

Circadian rest-activity rhythm and longitudinal brain changes underlying late-life cognitive decline

So Yeon Jeon, MD, PhD,^{1,2} Min Soo Byun, MD, PhD,^{3,4} Dahyun Yi, PhD,⁵ Gijung Jung, PhD,³ Jun-Young Lee, MD, PhD,⁶ Yu Kyeong Kim, MD, PhD,⁷ Chul-Ho Sohn, MD, PhD,^{8,9} Koung Mi Kang, MD, PhD,⁹ Yu Jin Lee, MD, PhD^{3,4} and Dong Young Lee, MD, PhD^{3,4,5*} and for the KBASE Research Group^a

Aim: The neurobiological substrates underlying the relationship of circadian rest-activity rhythm (RAR) alteration with accelerated late-life cognitive decline are not clearly understood. In the present study, the longitudinal relationship of objectively measured circadian RAR with *in vivo* Alzheimer disease (AD) pathologies and cerebrovascular injury was investigated in older adults without dementia.

Methods: The present study included 129 participants without dementia who participated in the KBASE (Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease) cohort. All participants underwent actigraphy at baseline and two consecutive [¹¹C] Pittsburgh compound-B positron emission tomography (PET), [¹⁸F] fluorodeoxyglucose-PET, magnetic resonance imaging, and Mini-Mental State Examination (MMSE) at baseline and at a 2-year follow-up assessment. The associations of circadian RAR with annualized change in neuroimaging measures including global amyloid-beta retention, AD-signature region cerebral glucose metabolism (AD-CM), and white matter hyperintensity volume were examined.

Results: Delayed acrophase at baseline was significantly associated with greater annualized decline of AD-CM over a 2-year period, but not with that of other neuroimaging measures. In contrast, other circadian RAR parameters at baseline had no association with annualized change of any neuroimaging measures. Annualized decline of AD-CM was also significantly positively associated with the annual change in MMSE scores. Furthermore, a mediation analysis showed that greater reduction in AD-CM mediated the effect of delayed acrophase at baseline on faster decline of MMSE score.

Conclusion: The findings indicate that delayed acrophase in late life may cause or predict hypometabolism at AD-signature brain regions, which underlies cognitive decline in the near future.

Keywords: Alzheimer disease, cognitive decline, neurodegeneration, older adults, rest-activity rhythm.

<http://onlinelibrary.wiley.com/doi/10.1111/pcn.13521/full>

Circadian rhythms are near 24-h oscillations in behavioral, physiological, and cellular processes.¹ Disruptions in circadian rhythm are common in aging adults; however, it is more severe in patients with Alzheimer disease (AD) dementia.² Circadian rest-activity rhythm (RAR) is a representative behavioral marker of the circadian rhythm system, and its alterations have been repeatedly described in symptomatic patients with AD.^{3–6} More importantly, a growing number of longitudinal studies reported that RAR dysfunctions including decreased total activity,^{7,8} fragmented rhythm,⁸ and advanced⁹ or delayed phase^{8,10,11} were associated with increased future risk of AD dementia or cognitive decline in cognitively unimpaired adults.^{8–11}

Nevertheless, the neurobiological substrates underlying the relationship of circadian RAR alteration with accelerated cognitive decline are not clearly understood. A cross-sectional clinical study¹²

that investigated the association of circadian rest-activity phase with cerebrospinal fluid AD biomarkers indicated that circadian phase alteration is not associated with amyloid-beta (A β) or tau accumulation in individuals without dementia. A laboratory study¹³ using human fibroblasts and brain samples reported that delayed acrophase of *Bmal 1* gene transcription was observed in cells from patients with AD compared with those from cognitively intact individuals. *Bmal 1* gene is a well-known key circadian transcriptional regulator or master clock gene.¹⁴ A series of preclinical studies^{15–18} also demonstrated that reduction of *Bmal 1* gene expression exacerbated neurodegeneration *via* cortical astrogliosis, oxidative damage, and synaptic degeneration, supporting the close link between circadian phase alteration and neurodegeneration. However, little information is yet available on the relationship between alterations of circadian RAR

¹ Department of Psychiatry, Chungnam National University Hospital, Daejeon, Republic of Korea

² Department of Psychiatry, Chungnam National University College of Medicine, Daejeon, Republic of Korea

³ Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Republic of Korea

⁴ Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea

⁵ Institute of Human Behavioral Medicine, Medical Research Centre, Seoul National University, Seoul, South Korea

⁶ Department of Neuropsychiatry, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea

⁷ Department of Nuclear Medicine, SMG-SNU Boramae Medical Center, Seoul, South Korea

⁸ Department of Radiology, Seoul National University College of Medicine, Seoul, South Korea

⁹ Department of Radiology, Seoul National University Hospital, Seoul, South Korea

* Correspondence: Email: seifpsy@snu.ac.kr

^a The coinvestigators of the KBASE Research Group are listed elsewhere (<http://kbase.kr>).

and longitudinal brain changes underlying cognitive decline in older adults. To our knowledge, no study has investigated the association of baseline circadian RAR and longitudinal changes of neuroimaging measures for AD pathology or cerebrovascular injury.

In this context, we aimed to examine the relationship of circadian RAR at baseline with the longitudinal brain changes related to cognitive impairment over a 2-year period in older adults without dementia. Circadian RAR was objectively evaluated using actigraphy. In regard to brain alterations associated with late-life cognitive decline, cerebral A β deposition and neurodegeneration in AD-signature regions were measured by [^{11}C] Pittsburg compound-B (PiB) positron emission tomography (PET) and [^{18}F] fluorodeoxyglucose (FDG) PET, respectively. Cerebral white matter hyperintensity (WMH) volume on magnetic resonance imaging (MRI) was used as a measure of cerebrovascular injury.¹⁹

Methods

Participants

This study was part of KBASE (Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease), a prospective cohort study that has been ongoing since 2014.²⁰ As of July 2018, 451 individuals without dementia (297 cognitively normal [CN] individuals and 154 individuals with mild cognitive impairment [MCI]) between 55 and 90 years of age were recruited and underwent baseline evaluation including comprehensive clinical assessment, PiB-PET, MRI, and FDG-PET. Among them, 192 patients additionally received actigraphy monitoring. Of these, 10 were excluded because of inadequate collection of actigraphy data. Among them ($n = 182$), we finally included 129 participants (100 CN and 29 MCI), who had completed 2-year follow-up PiB-PET, MRI, and FDG-PET scan for the current study (Fig. 1). Participants of the KBASE were recruited through four recruitment sites across Seoul, South Korea. Eligible patients who participated in a dementia screening program at two public dementia prevention and management centers or who visited memory clinics at two university hospitals (i.e., Seoul National University Hospital [SNUH] and Seoul National University-Seoul Metropolitan Government [SNU-SMG] Boramae Medical Center) across Seoul, South Korea, were informed about study participation. Among them, those who volunteered were invited for an assessment of eligibility. Community volunteers were also recruited through online website advertisements, posters, and brochures provided at main recruitment sites and word of mouth (recommendations from other participants, family members, friends, or acquaintances). The details of KBASE characteristics including recruitment have been previously described.²⁰

The CN group consisted of participants with a Clinical Dementia Rating (CDR) score of 0 and no diagnosis of MCI or dementia. The

MCI group consisted of individuals who met the following inclusion criteria according to the core clinical criteria for the diagnosis of MCI, as recommended by the National Institute of Aging and Alzheimer's Association guidelines²¹: (i) memory complaint corroborated by self, an informant, or a clinician; (ii) objective memory impairment for age, educational year, and sex; (iii) largely intact functional activities; and (iv) without dementia. All individuals with MCI had a global CDR score of 0.5. In terms of criterion (ii) for MCI, all participants with MCI had a performance score of at least 1.0 standard deviations (SDs) below the respective age, educational year, and sex-specific mean for at least one of the four episodic memory tests included in CERAD-K (the Korean version of Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological battery (Word List Memory, Word List Recall, Word List Recognition, and Constructional Recall test).²² The exclusion criteria were the following: (i) presence of a major psychiatric illness; (ii) significant neurological or medical conditions that could affect mental function; (iii) contraindications for MRI (e.g., pacemaker or claustrophobia); (iv) illiteracy; (v) the presence of significant visual/hearing difficulties and/or severe communication or behavioral problems that would render clinical examinations or brain scans difficult; and (vi) taking an investigational drug.

Standard protocol approvals, registrations, and patient consent

The study protocol was approved by the institutional review boards of Seoul National University Hospital (C-1401-027-547) and SNU-SMG Boramae Center (26-2015-60) in Seoul, South Korea, and conducted in accordance with the recommendations of the current version of the Declaration of Helsinki. All participants provided written informed consent prior to participation. This study followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for cohort studies.

Clinical assessments

All participants received standardized clinical and neuropsychological assessments at baseline by trained psychiatrists. The assessments were based on the KBASE clinical assessment protocol, which incorporated the CERAD-K.²³ The global cognition of each participant was assessed using the Korean version of the Mini-Mental State Examination (MMSE)²⁴ at both baseline and 2-year follow-up.

Measurement of circadian RAR data

Circadian RAR data were collected at baseline using the home-based Actiwatch 2 (Philips Respironics), which the participants wore on their nondominant wrist for eight consecutive days. Participants wore Actiwatch 2 on the day of the PiB-PET scan. Records with data from

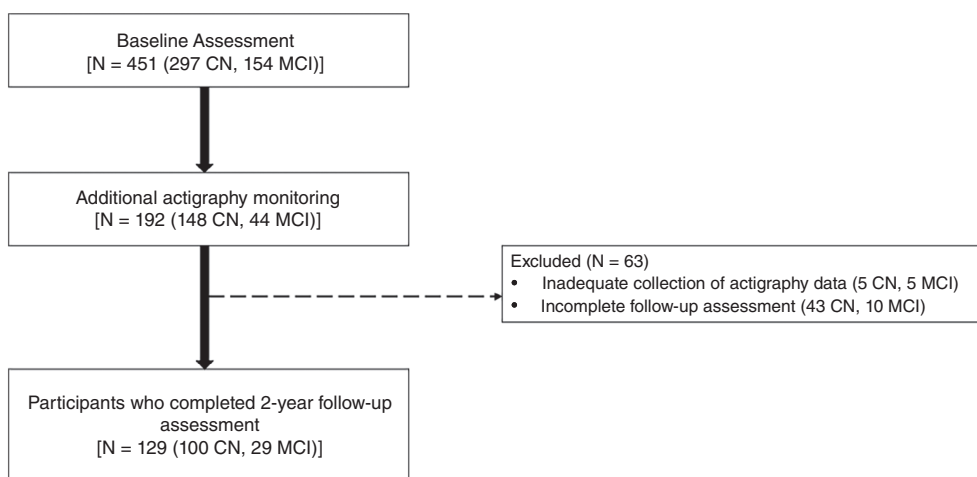


Fig. 1 Flow chart for the enrollment of study participants. CN, cognitively normal; MCI, mild cognitive impairment.

three or more consecutive days (mean duration: 180.4 ± 24.8 h) were included in the analyses, and takeoff was manually excluded by one researcher based on a sleep diary.²⁵ Circadian rest-activity variables were derived using Actiware version 6.0.9 with a high-sensitivity low threshold wake cutoff of 20, which is more sensitive to detecting sleep disturbances in older adults.²⁶ Cosinor analyses were conducted to process the circadian RAR data. Four circadian parameters were calculated from the cosinor analysis: midline estimation of statistic of rhythm (MESOR, overall average level of activity), amplitude (half of the peak-to-nadir difference), acrophase (timing of peak activity during the day), and *F* statistics (rhythmicity representing the robustness of circadian activity).²⁵ Additional details on cosinor analyses were provided in a previous report by our study group.²⁷

Measurement of cerebral A β deposition

All participants underwent simultaneous three-dimensional [¹¹C] PiB-PET and three-dimensional T1-weighted MRI using a 3.0T Biograph mMR (PET-MR) scanner (Siemens) at baseline and at a 2-year follow-up visit. The details of PiB-PET image acquisition and preprocessing were previously described.²⁸ An automatic anatomic labeling algorithm²⁹ and a region combining method³⁰ were applied to determine regions of interests (ROIs) to characterize the PiB retention level in the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal regions. A global A β retention value was the mean standardized uptake value ratio (SUVR) for all voxels of the four ROIs, calculated by dividing the mean uptake value of a reference region. Given the aims of the study to investigate longitudinal changes, for all PiB-PET scans (both baseline and follow-up), the SUVRs were calculated using a reference region that included the inferior cerebellar gray matter of the Spatially Unbiased Infratentorial Template for the cerebellum atlas,³¹ cerebellar white matter (thresholded at 50%),³² pons, and cerebrum white matter (threshold at 95% and eroded by three voxels).^{33,34} Extracted SUVRs were used to derive the annualized change of A β retention.

Measurement of AD-signature cerebral glucose metabolism

All participants also underwent 3D FDG-PET imaging using the abovementioned PET-MR machine at baseline and at a 2-year follow-up visit. After intravenous administration of 0.1 mCi/Kg of [¹⁸F]-FDG radioligands, patients fasted for at least 6 h and rested in a waiting room for 40 min prior to the scans. The PET data acquired in list mode (5 min \times 4 frames) were processed for routine corrections such as uniformity, ultrashort echo time-based attenuation, and decay corrections. Inspection of the data for any significant head movements was performed and the data were reconstructed into a 20-min summed image using iterative methods (six iterations with 21 subsets). Image processing was performed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 2014a (Mathworks). More specifically, static FDG-PET images were first coregistered to individual T1 structural images, and transformation parameters for the spatial normalization of individual T1 images to a standard montreal neurological institute (MNI) template were obtained to be used for spatial normalization of the PET images into the MNI template. Intensity normalization was performed using the pons as the reference region after smoothing with a 12-mm Gaussian filter. Voxel-weighted mean SUVR was extracted from the AD-signature FDG ROIs known to be sensitive to metabolic changes associated with AD,³⁵ which include the right and left angular gyri, bilateral posterior cingulate cortex, and left middle/inferior temporal gyrus. The AD-signature region cerebral glucose metabolism (AD-CM) was defined as a voxel-weighted mean SUVR of the AD-signature FDG ROIs.

Measurement of WMH volume

All participants underwent MRI scans with fluid-attenuated inversion recovery using the abovementioned PET-MER scanner. We followed the validated automatic procedure previously reported.^{36,37} Briefly,

the procedure consisted of 11 steps: spatial coregistration of T1 and fluid-attenuated inversion recovery (FLAIR) images, fusion of T1 and FLAIR images, T1 segmentation, attainment of transformation parameters, deformation and obtainment of the white matter mask, obtainment of FLAIR within the white matter mask, intensity normalization of the masked FLAIR, nomination of candidate WMH with a designated threshold, creation of a junction map, and elimination of the junction. Two modifications in the current processing procedure compared with the original study were as follows³⁷: (i) an optimal threshold of 70 was applied because it was more suitable for current data compared with the threshold of 65 used in the original study; and (ii) we did not use diffusion-weighted imaging in the current automated procedure given that participants with acute cerebral infarcts were enrolled in the original study.³⁷ Using the final WMH candidate image, the WMH volume was extracted in the native space for each patient.

Statistical analysis

Multivariate linear regressions were performed with annualized change of neuroimaging measures as the dependent variable and circadian RAR variables as independent variables after controlling for age, sex, apolipoprotein ϵ 4 (APOE4) positivity, and baseline MMSE. Annualized change of a neuroimaging measure for each participant

Table 1. Sample characteristics

	Total (N = 129)
Demographic and clinical	
Age at baseline	69.3 \pm 7.7 [55, 83]
Women	70 (54.3)
Education, year	12.0 \pm 4.6 [0, 21]
APOE4 carrier	26 (20.2)
Baseline MMSE	26.2 \pm 3.4 [15, 30]
Annualized Δ MMSE	-0.1 \pm 1.1 [-4.0, 3.4]
MCI	29 (22.5)
Follow-up interval (months)	27.0 \pm 1.9 [21, 33]
Circadian rest-activity rhythm variables	
Acrophase, Dec. hrs.	14.17 \pm 1.60 [10.0, 18.5]
MESOR, counts	180.10 \pm 54.97 [76.9, 341.9]
Amplitude, counts	137.42 \pm 51.89 [39.1, 295.8]
<i>F</i> statistics	2013.88 \pm 1117.30 [310.7, 6978.2]
AD imaging biomarkers	
Baseline A β deposition	0.83 \pm 0.19 [0.65, 1.67]
Annualized Δ A β deposition	0.00 \pm 0.03 [-0.08, 0.19]
Baseline AD-CM	1.40 \pm 0.13 [0.95, 1.85]
Annualized Δ AD-CM	-0.05 \pm 0.07 [-0.23, 0.17]
Baseline WMH (mm ³)	12 938.91 \pm 11 373.91 [0, 55 687]
Annualized Δ WMH (mm ³)	28.62 \pm 6191.51 [-20 472.46, 18 358.00]

Note: Values are presented as number (percentage) or mean \pm standard deviation [minimum, maximum].
Abbreviation: Acrophase, time of peak activity; AD-CM, AD-signature region cerebral glucose; APOE4, apolipoprotein ϵ 4; A β , amyloid-beta; Dec. hours, decimal hours (e.g. 14.5 = 2:30 pm); *F* statistic represents rhythmicity; MCI, mild cognitive impairment; MESOR, midline estimating statistic of rhythm; MMSE, Mini-Mental State Examination; SD, standard deviation; WMH, white matter hyperintensity.

was calculated by the subtraction of imaging values at follow-up visit minus those at baseline visit divided by time difference between the two visits in years.³⁸ We evaluated model assumptions of normality using Q-Q plots and residual versus fitted plots, and homoscedasticity by examining the nonconstant variance score test and confirmed that the assumptions were all satisfied. To overcome the issues of multiple comparisons, Bonferroni-corrected *P*-values, calculated by multiplying *P*-values by the number of comparisons (= 12), were used. In addition, multiple regression analyses were conducted to examine the relationship between annualized change of the MMSE and neuroimaging measure(s), which showed significant association with RAR variable(s) in the above analyses. Age, sex, educational year, APOE4 positivity, and baseline MMSE score were included as covariates. We also examined whether the association between the RAR variable and MMSE change was mediated by the change of neuroimaging measure, which showed a significant association with circadian variables using model 4 in the PROCESS program.³⁹ Circadian RAR variable was set as predictor, annualized change of MMSE was set as outcome, and neuroimaging measure was set as mediator. Inferences were determined by 95% bias-corrected bootstrap confidence intervals for 10 000 bootstrap samples. If the 95% confidence interval did not contain zero, an effect was considered significant. In addition, for exploratory purposes, when any relationship between the RAR variable and neuroimaging measure was significant, moderation effects of age, sex, APOE4 positivity, and clinical diagnosis were investigated using the multiple regression analysis, including each of the variables × circadian rhythm variable interaction term (e.g., age × acrophase) as an additional independent variable. All statistical analyses were performed using IBM SPSS Statistics 21 (SPSS Inc.) and the statistical significance was defined as *P* < 0.05 if not otherwise specified.

Results

Characteristics of the study population

The mean age (±SD) of all 129 participants was 69.3 ± 7.7 years at baseline assessment. Of the 129 participants, 70 (54.3%) were women and 29 (22.5%) had MCI at baseline. Table 1 shows demographic variables, RAR variables, and AD imaging biomarkers variable. The mean follow-up interval (±SD) was 27.0 ± 1.9 months.

Association between circadian RAR variables at baseline and annualized changes of neuroimaging measures

Delayed acrophase at baseline was significantly associated with greater annualized decline of AD-CM ($\beta = -0.256$, $P = 0.004$), even after applying the Bonferroni-corrected *P*-value (i.e., corrected $P = 0.048$ [= 0.004×12]) (Table 2, Fig. 2a), but not with the change of A β accumulation and WMH (Table 2). The other three RAR variables did not have a significant association with any neuroimaging measures (Table 2).

Relationship between annualized decline of AD-CM and annualized change of cognition

In order to investigate whether the decline of AD-CM, which showed a significant relationship with delayed acrophase at baseline, underlies longitudinal cognitive impairment, we further analyzed the association between AD-CM decline and MMSE score reduction over a 2-year period. The annualized decline of AD-CM showed a significant positive association with annualized reduction of MMSE scores ($\beta = 0.182$, $P = 0.040$) (Fig. 2(b)).

Mediation of annualized decline of AD-CM for the effect of delayed acrophase on cognitive decline

We performed a mediation analysis to test whether annualized decline of AD-CM (mediator) mediated the relationship between acrophase (predictor) and annualized change of MMSE score (outcome). As shown in Fig. 3, the effect of acrophase at baseline on annualized change of MMSE score was mediated by annualized decline of AD-CM. Before entering the AD-CM in the model, delayed acrophase was significantly associated with faster decline in MMSE score ($\beta = -0.201$, $P = 0.027$). When AD-CM was included in the model, the direct effect (acrophase → annualized MMSE) became nonsignificant ($P = 0.053$), while the indirect effect (acrophase → annualized AD-CM → annualized MMSE) was significant (B[Boot 95% CI] = $-0.037[-0.083$ to $-0.002]$) (Fig. 3) showing that annualized decline of AD-CM mediates the relationship between delayed acrophase and greater cognitive decline.

Table 2. Association of circadian rest-activity rhythm variables with annualized change in neuroimaging measures

Dependent variables	Independent variable	β (95% CI)	<i>t</i>	<i>P</i> -value [†]	Corrected <i>P</i> -value [‡]
Annualized Δ A β	Acrophase	0.108 (−0.067, 0.281)	1.234	0.220	NS
	MESORS	−0.040 (−0.229, 0.152)	−0.421	0.674	NS
	Amplitude	−0.056 (−0.247, 0.138)	−0.576	0.565	NS
	F-statistics	−0.106 (−0.286, 0.063)	−1.290	0.199	NS
Annualized Δ AD-CM	Acrophase	−0.256 (−0.434, −0.081)	−2.941	0.004*	0.048*
	MESORS	0.113 (−0.080, 0.297)	1.162	0.248	NS
	Amplitude	0.052 (−0.143, 0.253)	0.527	0.599	NS
	F-statistics	0.084 (−0.091, 0.259)	0.934	0.352	NS
Annualized Δ WMH	Acrophase	0.088 (−0.931, 0.272)	0.965	0.336	NS
	MESORS	0.011 (−0.190, 0.208)	0.108	0.914	NS
	Amplitude	0.117 (−0.077, 0.319)	1.204	0.231	NS
	F-statistics	0.133 (−0.052, 0.323)	1.440	0.152	NS

Note: Covariates of linear regression model are age, sex, apolipoprotein ϵ 4 (APOE4) positivity, and baseline MMSE.

[†]Value before Bonferroni correction.

[‡]The *P*-value was Bonferroni-corrected by multiplying the *P*-values by the number of comparison (= 12).

*Statistically significant ($P < 0.05$).

Abbreviation: Acrophase, time of peak activity; AD-CM, AD-signature region cerebral glucose; A β , amyloid-beta; CI, confidence interval; Dec, hours, decimal hours (e.g. 14.5 = 2:30 pm); *F* statistic represents rhythmicity; MESOR, midline estimating statistic of rhythm; MMSE, Mini-Mental State Examination; NS, not significant; WMH, white matter hyperintensity.

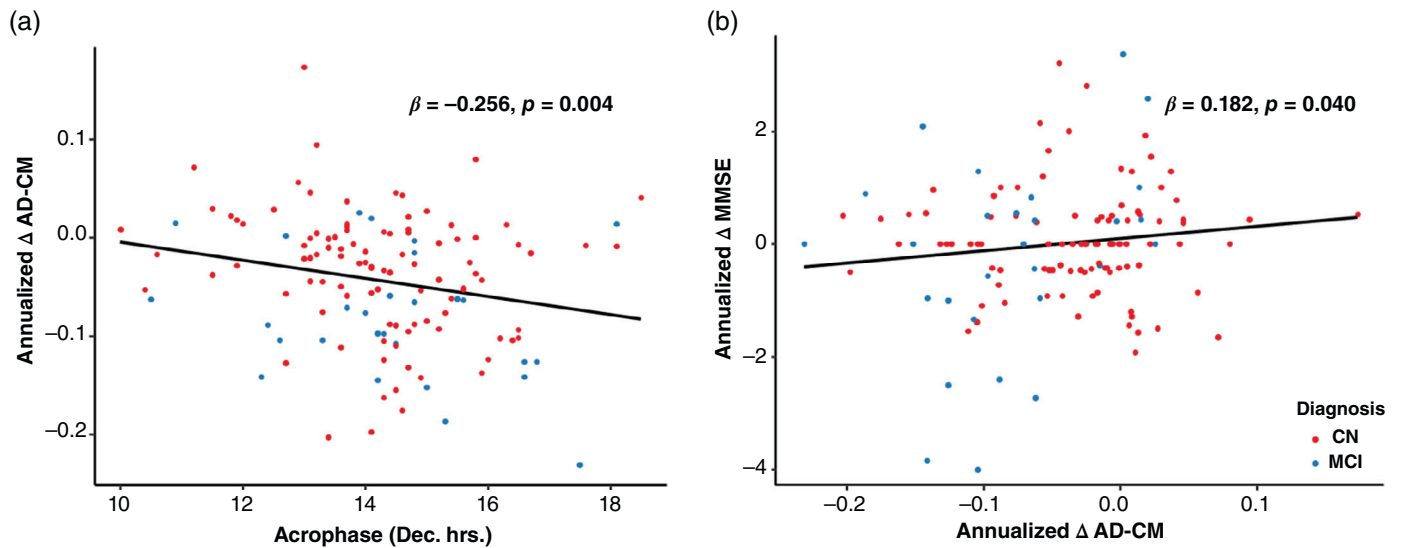


Fig. 2 (a) Association between delayed acrophase and annualized change of Alzheimer disease-signature region cerebral glucose (AD-CM), and (b) association between annualized change of AD-CM and those of Mini-Mental Status Examination (MMSE) score. Multiple linear regression analyses were performed after controlling for age, sex, apolipoprotein e4 (APOE4) positivity and baseline MMSE. Acrophase, time of peak activity; Dec. hours, decimal hours (e.g. 14.5 = 2:30 pm); CN, cognitive normal; MCI, mild cognitive impairment; Dec. hours, decimal hours (e.g. 14.5 = 2:30 pm).

Effect of age, sex, APOE4, and clinical diagnosis on the relationship between delayed acrophase at baseline and annualized decline of AD-CM

Any interaction between delayed acrophase at baseline and age, sex, APOE4, and clinical diagnosis was nonsignificant (Table 3). Although the interactions were not significant, we performed further subgroup analyses for the purpose of exploration and the results are presented in the Table S1.

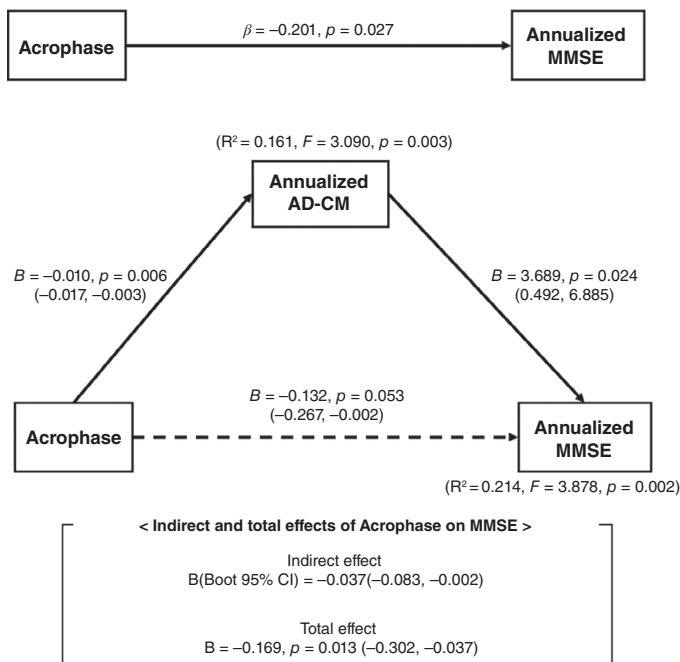


Fig. 3 Mediation model of annualized decline of Alzheimer disease-signature region cerebral glucose (AD-CM) for the effect of delayed acrophase on cognitive decline. Adjusted for age, sex, educational year, apolipoprotein e4 (APOE4) positivity, and baseline Mini-Mental Status Examination (MMSE) score. Bold lines indicate significant association. Brackets indicate 95% confidence intervals calculated using bootstrap method (10 000 resampling). Acrophase, time of peak activity; Dec. hours, decimal hours (e.g. 14.5 = 2:30 pm).

Discussion

In the present study, we examined the relationship between circadian RAR alteration and longitudinal neuroimaging biomarkers in older adults without dementia. We found that delayed acrophase was associated with greater AD-CM decline over a 2-year period. We additionally observed that AD-CM decline mediated the influence of delayed acrophase on the reduction of MMSE score.

Our results revealed that the delayed acrophase at baseline was associated with greater AD-CM decline over 2 years. Although it is difficult to clearly explain the mechanism underlying the connection between delayed acrophase and accelerated AD-CM reduction, several recent studies provide some clues regarding the mechanism: first, one exploratory study reported that changes of circadian phase, either phase advanced or phase delayed, resulted in disturbance of glucose-insulin metabolism in older adults.⁴⁰ More specifically, phase delay was associated with reduced effectiveness of insulin-mediated glucose uptake, possibly resulting in insulin resistance. Similarly, other studies demonstrated that shift workers⁴¹ and individuals exposed to circadian misalignment protocol⁴² showed a systematic increase in glucose and insulin, which could contribute to glucose intolerance and increased insulin resistance.⁴³ Abnormal glucose metabolism and insulin resistance in the peripheral system are also well-correlated with decreased cerebral glucose uptake.^{44,45} Second, a previous post-mortem brain study⁴⁶ suggested that the elevation of Circadian Locomotor Output Cycles Kaput (CLOCK)/Brain and Muscle ARNT-like 1 (BMAL1), i.e., master heterodimeric transcription factors, which act as a positive regulator of the biological circadian clock, induces the impairment of aerobic glycolysis in astrocytes.⁴⁷ Because aerobic glycolysis in astrocytes is a critical metabolic pathway that processes the utilization of glucose to generate lactate as a primary energy source for neurons,⁴⁸ delayed acrophase may affect AD-CM by altering aerobic glycolysis in astrocytes.

We found a significant association of delayed acrophase with greater MMSE decline. The finding is generally consistent with the results from several longitudinal studies that delayed acrophase was associated with greater cognitive decline and increased risk of MCI and dementia,^{8,10,49} although there was a conflicting report that showed no association between acrophase and conversion from normal cognition to MCI and dementia.⁷ Several studies also reported that greater reduction of AD-CM was correlated with faster cognitive decline.^{35,50,51} In line with those previous findings, our mediation

Table 3. Moderation effect of age, sex, APOE4, and clinical diagnosis on the relationship between acrophase and annualized Δ AD-CM

Variable or interaction	β (95% CI)	<i>t</i>	<i>P</i> -value
Acrophase	-0.252 (-0.424 to -0.078)	-1.754	0.082
Age	-0.168 (-0.340 to 0.008)	0.209	0.835
Acrophase \times age	-0.040 (-0.208 to 0.140)	-0.424	0.672
Acrophase	-0.242 (-0.406 to -0.062)	-2.827	0.005
Sex	-0.132 (-0.300 to 0.039)	-0.978	0.263
Acrophase \times sex	0.077 (-0.086 to 0.255)	0.970	0.334
Acrophase	-0.253 (-0.418 to -0.073)	-2.345	0.021
APOE4	0.022 (-0.149 to 0.202)	0.410	0.682
Acrophase \times APOE4	-0.032 (-0.212 to 0.140)	-0.385	0.701
Acrophase	-0.220 (-0.390 to 0.042)	-0.012	0.999
Clinical diagnosis	-0.248 (-0.208 to 0.071)	-0.142	0.887
Acrophase \times clinical diagnosis	-0.004 (-0.019 to 0.118)	-0.505	0.614

Note: The linear regression model included acrophase, age (or sex or apolipoprotein e4 [APOE4] or clinical diagnosis), and the interaction between acrophase and age (or sex or APOE4 or clinical diagnosis) treated as independent variables; age (<70 years vs \geq 70 years), sex, APOE4 status, and baseline Mini-Mental State Examination (MMSE) were treated as covariates when appropriate, and annualized Δ AD-CM treated as the dependent variable.

Abbreviation: Acrophase, time of peak activity; AD-CM, AD-signature region cerebral glucose; CI, confidence interval; Dec. hours, decimal hours (e.g. 14.5 = 2:30 pm).

analysis additionally demonstrated that AD-CM decline mediated the association between delayed acrophase and cognitive decline in older adults without dementia.

While some cross-sectional studies using actigraphic measurements reported that RAR fragmentation¹² and advanced phase⁵² in cognitively unimpaired older adults and phase delay⁵³ in cognitively impaired individuals were related with cerebral A β deposition, we did not find any association between baseline RAR variables and longitudinal changes of A β accumulation. Although direct comparison is difficult because of different study design (cross-sectional vs longitudinal), a 2-year follow-up period of our study may not be enough to reveal the association of RAR alteration with prospective A β accumulation.

In addition, we found significant associations of acrophase with the annualized decline of AD-CM and cognitive impairment, under the assumption of linear relationships. However, some studies on the effects of circadian RAR variables suggest a U- or L-shaped relationship between RAR variables and outcome measures.^{8,9} Further investigations considering nonlinear relationships may be helpful for a more detailed understanding about the effect of the RAR variables on brain pathology and cognition.

Furthermore, the association was not found between circadian rest-activity measures and longitudinal change of WMH volume. Although in several studies where actigraphy was used, WMH volume was reportedly associated with circadian rhythm stability⁵⁴ and fragmentation.⁵⁵ The difference in study design (cross-sectional vs longitudinal) or characteristics of study participants, such as number of patients and proportion of patients with high vascular risk burden, may have contributed to the discrepancy. In the two previous studies conducted by Zuurbier et al.⁵⁵ and Oosterman et al.,⁵⁴ a cross-sectional design was used. In addition, the study by Zuurbier et al. included 970 older adults, which was significantly greater than the number of participants in the present study. To the best of our knowledge, the relationship between objectively measured delayed acrophase, longitudinal decline of brain metabolism in AD-signature brain regions, and cognitive decline is a novel finding. However, the present study had several limitations. First, measurement of circadian rest-activity variables was performed only once at baseline, and the values for the variables were assumed as fixed over a 2-year period. Consequently, intraindividual changes in circadian rest-activity variables

during the period were not reflected in the analyses. Second, the longitudinal follow-up duration was relatively short, which might have caused detection of subtle longitudinal brain changes difficult. In addition, given the potentially bidirectional relationship between RAR and brain changes,⁵⁶ a 2-year follow-up duration may be not enough to exclude the possibility of reverse causation (i.e., RAR alterations caused by brain changes already in progress). Further studies with longer follow-up are needed to overcome the limitations. Third, we did not consider day-of-week⁵⁷ and seasonal effects,⁵⁸ which could affect the circadian rhythm variable. However, day-of-week effects might not be serious in our study considering that it was reported to be nonsignificant in old adults.⁵⁹ Finally, we used AD-CM, but not cortical thickness or other structural brain change, as a neurodegeneration measure. Further studies using structural brain changes as outcome measures could provide additional valuable information.

Conclusions

The present study results indicate that delayed acrophase in late life may cause or predict the progression of hypometabolism in AD-signature brain regions, which underlies cognitive decline in the near future.

Acknowledgment

This study was supported by a grant from the Ministry of Science and ICT, Republic of Korea (grant number: NRF2014M3C7A1046042), a grant from the Ministry of Health and Welfare, Republic of Korea (HI18C0630 and HI19C0149), a grant from the Seoul National University Hospital, Republic of Korea (number 3020200030), and a grant from the National Institute of Aging (U01AG072177). The funding source had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or decision to submit it for publication.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Study concept and design: S.Y.J., and D.Y.L.; acquisition, analysis, and interpretation of data: S.Y.J., M.S.B., D.Y., G.J., J.Y.L., Y. K. K., C.H. S., K.M.K., Y.J.L., and D.Y.L.; drafting the manuscript for

intellectual content: S.Y.J. and D.Y.L.; and statistical analysis: S.Y.J. and D.Y.L.

Data availability statement

The data sets generated and analyzed during the present study are not publicly available, owing to ethics considerations and privacy restrictions. Data may be obtained from the corresponding author after approval by the institutional review board of the Seoul National University Hospital, South Korea, has been sought.

References

- Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature* 2002; **418**: 935–941.
- Hood S, Amir S. The aging clock: Circadian rhythms and later life. *J. Clin. Invest.* 2017; **127**: 437–446.
- Gehrman P, Marler M, Martin JL, Shochat T, Corey-Bloom J, Ancoli-Israel S. The relationship between dementia severity and rest/activity circadian rhythms. *Neuropsychiatr. Dis. Treat.* 2005; **1**: 155–163.
- Witting W, Kwa I, Eikelenboom P, Mirmiran M, Swaab D. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biol. Psychiatry* 1990; **27**: 563–572.
- Harper DG, Volicer L, Stopa EG, McKee AC, Nitta M, Satlin A. Disturbance of endogenous circadian rhythm in aging and Alzheimer disease. *Am. J. Geriatr. Psychiatry* 2005; **13**: 359–368.
- Wang JL, Lim AS, Chiang WY *et al.* Suprachiasmatic neuron numbers and rest-activity circadian rhythms in older humans. *Ann. Neurol.* 2015; **78**: 317–322.
- 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**: e96–e105.
- 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**: 722–732.
- 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**: 2136–2143.
- Bokenberger K, Ström P, Dahl Aslan AK *et al.* Association between sleep characteristics and incident dementia accounting for baseline cognitive status: A prospective population-based study. *J. Gerontol. Ser A Biomed. Sci. Med. Sci.* 2017; **72**: 134–139.
- Lee PM, Kwok BH, Ma JY, Tse LA. A population-based prospective study on rest-activity rhythm and mild cognitive impairment among Hong Kong healthy community-dwelling older adults. *Neurobiol. Sleep Circadian Rhythms* 2021; **10**: 100065.
- Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju Y-ES. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurol.* 2018; **75**: 582–590.
- Cronin P, McCarthy MJ, Lim AS *et al.* Circadian alterations during early stages of Alzheimer's disease are associated with aberrant cycles of DNA methylation in BMAL1. *Alzheimers Dement.* 2017; **13**: 689–700.
- Partch CL, Green CB, Takahashi JS. Molecular architecture of the mammalian circadian clock. *Trends Cell Biol.* 2014; **24**: 90–99.
- Duncan M. Interacting influences of aging and Alzheimer's disease on circadian rhythms. *Eur. J. Neurosci.* 2020; **51**: 310–325.
- Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science* 2016; **354**: 1004–1008.
- Musiek ES, Lim MM, Yang G *et al.* Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. *J. Clin. Invest.* 2013; **123**: 5389–5400.
- Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of Alzheimer disease. *Exp. Mol. Med.* 2015; **47**: e148.
- Williamson W, Lewandowski AJ, Forkert ND *et al.* Association of cardiovascular risk factors with MRI indices of cerebrovascular structure and function and white matter hyperintensities in young adults. *JAMA* 2018; **320**: 665–673.
- Byun MS, Yi D, Lee JH *et al.* Korean brain aging study for the early diagnosis and prediction of Alzheimer's disease: Methodology and baseline sample characteristics. *Psychiatry Investig.* 2017; **14**: 851–863.
- Albert MS, DeKosky ST, Dickson D *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011; **7**: 270–279.
- Lee DY, Lee KU, Lee JH *et al.* A normative study of the CERAD neuropsychological assessment battery in the Korean elderly. *J. Int. Neuropsychol. Soc.* 2004; **10**: 72–81.
- Lee JH, Lee KU, Lee DY *et al.* Development of the Korean version of the consortium to establish a registry for Alzheimer's disease assessment packet (CERAD-K): Clinical and neuropsychological assessment batteries. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 2002; **57**: P47–P53.
- Lee DY, Lee KU, Lee JH *et al.* A normative study of the mini-mental state examination in the Korean elderly. *J. Korean Neuropsychiatr. Assoc.* 2002; **41**: 508–525.
- Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep* 2003; **26**: 342–392.
- van de Wouw E, Evenhuis HM, Ehteld MA. Comparison of two types of Actiwatch with polysomnography in older adults with intellectual disability: A pilot study. *J. Intellect. Dev. Disabil.* 2013; **38**: 265–273.
- Hwang JY, Byun MS, Choe YM *et al.* Moderating effect of APOE ε4 on the relationship between sleep-wake cycle and brain β-amyloid. *Neurology* 2018; **90**: e1167–e1173.
- Park JC, Han SH, Yi D *et al.* Plasma tau/amyloid-β1–42 ratio predicts brain tau deposition and neurodegeneration in Alzheimer's disease. *Brain* 2019; **142**: 771–786.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; **15**: 273–289.
- Reiman EM, Chen K, Liu X *et al.* Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* 2009; **106**: 6820–6825.
- Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the human cerebellum. *Neuroimage* 2009; **46**: 39–46.
- Van Baarsen KM, Kleinnijenhuis M, Jbabdi S, Sotiropoulos SN, Grotenhuis JA, van Walsum AVC. A probabilistic atlas of the cerebellar white matter. *Neuroimage* 2016; **124**: 724–732.
- Lowe VJ, Lundt ES, Senjem ML *et al.* White matter reference region in PET studies of 11C-Pittsburgh compound B uptake: Effects of age and amyloid-β deposition. *J. Nucl. Med.* 2018; **59**: 1583–1589.
- Schwarz CG, Senjem ML, Gunter JL *et al.* Optimizing PiB-PET SUVR change-over-time measurement by a large-scale analysis of longitudinal reliability, plausibility, separability, and correlation with MMSE. *Neuroimage* 2017; **144**: 113–127.
- Landau SM, Harvey D, Madison CM *et al.* Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol. Aging* 2011; **32**: 1207–1218.
- Byun MS, Jung JH, Sohn BK *et al.* Neuroticism, conscientiousness, and in vivo Alzheimer pathologies measured by amyloid PET and MRI. *Psychiatry Clin. Neurosci.* 2020; **74**: 303–310.
- Tsai JZ, Peng SJ, Chen YW *et al.* Automated segmentation and quantification of white matter hyperintensities in acute ischemic stroke patients with cerebral infarction. *PLoS One* 2014; **9**: e104011.
- Jack CR Jr, Wiste HJ, Schwarz CG *et al.* Longitudinal tau PET in ageing and Alzheimer's disease. *Brain* 2018; **141**: 1517–1528.
- Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach.* New York: Guilford Publications; 2017.
- Gonnissen HK, Rutters F, Mazuy C, Martens EA, Adam TC, Westerterp-Plantenga MS. Effect of a phase advance and phase delay of the 24-h cycle on energy metabolism, appetite, and related hormones. *Am. J. Clin. Nutr.* 2012; **96**: 689–697.
- Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc. Natl. Acad. Sci.* 2009; **106**: 4453–4458.
- Morris CJ, Yang JN, Garcia JI *et al.* Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proc. Natl. Acad. Sci.* 2015; **112**: E2225–E2234.
- Dinneen S, Alzaid A, Miles J, Rizza R. Metabolic effects of the nocturnal rise in cortisol on carbohydrate metabolism in normal humans. *J. Clin. Invest.* 1993; **92**: 2283–2290.
- Willette AA, Bendlin BB, Starks EJ *et al.* Association of insulin resistance with cerebral glucose uptake in late middle-aged adults at risk for Alzheimer disease. *JAMA Neurol.* 2015; **72**: 1013–1020.

45. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch. Neurol.* 2011; **68**: 51–57.
46. Yoo ID, Park MW, Cha HW *et al.* Elevated CLOCK and BMAL1 contribute to the impairment of aerobic glycolysis from astrocytes in Alzheimer's disease. *Int. J. Mol. Sci.* 2020; **21**: 7862.
47. Buhr ED, Takahashi JS. Molecular components of the mammalian circadian clock. In: Kramer A, Mrosovsky M, eds. *Circadian Clocks*. Berlin Heidelberg, Germany: Springer-Verlag; 2013; 3–27.
48. Magistretti PJ, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. *Neuron* 2015; **86**: 883–901.
49. Covell GE, Dhawan PS, Iannotti JK *et al.* Disrupted daytime activity and altered sleep-wake patterns may predict transition to mild cognitive impairment or dementia: A critically appraised topic. *Neurologist* 2012; **18**: 426–429.
50. De Leon M, Convit A, Wolf O *et al.* Prediction of cognitive decline in normal elderly subjects with 2-[18F] fluoro-2-deoxy-D-glucose/positron-emission tomography (FDG/PET). *Proc. Natl Acad. Sci.* 2001; **98**: 10966–10971.
51. Mosconi L, De Santi S, Li J *et al.* Hippocampal hypometabolism predicts cognitive decline from normal aging. *Neurobiol. Aging* 2008; **29**: 676–692.
52. Park JE, Lee YJ, Byun MS *et al.* Differential associations of age and Alzheimer's disease with sleep and rest-activity rhythms across the adult lifespan. *Neurobiol. Aging* 2021; **101**: 141–149.
53. Roh HW, Choi JG, Kim NR *et al.* Associations of rest-activity patterns with amyloid burden, medial temporal lobe atrophy, and cognitive impairment. *EBioMedicine* 2020; **58**: 102881.
54. Oosterman J, Van Harten B, Vogels R *et al.* Distortions in rest-activity rhythm in aging relate to white matter hyperintensities. *Neurobiol. Aging* 2008; **29**: 1265–1271.
55. Zuurbier LA, Ikram MA, Luik AI *et al.* Cerebral small vessel disease is related to disturbed 24-h activity rhythms: A population-based study. *Eur. J. Neurol.* 2015; **22**: 1482–1487.
56. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol.* 2019; **18**: 307–318.
57. Roenneberg T, Pilz LK, Zerbini G, Winnebeck EC. Chronotype and social jetlag: A (self-) critical review. *Biology* 2019; **8**: 54.
58. Honma K, Honma S, Kohsaka M, Fukuda N. Seasonal variation in the human circadian rhythm: Dissociation between sleep and temperature rhythm. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 1992; **262**: R885–R891.
59. Chipperfield JG. Everyday physical activity as a predictor of late-life mortality. *Gerontologist* 2008; **48**: 349–357.

Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.