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Rest-activity rhythms and cognitive impairment and dementia in older women: Results from The Women's Health Initiative

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Abstract

Introduction—Growing evidence suggests that impairment in rest-activity rhythms may be a risk factor for cognitive decline and impairment in the aging population. However, previous studies included only a limited set of rest-activity metrics and produced mixed findings. We studied a comprehensive set of parametric and nonparametric characteristics of rest-activity rhythms in relation to mild cognitive impairment (MCI) and probable dementia in a cohort of older women.

Methods—The prospective analysis included 763 women enrolled in two ancillary studies of the Women's Health Initiative (WHI): the WHI Memory Study-Epidemiology of Cognitive Health

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Outcomes and Objective Physical Activity and Cardiovascular Health studies. The association between accelerometry-based rest-activity parameters and centrally adjudicated MCI and probable dementia were determined using Cox regression models adjusted for sociodemographic characteristics, lifestyle factors, and comorbidities.

Results—Overall, the results support a prospective association between weakened rest-activity rhythms (e.g., reduced amplitude and overall rhythmicity) and adverse cognitive outcomes. Specifically, reduced overall rhythmicity (pseudo F statistic), lower amplitude and activity level (amplitude/relative amplitude, mesor and activity level during active periods of the day (M10)), and later activity timing (acrophase and midpoint of M10) were associated with higher risk for MCI and probable dementia. Women with lower amplitude and mesor also exhibited faster cognitive decline over follow-up.

Conclusion—Weakened rest-activity rhythms may be predictive markers for cognitive decline, MCI and dementia among older women.

Keywords

rest-activity rhythm; circadian rhythm; sleep; physical activity; cognitive impairment; dementia; older women

Introduction

Many human behaviors exhibit diurnal fluctuations that are orchestrated by the internal circadian timing system and influenced by external stimuli such as light, work schedules, and social patterns. [1] A prominent example of human diurnal behavior is the rest-activity rhythm, and alterations in rest-activity rhythms have been linked to many chronic diseases. [2,3] The process of aging is associated with decline in circadian output and shift in circadian phase, [4,5] leading to impairment in rest-activity rhythms in older adults. Some evidence suggests that older women may be disproportionally affected by circadian dysfunction and related diseases. [4,6]

A limited but growing number of epidemiological studies have reported that weakened rest-activity rhythms, typically manifested as lower amplitude, reduced overall rhythmicity, increased variability but decreased stability, and altered timing, were associated with higher risk of dementia and/or mild cognitive impairment (MCI). [7–11] The two main methods for characterizing rest-activity rhythms are cosine-based parametric models [12] and nonparametric algorithms.[13] The former assumes a cosine or cosine-like shape of daily activity patterns and produces rhythmic measures such as amplitude (0.5*difference between the peak and nadir of daily activity levels), mean estimating statistic of rhythm (mesor), acrophase (timing of activity peak) and overall rhythmicity. In contrast, the nonparametric methods have no underlying assumption about activity patterns and derive metrics that measure specific aspects of the rest-activity cycles, such as stability, variability/fragmentation, and activity levels and timing during the most and least active periods of the rest-activity cycle. The two methods are complementary to each other and together offer a more comprehensive assessment of the rest-activity rhythm. However, most of the previous studies only used either the parametric or nonparametric method, and even when both

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methods were applied, [9] the list of metrics examined tended to be limited. Therefore, there is a need for additional investigation combining both approaches and therefore including a more complete set of rest-activity characteristics to study their relationships with risk of dementia and cognitive impairment in older populations.

We examined associations of rest-activity characteristics with incident probable dementia and MCI in the Women's Health Initiative (WHI) study. Our study included both parametric and nonparametric methods and thus employed an agnostic approach to examine multiple aspects of the rest-activity rhythm. We hypothesized that patterns of weakened rest-activity rhythms would be associated with higher risk of MCI and probable dementia in older women.

Methods

Study population

The WHI is a longitudinal study focused on strategies to prevent major causes of disease and disability in older women. [14] The WHI had two major components, including an observational study and a clinical trial component that included three clinical trials. Consenting participants in both components have been followed up in multiple WHI Extension Studies. The current analysis included women in two WHI ancillary studies: the Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) [15] and Objective Physical Activity and Cardiovascular Health (OPACH) [16] studies.

WHIMS-ECHO is an extension of the original WHIMS study, which enrolled cognitively unimpaired women ages 65–79 years in the WHI Hormone Therapy trial from 1996 to 1999 and followed them through 2007 for cognitive outcomes. [15] In 2008, WHIMS transitioned to WHIMS-ECHO, which conducted annual telephone-based cognitive assessments. A total of 2922 women consented to the study and have been followed up for cognitive outcomes through Dec 31, 2019 at the time of this analysis. OPACH was initiated in 2012, and its primary aim was to investigate physical activity and sedentary behaviors in relation to cardiovascular and other health outcomes. The OPACH study enrolled 7,048 women, and among them, 6,489 provided accelerometry data between 2012 and 2014. A total of 1,503 women were in both OPACH and WHIMS-ECHO. Of these, we excluded women with missing rest-activity characteristics (N=211), or who had less than four days with at least 18 hours of recording (N=392), or whose follow-up time ended before accelerometry data were collected (N=137). The final analytic cohort included 763 women (see Figure 1).

Accelerometry-measured rest-activity characteristics

Participants were asked to wear an ActiGraph GT3X+ (Pensacola, Florida) triaxial accelerometer on their right hip for 7 consecutive days during waking and sleeping hours, and only to remove the device when swimming or bathing. Movement was recorded in 15-second epochs, and activity counts were derived from vector magnitudes of all three axes. We used the triaxial movement measure to derive rest-activity characteristics using both parametric and non-parametric methods.

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Detailed descriptions of as well as main findings for each rest-activity parameter are presented in Supplementary Table 1. Briefly, parametric rest-activity characteristics were derived using the extended cosine model. [12] This model applies an anti-logistic transformation to fit activity data to a modified cosine curve and has been suggested to have advantages over regular cosinor models, because it provides better model fit for older adults whose activity patterns often deviate from a standard cosine curve.[12] The extended cosine model derives multiple parameters, including amplitude, mesor, pseudo F statistic (overall rhythmicity), and acrophase. For deriving non-parametric rest-activity characteristics, we applied the previously published methods to activity data summarized into 1-hour intervals. [13] Nonparametric parameters included intradaily variability (IV), interdaily stability (IS), relative amplitude, average hourly activity during the 5 consecutive hours of the day with the lowest activity (L5), average hourly activity during the 10 consecutive hours of the day with the highest activity (M10), midpoint of L5 and midpoint of M10. All rest-activity variables were further categorized with the category indicating the strongest rhythmicity and thus the lowest hypothesized risk for incident MCI and probable dementia serving as the reference. Specifically, amplitude, mesor, pseudo-F statistic, IS, M10 and RA were divided into quartiles with the highest quartile (Q4) as the reference. IS and L5 were also divided into quartiles but the lowest quartile served as the reference. Finally, acrophase, midpoint of M10 and midpoint of L5 were divided into three groups (early (Q1), normal (Q2–3), and late (Q4), with the normal group serving as the reference.

Cognitive outcomes

All women were cognitively unimpaired at baseline. The WHIMS-ECHO protocol for cognitive assessment and ascertainment of probable dementia and MCI has been described in depth previously. [15,17] Briefly, certified staff conducted annual centralized telephone-administered cognitive assessments, including the Telephone Interview for Cognitive Status-modified (TICS-m), [18] East Boston Memory Test, [19] Oral Trail Making Test, [20] Verbal Fluency-Animals test, [21] and Digit Span Test [22]. If a participant scored below 31 on the TICS-m, the Dementia Questionnaire [23] was administered to a friend or family member to assess the participant's observed cognitive and functional performance. All data were sent to the WHIMS Clinical Coordinating Center for review and central adjudication of final classification (MCI, probable dementia, or no cognitive impairment) by a panel of specialists with experience in diagnosing cognitive impairment. MCI diagnosis was based on Petersen's criteria, [24] and probable dementia diagnosis was based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria. [25]

Covariates

Covariates ascertained the closest in time to the baseline of our analysis (2012–2014) were included in our analysis. Sociodemographic characteristics included age, race, ethnicity, education, and income. Lifestyle covariates included self-reported smoking and alcohol intake. Weight and height were measured by trained staff. Body-mass index (BMI) was calculated as weight (kg) / height^2 (m^2). Physical activity levels measured as total steps per day and total sleep time in hours were derived based on accelerometry data, as previously described. [16,26,27] Physical function was assessed by the Established Populations for Epidemiological Studies in the Elderly short physical performance

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battery (SPPB).[28] Finally, we derived a variable indicating the number of comorbidities (cancer, cerebrovascular disease, cardiovascular disease, diabetes, frequent falls, depression, osteoarthritis and chronic obstructive pulmonary disease) among OPACH participants.

Statistical analysis

We used Cox proportional hazards regression models to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for the risk of developing incident MCI or probable dementia, comparing each category of rest-activity characteristic to the reference. We evaluated and confirmed the proportional hazards assumption using the Wald χ procedure by including interaction terms with time. Separate models were fit for each rest-activity characteristic. Follow-up time was calculated from the start of the OPACH study until the date of the cognitive assessment at which a woman was first determined to have either MCI or probable dementia or the date of the last cognitive assessment, whichever occurred first. We presented results in three models. Model 1 was the minimal model adjusted for age alone. Model 2 was adjusted for age, education, race/ethnicity, intervention arm assignment, BMI, smoking, alcohol use, number of comorbidities and SPPB scores. Model 2 is considered as our main model. To assess to what degree the association between rest-activity parameters and cognitive outcomes was explained by individual behavioral components of the rest-activity rhythm (i.e., physical activity, sleep), we performed sensitivity analysis (Model 3) additionally adjusted for accelerometry-measured physical activity (total step count/day, quartile) and total sleep time (quartile). None of the variables had >10% missing, and missing values were coded as a separate group (groupings of each covariate are presented in table footnotes). We used mixed-effects linear regression models to investigate associations between rest-activity characteristics and trajectories of global cognitive function using TICS-m total scores with an interaction term between follow-up time and rest-activity characteristics. The models were adjusted for the same covariates in Model 2, and included a random intercept and allowed for random slopes for follow-up time.

We performed several sensitivity analyses to assess the robustness of our results. First, we excluded participants who developed MCI or probable dementia within two years of follow up to assess the potential of reverse causation. Second, we conducted analysis with MCI and probable dementia as the separate outcome. Third, we carried out stratified analysis according to carrier status of the *APOE* ε4 allele among White women (the *APOE* genotype was measured only among White women [29]). Finally, we examined the relationship between rest-activity characteristics and MCI and probable dementia in subgroups stratified by age using a median split (83.5 years). All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

Results

Baseline study characteristics according to quartiles of pseudo F statistic are presented in Table 1. When compared to the highest quartile, women in lower quartiles were older, had higher BMI and lower daily step count, and were more likely to be non-drinkers and report fair or poor self-rated health.

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During an average 4.5 years (standard deviation, 2.2 years) of follow-up, 193 women developed MCI (N=120) or probable dementia (N=73). We found that all parametric rest-activity rhythm parameters were associated with MCI and dementia risk (Table 2). Specifically, the risk was 2.28 (95% CI: 1.43–3.63, *p-trend*: *0.0004*), 2.45 (1.52–3.94, *0.001*) and 1.80 (1.12–2.88, *0.02*) times higher among women in the lowest quartiles of amplitude, mesor, and pseudo F statistic, respectively, when compared to those in the highest quartile (Table 2, Model 2). In addition, when compared to women in the normal group of acrophase, those in the early group were 33% less likely to develop MCI and probable dementia (HR: 0.67, 95% CI: 0.46, 0.99). After additionally adjusting for physical activity and total sleep time (Table 2, Model 3), the strengths of associations were modestly attenuated but observed overall patterns remained similar to results from the main model. In longitudinal analyses examining cognitive trajectories, we found a significant interaction between follow-up time and amplitude and mesor (*p-interaction*, *0.02* and *0.005*, respectively), suggesting differences in the slope of cognitive decline across different categories of these two rest-activity characteristics (Figure 2). Specifically, when compared to the highest quartile, women in lower quartiles of amplitude and mesor exhibited a steeper decline in TICS-m scores over 4 years of follow up.

Associations between non-parametric rest-activity rhythm parameters and incident MCI and probable dementia are presented in Table 3. We found that lower RA, M10, and a later midpoint of L5 were associated with higher incident MCI and probable dementia ((HR $_{\text{Q1 vs. Q4}}$ (95% CI): 1.67 (1.06–2.62), *p-trend*, *0.04* for RA and 2.01 (1.25, 3.23), *0.002* for M10, HR $_{\text{late vs. normal}}$ (95% CI), (1.51 (1.06, 2.14) for midpoint of L5). In addition, we also found a suggestive trend between a later midpoint of M10 and higher incidence of MCI and probable dementia (*p-trend*: *0.03*). These results were attenuated after additionally adjusting for physical activity and sleep (Table 3, Model 3). None of the nonparametric parameters showed a significant interaction with follow-up time in relation to the continuous TICS-m score, suggesting a similar rate of cognitive decline among different categories of rest-activity parameters.

We conducted sensitivity analysis by excluding cases of MCI and probable dementia that occurred within the first 2 years of follow up (N=47) (Supplementary Table 2-3). We found that, after exclusion, associations were attenuated but remained similar for amplitude, mesor, pseudo F statistic and M10. The exclusion had little impact on the results for acrophase, RA and midpoints for L5 and M10. In analysis focusing on MCI and probable dementia as separate outcomes, we found suggestive evidence indicating potential differences in their respective associations with rest-activity characteristics (Supplementary Table 4). For example, when both effect sizes and p-values are taken into consideration, amplitude showed a stronger association with MCI while pseudo F statistic showed a stronger association with probable dementia. However, the results were mixed and did not suggest consistently stronger associations with one outcome versus the other. In subgroup analysis among White women stratified by *APOE* ε4 status, we found that the results among non-carriers (N=572) were largely similar to those in the overall sample, while results among carriers (N=119) were less stable and with large confidence intervals due to small sample size (data not shown). Finally, in subgroup analysis stratified by age, the associations between rest-activity characteristics and incident MCI and probable dementia were generally similar between

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age groups, and none of the *p-for-interaction* suggested a statistically significant modifying effect due to age (data not shown).

Discussion

Among older women, we reported associations of multiple parametric and non-parametric rest-activity parameters with incident cognitive impairment and decline. Specifically, we found that weakened rest-activity characteristics as measured by variables derived from the extended cosine model (i.e., smaller amplitude, lower mesor, and reduced pseudo F statistic or overall rhythmicity) and nonparametric algorithms (i.e., smaller RA and lower M10) were associated with higher incidence of MCI and probable dementia. Moreover, women with smaller amplitude and lower mesor exhibited faster cognitive decline over follow-up. In addition, we found evidence suggesting a positive association between the timing or phase of rest-activity rhythms, as measured by both parametric (i.e., acrophase) and nonparametric variables (i.e., midpoint of M10), and incidence of MCI and PD.

Associations between weakened rhythmicity as measured by parametric variables and incidence of MCI and probable dementia are consistent with results from several previous studies, particularly those from the Study of Osteoporotic Fractures (SOF), a cohort of older women with similar characteristics to those in the WHI. Among 1,283 women in the SOF with an average of 4.9 years of follow up, the analysis showed that lowest quartiles of amplitude, mesor and pseudo F statistic were associated with higher incidence of MCI and dementia. [7] A follow-up study in SOF also found that a lower amplitude and mesor were associated with worse cognitive decline after five years of follow-up. [30] Similar findings with parametric rhythmic measures were also reported in the Osteoporotic Fractures in Men (MrOS) cohort, [8] with lower amplitude and pseudo F statistic both associated with higher dementia risk. A recent analysis in the Rush Memory and Aging Project (RMAP) also reported an association between lower amplitude and higher risk for Alzheimer's Disease; [9] however, no association was observed for acrophase. Because this study used a regular cosine regression, instead of the extended cosine model to assess rest-activity rhythms, it did not assess overall rhythmicity (i.e., pseudo F statistic) in relation to cognitive outcomes. Studies on nonparametric rest-activity measures have been more limited and produced mixed results. In a recent analysis in SOF, of all the nonparametric variables (i.e., IV, IS, RA, L5 and L10), only RA was associated with incident dementia. In the RMAP, higher IV predicted an overall higher risk of Alzheimer's disease. Among those with MCI at baseline, both higher IV and lower IS were associated with higher risk of Alzheimer's disease. [9] However, similar findings were not observed either in our analysis, or an analysis in the Rotterdam Study, which reported no association between IV or IS and dementia risk. [11] The discrepancy among these studies may be due to chance alone, or attributable to differences in sample size, study population, geographic location and differences in outcome assessment (e.g., WHIMS examined only all-cause dementia, whereas the RMAP examined Alzheimer's Disease). Overall, these findings support a link between weakened rest-activity rhythms as characterized by lower amplitude and overall rhythmicity and cognitive impairment and decline in older adults.

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Timing is an important aspect of diurnal behaviors. We found that, overall, the results for both parametric and nonparametric variables suggested a positive trend linking a later timing of the activity (acrophase and M10) and rest (L5) periods of the day with higher risk of MCI and probable dementia. Previous findings on the timing of rest-activity rhythms and cognitive health were mixed. In SOF, while a later acrophase (>15:51) was associated with a 67% increase in the incidence of MCI and dementia, when compared to the reference group (13:34–15:51), the study did not observe a linear trend similar to ours, but instead a suggestive U-shaped association. [7] In the SOF analysis focusing on nonparametric variables, the authors reported no association between M10 midpoint and dementia incidence. However, they found that an *earlier* L5 (<1:42 AM) was associated with higher incidence of dementia. [10] Analysis in the MrOS study reported an association between an early acrophase (<12:28) and higher risk of dementia. [8] Finally, no association was found between L5 onset and dementia risk in the Rotterdam Study. [11] The inconsistent and sometimes contradictory findings from different studies warrant further investigation on the dose-dependent relationship between rest-activity rhythm timing and cognitive outcomes. Previous studies were conducted in populations with potentially different distributions of rest/activity timing, and used different criteria to categorize them into early, normal and late groups. Such heterogeneity in sample distributions and the operationalization of exposure variables may have contributed to the inconsistency in their findings.

Several lines of evidence have suggested that impaired circadian function may play a role in neurodegenerative diseases such as dementia. [2] First, circadian disruption may lead to sleep deficiency and reduce sleep-dependent removal of key proteins involved in dementia pathology, such as Aβ and Tau. [31] Moreover, circadian disruption may directly impact the dynamics of Aβ via altered protein homeostasis and quality control [32,33] and influence protein clearance by modulating the permeability of the blood-brain barrier, [34] both of which may lead to pro-neurodegenerative aggregation of harmful proteins and peptides. In addition, deletion of core clock genes in animal models led to oxidative damage, synapse degeneration, and impaired neuronal connectivity in the brain, even when the sleep-wake rhythm remained intact, suggesting a direct role of circadian rhythms in neurodegenerative pathogenesis. [35] Finally, several previous studies have linked weakened rest-activity patterns, such as a lower amplitude and overall rhythmicity, to insulin resistance, type 2 diabetes, and chronic inflammation in older populations. [36–40] As both metabolic dysfunction and chronic inflammation are well established risk factors for dementia, [41] it is plausible that the disrupted circadian rhythms may lead to elevated risk of dementia via metabolic and inflammatory dysregulation. Although the aforementioned evidence supports a role of circadian disruption in dementia risk, it is important to note that there may be a bidirectional relationship between neurodegenerative diseases and circadian impairment. [2,9] In the RMAP, it was reported that the pathological development of Alzheimer's disease after the diagnosis of MCI was associated with a more rapid decline in rest-activity rhythmicity over time. [9] In addition, neuronal loss in brain regions involved in circadian regulation (e.g., suprachiasmatic nucleus) was observed in patients with Alzheimer's disease. [42] The aging process itself may also lead to changes in both circadian rhythms and cognitive function, leading to an observed correlation between the two. In summary, the association between rest-activity rhythm patterns and MCI and dementia observed in our study and other studies

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may be driven by multiple causes, and future studies, particularly well-controlled human intervention studies and animal experiments, are needed to elucidate the various underlying mechanisms. In particular, the field may benefit from research designed to evaluate the potential cognitive benefits of strategies that aimed at improving rest-activity rhythmicity, such as enhanced sleep hygiene, timed exercise, and light therapy.

Although the mechanisms linking rest-activity patterns with cognitive function in older populations remain to be determined, evidence from our study and previous longitudinal analyses suggest that rest-activity parameters may be useful predictive markers of the risk of dementia and cognitive decline. In particular, ours is the first study that included a comprehensive list of both parametric and nonparametric variables to characterize the rest-activity rhythm. Overall, when compared with nonparametric algorithms, the parametric models appeared to produce measures of rest-activity rhythms that were more robust in predicting the risk of dementia and MCI in various studies. Future studies should systematically quantify the relative importance and predictive power of various rest-activity variables in the context of cognitive health. Moreover, as mentioned above, the modeling of nonlinear relationships and choice of cutoff points may also influence the performance of regression models. Several machine learning methods have been previously proposed to systematically evaluate multiple measures of correlated behavioral patterns such as sleep, physical activity and rest-activity rhythms to identify the strongest predictors for health outcomes. [43]

Strengths of our study include its longitudinal design, clinically adjudicated cognitive outcomes, and objective and comprehensive measures of rest-activity rhythms. Excluding incident cases that developed within two years after baseline, and finding largely similar results suggested that rest-activity rhythm characteristics are not merely correlated with existing cognitive impairment, but may predict future risks of MCI and dementia.

Our study also has several limitations. First, most of our study participants were in their 80s at baseline. This may introduce survival bias, as women who developed cognitive impairment before baseline were excluded from the analysis. Second, previous studies indicated that sleep patterns in middle age were an important predictor of dementia risk later in life [44], while our analysis was limited to older women. Third, rest-activity patterns are not static and may change over time as a result of aging-related and/or other factors. [45] However, we only had one-time measurement of rest-activity rhythms, and were not able to assess whether changes in rest-activity characteristics are associated with cognitive outcomes. Fourth, rest-activity patterns are influenced by both internal circadian clocks and external factors. However, we did not have biomarkers of internal circadian rhythms, or measures of important environmental cues, such as light exposures, daily schedule, and social obligations. Thus, we were not able to pinpoint the upstream determinants of altered rest-activity patterns that may contribute to cognitive decline. Finally, women in our study were predominantly White and of relatively high socioeconomic status, and thus our study findings may not be generalizable to other populations.

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Conclusion

We found that multiple rest-activity parameters were associated with risk of cognitive impairment and decline in the WHI. Additional research, including intervention studies in humans, are needed to clarify the direction of the association and pinpoint underlying mechanisms linking rest-activity rhythms with cognitive health. Moreover, our results combined with findings from earlier studies suggest that accelerometry-based rest-activity measures may be used, in conjunction with other biomarkers, for predicting cognitive decline and cognitive impairment in older populations. Future studies should focus on developing statistical algorithms and platforms for data collection and analysis for risk prediction and management in clinical settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol. 2010;72:517–549. [PubMed: 20148687]
2. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. Lancet Neurol. 2019;18(3):307–318. [PubMed: 30784558]
3. Duffy JF, Zitting KM, Chinoy ED. Aging and Circadian Rhythms. Sleep Med Clin. 2015;10(4):423–434. [PubMed: 26568120]
4. Nakamura TJ, Nakamura W, Yamazaki S, et al. Age-related decline in circadian output. J Neurosci. 2011;31(28):10201–10205.
5. Dijk DJ, Duffy JF. Circadian regulation of human sleep and age-related changes in its timing, consolidation and EEG characteristics. Ann Med. 1999;31(2):130–140. [PubMed: 10344586]
6. Stone KL, Xiao Q. Impact of Poor Sleep on Physical and Mental Health in Older Women. Sleep Med Clin. 2018;13(3):457–465. [PubMed: 30098759]
7. Tranah GJ, Blackwell T, Stone KL, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol. 2011;70(5):722–732. [PubMed: 22162057]

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8. Rogers-Soeder TS, Blackwell T, Yaffe K, et al. Rest-Activity Rhythms and Cognitive Decline in Older Men: The Osteoporotic Fractures in Men Sleep Study. J Am Geriatr Soc. 2018;66(11):2136–2143. [PubMed: 30136716]
9. Li P, Gao L, Gaba A, et al. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. Lancet Healthy Longev. 2020;1(3):e96–e105. [PubMed: 34179863]
10. Posner AB, Tranah GJ, Blackwell T, et al. Predicting incident dementia and mild cognitive impairment in older women with nonparametric analysis of circadian activity rhythms in the Study of Osteoporotic Fractures. Sleep. 2021;44(10):zsab119.
11. Lysen TS, Luik AI, Ikram MK, Tiemeier H, Ikram MA. Actigraphy-estimated sleep and 24-hour activity rhythms and the risk of dementia. Alzheimers Dement. 2020;16(9):1259–1267. [PubMed: 32558256]
12. Marler MR, Gehrman P, Martin JL, Ancoli-Israel S. The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. Statistics in medicine. 2006;25(22):3893–3904. [PubMed: 16381069]
13. Van Someren EJ, Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiol Int. 1999;16(4):505–518. [PubMed: 10442243]
14. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. Ann Epidemiol. 2003;13(9 Suppl):S5–17. [PubMed: 14575938]
15. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. Control Clin Trials. 1998;19(6):604–621. [PubMed: 9875839]
16. LaCroix AZ, Rillamas-Sun E, Buchner D, et al. The Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) Study. BMC Public Health. 2017;17(1):192. [PubMed: 28193194]
17. Rapp SR, Legault C, Espeland MA, et al. Validation of a cognitive assessment battery administered over the telephone. J Am Geriatr Soc. 2012;60(9):1616–1623. [PubMed: 22985137]
18. Welsh KA, Breitner JCS, Magruderhabib KM. Detection of Dementia in the Elderly Using Telephone Screening of Cognitive Status. Neuropsy Neuropsy Be. 1993;6(2):103–110.
19. Scherr PA, Albert MS, Funkenstein HH, et al. Correlates of cognitive function in an elderly community population. Am J Epidemiol. 1988;128(5):1084–1101. [PubMed: 3189282]
20. Ricker JH, Axelrod BN. Analysis of an Oral Paradigm for the Trail Making Test. Assessment. 1994;1(1):47–52. [PubMed: 9463499]
21. Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. New York, NY: Oxford University Press; 2004.
22. Wechsler D. Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R). New Yor, NY: Psychological Corporation; 1981.
23. Kawas C, Segal J, Stewart WF, Corrada M, Thal LJ. A validation study of the Dementia Questionnaire. Arch Neurol. 1994;51(9):901–906. [PubMed: 8080390]
24. Petersen RC, Smith GE, Ivnik RJ, Kokmen E, Tangalos EG. Memory function in very early Alzheimer's disease. Neurology. 1994;44(5):867–872. [PubMed: 8190289]
25. Bell CC. DSM-IV: diagnostic and statistical manual of mental disorders. JAMA. 1994;272(10):828–829.
26. Evenson KR, Wen F, Herring AH, et al. Calibrating physical activity intensity for hip-worn accelerometry in women age 60 to 91 years: The Women's Health Initiative OPACH Calibration Study. Prev Med Rep. 2015;2:750–756. [PubMed: 26527313]
27. Full KM, Gallo LC, Malhotra A, et al. Modeling the cardiometabolic benefits of sleep in older women: exploring the 24-hour day. Sleep. 2020;43(1):zsz205.
28. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci. 2000;55(4):M221–231. [PubMed: 10811152]

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29. Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet. 2012;44(8):955–959. [PubMed: 22820512]
30. Walsh CM, Blackwell T, Tranah GJ, et al. Weaker circadian activity rhythms are associated with poorer executive function in older women. Sleep. 2014;37(12):2009–2016. [PubMed: 25337947]
31. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013;342(6156):373–377. [PubMed: 24136970]
32. Kress GJ, Liao F, Dimitry J, et al. Regulation of amyloid-beta dynamics and pathology by the circadian clock. J Exp Med. 2018;215(4):1059–1068. [PubMed: 29382695]
33. Huang G, Zhang F, Ye Q, Wang H. The circadian clock regulates autophagy directly through the nuclear hormone receptor Nr1d1/Rev-erbalpha and indirectly via Cebpb/(C/ebpbeta) in zebrafish. Autophagy. 2016;12(8):1292–1309. [PubMed: 27171500]
34. Zhang SL, Yue Z, Arnold DM, Artiushin G, Sehgal A. A Circadian Clock in the Blood-Brain Barrier Regulates Xenobiotic Efflux. Cell. 2018;173(1):130–139 e110. [PubMed: 29526461]
35. Musiek ES, Lim MM, Yang G, et al. Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. J Clin Invest. 2013;123(12):5389–5400. [PubMed: 24270424]
36. Sohail S, Yu L, Bennett DA, Buchman AS, Lim AS. Irregular 24-hour activity rhythms and the metabolic syndrome in older adults. Chronobiol Int. 2015;32(6):802–813. [PubMed: 26061588]
37. Luik AI, Zuurbier LA, Hofman A, Van Someren EJ, Tiemeier H. Stability and fragmentation of the activity rhythm across the sleep-wake cycle: the importance of age, lifestyle, and mental health. Chronobiol Int. 2013;30(10):1223–1230. [PubMed: 23971909]
38. Xiao Q, Qian J, Evans DS, et al. Cross-sectional and Prospective Associations of Rest-Activity Rhythms With Metabolic Markers and Type 2 Diabetes in Older Men. Diabetes Care. 2020;43(11):2702–2712. [PubMed: 32887712]
39. Morris CJ, Purvis TE, Hu K, Scheer FA. Circadian misalignment increases cardiovascular disease risk factors in humans. Proc Natl Acad Sci U S A. 2016;113(10):E1402–1411. [PubMed: 26858430]
40. Xiao Q, Qian J, Evans DS, et al. Cross-Sectional and Prospective Associations of Rest-Activity Rhythms with Circulating Inflammatory Markers in Older Men. J Gerontol A Biol Sci Med Sci. 2021.
41. Crous-Bou M, Minguillon C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res Ther. 2017;9(1):71. [PubMed: 28899416]
42. Wang JL, Lim AS, Chiang WY, et al. Suprachiasmatic neuron numbers and rest-activity circadian rhythms in older humans. Ann Neurol. 2015;78(2):317–322. [PubMed: 25921596]
43. Wallace ML, Stone K, Smagula SF, et al. Which Sleep Health Characteristics Predict All-Cause Mortality in Older Men? An Application of Flexible Multivariable Approaches. Sleep. 2018;41(1).
44. Sabia S, Fayosse A, Dumurgier J, et al. Association of sleep duration in middle and old age with incidence of dementia. Nat Commun. 2021;12(1):2289. [PubMed: 33879784]
45. Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. Sleep Med Rev. 2007;11(6):429–438. [PubMed: 17936039]

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Key Points

- We report associations of multiple parametric (i.e., amplitude, mesor, pseudo F statistic, acrophase) and non-parametric rest-activity (i.e., relative amplitude, activity during the most active 10 hours of the day (M10), midpoint of M10) parameters with incident cognitive impairment and dementia, as well as cognitive decline in older women.
- Specifically, weakened rest-activity rhythms, manifested as lower amplitude and reduced overall rhythmicity, are associated with a higher incidence of mild cognitive impairment (MCI) and probable dementia (PD).
- We report evidence suggesting a positive association between the timing or phase of rest-activity rhythms (i.e., acrophase and midpoint of M10), and incidence of MCI and PD.

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Why Does this Paper Matter

Accelerometry-based rest-activity measures may be used as predictive markers of future cognitive decline and cognitive impairment in older women.

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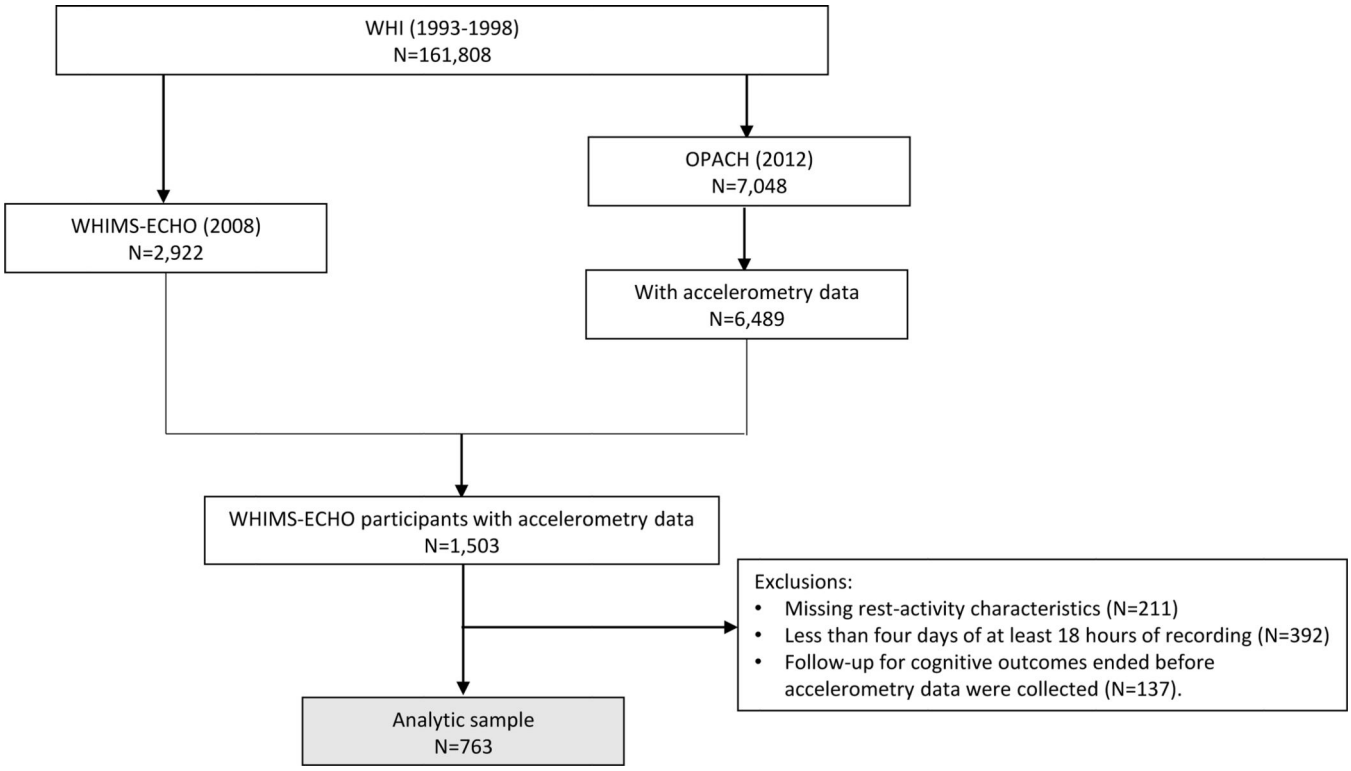

Figure 1.

Flow chart showing the progression of participants. Abbreviations: OPACH, Objective PA and Cardiovascular Health in Older Women; WHI, Women's Health Initiative; WHIMS-ECHO, Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes

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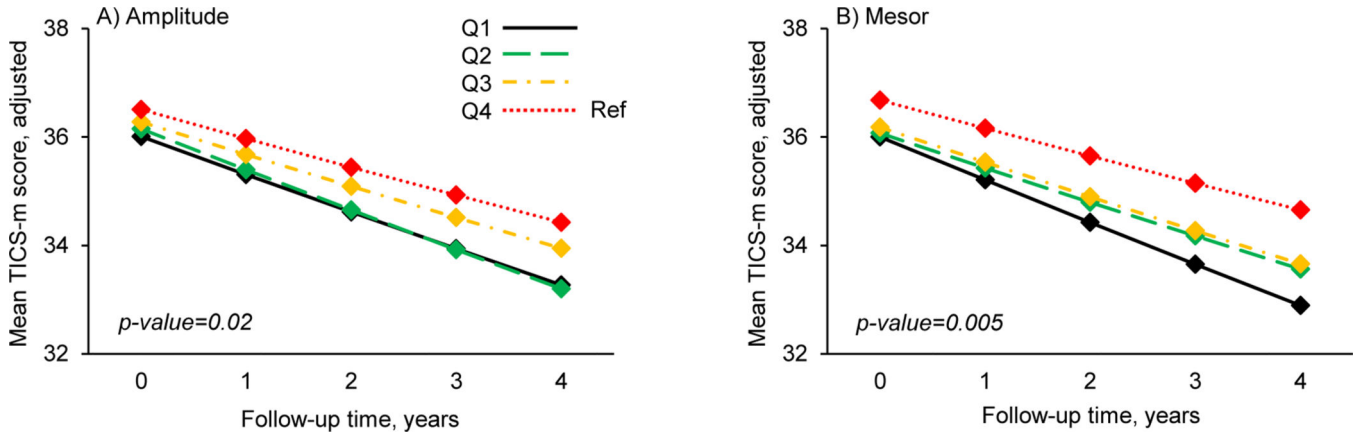

Figure 2.

Trajectories of TICS-m scores by A) Amplitude and B) Mesor in the WHI OPACH and WHIMS-ECHO Study (N=763). Models were [b] adjusted for age (continuous), education (less than high school, vocational or training school, some college or associate, college, graduate school), race/ethnicity (White, Black, Hispanic), intervention arm (HRT (estrogen only, progestin only, estrogen + progestin, control), dietary modification arm (not randomized, intervention, control), calcium and vitamin D arm (not randomized, intervention, control)), BMI (<25, 25–29.9, 30–34.9, 35+, missing), smoking (yes, no, missing), alcohol use (never, <1 drink/week, 1–2 or 3–4 drink/week, 4+ drink/week), number of comorbidities (0, 1, 2, 3+), SPPB score (<7, 7–9, 10–12). P-values represent the interaction between rest-activity characteristics and follow-up time. Abbreviations: BMI, body-mass index; CI, confidence intervals; HR, hazard ratio; OPACH, Objective PA and Cardiovascular Health in Older Women; SD, standard deviation; SPPB, Short Physical Performance Battery; TICS-m, Modified Telephone Interview for Cognitive Status; WHI, Women's Health Initiative; WHIMS-ECHO, Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes.

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Table 1.

Baseline characteristics by quartiles of pseudo F statistic in the WHI OPACH and WHIMS-ECHO studies (N=763).

	Pseudo F statistic				
	Q1	**Q2**	**Q3**	**Q4**	***p-value*** [b]
Age, mean (SD)	84.6 (3.3)	84.4 (3.3)	84.1 (3.4)	83.2 (2.7)	*<.0001*
Age, year, %					*0.02*
75–79	7.9	6.3	6.8	8.9	
80–84	51.1	52.4	57.1	67.5	
85–90	33.7	34.6	29.8	22.0	
90+	7.4	6.8	6.3	1.6	
Education, college or higher, %	37.9	42.9	43.5	42.4	*0.83*
White, %	89.5	93.7	94.8	94.2	*0.17*
Smoking, never, %	89.5	89.0	93.2	93.7	*0.55*
Alcohol, non-drinker, %	39.0	29.8	28.3	24.1	*0.005*
Body mass index, kg/m^2, mean (SD)	29.7 (5.7)	27.8 (5.0)	26.5 (5.0)	24.8 (4.1)	*<.0001*
ApoE e4 carrier, [b] %	18.4	15.7	13.6	15.2	*0.64*
Total steps per day, mean (SD)	1687 (851)	2457 (1072)	3167 (1242)	4636 (2056)	*<.0001*
Total sleep time per day, mean (SD)	8.5 (1.2)	8.3 (1.1)	8.4 (1.0)	8.4 (0.9)	*0.16*
Number of comorbidities, 3+, [c] %	33.7	25.7	18.3	15.2	*0.001*
Poor physical function, SPPB score<7, %	47.9	20.9	22.0	15.7	*<.0001*

[a] p-values were derived from chi-square test for categorical variables and ANOVA for continuous variables.

[b] measured among White women only.

[c] Comorbidities included cancer, cerebrovascular disease, cardiovascular disease, diabetes, frequent falls, depression, osteoarthritis and chronic obstructive pulmonary disease.

Abbreviations: ANOVA, Analysis of variance; OPACH, Objective PA and Cardiovascular Health in Older Women; SD, standard deviation; SPPB, Short Physical Performance Battery; WHI, Women's Health Initiative; WHIMS-ECHO, Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes.

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Table 2

Associations (HR (95% CI)) between rest-activity rhythm characteristics derived from extended cosine models and incident probable dementia and mild cognitive impairment in the WHI OPACH and WHIMS-ECHO studies (N=763).

			Incident Probable Dementia and Mild Cognitive Impairment		
Rest-activity parameters	**Mean (SD)**	**N**	**Model 1** [a]	**Model 2** [b]	**Model 3** [c]
Amplitude					
Q1	42.83 (12.49)	57	2.15 (1.40, 3.29)	2.28 (1.43, 3.63)	1.84 (1.07, 3.15)
Q2	72.82 (7.07)	54	1.62 (1.05, 2.49)	1.58 (1.02, 2.46)	1.38 (0.84, 2.28)
Q3	101.48 (10.97)	47	1.38 (0.89, 2.14)	1.36 (0.87, 2.13)	1.35 (0.84, 2.16)
Q4	217.39 (202.91)	35	ref	ref	ref
p-trend			*0.0003*	*0.0004*	*0.04*
Mesor					
Q1	35.40 (7.41)	55	2.38 (1.53, 3.73)	2.45 (1.52, 3.94)	1.92 (1.10, 3.35)
Q2	53.38 (4.40)	52	1.70 (1.08, 2.66)	1.63 (1.03, 2.59)	1.46 (0.86, 2.45)
Q3	70.41 (6.19)	55	1.90 (1.22, 2.95)	1.80 (1.15, 2.81)	1.69 (1.05, 2.73)
Q4	133.22 (108.14)	31	ref	ref	ref
p-trend			*0.0006*	*0.001*	*0.06*
Pseudo F statistic					
Q1	198.11 (69.05)	49	1.60 (1.04, 2.45)	1.80 (1.12, 2.88)	1.33 (0.78, 2.26)
Q2	394.21 (55.62)	55	1.45 (0.96, 2.20)	1.46 (0.95, 2.24)	1.18 (0.73, 1.90)
Q3	605.62 (75.29)	50	1.30 (0.85, 1.98)	1.39 (0.90, 2.13)	1.29 (0.83, 2.03)
Q4	1146.87 (742.04)	39	ref	ref	ref
p-trend			*0.03*	*0.02*	*0.40*
Acrophase [d]					
Early	11.12 (1.53)	35	0.67 (0.46, 0.99)	0.70 (0.48, 1.04)	0.72 (0.48, 1.07)
Normal	13.60 (0.50)	100	ref	ref	ref
Late	15.53 (1.03)	58	1.28 (0.92, 1.77)	1.20 (0.86, 1.69)	1.11 (0.79, 1.57)
p-trend			*0.003*	*0.02*	*0.06*

[a] adjusted for age (continuous).

[b] adjusted for age (continuous), education (less than high school, vocational or training school, some college or associate, college, graduate school), race/ethnicity (White, Black, Hispanic), intervention arm (HRT (estrogen only, progestin only, estrogen + progestin, control), dietary modification arm (not randomized, intervention, control), calcium and vitamin D arm (not randomized, intervention, control)), BMI (<25, 25–29.9, 30–34.9, 35+, missing), smoking (yes, no, missing), alcohol use (never, <1 drink/week, 1–2 or 3–4 drink/week, 4+ drink/week), number of comorbidities [e] (0, 1, 2, 3+), SPPB score (<7, 7–9, 10–12).

[c] adjusted for variables in Model 2 and total daily steps (quartile) and total sleep time (<7, 7-<8, 8-<9, 9+ hours).

[d] early, normal and late groups defined as Q1 (≤12:42), Q2–3 (12:43–14:29), and Q4 (≥14:30), respectively.

[e] Comorbidities included cancer, cerebrovascular disease, cardiovascular disease, diabetes, frequent falls, depression, osteoarthritis and chronic obstructive pulmonary disease.

Abbreviations: BMI, body-mass index; CI, confidence intervals; HR, hazard ratio; HRT, hormone replacement therapy; OPACH, Objective PA and Cardiovascular Health in Older Women; SD, standard deviation; SPPB, Short Physical Performance Battery; WHI, Women's Health Initiative; WHIMS-ECHO, Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes.

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Table 3

Associations (HR (95% CI)) between rest-activity rhythm characteristics derived from nonparametric algorithms and incident probable dementia and mild cognitive impairment in the WHI OPACH and WHIMS-ECHO studies (N=763).

			Incident Probable Dementia and Mild Cognitive Impairment		
Rest-activity parameters	**Mean (SD)**	**N**	**Model 1** [a]	**Model 2** [b]	**Model 3** [c]
Interdaily stability					
Q1	0.35 (0.05)	46	1.25 (0.82, 1.91)	1.33 (0.85, 2.08)	1.16 (0.73, 1.83)
Q2	0.45 (0.02)	53	1.28 (0.85, 1.92)	1.43 (0.93, 2.21)	1.28 (0.83, 1.96)
Q3	0.53 (0.02)	52	1.37 (0.91, 2.06)	1.47 (0.96, 2.25)	1.33 (0.87, 2.04)
Q4	0.63 (0.06)	41	ref	ref	ref
p-trend			*0.37*	*0.25*	*0.58*
Intradaily variability					
Q1	0.84 (0.09)	46	ref	ref	ref
Q2	1.07 (0.05)	51	1.07 (0.71, 1.59)	1.18 (0.78, 1.78)	1.07 (0.71, 1.62)
Q3	1.25 (0.06)	44	0.90 (0.59, 1.36)	0.99 (0.65, 1.53)	0.85 (0.54, 1.32)
Q4	1.57 (0.18)	51	1.23 (0.82, 1.85)	1.41 (0.91, 2.18)	1.16 (0.73, 1.83)
p-trend			*0.48*	*0.24*	*0.79*
Relative amplitude					
Q1	0.64 (0.11)	52	1.64 (1.08, 2.49)	1.67 (1.06, 2.62)	1.39 (0.86, 2.24)
Q2	0.81 (0.03)	49	1.34 (0.88, 2.04)	1.42 (0.91, 2.20)	1.26 (0.81, 1.99)
Q3	0.87 (0.02)	52	1.46 (0.96, 2.21)	1.45 (0.94, 2.23)	1.47 (0.95, 2.28)
Q4	0.93 (0.02)	39	ref	ref	ref
p-trend			*0.04*	*0.04*	*0.30*
L5					
Q1	3.95 (126)	44	ref	ref	ref
Q2	7.13 (0.79)	53	1.30 (0.87, 1.95)	1.26 (0.83, 1.91)	1.35 (0.89, 2.05)
Q3	9.92 (0.95)	45	1.04 (0.69, 1.58)	1.03 (0.67, 1.57)	1.14 (0.74, 1.76)
Q4	17.12 (5.27)	50	1.30 (0.86, 1.94)	1.25 (0.82, 1.90)	1.27 (0.83, 1.95)
p-trend			*0.41*	*0.51*	*0.42*
M10					
Q1	56.83 (12.45)	52	1.70 (1.12, 2.60)	2.01 (1.25, 3.23)	1.31 (0.71, 2.41)
Q2	87.57 (7.65)	56	1.56 (1.03, 2.36)	1.60 (1.03, 2.47)	1.18 (0.68, 2.03)
Q3	114.39 (8.51)	46	1.22 (0.79, 1.87)	1.25 (0.81, 1.94)	1.05 (0.64, 1.72)
Q4	163.95 (32.86)	39	ref	ref	ref
p-trend			*0.006*	*0.002*	*0.33*
Midpoint of L5 [d]					
Early	1.14 (0.99)	45	0.95 (0.67, 1.37)	1.04 (0.72, 1.50)	1.08 (0.74, 1.56)
Normal	2.87 (0.49)	59	ref	ref	ref
Late	4.78 (0.88)	59	1.55 (1.11, 2.16)	1.51 (1.06, 2.14)	1.41 (0.99, 2.02)
p-trend			*0.01*	*0.07*	*0.19*

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		Incident Probable Dementia and Mild Cognitive Impairment			
Rest-activity parameters	**Mean (SD)**	**N**	**Model 1** [a]	**Model 2** [b]	**Model 3** [c]
Midpoint of M10 [e]					
Early	11.16 (1.02)	36	0.69 (0.47, 1.02)	0.68 (0.46, 1.01)	0.74 (0.50, 1.09)
Normal	12.83 (0.53)	102	ref	ref	ref
Late	15.07 (1.39)	55	1.22 (0.88, 1.69)	1.12 (0.79, 1.58)	1.14 (0.80, 1.62)
p-trend			*0.009*	*0.03*	*0.06*

[a] adjusted for age (continuous).

[b] adjusted for age (continuous), education (less than high school, vocational or training school, some college or associate, college, graduate school), race/ethnicity (White, Black, Hispanic), intervention arm (HRT (estrogen only, progestin only, estrogen + progestin, control), dietary modification arm (not randomized, intervention, control), calcium and vitamin D arm (not randomized, intervention, control)), BMI (<25, 25–29.9, 30–34.9, 35+, missing), smoking (yes, no, missing), alcohol use (never, <1 drink/week, 1–2 or 3–4 drink/week, 4+ drink/week), number of comorbidities [f] (0, 1, 2, 3+), SPPB score (<7, 7–9, 10–12).

[c] adjusted for variables in Model 2 and total daily steps (quartile) and total sleep time (<7, 7-<8, 8-<9, 9+ hours).

[d] early, normal and late groups defined as Q1 (≤02:00), Q2–3 (02:01–03:47), and Q4 (≥03:48), respectively.

[e] early, normal and late groups defined as Q1 (≤11:54 PM), Q2–3 (11:55–13:47), and Q4 (≥13:48), respectively.

[f] Comorbidities included cancer, cerebrovascular disease, cardiovascular disease, diabetes, frequent falls, depression, osteoarthritis and chronic obstructive pulmonary disease.

Abbreviations: BMI, body-mass index; CI, confidence intervals; HR, hazard ratio; HRT, hormone replacement therapy; OPACH, Objective PA and Cardiovascular Health in Older Women; SD, standard deviation; SPPB, Short Physical Performance Battery; WHI, Women's Health Initiative; WHIMS-ECHO, Women's Health Initiative Memory Study-Epidemiology of Cognitive Health Outcomes.