Sleep-wake behaviors associated with cognitive performance in middle-aged participants of the Hispanic Community Health Study / Study of Latinos

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Abstract

Objectives: Many sleep-wake behaviors have been associated with cognition. We examined a panel of sleep-wake/activity characteristics to determine which are most robustly related to having low cognitive performance in midlife. Secondarily, we evaluate the predictive utility of sleep-wake measures to screen for low cognitive performance.

Methods: The outcome was low cognitive performance defined as being >1 SD below average age/sex/education internally-normalized composite cognitive performance levels assessed in the Hispanic Community Health Study/Study of Latinos. Analyses included 1,006 individuals who had sufficient sleep-wake measurements about two years later (mean age=54.9, standard deviation (SD)=5.1; 68.82% female). We evaluated associations of 31 sleep-wake variables with low cognitive performance using separate logistic regressions.

Results: In individual models, the strongest sleep-wake correlates of low cognitive performance were measures of weaker and unstable 24-hour rhythms; greater 24-hour fragmentation; longer time-in-bed; and lower rhythm amplitude. One standard deviation worse on these sleep-wake factors was associated with ~20–30% greater odds of having low cognitive performance. In an internally cross-validated prediction model, the independent correlates of low cognitive performance were: lower Sleep Regularity Index scores; lower pseudo-F statistics (modellability of 24-hour rhythms); lower activity rhythm amplitude; and greater time in bed. Area under the curve was low/moderate (64%) indicating poor predictive utility.

Conclusion: The strongest sleep-wake behavioral correlates of low cognitive performance were measures of longer time-in-bed and irregular/weak rhythms. These sleep-wake assessments were not useful to identify previous low cognitive performance. Given their potential modifiability, experimental trials could test if targeting midlife time-in-bed and/or irregular rhythms influences cognition.

Keywords

cognitive aging; cognitive performance; sleep; sleep-wake rhythms; Hispanic/Latino

Sleep-wake behaviors may be viable targets for experimental dementia prevention trials, given that sleep-wake behavior is modifiable[1–4], and because there are plausible mechanisms by which sleep and circadian dysfunction affect brain health[5–7]. A range of 24-hour sleep-wake behavioral domains/factors have been prospectively associated with worse cognitive outcomes in aging (as reviewed[8]; also see more recent prospective studies such as [9–11]). To prioritize candidates for future trials (that target sleep-wake factors to test effects on dementia biomarkers/cognition), observational evidence is needed regarding which sleep-wake factors most robustly/independently correlate with low cognitive function.

Current evidence does not allow direct within-study/sample comparisons, across a broad panel of domains and measures, regarding which sleep-wake/activity factors are most robustly/independently correlated with cognitive dysfunction. Several past studies have examined night-time (sleep duration)[12,13] and daytime (e.g., low activity)[14] predictors of dementia separately. Other studies have shown that measures of 24-hour sleep-wake/rest-activity disruption are associated with the incidence of cognitive impairment independent of sleep and activity[10,11,15–17]. In these studies, various measures have been used across publications to examine similar domains/concepts. For example, both extended-cosine based[16] and non-parametric approaches[17] have been used to predict future cognitive impairment; both non-parametric interdaily stability[18] and the Sleep Regularity Index[19] have been proposed to assess 24-hour sleep-wake rhythmicity; and both detrended fluctuation analysis[10] and intraday variability[11] variables have been used to link 24-hour fragmentation with dementia risk.

There is a particular need for evidence regarding which, of the sleep-wake domains/factors that have been linked with cognition in older adults[9–17], are related to low cognitive performance in midlife. Identifying modifiable factors associated with low cognitive performance in midlife is important, given that poor performance on neuropsychological test batteries in midlife/early late-late life is associated with higher dementia risk[20,21]. For example, being in the lowest quartile on a composite cognitive performance variable, assessed in midlife when the sample age was around 55 years old on average, was associated with an estimated 3.8 (95% confidence interval: 2.5–6.0) times the odds of developing dementia over 20 years later [20]. Midlife is an important period from which to initiate selective prevention approaches[22]. Since dementia can have a decades long incubation period, it is plausible that relationships between signs of sleep-wake behavioral disruption and cognitive pathology already exist by midlife.

Evidence regarding which sleep-wake factors are associated with cognition in midlife, especially in high-risk and minority groups, is currently limited. The above-cited studies on sleep-wake patterns and cognitive outcomes utilized samples that were older and predominately non-Hispanic white. Less research in this area has focused on Hispanic/Latinos. The number and proportion of people with dementia of Hispanic/Latino ancestry in the United States is expected to grow dramatically in the next three decades[23,24]. Recent research has identified associations of both sleep duration and actigraphy-estimated sleep onset latency with cognition in Hispanic/Latinos[25,26]. But we are unaware of prior studies that have characterized the relationships between an in-depth panel of multidimensional sleep-wake behaviors in relation to low cognitive function in midlife Hispanic/Latinos.

In addition, while the prior studies reviewed above have shown statistical associations between sleep-wake variables and cognitive outcomes, it is not known whether simple sleep-wake measures have any utility for detecting cases of lower cognitive function. The presence of a statistical association between two factors (e.g., levels of sleep factor X are higher in people with disease Y) does not mean that one factor can be used to provide valid discrimination/prediction of the other (e.g., high levels of sleep factor X accurately determine who has disease Y)[27,28]. If sleep-wake measures were useful to screen for low cognitive performance in midlife, they may be helpful to narrow the pool of individuals who should undergo traditional in-depth neuropsychological screening in midlife.

To address these gaps in the literature, our first aim was to explore the associations between a multidimensional panel of sleep-wake behavioral factors with low cognitive performance among Hispanic/Latinos in midlife. Analyses ranked the effect sizes and assessed the statistical independence of a panel of 24-hour sleep-wake measures in relation to the outcome of low midlife cognitive performance. Second, we evaluated the predictive utility of sleep-wake measures for detecting low cognitive performance using LASSO regression.

Methods

Participants:

This study was a secondary data analysis including a subset of participants from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). From 2008–2011, the HCHS/SOL enrolled 16,415 participants age 18–74 years at screening, from four sites in the United States (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA). As described previously[29], the HCHS/SOL was designed to be representative of Hispanic/Latino adults in the target communities and employed a two-stage probability sampling approach with deliberate oversampling of specific groups and sampling weights for analyses. However, this paper focuses on measures that were available in a relatively small subset of the overall sample (n=1,006; see below). Therefore, we do not use sampling weights as we do not intend for or imply that this sample necessarily represents the entire HCHS/SOL or target Hispanic/Latino population.

Based on our aims, our analytic sample was first restricted to participants age 45+ years of age who had sufficient data to determine education-normalized performance on all four neuropsychological assessments (n=8,703). Of these HCHS/SOL parent study participants, a total of 1,260 had enrolled in the Sueño Ancillary Study (conducted from 2010–2013; only included people up to age 65), which provided data for the sleep-wake measures analyzed here. The Sueño study included people who were willing to undergo sleep assessments for the study, and excluded those who reported severe sleep disorders at baseline defined as apnea hypopnea index < 50 events/hr on home sleep testing, no clinical treatment for sleep apnea, and no clinical diagnosis of narcolepsy. We further excluded 151 participants who did not meet the quality control standard for their sleep-wake behavioral data (as described below). Of these 1,109 individuals, 1,006 also had complete self-report sleep data and were included in the analysis. All study procedures were approved by the Institutional Review Boards of the participating institutions. Participants provided written informed consent.

Objective sleep-wake behavioral measures:

In the Sueño study, participants were asked to wear an Actiwatch Spectrum device (Philips Respironics) on the non-dominant wrist for seven days (mean recording length = 7.83 days, standard deviation = 0.96). During the actigraphy recording period, participants completed a sleep diary, which was used as described previously to identify the rest/sleep period[30]. Participants also completed questionnaires regarding their sleep. Participants were excluded from the analysis if they had less than 3 continuous good days of actigraphy data, with good days defined as missing no more than 4 hours per day and missing no data in the main rest/sleep interval. These quality control criteria were ascertained independently then adjudicated by the second author and a research assistant trained in the protocol.

Consistent with sleep-wake health as a multidimensional construct (e.g., R[U] SATED which is meant to stand for "Regularity," "Satisfaction," "Alertness," "Timing," "Efficiency," and "Duration")[31], we considered sleep-wake/activity factors within eight broadly defined conceptual domains (information in Table 1). Main sleep periods and naps were manually identified from the actigraphy data using an approach that has been validated against polysonmography[32]. These data were used to calculate both daytime and night-time sleep variables. We also used circadian rest-activity rhythm variables from commonly applied extended-cosine[33] (R package 'RAR') and non-parametric approaches[34,35]. We used custom R code to calculate the hourly intradaily variability metric using all the data as described previously[35] and using the entire (not subsampled) time series variance in the denominator as described previously[36]. As additional regularity measures, we used recently developed metrics including: the Sleep Regularity Index[19] (higher indicates greater sleep regularity), Composite Phase Deviation (index based on daily mid-sleep and average midsleep timing; higher reflects less regularity)[37], and Residual Circadian Spectrum[38] (which decomposes error from the extended cosine model into low, medium, and high frequency deviations). As another measure related to ultradian variability/fragmentation, we used the scaling exponent from detrended fluctuation analysis[10] (higher reflects less ultradian variation) calculated with the R package 'nonlinearTseries' function 'dfa.'

Other health factor predictor variables:

We also included several self-reported measures collected at the Sueño visit that were relevant based on their potential associations with midlife cognition. These were: medical histories of chronic medical conditions (hypertension, coronary heart disease, stroke, and diabetes); anxiety symptom severity (10-item Spielberger State-trait anxiety index [39]); depression symptom severity (measured with the 10-item Center for Epidemiological Studies Depression Scale[40]). We also examined daytime sleepiness (total scores on the Epworth Sleepiness Scale[41]) and insomnia severity (Insomnia Severity Index[42] total scores).

Neuropsychological outcome measure:

Low cognitive performance was defined as being > 1 standard deviation below the mean on a composite cognitive performance variable. This composite cognitive performance variable was calculated as in similar work[43], such that lower than expected performance was defined after removing effects of age, sex, and education. To do so, we averaged, then z-scored, internally standardized age/sex/education normalized scores on four cognitive assessments.

The four “pen and paper”/“face-to-face” cognitive assessments, administered by study staff in Spanish or English, were: (1) total scores from the Digit Symbol Substitution Test[44] (assessing sustained attention/processing speed); (2) three learning trial total scores from the Spanish-English Verbal Learning Test[45] (assessing learning); (3) delayed recall on the Spanish-English Verbal Learning Test (assessing delayed memory); and (4) the total number of words named on a word fluency test[46] (assessing verbal fluency). Note that these cognitive tests were administered at baseline, which averaged 2.1 years (SD=0.4) before the Sueño visit.

All test scores were first internally standardized based on age/sex/education norms. We computed means and standard deviations for each test within age/sex/education strata using data from the 8,703 HCHS/SOL participants who had age, education, and cognitive test data. For normalizing purposes, age was treated as a four-level categorical variable (45–49 years, 50–54 years, 55–59 years, and 60–64 years), whereas sex and education were defined as shown in Table 2. For each test, we computed Z-scores (in standard deviation units) based on these age/sex/education strata norms.

Covariates:

We considered several non-modifiable factors as covariates in all models, as they represent potential confounding variables. These were age (expressed continuously), sex, self-reported heritage (groups defined as in Table 2), cognitive test administration language, study site, and time between baseline cognitive testing and the sleep assessments.

Statistical analyses:

Low cognitive performance, defined as being > 1 standard deviation below the mean on a composite cognitive performance variable, was the outcome. All continuous predictor variables were standardized (mean=0 and standard deviation=1) prior to analysis to facilitate effect size comparisons. We used separate logistic regression models for each of the predictor variables. All models adjusted for the covariates listed above. There were 31 sleep-wake/activity variables and 6 other health factors. We accounted for these 37 comparisons of interest by reporting Benjamini-Hochberg False Discovery Rates[47]. We illustrate the odds ratios and confidence intervals on a forest plot that was generated using the R package ‘forestploter.’

In the multivariable analysis, we used Least Absolute Shrinkage and Selection Operator (LASSO) implemented using the R package ‘glmnet’ to fit regression models. In the LASSO, we forced all the covariates into the model. We only entered predictor variables if their FDR from logistic regression was less than 10%. We did this prescreening to ensure that the LASSO model was driven by factors that are also associated with cognition when considered alone. Three LASSO models were constructed to compare the relative predictive utility of: (1) sleep-wake variables; (2) aforementioned other health factors; (3) both sleep-wake variables and other health factors. We report overall predictive utility using the area under the curve (AUC) calculated with five-fold cross-validation. The five-fold cross-validation involves dividing the dataset into five subsets, training the LASSO model on four of the subsets, and evaluating its performance on the remaining subset. This process is

repeated multiple times, utilizing each subset for both training and testing, to obtain a more reliable evaluation of the performance of the model. To provide further evidence of low predictive performance, we constructed Random Forest and Support Vector Machine using the R packages ‘randomForest’ and ‘e1071’, respectively. However, both machine learning techniques produced similarly poor performance and therefore only LASSO model reported based on its relatively better interpretability.

Results

Sample characteristics:

The sample was 68% female and about 55 years old on average. See Table 2 for additional sample characteristics.

Individual sleep-wake/activity variables related to low cognitive performance:

None of the actigraphy/score sleep timing, efficiency, or daytime sleep variables were statistically associated with cognitive performance status in this sample (Table 3, Figure 1). In addition, self-reported insomnia severity was not associated with low cognitive performance.

There were statistically significant associations between measures of lower 24-hour regularity, higher ultradian fragmentation, longer time in bed (from diary), and lower activity levels with higher odds of having low cognitive performance (Table 3). Of these sleep-wake/activity variables that were statistically associated with low cognitive performance, confidence intervals for effect size (odds ratio) estimates were all in the small range and widely overlapping (Figure 1). For example, per standard deviation higher relative amplitude and Sleep Regularity Index Scores, the odds of having low cognitive performance were ~20% lower (95% confidence interval (CI) odds ratio: 0.67–0.93). That said, the numerically largest and most statistically robust correlate of low cognitive performance were measures which captured rest-activity (sleep-wake) rhythms. For example, per standard deviation higher log transformed rest-activity rhythm amplitude, the odds of having low cognitive performance were estimated to be 31% lower (False Discovery Rate < 0.001; 95% CI odds ratio: 0.58–0.81).

Independence of sleep-wake variables and predictive validity:

Based on evidence for their associations with cognition, we selected the 12 variables highlighted in Table 3 for entry into the LASSO model (in addition to the covariates listed above, which we forced into all models). The cross-validated overall prediction accuracy was low-to-moderate (Table 4; AUC=64%).

The sleep-wake variables retained by the LASSO model that were independently associated with low cognitive performance were: measures of higher 24-hour regularity (the Sleep Regularity Index and pseudo-F statistic), longer time in bed, and lower activity rhythm amplitude. Alternative modelling approaches, e.g., including using Random Forest Models and Support Vector Machines produced similar results indicative of overall low-to-moderate AUC.

Analyses using low performance on the individual subsets as the outcome:

Finally, we sought to determine if associations between the identified sleep-wake factors and low overall cognitive performance were driven by particular cognitive tests. Each of the sleep-wake factors identified as independent correlates of low cognitive performance were examined in a set of separate logistic regression analyses which used low performance (>1 standard deviation below normed levels) on each cognitive test for their outcomes. Similar associations were detected between all measures of regularity/activity rhythm amplitude with each subtest as compared with the overall performance variable (see widely overlapping confidence intervals). Longer time in bed appeared to be potentially more robustly associated with the overall cognitive performance variable (Table 3, e.g., OR=1.25 (1.05, 1.50) than the individual subtests (Supplemental Table 1, e.g., OR=1.14 (9% CI: 0.95, 1.37).

Discussion

By leveraging a multi-domain panel of sleep-wake/activity factors and using multivariable modelling, our study was able to identify sleep-wake measures that were independently associated with low cognitive performance in midlife. It is also notable that we did not observe associations between sleep duration, sleep fragmentation, daytime napping, or insomnia symptoms with low cognitive performance. Our main findings were that less regular sleep-wake patterns, longer time in bed, and lower activity rhythm amplitude were all independently associated with having lower than expected cognitive performance among US Hispanic/Latino adults aged 45–64 years. These observations mirror findings from prior prospective studies of older adults that have shown associations between measures of irregular/weak activity rhythms with future cognitive decline[16,17]; and longer time in bed with associated with future dementia risk[9]. Given that low cognitive performance in midlife is a risk factor for future dementia[20,21], the associated sleep-wake behavioral factors (long time-in-bed and weak/irregular rhythms) may be important candidates for future trials examining whether targeting these sleep-wake factors in midlife reduce the risk of cognitive decline and dementia.

It is important to note limitations related to the current study's observational, correlative, design. Our findings linked sleep-wake and cognitive data from single timepoints in midlife. As noted above, data from our study can be interpreted in the context of prior literature linking the identified sleep-wake factors[9,16,17] and low midlife cognitive performance[20,21] with future dementia risk. But the data presented here do not directly link these sleep-wake factors with dementia. In addition, findings were based on a single, relatively short-term, assessment of sleep-wake patterns. Future longitudinal studies are needed to clarify the temporal relationships between sleep-wake factors, their changes over time, cognition, potential mediating factors (e.g., psychological, lifestyle, and/or cardiometabolic factors), and the development of dementia. It is also important to note that all observational studies are subject to residual confounding and cannot ascertain causality (e.g., we cannot determine if sleep-wake variables influence cognitive performance; or if underlying/measured factors influence both sleep-wake behavior and cognition). Therefore, experimental studies are needed to determine if targeting these aspects of sleep-wake/activity disruption (irregular

sleep-wake patterns, long time in bed, low activity rhythm amplitude) in midlife causally alters the course of brain/cognitive aging and forestalls or prevents dementia.

Such future trials are plausible based on: (1) these sleep-wake factors being potentially modifiable; and (2) there being plausible mechanisms by which modifying these behavioral factors could improve the trajectory of cognitive function. Regarding modifiability of these sleep-wake factors, several options are currently available for testing, e.g.: a transdiagnostic intervention, called the Transdiagnostic Intervention for Sleep and Circadian Dysfunction, has been recently shown to increase actigraphy measures of regularity[4]; approaches to restrict time in bed are already widely used as part of first line treatment for insomnia[48]; and behavioral approaches like prescribed exercise and behavioral activation may be useful to increase activity rhythm amplitude. With regard to plausible mechanisms: both inactivity[49] and irregular sleep-wake rhythms[50,51] affect cardiometabolic risk factors that can lead to neurodegeneration[52,53] and cerebrovascular disease[54,55]; and excessive time in bed may reduce the amount of time spent physically, socially, or mentally engaged.

With regard to our secondary aim, we found that even including health conditions and sleep-wake measures, models could not accurately predict who had low cognitive performance in this sample. This observation suggests that, while there may be associations (suggesting possibly etiological relationships) between sleep-wake disruption and cognition, these measures of sleep-wake disruption were not a useful surrogate for neuropsychological-based testing. It is important to note one major limitation of our prediction aim is that low cognitive performance was determined an average of about two years before sleep was measured. As a result, this could have diluted the strength of association and reduced predictive validity as compared with identifying truly concurrent low cognitive performance. Prediction results may vary when using these or other sleep predictors (e.g., sleep electrophysiology) for predicting different outcomes and in different timeframes (e.g., hippocampal volume or future dementia diagnosis). Overall, our sample and these findings are not necessarily be generalizable to other populations. Future studies employing similar methodological approaches will be needed to replicate and potentially confirm: (a) whether these are indeed key sleep-wake factors related to midlife cognition across ethnic/geographic groups; and (b) that in general, although there are associations between these factors, sleep-wake measures are not clinically useful for identifying people with low cognitive performance.

In conclusion, we have identified aspects of sleep-wake disruption that are related to low cognitive performance in midlife independent of each other and other dementia risk factors (including self-reported stroke, hypertension, diabetes, and anxiety). These findings mirror associations of sleep-wake rhythm disruption and cognitive decline in older adults. Thus, we have provided evidence that relationships between sleep-wake disruption and low cognitive function exist in the decade before older adulthood. Future studies are needed to determine if targeting these sleep-wake factors, i.e., promoting regular/strong sleep-wake activity patterns and reducing time in bed, can help protect brain health and reduce dementia risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The data underlying this article will be shared on reasonable request to the corresponding author and HCHS/SOL Study Administration.

References

1. Riede SJ, van der Vinne V, Hut RA. The flexible clock: predictive and reactive homeostasis, energy balance and the circadian regulation of sleep–wake timing. Journal of Experimental Biology 2017; 220 (5): 738–749. [PubMed: 28250173]
2. Reebs SG, Mrosovsky N. Effects of induced wheel running on the circadian activity rhythms of Syrian hamsters: entrainment and phase response curve. J Biol Rhythms 1989; 4 (1): 39–48. [PubMed: 2519579]
3. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. Journal of biological rhythms 2006; 21 (6): 482–493. [PubMed: 17107938]
4. Harvey AG, Dong L, Hein K, et al. A randomized controlled trial of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) to improve serious mental illness outcomes in a community setting. Journal of consulting and clinical psychology 2021; 89 (6): 537–550. [PubMed: 34264701]
5. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science (New York, NY) 2013; 342 (6156): 373–377.
6. Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. Nature Communications 2020; 11 (1): 4411.
7. Sommer R, Yu L, Schneider JA, Bennett DA, Buchman AS, Lim ASP. Disrupted Rest-Activity Rhythms and Cerebral Small Vessel Disease Pathology in Older Adults. Stroke 2021; 52 (7): 2427–2431. [PubMed: 33902300]
8. Smagula SF, Gujral S, Capps CS, Krafty RT. A Systematic Review of Evidence for a Role of Rest-Activity Rhythms in Dementia. Frontiers in Psychiatry 2019; 10 (778).
9. 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.
10. Li P, Yu L, Lim ASP, et al. Fractal regulation and incident Alzheimer's disease in elderly individuals. Alzheimer's & dementia : the journal of the Alzheimer's Association 2018; 14 (9): 1114–1125.

11. 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. The Lancet Healthy longevity 2020; 1 (3): e96–e105. [PubMed: 34179863]
12. 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]
13. Shi L, Chen SJ, Ma MY, et al. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Med Rev 2018; 40: 4–16. [PubMed: 28890168]
14. Del Pozo Cruz B, Ahmadi M, Naismith SL, Stamatakis E. Association of Daily Step Count and Intensity With Incident Dementia in 78 430 Adults Living in the UK. JAMA Neurol 2022; 79 (10): 1059–1063. [PubMed: 36066874]
15. 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]
16. 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]
17. Xiao Q, Sampson JN, LaCroix AZ, et al. Nonparametric Parameters of 24-Hour Rest-Activity Rhythms and Long-Term Cognitive Decline and Incident Cognitive Impairment in Older Men. J Gerontol A Biol Sci Med Sci 2022; 77 (2): 250–258. [PubMed: 34558603]
18. Zuurbier LA, Ikram MA, Luik AI, et al. Cerebral small vessel disease is related to disturbed 24-h activity rhythms: a population-based study. European Journal of Neurology 2015: n/a-n/a.
19. Lunsford-Avery JR, Engelhard MM, Navar AM, Kollins SH. Validation of the Sleep Regularity Index in Older Adults and Associations with Cardiometabolic Risk. Scientific Reports 2018; 8 (1): 14158. [PubMed: 30242174]
20. Knopman DS, Gottesman RF, Sharrett AR, et al. Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: The Atherosclerosis Risk in Communities Study. Alzheimers Dement 2018; 14 (11): 1406–1415. [PubMed: 29763593]
21. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. Neurology 2015; 85 (10): 898–904. [PubMed: 26109713]
22. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet (London, England) 2020; 396 (10248): 413–446. [PubMed: 32738937]
23. Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged ≥65 years. Alzheimers Dement 2019; 15 (1): 17–24. [PubMed: 30243772]
24. Quiroz YT, Solis M, Aranda MP, et al. Addressing the disparities in dementia risk, early detection and care in Latino populations: Highlights from the second Latinos & Alzheimer's Symposium. Alzheimer's & Dementia 2022; 18 (9): 1677–1686.
25. Agudelo C, Tarraf W, Wu B, et al. Actigraphic sleep patterns and cognitive decline in the Hispanic Community Health Study/Study of Latinos. Alzheimers Dement 2021; 17 (6): 959–968. [PubMed: 33350583]
26. Alberto R, Wassim T, Martha D, et al. Sleep duration is associated with worse neurocognitive function in Hispanic/Latinos: Results of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (P1.100). Neurology 2015; 84 (14 Supplement): P1.100.
27. Poldrack RA, Huckins G, Varoquaux G. Establishment of Best Practices for Evidence for Prediction: A Review. JAMA Psychiatry 2020; 77 (5): 534–540. [PubMed: 31774490]
28. Varga TV, Niss K, Estampador AC, Collin CB, Moseley PL. Association is not prediction: A landscape of confused reporting in diabetes - A systematic review. Diabetes Res Clin Pract 2020; 170: 108497. [PubMed: 33068662]
29. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010; 20 (8): 642–649. [PubMed: 20609344]

30. Patel SR, Weng J, Rueschman M, et al. Reproducibility of a Standardized Actigraphy Scoring Algorithm for Sleep in a US Hispanic/Latino Population. Sleep 2015; 38 (9): 1497–1503. [PubMed: 25845697]
31. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep 2014; 37 (1): 9–17. [PubMed: 24470692]
32. Kushida CA, Chang A, Gadkary C, Guilleminault C, Carrillo O, Dement WC. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Med 2001; 2 (5): 389–396. [PubMed: 14592388]
33. 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. Stat Med 2006; 25 (22): 3893–3904. [PubMed: 16381069]
34. van Someren EJ, Hagebeuk EE, Lijzenga C, et al. Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biol Psychiatry 1996; 40 (4): 259–270. [PubMed: 8871772]
35. Suibkitwanchai K, Sykulski AM, Perez Algorta G, Waller D, Walshe C. Nonparametric time series summary statistics for high-frequency accelerometry data from individuals with advanced dementia. PloS one 2020; 15 (9): e0239368–e0239368. [PubMed: 32976498]
36. Fossion R, Rivera AL, Toledo-Roy JC, Ellis J, Angelova M. Multiscale adaptive analysis of circadian rhythms and intradaily variability: Application to actigraphy time series in acute insomnia subjects. PLoS One 2017; 12 (7): e0181762. [PubMed: 28753669]
37. Fischer D, Vetter C, Roenneberg T. A novel method to visualise and quantify circadian misalignment. Sci Rep 2016; 6: 38601. [PubMed: 27929109]
38. Krafty RT, Fu H, Graves JL, Bruce SA, Hall MH, Smagula SF. Measuring Variability in Rest-Activity Rhythms from Actigraphy with Application to Characterizing Symptoms of Depression. Stat Biosci 2019; 11 (2): 314–333. [PubMed: 31788133]
39. CD S State-trait anxiety inventory. In: John Wiley & Sons I, ed. The Corsini Encyclopedia of Psychology Hoboken, NJ, USA2010.
40. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). American journal of preventive medicine 1994; 10 (2): 77–84. [PubMed: 8037935]
41. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991; 14 (6): 540–545. [PubMed: 1798888]
42. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001; 2 (4): 297–307. [PubMed: 11438246]
43. Smagula SF, Zhang G, Gujral S, et al. Association of 24-Hour Activity Pattern Phenotypes With Depression Symptoms and Cognitive Performance in Aging. JAMA Psychiatry 2022; 79 (10): 1023–1031. [PubMed: 36044201]
44. Wechsler D WAIS Manual – Third Edition New York: Psychological Corporation; 1997.
45. González HM, Mungas D, Reed BR, Marshall S, Haan MN. A new verbal learning and memory test for English- and Spanish-speaking older people. J Int Neuropsychol Soc 2001; 7 (5): 544–555. [PubMed: 11459106]
46. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment (5th ed.). Neuropsychological assessment (5th ed.). 2012.
47. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B (Methodological) 1995; 57 (1): 289–300.
48. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2021; 17 (2): 255–262. [PubMed: 33164742]
49. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes 2007; 56 (11): 2655–2667. [PubMed: 17827399]
50. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 2009; 106 (11): 4453–4458. [PubMed: 19255424]

51. West AC, Smith L, Ray DW, Loudon ASI, Brown TM, Bechtold DA. Misalignment with the external light environment drives metabolic and cardiac dysfunction. Nature Communications 2017; 8 (1): 417.

52. Moheet A, Mangia S, Seaquist ER. Impact of diabetes on cognitive function and brain structure. Annals of the New York Academy of Sciences 2015; 1353: 60–71. [PubMed: 26132277]

53. Fiford CM, Nicholas JM, Biessels GJ, Lane CA, Cardoso MJ, Barnes J. High blood pressure predicts hippocampal atrophy rate in cognitively impaired elders. Alzheimers Dement (Amst) 2020; 12 (1): e12035. [PubMed: 32587882]

54. Wang DQ, Wang L, Wei MM, et al. Relationship Between Type 2 Diabetes and White Matter Hyperintensity: A Systematic Review. Front Endocrinol (Lausanne) 2020; 11: 595962. [PubMed: 33408693]

55. White WB, Wakefield DB, Moscufo N, et al. Effects of Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People (INFINITY). Circulation 2019; 140 (20): 1626–1635. [PubMed: 31607143]

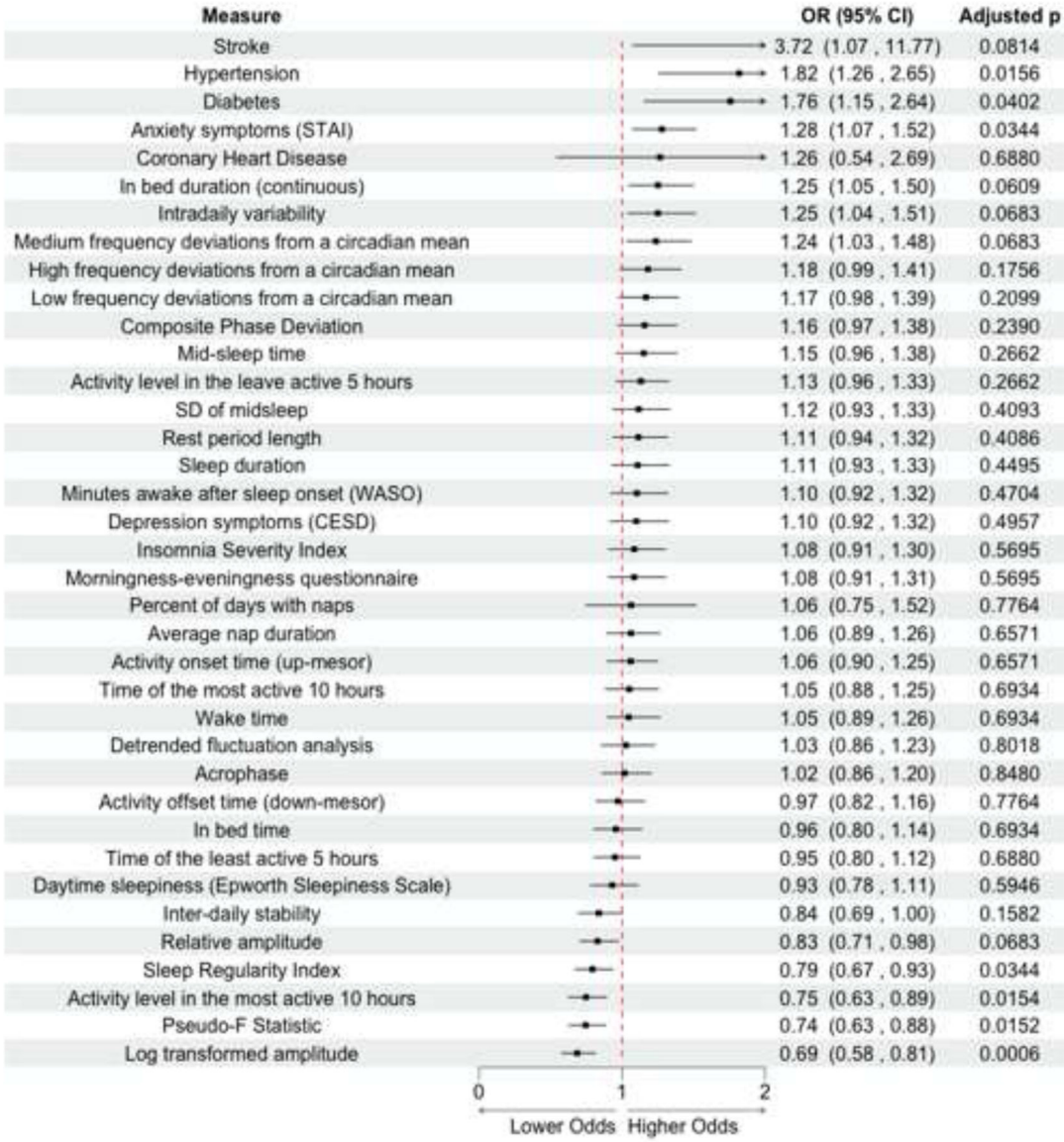

Figure 1.

Associations of each individual sleep-wake measures with low cognitive performance ranked by effect sizes.

All odds ratios are from separate models that are adjusted for age, sex, test administration language, time between cognitive and sleep visits, study site, and heritage. False Discovery Rate adjusted p-values are reported.

Table 1.

List of domains, measures, and data sources for each predictor used

Domains	Measures	Data Source
24-hour regularity	Medium frequency deviations from a circadian mean	Actigraphy
	Low frequency deviations from a circadian mean	Actigraphy
	Composite Phase Deviation	Scored actigraphy data
	SD of midsleep	Scored actigraphy data
	Inter-daily stability	Actigraphy
	Relative amplitude	Actigraphy
	Sleep Regularity Index	Scored actigraphy data
	Pseudo-F Statistic	Actigraphy
Ultradian fragmentation	Intradaily variability	Actigraphy
	High frequency deviations from a circadian mean	Actigraphy
	Detrended fluctuation analysis	Actigraphy
Timing	Mid-sleep time	Scored actigraphy data
	Activity onset time (up-mesor)	Actigraphy
	Morningness-eveningness questionnaire	Self-report
	Time of the most active 10 hours	Actigraphy
	Wake time	Scored actigraphy data
	Acrophase	Actigraphy
	Activity offset time (down-mesor)	Actigraphy
	Time of the least active 5 hours	Actigraphy
	In bed time	Diary
Duration	In bed duration (continuous)	Diary
	Rest period length	Actigraphy
	Sleep duration	Scored actigraphy data
Efficiency	Activity level in the leave active 5 hours	Actigraphy
	Wake after sleep onset (WASO)	Scored actigraphy data
Daytime sleep	Any napping	Scored actigraphy data
	Average nap duration	Scored actigraphy data
	Daytime sleepiness (Epworth Sleepiness Scale)	Self-report
Activity level	Activity level in the most active 10 hours	Actigraphy
	Log transformed rhythm amplitude	Actigraphy
Satisfaction	Insomnia Severity Index	Self-report
Health factors	Stroke	Self-report
	Hypertension	Self-report
	Diabetes	Self-report
	Anxiety symptoms (STAI)	Self-report
	Coronary Heart Disease	Self-report
	Depression symptoms (CESD)	Self-report

Table 2.

Analytic sample demographic and descriptive information (n=1006)

Age in years, mean (standard deviation)	55 (5)
Sex	
Female	67.5 (679)
Male	32.5 (327)
Heritage	
Central American	13.1 (132)
Cuban	19.4 (195)
Dominican	13.2 (133)
Mexican	24.4 (245)
Puerto Rican	20.9 (210)
South American	9.0 (91)
Test administration language	
Spanish	15.7 (158)
English	84.3 (848)
Education	
No high school diploma or GED	32.6 (277)
At most a High school diploma or GED	23.1 (196)
Greater than high school (or GED) education	44.4 (377)
Years between baseline and the sleep visit, mean (standard deviation)	2.1 (4.0)
Cognitive Test Scores (before standardization)	
Digit Symbol Substitution Test total score	36.4 (12.7)
Three learning trial total sore (SEVLT)	23.9 (5.4)
Delayed recall (SEVLT)	8.7 (2.9)
Total number of words (Word Fluency Test)	19.0 (7.2)

Percent (n) shown unless otherwise noted. Acronym: SEVLT, Spanish-English Verbal Learning Test

Table 3.

Associations between each sleep-wake/activity variable and low cognitive performance

Domains	Measures	OR (95% CI)	Adjusted p-value
24-hour regularity	Medium frequency deviations from a circadian mean	1.24 (1.03, 1.48)	0.068
	Low frequency deviations from a circadian mean	1.17 (0.98, 1.39)	0.210
	Composite Phase Deviation	1.16 (0.97, 1.38)	0.239
	SD of midsleep	1.12 (0.93, 1.33)	0.409
	Inter-daily stability	0.84 (0.69, 1.00)	0.158
	Relative amplitude	0.83 (0.71, 0.98)	0.068
	Sleep Regularity Index	0.79 (0.67, 0.93)	0.034
	Pseudo-F Statistic	0.74 (0.63, 0.88)	0.015
Ultradian fragmentation	Intradaily variability	1.25 (1.04, 1.51)	0.068
	High frequency deviations from a circadian mean	1.18 (0.99, 1.41)	0.176
	Detrended fluctuation analysis	1.03 (0.86, 1.23)	0.802
Timing	Mid-sleep time	1.15 (0.96, 1.38)	0.266
	Activity onset time (up-mesor)	1.06 (0.90, 1.25)	0.657
	Morningness-eveningness questionnaire	1.08 (0.91, 1.31)	0.570
	Time of the most active 10 hours	1.05 (0.88, 1.25)	0.693
	Wake time	1.05 (0.89, 1.26)	0.693
	Acrophase	1.02 (0.86, 1.20)	0.848
	Activity offset time (down-mesor)	0.97 (0.82, 1.16)	0.776
	Time of the least active 5 hours	0.95 (0.80, 1.12)	0.688
	In bed time	0.96 (0.80, 1.14)	0.693
Duration	In bed duration (continuous)	1.25 (1.05, 1.50)	0.061
	Rest period length	1.11 (0.94, 1.32)	0.409
	Sleep duration	1.11 (0.93, 1.33)	0.450
Efficiency	Activity level in the leave active 5 hours	1.13 (0.96, 1.33)	0.266
	Wake after sleep onset (WASO)	1.10 (0.92, 1.32)	0.470
Daytime sleep	Any napping	1.06 (0.75, 1.52)	0.776
	Average nap duration	1.06 (0.89, 1.26)	0.657
	Daytime sleepiness (Epworth Sleepiness Scale)	0.93 (0.78, 1.11)	0.595
Activity level	Activity level in the most active 10 hours	0.75 (0.63, 0.89)	0.015
	Log transformed rhythm amplitude	0.69 (0.58, 0.81)	0.001
Satisfaction	Insomnia Severity Index	1.08 (0.91, 1.30)	0.570
Health factors	Stroke	3.72 (1.07, 11.8)	0.081
	Hypertension	1.82 (1.26, 2.65)	0.016
	Diabetes	1.76 (1.15, 2.64)	0.040
	Anxiety symptoms (STAI)	1.28 (1.07, 1.52)	0.034
	Coronary Heart Disease	1.26 (0.54, 2.69)	0.688
	Depression symptoms (CESD)	1.10 (0.92, 1.32)	0.496

Notes: (1) All OR (odds ratios) are from separate models that are adjusted for age, sex, heritage, test administration language, time between cognitive and sleep visits, and study site; (2) p-values adjusted for multiple comparisons using the Benjamini-Hochberg method; and (3) shading indicates variable was selected into the multivariable modeling

Table 4.

Variables retained by the final LASSO model

Domains	Measures	β
24-hour regularity	Sleep Regularity Index	−0.06
	Pseudo-F Statistic	−0.04
Duration	In bed duration	0.13
Activity level	Log transformed rhythm amplitude	−0.22
Health factors	Stroke	0.87
	Hypertension	0.34
	Diabetes	0.22
	Anxiety symptoms (STAI)	0.13

The model also included covariates (forced into model: age, sex, heritage, test administration language, time between cognitive and sleep visits, and study site)