15:17, 16:47)	44 (12.8)	1.02 (0.74–1.41)	1.04 (0.75–1.44)	1.06 (0.77–1.47)

Notes: CI = confidence interval; IQR = interquartile range; 3MS = Modified Mini-Mental State examination; L5 = activity during the least active 5 hours; M10 = activity during the most active 10 hours; OR = odds ratio; PASE = Physical Activity Scale for the Elderly. Model 1: adjusted for age (≤70, >70–75, >75–80, >80–85, >85) and baseline 3MS score (continuous). Model 2: adjusted for variables in Model 1 and study site (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; San Diego, CA), education (less than high school, high school, some college, college, more than college), race (White, non-White), body mass index (<25, 25–<30, 30+), smoking status (current, past, never), alcohol consumption (<1, 1–13, 14+ drink/week), coffee intake (0, 1, 2, >2 cups/day), self-reported health (good or excellent, fair or lower), depression (yes, no), diabetes (yes, no), hypertension (yes, no), cardiovascular disease (yes, no), sleep medication use (yes, no), and the season of actigraphy data collection (Dec–Feb, Mar–May, Jun–Aug, and Sep–Nov). Model 3: adjusted for variables in Model 2 and PASE scores, total sleep time, sleep efficiency, and daytime napping (all in quartiles).

*Relative amplitude was calculated as (M10 – L5)/(M10 + L5).

†Early and late groups were defined as mean – 1 *SD* and mean + 1 *SD*, respectively.

in some participants years before the onset of symptoms, our findings suggest that rhythm disruption is unlikely a mere manifestation of dementia pathology, but may well precede cognitive impairment and thus could serve as an early biomarker of disease risk.

Our study extended the existing literature by identifying additional rest–activity patterns, particularly IV and IS, as potentially important risk factors for cognitive decline. Notably, our findings contrast with those from a recent analysis in the Rotterdam Study, which reported no association between baseline IV and IS and incident dementia in 1 322 older men and women (22). Although our study was similar to the Rotterdam Study with regard to rest–activity measurements, there are several differences that may have contributed to these inconsistent findings. For outcome assessment, the Rotterdam Study used a more stringent definition, only including those with severe impairment in cognitive performance (eg, 3MS score <26) or AD diagnosis as dementia cases. In total, they identified

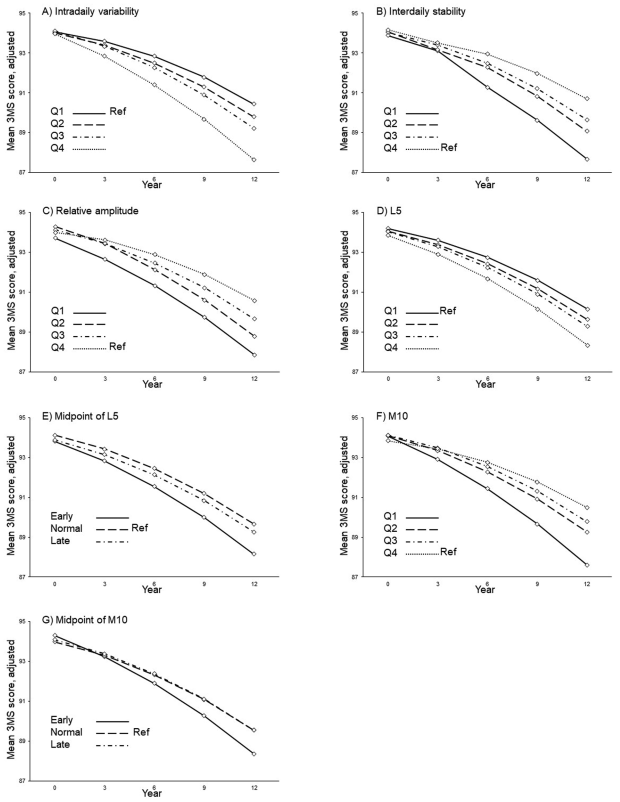

Figure 1. Trajectories of 3MS scores by categories of rest–activity rhythm parameters. Models were adjusted for age, season of actigraphy measurement, clinical site, race, education, body mass index, smoking, alcohol, coffee, depression, hypertension, diabetes, cardiovascular disease, self-reported health, and use of sleep medication. *p* values for interaction between year and rest–activity variables (**A–G**): .0003, .39, .0002, .13, .20, <.0001, .09. 3MS = Modified Mini-Mental State test; L5 = activity during the least active 5 hours; M10 = activity during the most active 10 hours. Relative amplitude was calculated as (M10 – L5)/(M10 + L5). Early and late groups of L5 and M10 were defined as mean – 1 *SD* and mean + 1 *SD*, respectively.

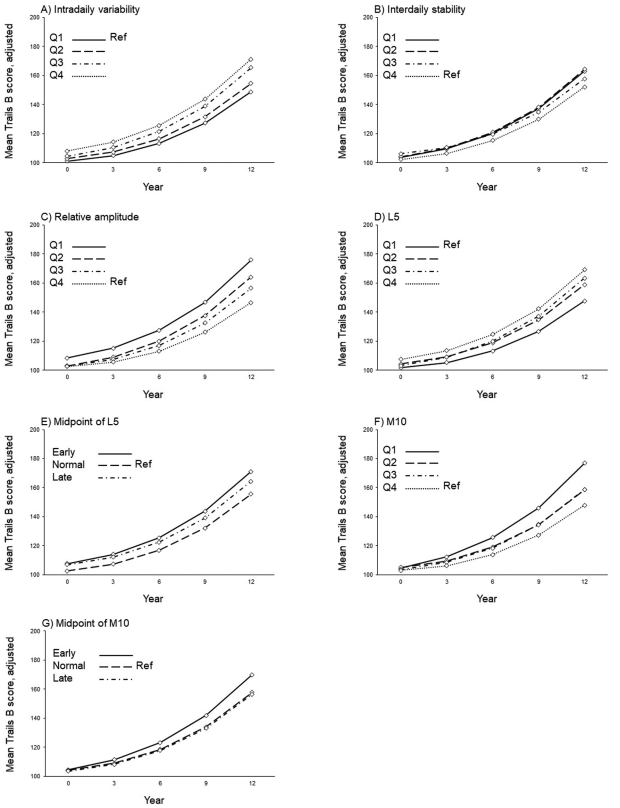

Figure 2. Trajectories of Trails B scores by categories of rest–activity rhythm parameters. Models were adjusted for age, season of actigraphy measurement, clinical site, race, education, smoking, alcohol, coffee, depression, hypertension, diabetes, cardiovascular disease, self-reported health, and use of sleep medication. *p* values for interaction between year and rest–activity variables (**A–G**): .07, .14, .001, .04, .42, <.0001, .16. 3MS = Modified Mini-Mental State test; L5 = activity during the least active 5 hours; M10 = activity during the most active 10 hours. Relative amplitude was calculated as (M10 – L5)/(M10 + L5). Early and late groups of L5 and M10 were defined as mean – 1 *SD* and mean + 1 *SD*, respectively.

60 incident cases over up to 11.2 years of follow-up, which may have limited statistical power to detect significant associations. Moreover, participants in the 2 studies differed in several aspects. For example, the Rotterdam Study included both men and women and the participants were younger (mean age, 66) than MrOS men at baseline (mean age, 76). Given the limited research and inconsistency in the literature, more studies are needed to clarify the relationship between rest–activity rhythms and cognitive outcomes. Moreover, it is important for future studies to evaluate if the relationship differs across sociodemographic groups as well as populations with different lifestyle behaviors and health status.

The relationship between rest–activity rhythms and cognition is likely bidirectional in nature. On the one hand, the pathogenesis of dementia, in general, and AD, in particular, is known to cause neurodegeneration in the suprachiasmatic nucleus, where the master circadian clock locates (34–36). On the other hand, circadian disruption and altered behavioral rhythms may also drive cognitive decline and lead to the development of dementia. For example, experimentally induced sleep deprivation in both humans and rodents led to the accumulation of amyloid-beta and -tau (37–39), 2 key proteins that play a crucial role in AD development. Moreover, circadian disruption has also been shown to induce metabolic disorder (40, 41), immune dysfunction, and inflammation (42, 43), all of which are well-established dementia risk factors (44). Although observational studies like ours are not designed to establish causality, our prospective design and the analysis focusing on changes in rest–activity patterns and subsequent cognitive decline, in particular, help clarify the temporal relationship between rest–activity rhythms and cognitive outcomes. Specifically, we found that a larger increase in rhythm fragmentation (IV) predicted a subsequent greater decline in global cognitive performance (3MS), even after adjusting for baseline IV. However, similar results were not found for measures of executive function (Trails B). These findings suggest that *changes* in rest–activity patterns may be a unique predictive marker of overall cognitive decline but not associated with an executive function specifically. In addition, the predictive value of rest–activity patterns may differ across different domains of cognition, a hypothesis that warrants additional investigation. Finally, a third explanation for the observed relationship between rest–activity rhythms and cognitive outcomes is confounding due to aging-related changes, as the underlying aging process may lead to changes in both rest–activity patterns and cognition. Although we adjusted for age in our models, residual confounding is still a possibility, given the observational design of our study. Thus, mechanistic studies are needed to fully understand the

Table 3. Associations Between Changes in Rest–Activity Rhythm Parameters Between Baseline (2003–2005) and Sleep Visit 2 (2009–2012) and Changes in Cognitive Scores Between Sleep Visit 2 and the Last Visit (2014–2016)

Changes in Rest–Activity Rhythm Parameters		Changes in 3MS Score				Changes in Trails B Score			
			β (95% CI)				β (95% CI)		
Categories	Mean (*SD*)	Mean (*SD*)	Model 1	Model 2	Model 3	Mean (*SD*)	Model 1	Model 2	Model 3
Interdaily variability									
Q1	−0.01 (0.10)	−0.50 (4.13)	ref	ref	ref	18.51 (51.53)	ref	ref	ref
Q2	0.18 (0.04)	−0.59 (4.16)	−0.09 (−1.22, 1.03)	−0.17 (−1.32, 0.97)	−0.15 (−1.32, −1.01)	15.31 (55.01)	−3.31 (−16.14, 9.52)	−3.97 (−17.24, 9.31)	−2.52 (−15.99, 10.96)
Q3	0.32 (0.04)	−1.46 (5.30)	−0.93 (−2.05, 0.20)	−1.01 (−2.15, 0.14)	−0.99 (−2.15, 0.16)	24.46 (57.42)	5.20 (−7.62, 18.03)	3.35 (−9.98, 16.67)	4.39 (−9.03, 17.82)
Q4	0.56 (0.17)	−1.93 (5.54)	−1.36 (−2.49, −0.23)	−1.46 (−2.60, −0.32)	−1.44 (−2.60, −0.27)	28.52 (56.95)	8.15 (−4.76, 21.06)	8.64 (−4.58, 21.86)	10.34 (−3.16, 23.84)
p for trend			.01	.01	.01		.11	.13	.08
Intradaily stability									
Q1	−0.26 (0.06)	−0.95 (4.84)	0.07 (−1.05, 1.19)	0.04 (−1.20, 1.11)	0.07 (−1.23, 1.37)	24.51 (54.32)	2.27 (−10.45, 15.08)	0.75 (−12.61, 14.11)	5.70 (−9.30, 20.70)
Q2	−0.15 (0.02)	−1.72 (5.08)	−0.70 (−1.83, 0.43)	−0.70 (−1.84, 0.43)	−0.61 (−1.84, 0.61)	25.84 (56.55)	3.46 (−9.35, 16.27)	4.15 (−8.93, 17.23)	7.98 (−6.12, 22.08)
Q3	−0.08 (0.02)	−0.81 (4.16)	0.18 (−0.95, 1.31)	−0.01 (−1.16, 1.14)	0.05 (−1.14, 1.24)	14.66 (51.72)	−7.46 (−20.29, 5.37)	−5.74 (−19.04, 7.55)	−3.21 (−16.94, 10.52)
Q4	0.04 (0.07)	−0.99 (5.25)	ref	ref	ref	21.78 (58.56)	ref	ref	ref
p for trend			.71	.64	.84		.39	.56	.23

Notes: 3MS = Modified Mini-Mental State test; CI = confidence interval; SD = standard deviation. Model 1: adjusted for age (≤75, >75–80, >80–85, >85). Model 2: adjusted for age (≤75, >75–80, >80–85, >85), study site (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; San Diego, CA), education (less than high school, high school, some college, college, more than college), race (White, non-White), body mass index (<25, 25–<30, 30+), smoking status (current or past, never), alcohol consumption (<1, 1–13, 14+ drink/week), coffee intake (0, 1, 2, >2 cups/day), self-reported health (good or excellent, fair or lower), depression (yes, no), diabetes (yes, no), hypertension (yes, no), cardiovascular disease (yes, no), sleep medication use (yes, no), and the season of actigraphy data collection (Dec–Feb, Mar–May, Jun–Aug, Sep–Nov). Model 3: adjusted for variables in Model 2 and baseline value of the rest–activity parameter (continuous).

underlying pathways that drive the association between rest–activity rhythms and cognitive outcomes. Moreover, we also encourage future studies to evaluate the potential cognitive benefits of interventions aimed at improving circadian rhythmicity, such as timed light exposure, carefully designed exercise and meal schedules, and improved sleep hygiene.

Our study has several strengths. We examined a large cohort of men with repeated cognitive assessments over a long follow-up. Moreover, we were able to not only examine cognitive impairment, but also evaluate cognitive trajectories over an extended period. Finally, we controlled for sleep and physical activity, showing that overall rhythmic characteristics such as IV may predict cognitive outcomes independent of the individual behavior components of the rest–activity rhythm.

Our study also has several limitations. First, MrOS participants are all men, predominantly White and from relatively high socioeconomic background. Therefore, our results may not apply to women or underrepresented populations. In addition, we did not have either measurement of the internal circadian clock such as melatonin or information on environmental factors that shape people's activity patterns. Therefore, we were not able to determine the relative contributions of intrinsic versus external factors. Moreover, we did not have clinically adjudicated dementia and relied on cognitive tests and self-reported information for outcome assessment. Although this definition has been successfully used in prior MrOS studies to define cognitive impairment more severe than what would be observed with the normal cognitive aging process (31), outcome misclassification is a possibility and future research would benefit from more rigorously ascertained clinical outcomes. We used time of study visits to define the occurrence of outcomes, which may not accurately reflect the timing when participants developed cognitive impairment. In addition, we did not have information on dementia subtypes. Finally, due to the relatively large number of regression models we ran for 7 exposures and 3 outcomes included in this study, it is possible that some of the results were chance findings and require replication and confirmation in future studies.

In conclusion, our study contributes to the growing literature supporting the role of circadian disruption in cognitive decline in older adults. In particular, we showed that weakened rest–activity rhythms characterized by higher fragmentation, lower stability, and amplitude may be predictors of cognitive impairment in older men and may potentially serve as digital biomarkers for underlying cognitive health in the clinical setting. Future studies should examine these relationships in more diverse populations, elucidate the underlying mechanisms, and evaluate the potential benefit of improving circadian function on cognitive health.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

Author Contributions

Study concept and design: Q.X., A.Z.L., K.Y., and K.S. Statistical analysis: Q.X. Draft manuscript: Q.X. Critical revision of the manuscript for important intellectual content: All.

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