Published in final edited form as:

Ann Neurol. 2011 November ; 70(5): 722–732. doi:10.1002/ana.22468.

Circadian activity rhythms and risk of incident dementia and MCI in older women

Gregory J. Tranah, PhD^a, Terri Blackwell, MA^a, Katie L. Stone, PhD^a, Sonia Ancoli-Israel, PhD^b, Misti L. Paudel, MPH^c, Kristine E. Ensrud, MD^{c,d,e}, Jane A. Cauley, DrPH^f, Susan Redline, MD^g, Teresa A. Hillier, MD^h, Steven R Cummings, MD^a, and Kristine Yaffe, MDⁱ for the SOF Research Group

^aCalifornia Pacific Medical Center Research Institute, San Francisco, CA

^bDepartment of Psychiatry, University of California San Diego, San Diego, CA

^cDivision of Epidemiology and Community Health, University of Minnesota, MN

^dCenter for Chronic Disease Outcomes Research, Minneapolis VA Medical Center, Minneapolis, MN

^eDepartment of Medicine, University of Minnesota, Minneapolis, MN

^fDepartment of Epidemiology, University of Pittsburgh, Pittsburgh, PA

^gDepartment of Medicine, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

^hKaiser Permanente Center for Health Research Northwest/Hawaii, Portland, OR

ⁱDepartments of Psychiatry, Neurology, and Epidemiology, University of California, San Francisco and the San Francisco VA Medical Center, San Francisco, CA

Abstract

Objective—Previous cross-sectional studies have observed alterations in activity rhythms in dementia patients but the direction of causation is unclear. We determined whether circadian activity rhythms measured in community-dwelling older women are prospectively associated with incident dementia or mild cognitive impairment (MCI).

Corresponding Author: Gregory Tranah, PhD, California Pacific Medical Center Research Institute, San Francisco Coordinating Center, UCSF, 185 Berry Street, Lobby 4, Suite 5700, San Francisco, CA 94107-1728, gtranah@sfcc-cpmc.net.

Conflict of Interest: JA Cauley receives research funding and consulting fees from Novartis Pharmaceuticals.

KE Ensrud is a federal employee of the Veterans Affairs Medical Center in Minneapolis, MN and has received research support from California Pacific Medical Center, who receives funding from Roche Molecular Systems.

S Cummings, K Stone, T Blackwell and G Tranah are employees of the California Pacific Medical Center and receive research support from Roche Molecular Systems.

S Ancoli-Israel has disclosed that she has received grants for educational activities from Sepracor, and Litbebook, Inc. She has served as an advisor or consultant to Ferring Pharmaceuticals Inc., GlaxoSmithKline, Merck, NeuroVigil, Inc., Neurocrine Biosciences, Pfizer, Philips Respironics, sanofi-aventis, Sepracor, Inc., Schering-Plough.

M Paudel, S Redline and T Hillier have no conflicts of interest.

Author Contributions: G Tranah participated in the conception and design of the project and drafted and revised the manuscript. T Blackwell conducted all statistical analyses and participated in interpretation of data analyses and critical revision of the manuscript. K Stone and K Yaffe obtained funding and participated in the acquisition of data, interpretation of data analyses, and critical revision of the manuscript. KE Ensrud participated in the acquisition of data, interpretation of data analyses, and critical revision of the manuscript. M Paudel, JA Cauley, T Hillier and S Cummings participated in interpretation of data analyses and critical revision of the manuscript. S Ancoli-Israel and S Redline participated in the conception and design of the project, interpretation of data, and critical revision of the manuscript.

Method—Activity rhythm data were collected from 1,282 healthy community-dwelling women from the Study of Osteoporotic Fractures cohort (mean age 83 years) with wrist actigraphy for a minimum of three 24-hour periods. Each participant completed a neuropsychological test battery and had clinical cognitive status (dementia, MCI, normal) adjudicated by an expert panel approximately 5 years later. All analyses were adjusted for demographics, BMI, functional status, depression, medications, alcohol, caffeine, smoking, health status, and co-morbidities.

Results—After 4.9 years of follow-up, 195 (15%) women had developed dementia and 302 (24%) had developed MCI. Older women with decreased activity rhythms had a higher likelihood of developing dementia or MCI when comparing those in the lowest quartiles of amplitude (Odds ratio[OR]=1.57, 95% CI, 1.09–2.25) or rhythm robustness (OR=1.57, 95% CI, 1.10–2.26) to women in the highest quartiles. An increased risk of dementia or MCI (OR=1.83, 95% CI, 1.29–2.61) was found for women whose timing of peak activity occurred later in the day (after 3:51PM) when compared to those with average timing (1:34PM–3:51PM).

Interpretation—Older, healthy women with decreased circadian activity rhythm amplitude and robustness, and delayed rhythms have increased odds of developing dementia and MCI. If confirmed, future studies should examine whether interventions (physical activity, bright light exposure) that influence activity rhythms will reduce the risk of cognitive deterioration in the elderly.

Introduction

Circadian rhythms are critically involved in control of sleep-wake cycles and numerous physiological processes. In addition, they may also play an important role in rhythms associated with cognitive processing including alertness, learning and memory. During waking, there are observed rhythms in synaptic plasticity^{1, 2}, focused attention and behavioral flexibility^{3, 4}. Aging is associated with altered circadian activity rhythms including decreased amplitude (peak activity)⁵, fragmentation or loss of rhythms^{6–11}, alterations in entrainment and decreased sensitivity to phase resetting signals, including light and sleep medications¹². The timing of activity also advances with age resulting in an earlier onset of sleepiness in the evening, and an earlier morning waking time⁷.

Circadian and sleep-wake rhythm abnormalities have been observed among those with a wide variety of medical conditions. Activity phase abnormalities in the elderly with dementia have been shown to predict a shorter survival¹³. Disturbances of the sleep-wake cycle, which are reflected in poor activity rhythms, are particularly pronounced in Alzheimer's disease (AD)^{14–16} and hypothesized to be one of the primary causes of institutionalization^{17, 18} along with shifts in daytime patterns¹⁹. Patients diagnosed with AD also exhibit circadian disturbances, including reduced amplitudes and phase delay of circadian variation in core body temperature and activity²⁰.

Little is known concerning the causes of age-related changes in circadian activity patterns in non-demented older adults and the *subsequent* effects of these changes on health and well-being. We previously reported that older community dwelling women and men with weak circadian activity rhythms have a higher mortality risk^{21, 22}. However, the relationship between circadian activity rhythms and subsequent development of dementia and MCI has not been studied in the elderly. This study, part of a longitudinal study of older community-dwelling women, was designed to test the hypothesis that circadian activity rhythms measured objectively by wrist actigraphy are prospectively associated with risk of dementia and MCI. The identification of risk factors that might lead to new interventions to slow the decline in cognitive function may benefit the health and well-being of older adults. Possible interventions may include physical activity and light exposure, which have both been

demonstrated to influence cognitive functioning and affective state ^{2, 16, 23–27}, strengthen circadian activity rhythms, and improve sleep synchronization in older adults ^{27–31}.

Subjects and Methods

Participants

Women were participants of the Study of Osteoporotic Fractures (SOF), a longitudinal epidemiologic study of 10,366 community-dwelling women age 65 or older, recruited from four study centers located in Baltimore, MD; Minneapolis, MN; Portland, OR; and the Monongahela Valley near Pittsburgh, PA. Women were excluded if they had a bilateral hip replacement or were unable to walk without assistance. The baseline SOF exams were conducted from 1986–88, when 9,704 Caucasian women were recruited ³² and from February 1997 to February 1998 when 662 African-American women were enrolled ³³. For this study, we included participants who completed wrist actigraphy study during SOF Exam 8 (2002–2004) and an expanded cognitive assessment during SOF Exam 9 (2006–2008) which included participants from three of four sites (MN, OR, and PA). Of the 2,549 women with actigraphy from the three clinic sites, 1,777 also participated in Exam 9. Of these, 1,320 provided sufficient data for assessment of cognitive impairment status. The cognitive status for twelve of these women was determined as indeterminate so they were unable to be included in the current analysis. We excluded 26 participants with probable dementia or cognitive impairment at visit 8 identified from self-report of a diagnosis of dementia (n=6); dementia medication use (n=8); and a Mini-Mental State Examination (MMSE) score <24 ³⁴ (n=16), with some overlap of criteria. The goal of the present analysis was to determine incident cognitive impairment from Exam 8 to Exam 9, so the twenty-six women who had possible cognitive impairment at Exam 8 were not included in the analysis, leaving an analysis cohort of 1,282 women. Self-reported dementia, use of dementia medications, and global cognitive test score were also part of the Visit 9 screening where MCI and dementia were assessed. The institutional review boards on human research approved the study at each institution, and all participating women provided written informed consent. The MCI-dementia measures were performed as part of the Women, Cognitive Impairment Study of Exceptional Aging (WISE) study, which along with sleep measures were funded as part of the ancillary study, Changes in Sleep and Cognition in Older Women (SOF Sleep and Cognition Study).

Actigraphy

Activity data were collected with the Sleep-watch-O (SleepWatch-O ®, Ambulatory Monitoring, Inc) actigraph, a small device worn on the nondominant wrist. Movement is measured by a piezoelectric linear accelerometer (sensitive to 0.003 g and above), which generates a voltage each time the actigraph is moved. These voltages are gathered continuously and summarized over 1-minute epochs. Women wore the actigraphs continuously for a minimum of three 24-hour periods (i.e., 72 hours). The orientation and sensitivity of the accelerometer are optimized for highly effective sleep-wake inference from wrist activity, which has been previously validated ^{35, 36}. The actigraph was initialized in the clinic prior to the home visit, and placed on the participant's wrist by the examiner during the home visit.

Circadian measurements derived from wrist actigraphy have been compared to measures derived from other methods considered reference standards ³⁷. For example, actigraphic sleep/wake predictions have the same circadian period as PSG sleep/wake scores ³⁸. Actigraph-identified bedtime, wake-up time, mid-sleep time and acrophase were all significantly correlated with the acrophase of urinary melatonin and core body temperature ^{39–41}. Actigraphy has also been used to effectively assess activity levels ^{42–44}.

Inter-scorer reliability for actigraphy has been previously found to be high in our group (intra-class coefficient = 0.95) and this measure has been shown to have good concordance with total sleep time from polysomnography ⁴⁵.

An extension to the traditional cosine model was used to map the circadian activity rhythm to the activity data ⁴⁶. The following activity rhythm parameters were calculated from the extended cosine curve: Amplitude, an indicator of the strength of the rhythm, is the peak to nadir difference in activity (measured in arbitrary units of activity [counts/min]); Mesor, mean level of activity (measured in arbitrary units of activity [counts/min]); Robustness of the circadian activity rhythm (pseudo-F statistic for goodness of extended cosine fit; higher pseudo-F values indicate stronger rhythms); and Acrophase, timing of peak activity measured as time of day. Circadian amplitude, mesor and robustness were examined based on quartile distributions. Acrophase was examined in terms of the deviation from the population mean. We identified three categories based on having a peak time of more than 1 standard deviation (SD) above and below the population mean for the study population. Phase advanced participants were defined as having an acrophase of <1:34PM (−1 SD from the mean) and phase delayed participants were defined as having an acrophase of >3:51PM (+1 SD from the mean). Continuous versions of these predictors were used in secondary analyses.

Cognitive Impairment Evaluation

Cognitive impairment was determined in a two-step process. First, women were screened for cognitive impairment at Exam 9 (approximately 5 years after the original wrist actigraphy data were collected) using one or more of the following criteria: 1) score <88 on the Modified Mini-Mental State Examination (3MS) ⁴⁷; 2) score <4 on the California Verbal Learning Test (CVLT) delayed recall ⁴⁸; 3) score ≥3.6 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ⁴⁹; 4) self-reported previous dementia diagnosis; or 5) nursing home residence. The 634 women who screened positive were evaluated at the next step, an assessment of clinical cognitive status. The remaining women who screened negative were considered to be cognitively normal.

Assessment of cognitive status was performed by a panel of clinical experts, which included a neurologist, two neuropsychologists, and a geropsychologist. Information used for assessment included the year 20 neuropsychological battery scores, prior cognitive test scores, demographics, medical history, medications, depression score, and functional status. The diagnosis of dementia was made based on DSM-IV criteria and likely dementia etiology (vascular dementia, AD, dementia due to multiple etiologies (mixed), or other) was also determined. MCI was diagnosed using a modified Petersen Criteria ^{50, 51}, which requires cognitive impairment that is insufficient to be dementia and generally intact functional status. Those who did not meet criteria for MCI or dementia were classified as being cognitively normal.

Other Measurements

All participants completed a self assessment questionnaire, which included questions about education level, medical history, self-reported health, smoking status, alcohol use, caffeine intake, and whether or not the participant walked for exercise. Functional status was assessed by collecting information on 6 instrumental activities of daily living (IADL), which included walking 2 to 3 blocks on level ground, climbing up to 10 steps, walking down 10 steps, preparing meals, doing heavy housework, and shopping for groceries or clothing. Further information on function was obtained from informants using the IQCODE ⁴⁹. The Geriatric Depression Scale (GDS) was used to assess depressive symptoms, with the standard cutoff of ≥6 symptoms used to define depression ⁵². Medication use was

ascertained by asking participants to bring all current prescription and nonprescription medications used in the past 30 days to their clinic visits. For women who completed a home visit, the interviewer gathered medication use information at the home. A computerized medication coding dictionary was used to categorize all medications⁵³. Body weight and height were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. A history of coronary heart disease was defined as a prior diagnosis of myocardial infarction, angina, congestive heart failure, or other heart disease. A history of medical conditions was defined as a prior physician diagnosis of stroke, diabetes, Parkinson's disease, cancer, chronic obstructive pulmonary disease (COPD), or coronary heart disease. All measurements were collected at visit 8, the baseline examination for this analysis.

Statistical analysis

Characteristics known to be related to activity rhythms or cognitive function were summarized using means and *SDs* for continuous data and counts and percentages for categorical data. We compared characteristics among categories of amplitude and acrophase using ANOVA for continuous covariates that were normally distributed, Kruskal-Wallis tests for skewed continuous data, and chi-square tests for categorical data.

To determine the relationship between circadian activity rhythms and incident dementia and MCI, we used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). To identify potential confounders, we considered a list of predictors thought to be associated with circadian activity rhythms and cognition, based on biological plausibility or previous studies. Variables that were significantly related ($p < 0.10$) to at least one activity rhythm predictor measure were included in the final multivariate analyses (age, clinic site, race, education, BMI, walking for exercise, functional status, depression score, benzodiazepine use, antidepressant use, sleep medication use, alcohol use, caffeine use, smoking, self-reported health status, and prior medical conditions). Women determined as having dementia were not included in the logistic models with the outcome of MCI. Sensitivity models were performed further adjusting the multivariate models by sleep efficiency to examine if the association of circadian activity rhythms and incident dementia or MCI was driven by underlying sleep fragmentation. Statistical analysis was performed using the statistical software program SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of the study population

Our cohort was composed of 1,282 women with both actigraphy data and the expanded cognitive assessment. In general, women in the lowest quartile of amplitude were more likely to be older and have a high BMI, more IADL impairments, more medical conditions, a history of hypertension, poor health and more likely to be taking antidepressants or benzodiazepines and to consume less alcohol and caffeine (Table 1). Those women with a phase-delayed circadian activity rhythm had a higher average BMI, were more likely to be a minority, had more IADL impairments, higher rates of smoking and fewer who walked for exercise (Table 2).

Circadian activity rhythms and incident dementia and MCI

After a mean of 4.9 years of follow-up, there were 195 (15%) women with adjudicated dementia and 302 (24%) with MCI. An approximately 50% adjusted higher odds of developing dementia or MCI versus those without any dementia or MCI was observed for those in the lowest quartiles ($n=320$) of amplitude (Odds ratio [OR]=1.57, 95% CI, 1.09–2.25) and robustness (OR=1.57, 95% CI, 1.10–2.26) when compared to those highest

quartiles (n=322) (Table 3). A significant linear trend was also observed as the odds of developing dementia or MCI increased from highest to lowest amplitude (p-trend, $p=0.023$). A linear trend is clear when examining ORs and 95% CIs from the bottom three quartiles of amplitude compared to the referent quartile 1: quartile 2, (OR=1.26, 95% CI, 0.89–1.78); quartile 3, (OR=1.30, 95% CI, 0.91–1.85); quartile 4, (OR=1.57, 95% CI, 1.09–2.25). Amplitude was significantly correlated with mesor ($r=0.81$) and the results for these measures were very similar.

Acrophase deviation was associated with increased odds of developing dementia or MCI (Table 3). A delayed acrophase, after 3:51PM (n=173, 13%), was associated with a significant increase in odds of developing dementia or MCI (OR=1.83, 95% CI, 1.29–2.61) when compared to the mean peak range of 1:34PM–3:51PM (n=927, 73%). An advanced acrophase, before 1:34PM (n=182, 14%), was associated with an elevated but non-significant odds of developing dementia or MCI (OR=1.37, 95% CI, 0.97–1.93) when compared to the mean peak range. All analyses were multivariate adjusted for age, clinic site, race, education, BMI, walking for exercise, functional status, depression, benzodiazepine and antidepressant use, sleep medication use, alcohol use, caffeine intake, smoking, self-reported health status, history of hypertension, and prior medical conditions.

Results for all models were largely unchanged after further adjustment for sleep efficiency. For example, a delayed acrophase continued to be associated with a significant increase in odds of developing dementia or MCI (OR=1.81, 95% CI, 1.27–2.58) when compared to the mean peak range and there continued to be a higher odds of developing dementia or MCI for those in the lowest quartile of amplitude (OR=1.55, 95% CI, 1.08–2.23) when compared to those in the highest quartile.

Discussion

We found that among 1,282 older women, variations in circadian activity rhythms were associated with increased odds of developing dementia or MCI, independent of multiple confounders. Lower amplitude, a less robust rhythm and a delayed timing of peak activity were consistently related to developing either dementia or MCI. These associations were independent of the sleep fragmentation (e.g. sleep efficiency) and sleep duration. To our knowledge, this is the first study to evaluate the relationship between circadian activity rhythms and subsequent development of dementia and MCI in participants from a community dwelling setting. If confirmed in other cohorts, these findings could lead to interventions that might delay the onset of MCI and dementia in the elderly.

The circadian timing system most likely affects memory, cognitive function, and behavior through a variety of neuroanatomical and neurophysiological mechanisms (reviewed⁵⁴). The circadian contribution to cognition may also arise from the synchronized activities of an integrated network of clocks in the brain under the direction of the suprachiasmatic nucleus (SCN) pacemaker⁵⁵. It is also possible that circadian activity rhythms are biomarkers of advanced physiological aging that provide additional risk over and beyond that of traditional covariates but which may have no direct causal association with dementia or MCI.

Daily rhythms in sleep-wake behavior and waking performance are generated by the interaction of multiple external and internal oscillators⁵⁶. From a cognitive perspective, neurobehavioral efficiency changes over the day to accommodate two interacting processes: the homeostatic sleep pressure, which increases with time spent awake, and the circadian pacemaker, which drives a nearly 24-hour endogenous oscillatory process⁵⁷. Optimal cognitive performance, therefore, depends on temporal alignment between sleep and clock-driven mechanisms. The complexity of this relationship is underscored by the discovery that

the SCN is not the only brain pacemaker⁵⁸ and that local semi-autonomous clocks are distributed across the brain, including cerebral cortex, hippocampus and cerebellum⁵⁹. The SCN plays a central role in determining the timing of sleep and wakefulness and simultaneously synchronizes the multitude of local brain clocks to a complementary circadian program⁵⁸. Compromise of the local clock machinery with age may reduce the efficiency of temporal adaptation and impair cognitive function. By way of example, jet lag and rotational shift work likely lead to a transient loss of phase coherence both among individual brain clocks possibly compromising circadian coordination leading to suboptimal cognitive performance^{60, 61}. In rodent models the SCN is subject to marked electrophysiological changes in aged animals⁶² while serotonergic neurotransmission in the SCN decreases with age⁶³. Diminished presence of vasopressin in the SCN and a deterioration of sleep-wake rhythms during aging and depression make it likely that the vasopressin neurons contribute considerably to the rhythmic output of the SCN⁶⁴. The SCN of elderly people show a disrupted annual cycle and reduced amplitude of vasopressin-expressing neurons in the human SCN. These data suggest that the biosynthesis of vasopressin in the human SCN exhibits a seasonal rhythm that becomes disturbed later in life⁶⁵.

Sleep and rhythm disturbances are common in many neurodegenerative diseases including AD^{66–68}, dementia⁶⁹ and Lewy body disease⁷⁰. The major sleep complaints associated with neurodegenerative diseases include insomnia, hypersomnia, parasomnia, excessive nocturnal motor activity, sleep apnea, and sleep-wake rhythm disturbances⁷¹. Sleep is disturbed early in the neurodegenerative process and sleep disturbances are observed in the presence of MCI^{72, 73}. Further, it has been suggested that sleep disturbance increases with severity of the neurodegeneration⁷⁴. While neurodegenerative diseases are believed to be proteinopathies resulting from excessive protein misfolding and intracellular protein aggregation, the role of sleep and rhythm disturbances in the neurodegenerative process has largely been unexplored. The accumulation of amyloid-beta in the brain extracellular space is a critical event in the pathogenesis of AD and both the sleep-wake cycle and the neuropeptide hormone orexin have been shown to play a role in regulating amyloid-beta dynamics⁷⁵. Orexins and their receptors are involved in a number of central⁷⁶ and peripheral functions⁷⁷ and play an important role in maintaining wakefulness by preventing unwanted transitions into sleep as seen in narcolepsy⁷⁸. Orexin knock-out mice and narcoleptic patients exhibit frequent transitions between vigilance states^{79–83}. Chronic overexpression of orexins in mice resulted in suppression of REM sleep during day time and fragmented non-REM sleep⁸⁴. Transgenic human prepro-orexin (*hPPO*) mice exhibit increased expression of hPPO and orexin-A in the hypothalamus and show a small reduction in REM sleep and differences in vigilance state during the light/dark transition periods⁸⁵. The effects of sleep deprivation and orexin modulation have also been examined in wild-type mice and human APP transgenic mice, which express a mutated form of human amyloid precursor protein (*hAPP*)⁷⁵. The quantity of amyloid-beta measured in brain interstitial fluid (ISF) correlated with wakefulness and orexin dynamics⁷⁵. Chronic sleep deprivation and orexin infusion both significantly increased ISF amyloid-beta while dual orexin receptor antagonist decreased plaque formation⁷⁵. These results suggest that sleep and rhythm disturbances may be fundamental contributors to neurodegeneration by exacerbating the aggregation of toxic proteins.

Circadian activity rhythms may also be biomarkers of altered rhythms that correlate with physiological advanced aging and morbidity not measured by conventional measures or captured in multivariable models. Weak circadian activity rhythms would not then have a direct causal association with dementia or MCI but would provide additional risk over and beyond that of traditional covariates. Previous studies suggest that some but not all peripheral circadian oscillators exhibit age-related changes in rhythmicity⁸⁶ and that some

of these tissues retained the capacity to oscillate but were not being appropriately driven in vivo (e.g. by physical activity or feeding)⁸⁷. The presence of arrhythmic peripheral tissues may be due to weakened behavioral and physiological rhythms that provide less effective signals to the peripheral oscillators⁸⁸. It is also possible that the age-related shift towards morningness age and related changes in patterns of subjective alertness may not due to a weakness of the master circadian clock, but rather to a weakened transduction of its output by means of deficits in the downstream mechanisms^{89–91}. For example advanced sleep phase cannot be completely explained by a general advance of the circadian timing system with age since normal circadian rhythms have been observed in other physiological parameters like core body temperature rhythms^{89, 90}. This suggests that the age-related shift towards morningness could rather reflect a weaker transduction of the circadian signal downstream from the circadian timing system. Therefore the change in phase relationships of behavioral and physiological rhythms may not be due to age-related changes in the entrained phase of the SCN itself but rather is because of age-related alterations in other rhythmic components of the circadian system⁸⁶. If it is the case that circadian desynchronization affects independent organ systems differently, as experimental systems have shown, and some peripheral oscillators retain their capacity to oscillate, then interventions to regulate circadian activity rhythm abnormalities including physical activity may be warranted in older adults.

This analysis had a number of strengths. We studied a large cohort of mostly community-dwelling older women with no inclusion requirements regarding circadian activity rhythms or sleep disorders or cognitive function. We adjusted for multiple possible confounders and used validated measures to assess rhythms and cognitive function. By excluding participants with probable dementia or cognitive impairment at visit 8 we were able to prospectively examine circadian activity rhythm patterns and 5 year incidence of dementia and MCI. This analysis also had several limitations. Findings are for older women and may not be generalizable to other populations such as men, institutionalized older women or younger women. The IADLs chosen for adjustment stress mobility-dependent activities rather than more “standard” aging-related IADLs. These IADLs, however, have been shown to have good face and prognostic validity in that they are associated with risk of falls⁹² in the SOF Study. We cannot rule out that some participants with subtle cognitive impairment were not excluded based on our Visit 8 exclusions. The individuals who agreed to wear the actigraph were somewhat healthier than those who did not. However, we expect that this would have biased our findings towards the null. The potential for residual confounding cannot be eliminated given the observational design of our study.

These findings suggest that activity rhythm abnormalities are prognostic of increased risk of developing dementia and MCI in older, cognitively healthy community-dwelling women. The mechanism behind this association of circadian activity rhythms and dementia and MCI cannot be addressed but emerging research suggests the possibility that altered circadian rhythms may influence a wide range of neurophysiological processes. Studies have shown that low light exposure is related to increased cognitive functioning¹⁶. Studies have also shown that bright light therapy is effective in strengthening and synchronized circadian activity rhythms and sleep in older adults^{27–29}. Other studies have shown that physical activity also has a positive effect on circadian activity rhythms^{30, 31}. In addition, exposure to ambient light is known to influence cognition and affective state^{2, 23–26} and bright light has phase-shifting properties that have been shown to improve cognitive performance²⁷. If confirmed in other cohorts, studies will be needed to examine whether interventions that influence circadian activity rhythms improve cognitive health in the healthy elderly. Alternatively, markers of circadian rhythm, whether causal or not, may serve as useful prognostic indicators in identifying individuals at risk for cognitive decline. Sleep interventions and light therapy in patients or rodent models have been shown to demonstrate

acute beneficial effects^{93, 94}. Identifying new approaches for interventions that slow the decline in cognitive function will potentially benefit the health and well-being of the elderly before the onset of cognitive impairment.

Acknowledgments

The Study of Osteoporotic Fractures (SOF) and SOF-WISE is supported by the National Institutes of Health funding (AG05407, AR35582, AG05394, AR35584, AR35583, AG005407, AG027576-22, AG005394-22A1, AR46238, AG08415, AG030474, AG027574-22A1, and AG026720-04). Dr. Kristine Yaffe is supported in part by the National Institute of Aging grant K24 AG 031155 and an Independent Investigator Award from the Alzheimer's Association.

This work was supported by grants from the NIH: AG026720, AG05407, AR35582, AG05394, AR35584, AR35583, AR46238, AG005407, AG08415, AG027576-22, AG005394-22A1, AG027574-22A1, AG030474.

Sponsor's Role – None.

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Appendix

Investigators in the Study of Osteoporotic Fractures Research Group: *San Francisco Coordinating Center (California Pacific Medical Center Research Institute and University of California San Francisco)*: SR Cummings (principal investigator), MC Nevitt (co-investigator), DC Bauer (co-investigator), DM Black (co-investigator), KL Stone (co-investigator), W Browner (co-investigator), R Benard, T Blackwell, PM Cawthon, L Concepcion, M Dockrell, S Ewing, M Farrell, C Fox, R Fullman, SL Harrison, M Jaime-Chavez, W Liu, L Lui, L Palermo, N Parimi, M Rahorst, D Kriesel, C Schambach, R Scott, J Ziarno. *University of Maryland*: MC Hochberg (principal investigator), R Nichols (clinic coordinator), S Link. *University of Minnesota*: KE Ensrud (principal investigator), S Diem (co-investigator), M Homan (co-investigator), P Van Coevering (program coordinator), S Fillhouer (clinic director), N Nelson (clinic coordinator), K Moen (assistant program coordinator), F Imker-Witte, K Jacobson, M Slindee, R Gran, M Forseth, R Andrews, C Bowie, N Muehlbauer, S Luthi, K Atchison. *University of Pittsburgh*: JA Cauley (principal investigator), LH Kuller (co-principal investigator), JM Zmuda (co-investigator), L Harper (project director), L Buck (clinic coordinator), M Danielson (project administrator), C Bashada, D Cusick, A Flaugh, M Gorecki, M Nasim, C Newman, N Watson. *The Kaiser Permanente Center for Health Research, Portland, Oregon*: T Hillier (principal investigator), K Vesco (co-investigator), K Pedula (co-investigator), J Van Marter (project director), M Summer (clinic coordinator), A MacFarlane, J Rizzo, K Snider, J Wallace.

Table 1
Comparing Characteristics of the SOF cohort among quartiles of amplitude (difference between peak to nadir activity).

Characteristic	Quartile 4 (N= 322)	Quartile 3 (N= 322)	Quartile 2 (N= 318)	Quartile 1 (N= 320)	p-value
Counts/Min.	>=4194	3588 – 4193	2984 – 3587	<2984	
Age, mean +/- SD, years	82.22 +/- 3.16	82.20 +/- 3.26	82.98 +/- 3.34	83.37 +/- 3.45	<0.01
BMI, mean +/- SD, kg/m2	26.41 +/- 4.30	26.88 +/- 4.46	27.76 +/- 4.70	28.97 +/- 5.40	<0.01
African-American	39 (12.11)	43 (13.35)	24 (7.55)	32 (10.00)	0.09
Education, mean +/- SD, years	12.79 +/- 2.68	12.88 +/- 2.63	12.85 +/- 2.49	12.86 +/- 2.53	0.97
Any LADL impairments (of 6)	102 (31.97)	130 (40.50)	162 (50.94)	206 (64.38)	<0.01
History of stroke	20 (6.21)	29 (9.01)	29 (9.12)	49 (15.31)	<0.01
History of diabetes	21 (6.52)	18 (5.59)	35 (11.01)	52 (16.25)	<0.01
History of coronary heart disease *	74 (22.98)	75 (23.29)	109 (34.28)	124 (38.75)	<0.01
History of COPD	33 (10.25)	39 (12.11)	34 (10.69)	49 (15.31)	0.19
History of hypertension	164 (50.93)	187 (58.07)	199 (62.58)	210 (65.63)	0.001
Current benzodiazepine user	10 (3.11)	23 (7.17)	22 (6.92)	33 (10.31)	<0.01
Current antidepressant user	29 (9.01)	23 (7.17)	29 (9.12)	55 (17.19)	<0.01
Current sleep medication user	6 (1.86)	2 (0.62)	1 (0.31)	5 (1.56)	0.18
Depression (GDS score >=6)	19 (5.92)	17 (5.30)	31 (9.75)	37 (11.56)	<0.01
Average drinks per day in past 30 days	1.41 +/- 2.81	1.26 +/- 3.02	0.97 +/- 2.38	0.76 +/- 3.01	<0.01
Average caffeine intake, mg/d	190.96 +/- 174.70	157.03 +/- 136.83	144.94 +/- 151.93	134.00 +/- 149.59	<0.01
Walks for exercise	151 (47.34)	148 (46.69)	120 (37.74)	111 (35.24)	<0.01
Self-reported health status, poor/very poor	2 (0.62)	2 (0.62)	3 (0.94)	9 (2.81)	<0.01
Actigraphic total sleep time, min, mean +/- SD	405.51 +/- 63.24	410.19 +/- 63.01	410.42 +/- 64.39	406.14 +/- 85.64	0.72
Actigraphic sleep efficiency, %	80.11 +/- 9.01	79.89 +/- 9.35	79.63 +/- 9.91	76.49 +/- 13.64	0.02

p-values for continuous variables are from ANOVA for normally distributed, Kruskal-Wallis for skewed.

p-values for categorical variables are from a chi-square test for homogeneity.

* Coronary heart disease is myocardial infarction, angina, congestive heart failure or other heart disease

** medical conditions include stroke, diabetes, Parkinson's disease, COPD, cancer, and coronary heart disease.

Table 2

Comparing Characteristics of the SOF cohort among categories of acrophase (time of peak daily activity).

Characteristic	<1:34PM (N= 182)	1:34PM to 3:51PM (N= 927)	>3:51PM (N= 173)	p-value
Age, mean $\pm$ SD, years	82.62 $\pm$ 3.26	82.75 $\pm$ 3.27	82.46 $\pm$ 3.76	0.55
BMI, mean $\pm$ SD, kg/m ²	27.50 $\pm$ 4.62	27.27 $\pm$ 4.71	28.72 $\pm$ 5.43	<0.01
African-American	15 (8.24)	95 (10.25)	28 (16.18)	0.03
Education, mean $\pm$ SD, years	12.75 $\pm$ 2.52	12.89 $\pm$ 2.56	12.70 $\pm$ 2.73	0.59
Any IADL impairments (of 6)	72 (39.78)	429 (46.43)	99 (57.23)	<0.01
Any medical condition**	108 (59.34)	517 (55.83)	109 (63.01)	0.18
History of stroke	20 (10.99)	86 (9.28)	21 (12.14)	0.45
History of diabetes	18 (9.89)	86 (9.28)	22 (12.72)	0.38
History of coronary heart disease*	46 (25.27)	281 (30.31)	55 (31.79)	0.33
History of COPD	25 (13.74)	100 (10.79)	30 (17.34)	0.04
History of hypertension	110 (60.44)	543 (58.58)	107 (61.85)	0.68
Current benzodiazepine user	9 (4.95)	60 (6.48)	19 (10.98)	0.05
Current antidepressant user	14 (7.69)	98 (10.58)	24 (13.87)	0.17
Current sleep medication user	2 (1.10)	12 (1.30)	0	0.32
Depression (GDS score ≥ 6)	17 (9.34)	71 (7.68)	16 (9.25)	0.64
Current smoker	3 (1.65)	16 (1.73)	10 (5.78)	<0.01
Average drinks per day in past 30 days	1.16 $\pm$ 2.94	1.07 $\pm$ 2.51	1.18 $\pm$ 4.04	0.14
Average caffeine intake, mg/d	161.46 $\pm$ 147.74	153.52 $\pm$ 154.55	169.54 $\pm$ 165.97	0.37
Walks for exercise	76 (41.99)	406 (44.27)	48 (28.07)	<0.01
Self-reported health status, poor/very poor	3 (1.65)	11 (1.19)	2 (1.16)	0.59
Actigraphic total sleep time, min, mean $\pm$ SD	408.31 $\pm$ 71.84	411.36 $\pm$ 66.51	390.12 $\pm$ 80.81	0.001
Actigraphic sleep efficiency, %	80.58 $\pm$ 9.13	79.28 $\pm$ 10.13	76.07 $\pm$ 14.33	0.02

p-values for continuous variables are from ANOVA for normally distributed, Kruskal-Wallis for skewed.

p-values for categorical variables are from a chi-square test for homogeneity

* Coronary heart disease is myocardial infarction, angina, congestive heart failure or other heart disease

** medical conditions include stroke, diabetes, Parkinson's disease, COPD, cancer, and coronary heart disease.

SOF=Study of Osteoporotic Fractures; MMSE=Mini-Mental State Examination; SD=standard deviation; IADL=instrumental activities of daily living.

Table 3

Associations between circadian activity rhythm quartiles and dementia and MCI.

N	MCI (n=302)	Dementia (n=195)	MCI + Dementia (n=497)
Amplitude (counts/min.)			
>=4194	1.00 (ref)	1.00 (ref)	1.00 (ref)
3588 – 4193	1.20 (0.80 – 1.81)	1.25 (0.77 – 2.02)	1.26 (0.89 – 1.78)
2984 – 3587	1.50 (1.00 – 2.25)	0.88 (0.53 – 1.45)	1.30 (0.91 – 1.85)
<2984	1.57 (1.02 – 2.42)	1.30 (0.80 – 2.12)	1.57 (1.09 – 2.25)
p-value for continuous predictor	0.046	0.26	0.020
Mesor (counts/min.)			
>=2437	1.00 (ref)	1.00 (ref)	1.00 (ref)
2149 – 2436	1.08 (0.72 – 1.61)	1.01 (0.62 – 1.65)	1.05 (0.74 – 1.49)
1861 – 2148	1.43 (0.95 – 2.15)	1.14 (0.70 – 1.86)	1.39 (0.98 – 1.98)
<1861	1.51 (0.99 – 2.28)	1.14 (0.70 – 1.85)	1.42 (0.99 – 2.02)
p-value for continuous predictor	0.08	0.94	0.11
Robustness (pseudo F-statistic)			
>=1152	1.00 (ref)	1.00 (ref)	1.00 (ref)
851 – 1151	1.20 (0.80 – 1.79)	1.70 (1.03 – 2.78)	1.39 (0.98 – 1.97)
595 – 850	1.31 (0.87 – 1.96)	1.27 (0.76 – 2.11)	1.32 (0.93 – 1.89)
<595	1.45 (0.96 – 2.20)	1.50 (0.90 – 2.48)	1.57 (1.10 – 2.26)
p-value for continuous predictor	0.30	0.32	0.13
Acrophase (hours)			
<1:34PM	1.29 (0.87 – 1.94)	1.37 (0.86 – 2.19)	1.37 (0.97 – 1.93)
1:34 PM to 3:51	1.00 (ref)	1.00 (ref)	1.00 (ref)
>3:51PM	1.73 (1.15 – 2.60)	1.67 (1.07 – 2.61)	1.83 (1.29 – 2.61)

* Adjusted for age, clinic site, race, education, depression, body mass index, self-reported walking for exercise, number of IADL impairments, benzodiazepine use, antidepressant use, sleep medication use, alcohol use, caffeine intake, smoking, self-reported health status, hypertension, and history of medical conditions.

** Participants classified as having dementia are not included in models with MCI as the outcome. Odds ratios represent comparison of cognitively normal to MCI/dementia.