Introduction:
Many biological functions are under circadian control, including release of certain hormones, temperature, blood pressure and heart rate, bone remodeling, sleep and activity cycles. Little is known concerning the causes of age-related changes in circadian patterns and the subsequent effects of these changes on health and well-being. With age, circadian rhythms phase advance resulting in an earlier onset of sleepiness in the evening, and an earlier morning waking time. Some older adults also show a decrease in rhythm amplitude. A disrupted or desynchronized circadian rhythm has been associated with medical illness, such as dementia and cancer. Disturbances of the sleep/wake cycle are particularly pronounced in Alzheimer's disease and hypothesized to be one of the primary causes of institutionalization. Other studies have related sleep disturbances to mortality, cognitive impairments and specific psychiatric diagnoses such as depression, dementia and Parkinson’s diseases.

Given these characteristic age-related changes in circadian patterns and the many systems that are modulated by the circadian clock, studies to determine the consequences of disruption of this cycle are needed. Evidence for an association between circadian rhythms and age-related illness is accumulating. However, evidence for an association between disrupted circadian activity rhythms and cognitive function is limited.

Research question:
Among older women, what is the relationship between circadian parameters measured by actigraphy and cognitive function?

Data:
Visit 8 actigraphy data: Amplitude, Mesor, pseudo-F statistic, and Acrophase.

Visit 8 Form data: MMSE score, Trails B test time and the following covariates: Age; Clinic Site; Race; BMI; Geriatric Depression Scale score; Functional Status (ADL/IADL), Alcohol use; Smoking; Caffeine intake; use of benzodiazepines, antidepressants, other hypnotics; self-reported exercise; self-reported health status; and medical comorbidities.

Visit 9 Form data: MMSE score, Trails B test time, adjudicated data on mild cognitive impairment (MCI) and dementia, and the following covariates: Age; Clinic Site; Race; BMI; Geriatric Depression Scale score; Functional Status (ADL/IADL), Alcohol use; Smoking; Caffeine intake; use of...
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benzodiazepines, antidepressants, other hypnotics; self-reported exercise; self-reported health status; and medical comorbidities.

Analysis Plan and Methods:

We propose to conduct:

(a) A cross-sectional analysis of the association between circadian activity rhythms and cognitive function at visit 8 and;
(b) A longitudinal analysis of the association between visit 8 circadian activity rhythms and change in cognitive function from visit 8 to visit 9 and;
(c) A longitudinal analysis of the association between visit 8 circadian activity rhythms and the risk of MCI or dementia.

Predictor variables: Circadian amplitude, mesor and pseudo-F statistic will be examined as continuous predictor variables and by quartiles. Acrophase will be examined in terms of the deviation from the mean or “healthy” peak timing of activity. We identified three categories based on having a peak time of more than 1.5 standard deviations (SDs) above and below the “healthy” mean for the study population. Phase advanced participants were defined as having an acrophase of <12:50PM (-1.5 SD from the mean) and phase delayed participants were defined as having an acrophase of >4:33PM (+1.5 SD from the mean).

Outcome variables: Trails B and MMSE will be examined as continuous predictor variables and using the following definitions of cognitive impairment: 1.5 SDs above the trails B mean, 1.5 SDs below the MMSE mean and <26 on the MMSE. The Visit 9 adjudicated cognitive outcomes of MCI and dementia will most likely be combined into one variable for cognitive impairment (MCI or dementia vs cognitively normal).

Analysis: We will use linear regression to examine the unadjusted and adjusted trends between linear and categorical circadian measures and trails B and MMSE. We will use logistic regression to examine the unadjusted and adjusted associations between quartiles of amplitude, mesor and pseudo-F statistic and cognitive impairment defined using trails B and MMSE using the top quartile of each predictor variable as the referent. We will use logistic regression to examine the unadjusted and adjusted associations between advanced and delayed acrophase and trails B and MMSE using the mean acrophase category as the referent.

To examine changes in cognitive function from visit 8 to visit 9 we will use random effects regression to determine the change in slope associated with each quartile of amplitude, mesor and pseudo-F statistic and acrophase deviation (advanced and delayed). To examine clinically meaningful differences in cognitive function from visit 8 to visit 9, cognitive impairment will be defined in the following ways: a decline in MMSE score of 3 or more points during follow-up and/or a follow-up score of <26, and a change of more than 1.5 standard deviations (SDs) above the mean for completion of the Trails B (eg. >278 seconds). Logistic regression models will also be used to examine the association of our visit 8 circadian rhythm predictors and cognitive impairment defined using the adjudicated data.

Data will be transformed as needed to ensure that model assumptions are met.
References: