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Differential associations of age and Alzheimer's disease with sleep and rest-activity rhythms across the adult lifespan

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ABSTRACT

This study aimed to identify differences between physiological age-related and Alzheimer's disease (AD)-related alterations in sleep and rest-activity rhythm. All participants ($n = 280$; 20–90 years) underwent clinical assessments, [^{11}C] Pittsburgh compound B–positron emission tomography, and actigraphic monitoring. In cognitively normal adults without cerebral amyloid-β, older age was associated with earlier timing of circadian phase and robust rest-activity rhythm, but sleep quantity and quality were mostly unaffected by age. While preclinical AD was associated with earlier circadian timing, clinical AD exhibited later timing of daily rhythm and increased sleep duration. In conclusion, our findings suggest that older age itself leads to a more regular daily activity rhythm, but does not affect sleep duration. While preclinical AD made the effects of age-related phase advance more prominent, clinical AD was related to later circadian timing and increased sleep duration.

1. Introduction

The human circadian system has evolved to synchronize with the 24-hour light-dark cycle (zeitgeber), and all biological processes in the body are affected by this internal clock (Van Someren and Riemersma-Van Der Lek, 2007). Sleep and rest-activity rhythms (RARs) are representative physiological functions controlled by the circadian system, and their dysfunction is closely related to various health problems such as cancers, metabolic disorders, and neurodegenerative diseases as well as aging itself (Abbott and Videnovic, 2016; Kloog et al., 2011; Parsons et al., 2015). Thus, it is important to differentiate age-related physiological differences in sleep and RAR clearly from their pathological alterations.

A meta-analysis on age-related differences in sleep parameters among community participants noted that older age was associated with reduced sleep duration and efficiency, frequent awakenings after sleep onset, and increased sleep latency (Ohayon et al., 2004). In case of RAR variables, which can usually be measured by actigraphy, their age-associated alterations have only been investigated in a few studies showing inconsistent findings (Huang et al., 2002; Luik et al., 2013; Mitchell et al., 2017), whereas a subjectively reported phase advance in older adults such as earlier timing of sleep

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and awakening has been reported frequently (Duffy et al., 2015). Most previous studies were conducted in general populations without isolating the influences of neurodegenerative conditions that are common in late-life, and Alzheimer's disease (AD) in particular (Duffy et al., 2015; Huang et al., 2002; Luik et al., 2013; Mitchell et al., 2017; Ohayon et al., 2004). Disruptions to sleep and RAR are frequent manifestations of clinical AD dementia (Lim et al., 2014; Witting et al., 1990). Moreover, recent studies have reported that such disruptions were found even in preclinical AD (Hwang et al., 2018; Ju et al., 2013; Musiek et al., 2018). The prevalence of preclinical AD, a condition with pathological amyloid-beta (Aβ) deposition in the brain without clinical symptoms, increases from 10% in cognitively normal (CN) adults aged 50 years to 44% in those aged 90 years (Jansen et al., 2015). Therefore, the previously reported findings on age-related sleep and RAR changes might be a mixture of pathological alterations caused by the AD process and purely physiological changes. A recent study reported effects of age on RAR that were independent of the influences of preclinical AD (Musiek et al., 2018). However, the study targeted only middle- and old-aged participants and did not include young adults; therefore, it could not reveal age-related differences in sleep and RAR throughout the adult lifespan.

Therefore, we first aimed to differentiate between physiological age-related and pathological AD-related alterations in sleep and RAR. The physiological effects of age on sleep and RAR throughout the adult lifespan (20–90 years) of CN individuals were investigated after excluding the influences of cerebral Aβ. Second, we examined the effects of preclinical AD on sleep and RAR in CN individuals aged over 55 years. Finally, we investigated the effects of clinical AD on sleep and RAR by comparing individuals with preclinical AD, those with mild cognitive impairment (MCI) due to AD, and those with AD dementia (ADD).

2. Methods and materials

2.1. Participants

All participants were involved in the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), which is an ongoing prospective cohort study that started in 2014. The primary goals of the KBASE are to search for new biomarkers of AD and to determine various life experiences that contribute to AD-related brain changes. The detailed protocols and characteristics of the samples have been reported previously (Byun et al., 2017).

As of March 2017, 758 volunteer individuals had been recruited. Among these, 591 participants were included in the baseline cohort after 167 individuals were excluded for the following reasons: any current serious medical, psychiatric, or neurological disorder that could affect cognitive functioning; the presence of a severe communication problem that would make a clinical examination difficult; contraindications for magnetic resonance imaging (MRI); absence of a reliable informant; and illiteracy. Among all participants who conducted baseline assessments, including [^{11}C] Pittsburgh compound B–positron emission tomography (PiB-PET), 280 participants additionally underwent actigraphy monitoring and 29 were excluded because of inadequate collection of actigraphic data. Finally, a total of 251 individuals were included in our analyses. Fig. 1 shows the participants' classification in accordance with clinical diagnosis and Aβ deposition status and target populations for each of the 3 study aims.

CN was defined as participants having a clinical dementia rating of 0 and no diagnosis of MCI or dementia. The details for the diagnosis of MCI and ADD were described in Supplemental Material. CN participants were divided by age group to characterize the age-specific changes in sleep and RAR as follows: young-to-middle (20–54 years), near-old (55–64 years), early-old (65–74 years), and late-old (75–90 years). The near-old group, in addition to the generally used old age subgroups (early and late-old), was included because such adults may experience significant physical and environmental changes, including retirement (Park et al., 2015), which may affect their rest-activity patterns.

The Institutional Review Board of Seoul National University Hospital and the SMG-SNU Boramae Medical Center in South Korea approved to conduct the present study, and all participants provided written informed consent before participation.

2.2. Demographic and clinical data

All participants underwent standardized clinical assessments performed by trained psychiatrists based on the KBASE clinical assessment protocol (Byun et al., 2017). Trained nurses asked questions about various sociodemographic factors including educational years, current employment status, and living environment (living alone or with family). They also assessed vascular risk factors (VRFs), including hypertension, diabetes mellitus, dyslipidemia, coronary heart disease, transient ischemic attack, and stroke, using a systematic interview with the participants and their family members. The VRF score was calculated as the number of VRFs present and is reported as a percentage (DeCarli et al., 2004). Global cognitive function was evaluated using the Korean version of the Mini-Mental State Examination, a part of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (Lee et al., 2004), and depressive symptoms were assessed using the Korean version of the Center for Epidemiologic Studies Depression (Cho and Kim, 1998). Current sleep-related problems were evaluated using sleep questionnaires including the Pittsburgh Sleep Quality Index (Buysse et al., 1989), the STOP questionnaire (Chung et al., 2008), RBD screening questionnaire (Stiasny-Kolster et al., 2007), and the Cambridge–Hopkins questionnaire for RLS (Allen et al., 2009).

2.3. Neuroimaging data

Simultaneous [^{11}C] PiB-PET and three-dimensional T1-weighted MRI scans were performed on all participants using a 3.0 T Biograph mMR (PET-MRI) scanner (Siemens, Washington, DC, USA): detailed descriptions of the imaging acquisition and preprocessing are described in a previous study (Byun et al., 2017). A global PiB retention value, a standardized uptake value ratio, was generated by dividing the mean value for all voxels within the region of interest (frontal, lateral parietal, posterior cingulate precuneus, and lateral temporal area) by the mean cerebellar uptake value in the same image (Lopresti et al., 2005). If the global standardized uptake value ratio was $>$1.21, it was considered as Aβ-positive (Aβ+). This was the cutoff value used to detect early Aβ deposition in the preclinical stage of AD (Villeneuve et al., 2015).

The volume of white matter hyperintensities (WMHs) was obtained using a validated automatic procedure (Tsai et al., 2014) with 2 kinds of modifications. An optimal threshold of 70 was applied compared with the threshold of 65 used in the original article as it was more suitable for the data. Final WMH candidate images were used to extract WMH volumes based on lobar region of interests in native space of each participant (Kochunov et al., 2001).

2.4. Sleep and RAR

Sleep and RAR data were collected using home-based Actiwatch 2 (Philips Respironics, Murrysville, PA, USA) on the nondominant wrist for more than 7 consecutive days; the monitor was started on

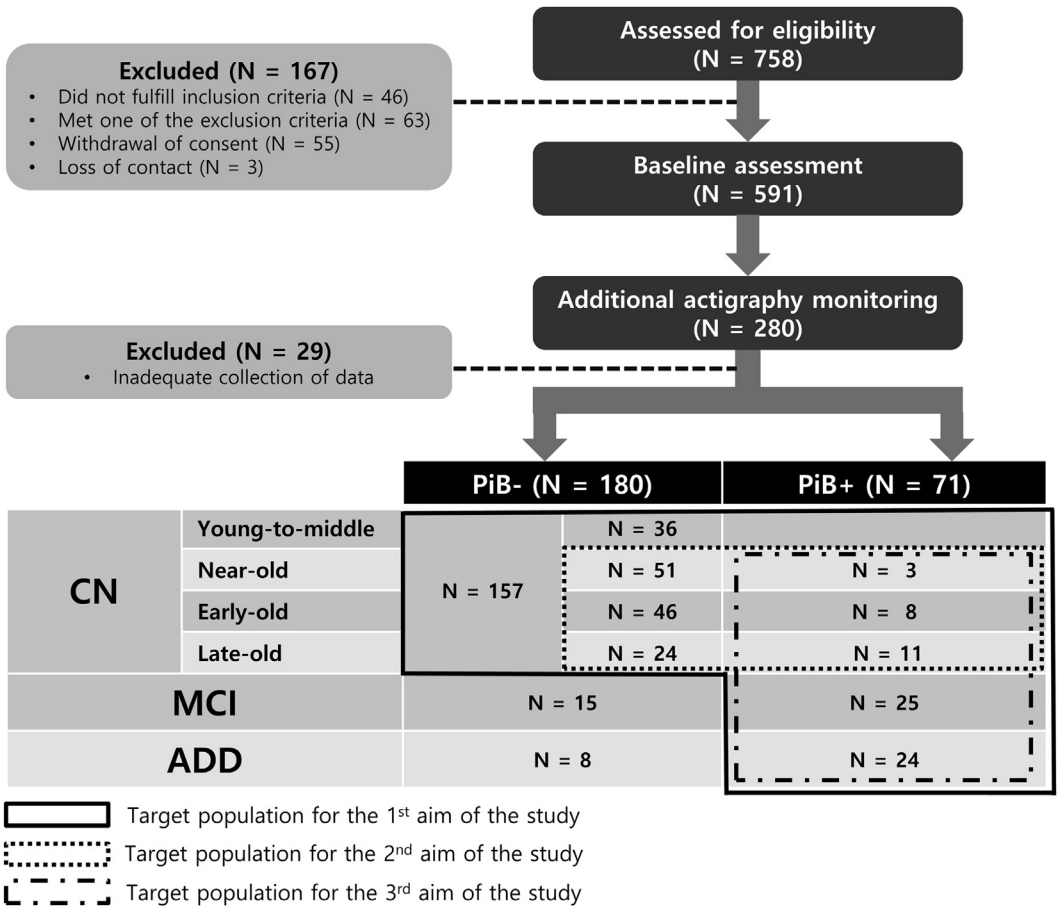

Fig. 1. Flow chart describing the target population in accordance with the study aims. Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia. There were 3 aims for the present study: (1) to investigate the physiological age-related differences on sleep and rest-activity rhythms across the adult lifespan (20–90 years) in cognitively normal adults excluding the influences of amyloid-β deposition, (2) to examine the effects of preclinical cerebral amyloid-β on sleep and rest-activity rhythms in cognitively normal adults aged over 55 years, and (3) to examine the effects of clinical Alzheimer's disease on sleep and rest-activity rhythms.

the same day as the PiB-PET scan. Take-off was manually excluded by one researcher based on a sleep diary, and records with at least 3 consecutive days of data (average period: 180.4 ± 24.8 hours) were included in the analyses (Ancoli-Israel et al., 2003). Sleep and RAR variables were calculated using Actiware, version 6.0.9 with a wake-threshold activity count >20, which is more sensitive for detecting sleep disturbances in older adults (van de Wouw et al., 2013).

Bedtime, wake-up time, total sleep time (TST), sleep onset latency, sleep efficiency, and wake time after sleep onset (WASO) were evaluated as sleep variables. Cosinor and nonparametric analyses were used to process the RAR data. The cosinor analysis included the mesor (overall average level of activity), acrophase (time of peak activity during the day), and F-statistics (measure of rhythmicity representing the robustness of circadian activity) (Ancoli-Israel et al., 2003). A nonparametric method based on raw activity counts was used to calculate interdaily stability (IS; an estimate of how closely the 24-hour RAR follows the 24-hour light-dark cycle), intradaily variability (an estimate of the fragmentation of the 24-hour RAR), and relative amplitude (RA; difference between M10 [activity counts during the most active 10-hour period] and L5 [activity counts during the least active 5-hour period]) in the average 24-h pattern (Goncalves et al., 2015). Additional details regarding cosinor and nonparametric analyses have been provided in the Supplemental Material.

2.5. Statistical analysis

The demographic and clinical characteristics are presented in accordance with Aβ-positivity. Aβ-negative (Aβ−) participants are presented by age (young-to-middle [20–54 years] vs. old [55–90 years]), whereas the Aβ-positive (Aβ+) group (55–90 years) is shown in accordance with clinical diagnosis (CN, MCI, and ADD). Aβ−CN and Aβ+ CN were designated as CN−and CN+, respectively. The young-to-middle CN−, old CN−, and overall Aβ+ groups were compared using analysis of variance for continuous variables and χ^2 tests for categorical variables.

General linear models were used to examine age-related differences in sleep and RAR in CN−. We used age groups and continuous age for assessment of independent variables. For the association of age groups with sleep and RAR, linear, quadratic, and cubic patterns were also assessed across age groups using polynomial contrasts to test whether age-related differences showed linear or nonlinear patterns.

The effects of preclinical and clinical AD (MCI and ADD) on sleep and RAR were also examined using general linear models, respectively. All models were adjusted for the following covariates: sex, educational level, employment status, vascular risk factors, global cognitive function, depressive symptoms, sleep-related problems, and apolipoprotein ε4 carrier status. Sleep-related problems were defined using sleep questionnaire data and converted to categorical

variables (yes or no) using cutoff values (Chung et al., 2008; Lee et al., 2015; Sohn et al., 2012) and diagnostic criteria (Allen et al., 2009). The volume of WMH was additionally adjusted to investigate the more specific influences of older age on sleep and RAR excluding the effects of cerebral vascular lesion as well as Aβ deposition in participants having WMH data (N = 140, 89.2%).

All statistical analyses were performed using SPSS Statistics, version 25 (IBM, Chicago, IL, USA). Two-sided tests were performed, and $p < 0.05$ was considered to indicate significance.

3. Results

3.1. Demographics and clinical characteristics

Of the 251 participants, 157 (62.5%) were CN− (Fig. 1). Table 1 shows that young-to-middle–aged CN–adults (mean [standard deviation], 37.86 [8.58] years) had a higher education level, employment rate, Mini-Mental State Examination score, and lower VRF score than older adults (≥55 years) with or without Aβ deposition. Older CN–adults (67.12 [7.34] years) were younger and had a higher employment rate and lower Center for Epidemiologic Studies Depression scores than overall Aβ+ participants, all of whom were 55 years and older (73.42 [6.70] years). Sleep-related problems measured by the questionnaires were not different among the 3 groups.

3.2. Age-related differences in sleep and RAR across the adult lifespan (20–90 years)

Among CN–adults, all phase-related variables showed significantly earlier timing with older age (bed time $F[1, 142] = 21.155, p < 0.001$; wake-up time $F[1, 142] = 19.934$, $p < 0.001$; acrophase $F[1, 142] = 36.890$, $p < 0.001$; Fig. 2), and these associations were confirmed in analyses with categorical age groups (Table 2). Older age was also associated with more consistent day-to-day circadian rhythms, as measured by IS, and more robust rest-activity patterns, as measured by RA in CN adults without Aβ deposition (IS $F[1, 142] = 9.524$, $p = 0.002$; RA $F[1, 142] = 4.650$, $p = 0.033$; Fig. 2). Analyses involving categorical age groups also showed increasing tendencies of IS and RA in older groups. However, these increases were no longer apparent in late-old–aged individuals. These nonlinear patterns were supported by polynomial contrast trend analyses: there were significant quadratic patterns in the RAR variables (IS [$t(141) = -2.800$, $p = 0.007$] and RA [$t(141) = -4.143$, $p < 0.001$]; Table 2).

Among the sleep quantity and quality variables, only WASO differed significantly in accordance with age ($F[1, 142] = 6.324$, $p = 0.013$) in CN–participants; the highest values were in the near-old group and then decreased in the early- and late-old groups (Table 2). Additional adjustment with WMH volume did not change the significant associations of age with sleep and RAR (Supplemental Material: Table S1).

3.3. Influences of preclinical Aβ deposition on sleep and RAR in CN individuals aged over 55 years

Sleep and RAR parameters were compared between CN− ($n = 121$) and CN+ (preclinical AD; $n = 22$) among participants aged over 55 years. After adjustments for age and the same covariates as in the first analyses, cerebral Aβ pathology was associated with an earlier wake-up time: CN+ participants woke up approximately

Table 1
Demographic and clinical variables of the participants in accordance with cerebral amyloid-β deposition

Parameter	Amyloid-β (−)[a]		Amyloid-β (+)			
	Young-to-middle–aged (20–54 y) N = 36	Old-aged (55–90 y) N = 121	All Aβ (+) (55–90 y) N = 71	CN N = 22	MCI N = 25	ADD N = 24
Demographic						
Age, year ±SD	37.86 ± 8.58[d,e]	67.12 ± 7.34[c,e]	73.42 ± 6.70[c,d]	73.59 ± 7.13	75.00 ± 6.20	71.63 ± 6.63
Female, number (%)	17 (47.22)	65 (53.72)	42 (59.15)	11 (50.00)	13 (52.00)	18 (75.00)
Education, year ±SD	15.03 ± 1.52[d,e]	11.82 ± 4.69[c]	11.15 ± 4.78[c]	13.23 ± 4.54	10.36 ± 4.30	10.08 ± 5.04
Employed, number (%)	24 (66.67)[d,e]	46 (38.02)[c,e]	12 (16.90)[c,d]	6 (27.27)	4 (16.00)	2 (8.33)
Living alone, number (%)	4 (12.12)	14 (11.57)	9 (12.68)	6 (27.27)	0 (0.00)	3 (12.50)
Clinical						
Cognitive diagnosis						
CN, number (%)	36 (100.00)	121 (100.00)	22 (30.99)	22 (100.00)	_	_
MCI, number (%)	_	_	25 (35.21)	_	25 (100.00)	_
Dementia, number (%)	_	_	24 (33.80)	_	_	24 (100.00)
Global CDR, median (IQR)	0.00 (0.00)[e]	0.00 (0.00)[e]	0.50 (0.50)[c,d]	0.00 (0.00)	0.00 (0.00)	1.00 (0.50)
MMSE-KC, median (IQR)	29.00 (2.00)[d,e]	28.00 (3.00)[c,e]	20.00 (8.00)[c,d]	27.50 (3.00)	20.00 (4.00)	17.00 (5.00)
CES-D, median (IQR)	23.00 (8.00)[d,e]	27.00 (9.00)[c,e]	29.00 (11.00)[c,d]	26.00 (9.00)	30.00 (11.00)	29.00 (11.00)
Sleep problems						
PSQI, median (IQR)	4.50 (2.80)	5.00 (2.00)	5.00 (4.00)	5.50 (5.30)	4.00 (3.00)	4.00 (4.50)
STOP, median (IQR)	0.00 (1.00)[d,e]	1.00 (1.00)[c]	1.00 (2.00)[c]	1.00 (1.30)	1.00 (2.00)	1.00 (1.80)
RBDSQ, median (IQR)	2.00 (3.00)	2.00 (3.00)	1.00 (2.00)	1.50 (3.30)	1.00 (2.00)	1.00 (4.30)
CH-RLSq, number (%)[b]	0 (0.00)	1 (0.80)	1 (1.40)	0 (0.00)	0 (0.00)	1 (4.17)
VRS, median (IQR)	0.00 (0.00)[d,e]	1.00 (2.00)[c]	1.00 (1.00)[c]	1.00 (1.00)	1.00 (1.00)	1.00 (2.00)
APOE ε4 carrier, number (%)	14 (38.89)[d]	21 (17.36)[c,e]	29 (41.43)[d]	5 (23.81)	8 (32.00)	16 (66.67)

Key: Aβ, amyloid-β; ADD, Alzheimer's disease dementia; CDR, clinical dementia rating; CES-D, Center for Epidemiologic Studies Depression Scale; CH-RLSq, Cambridge-Hopkins questionnaire for restless leg syndrome; CN, cognitively normal; IQR, interquartile range; MCI, mild cognitive impairment; MMSE-KC, Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet; PSQI, Pittsburgh Sleep Quality Index; RBDSQ, REM sleep behavior disorder screening questionnaire; SD, standard deviation; STOP, questionnaire for obstructive sleep apnea; VRS, composite score for present vascular risk factors such as hypertension, diabetes, dyslipidemia, coronary heart disease, transient ischemic attack, and stroke.

[a] Only cognitively normal adults are shown.
[b] Numbers of individuals diagnosed with restless leg syndrome using CH-RLSq.
[c] Significantly different from cognitively normal young-to-middle–aged adults without amyloid-β at $p < 0.05$.
[d] Significantly different from cognitively normal old-aged adults without amyloid-β at $p < 0.05$.
[e] Significantly different from old-aged adults with amyloid-β at $p < 0.05$.

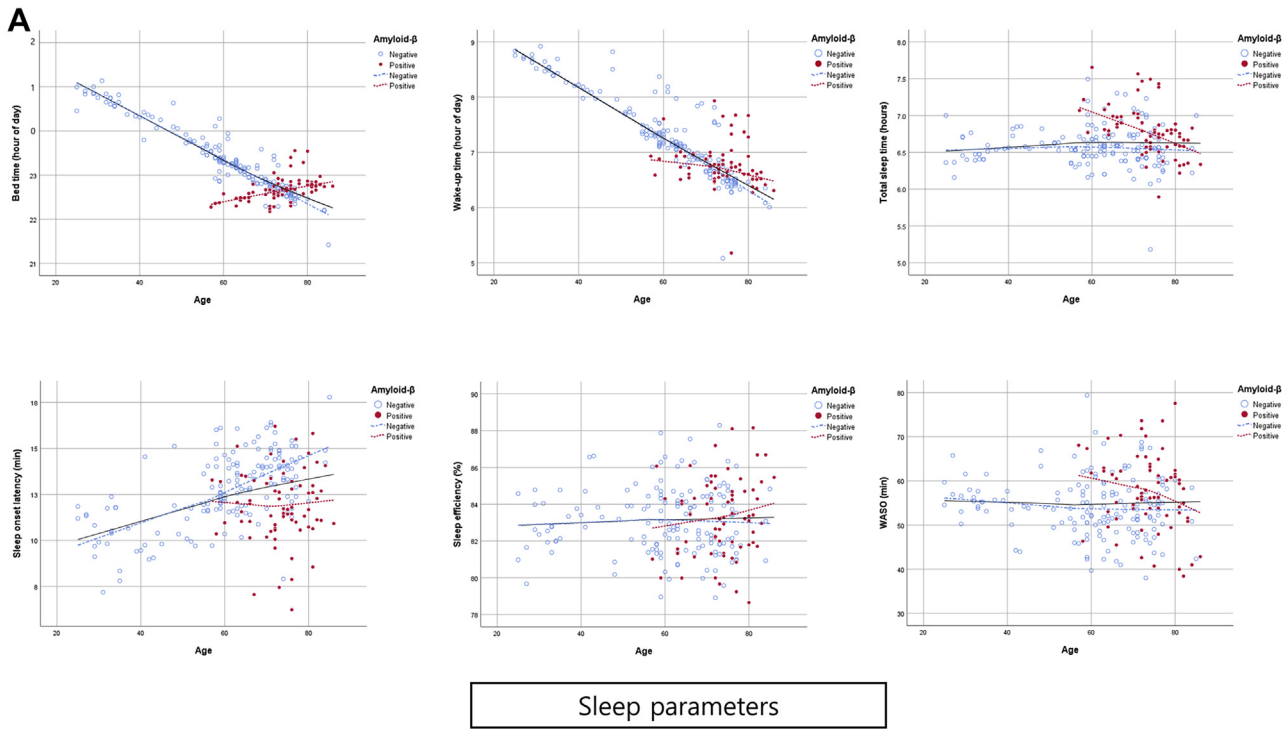

Fig. 2.

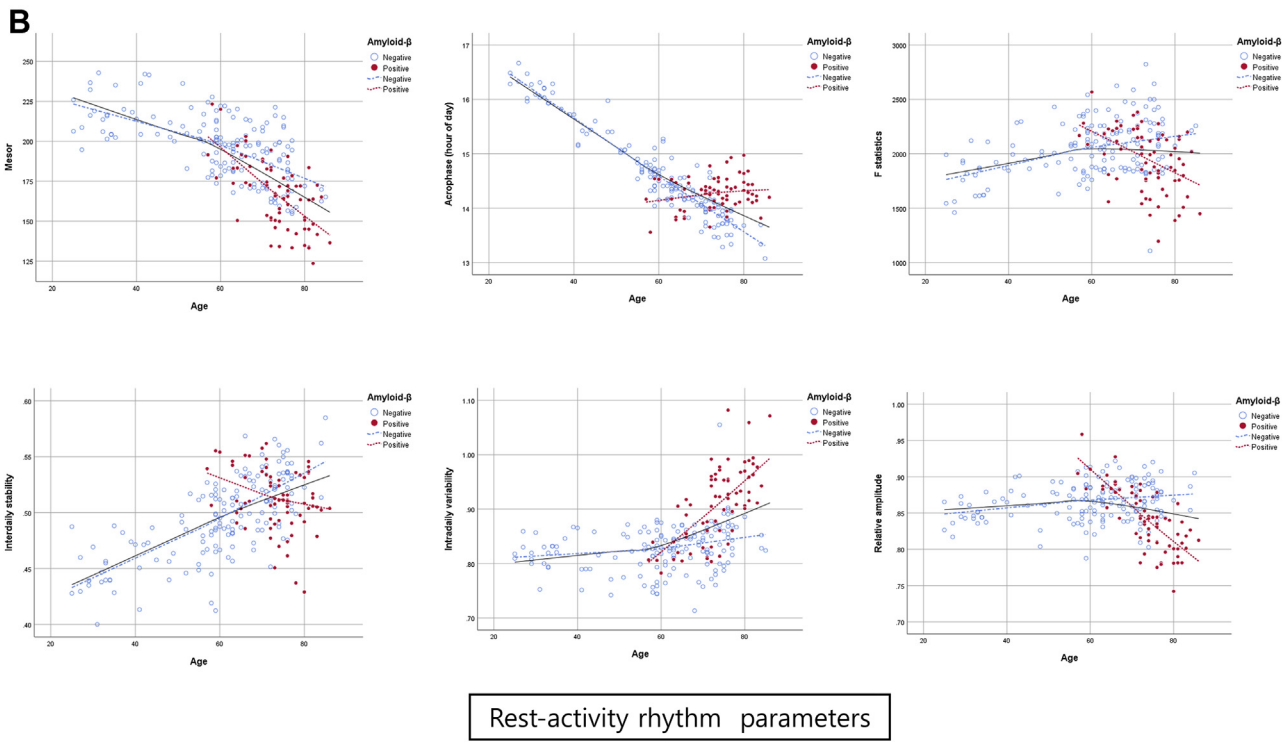

Fig. 2. Age-related differences in sleep and rest-activity rhythms throughout the adult lifespan with normal cognition (20–90 years) in accordance with Aβ deposition. A. Sleep parameters, B. Rest-activity rhythm parameters. Note: Data are presented as estimated marginal means with 95% confidence intervals obtained from a general linear model after adjustment for covariates including sex, employment status, vascular risk factor scores (VRS, the composite score for present vascular risk factors), global cognitive function (MMSE-KC, Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet), depression symptoms (CES-D, Center for Epidemiologic Studies Depression Scale), sleep problems defined by sleep questionnaire data converted to categorical variables (yes or no) using cutoff values and diagnostic criteria (PSQI, Pittsburgh Sleep Quality Index; STOP, questionnaire for obstructive sleep apnea; RBDSQ, REM sleep behavior disorder screening questionnaire; CH-RLSq, Cambridge-Hopkins questionnaire for restless leg syndrome), and APOE ε4 positivity. *Significantly different from young-to-middle–aged adults at $p < 0.05$.

Table 2
Age-related changes in sleep and rest-activity rhythm among cognitively normal adults without cerebral amyloid-β deposition

Parameter[a]	Young-to-middle (20–54 y) N = 36	Near-old (55–64 y) N = 51	Early-old (65–74 y) N = 46	Late-old (75–90 y) N = 24	F[b]	p	Post hoc
Sleep variables							
Bed time, Dec. hours	24.62 ± 1.28[b]	23.22 ± 1.05	22.57 ± 2.26	23.02 ± 1.17	9.173	< 0.001	a > b > c/a > d
Wake-up time, Dec. hours	8.28 ± 1.94	7.45 ± 1.60	6.57 ± 1.42	6.78 ± 1.47	5.472	0.001	a > b > c/a > d
Total sleep time, Dec. hours	6.41 ± 1.19	6.80 ± 1.18	6.50 ± 1.11	6.47 ± 1.13	1.275	0.285	
Sleep onset latency, minutes	10.42 ± 7.07	12.92 ± 15.42	14.32 ± 13.67	12.86 ± 10.86	0.100	0.960	
Sleep efficiency, %	83.25 ± 5.30	82.22 ± 5.32	83.83 ± 6.34	83.15 ± 5.87	1.661	0.178	
WASO, minutes	52.43 ± 19.01	60.24 ± 17.68	49.91 ± 21.43	52.63 ± 22.04	5.205	0.002	a, b > c, d
Rest-activity rhythm variables							
Cosinor variables							
MESOR, counts	212.89 ± 55.26	205.51 ± 53.37	191.73 ± 50.38	159.27 ± 47.25	2.839	0.050	a, b > d
Acrophase, Dec. hours	15.85 ± 1.56	14.56 ± 1.52	13.81 ± 1.30	14.02 ± 1.01	11.958	< 0.001	a > b > c, d
F-statistics	1865.07 ± 1032.40	2081.89 ± 1013.65	2161.28 ± 1135.15	1961.56 ± 1367.66	0.705	0.550	
Nonparametric variables							
Interdaily stability	0.457 ± 0.119	0.487 ± 0.120	0.542 ± 0.089	0.479 ± 0.123	4.037	0.009	a, b, d < c
Intradaily variability	0.828 ± 0.213	0.817 ± 0.177	0.819 ± 0.164	0.868 ± 0.273	0.068	0.977	
Relative amplitude	0.847 ± 0.109	0.875 ± 0.062	0.891 ± 0.063	0.830 ± 0.101	5.903	0.001	a < b, c/d < c

Key: acrophase, time of peak activity; Dec. hours, decimal hours (e.g., 14.5 = 2:30 pm); F-statistic represents rhythmicity; MESOR, midline estimating statistic of rhythm; WASO, wake-time after sleep onset.
[a]Significantly different from young-to-middle–aged adults, $p < 0.05$.
[b]Significantly different from near-old–aged adults, $p < 0.05$.
[c]Significantly different from early-old–aged adults, $p < 0.05$.
[d]Significantly different from late-old–aged adults, $p < 0.05$.
[a] Presented as mean ± SD.
[b] General linear model adjusted for covariates including sex, education, employment status, vascular risk factor scores (VRS, the composite score for present vascular risk factors), global cognitive function (MMSE-KC, Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet), depression symptoms (CES-D, Center for Epidemiologic Studies Depression Scale), sleep problems defined by sleep questionnaire data converted to categorical variables (yes or no) using cutoff values and diagnostic criteria (PSQI, Pittsburgh Sleep Quality Index; STOP, questionnaire for obstructive sleep apnea; RBDSQ, REM sleep behavior disorder screening questionnaire; CH-RLSq, Cambridge-Hopkins questionnaire for restless leg syndrome), and APOE ε4 positivity; df1 = 3, df2 = 141.

1 hour earlier than CN−. No other sleep or RAR variables differed in accordance with Aβ positivity (Table 3).

The effects of age on sleep and RAR also differed in older CN adults in terms of Aβ positivity. Analyses including the interaction term between age group and Aβ status showed differential influences of age on bed time [$F\{1, 210\} = 4.764$, $p = 0.030$], acrophase [$F\{1, 210\} = 4.691$, $p = 0.031$], and robustness of day and night activity (RA [$F\{1, 210\} = 10.045$, $p = 0.002$]) between participants

Table 3
Influences of amyloid-β deposition and clinical progression of Alzheimer's disease on sleep and rest-activity rhythm

	Amyloid β (−)	Amyloid β (+)			F (p)[b]	
Parameter[a]	CN N = 121	CN N = 22	MCI N = 25	ADD N = 24	CN- vs. CN+	CN+ vs. MCI+ vs. ADD
Sleep variables						
Bed time, Dec. hours	22.95 ± 1.66	22.62 ± 1.50	23.17 ± 1.61	22.21 ± 1.29	1.370 (0.244)	3.420 (0.040)
Wake-up time, Dec. hours	7.01 ± 1.55	6.08 ± 1.61[d]	7.17 ± 1.59[c]	6.98 ± 1.40	5.865 (0.017)	5.437 (0.007)
Total sleep time, Dec. hours	6.64 ± 1.15	6.29 ± 1.18[e]	6.59 ± 1.38	7.43 ± 1.88[c]	0.713 (0.400)	4.083 (0.022)
Sleep onset latency, minutes	13.44 ± 13.98	9.87 ± 9.52	14.51 ± 9.59	10.58 ± 6.57	0.899 (0.345)	1.474 (0.238)
Sleep efficiency, %	83.09 ± 5.84	84.42 ± 4.86	81.88 ± 5.16	84.12 ± 5.13	0.421 (0.518)	1.599 (0.211)
WASO, minutes	54.80 ± 20.59	51.94 ± 23.94	60.76 ± 19.27	58.38 ± 15.06	0.009 (0.924)	0.677 (0.512)
Rest-activity rhythm variables						
Cosinor variables						
MESOR, counts	191.18 ± 53.88	190.84 ± 52.85	160.32 ± 55.30	153.46 ± 58.26	1.400 (0.239)	2.404 (0.100)
Acrophase, Dec. hours	14.21 ± 1.36	13.60 ± 1.86[d]	14.79 ± 1.81[c]	14.30 ± 1.02	2.289 (0.133)	4.550 (0.015)
F-statistics	2103.26 ± 1132.18	1836.52 ± 803.54	1742.78 ± 831.48	2211.30 ± 1174.18	0.817 (0.368)	0.624 (0.539)
Nonparametric variables						
Interdaily stability	0.507 ± 0.113	0.511 ± 0.101	0.507 ± 0.146	0.523 ± 0.167	0.289 (0.592)	0.107 (0.899)
Intradaily variability	0.829 ± 0.196	0.891 ± 0.245	0.951 ± 0.256	0.874 ± 0.185	0.497 (0.482)	1.599 (0.211)
Relative amplitude	0.872 ± 0.075	0.865 ± 0.051	0.800 ± 0.149	0.866 ± 0.070	0.013 (0.909)	1.850 (0.167)

Key: acrophase, time of peak activity; ADD, Alzheimer's disease dementia; CN, cognitively normal; CN-, CN without amyloid-β deposition; CN+, CN with amyloid-β deposition; Dec. hours, decimal hours (e.g., 14.5 = 2:30 pm); F-statistic represents rhythmicity; MCI, mild cognitive impairment; MCI+, MCI with amyloid-β deposition; MESOR, midline estimating statistic of rhythm; WASO, wake-time after sleep onset.
[a] Presented as mean ± SD.
[b] General linear model adjusted for covariates including age, sex, education, employment status, vascular risk factor scores (VRS, the composite score for present vascular risk factors), global cognitive function (MMSE-KC, Mini-Mental State Examination in the Korean version of the CERAD Assessment Packet), depression symptoms (CES-D, Center for Epidemiologic Studies Depression Scale), sleep problems defined by sleep questionnaire data converted to categorical variables (yes or no) using cutoff values and diagnostic criteria (PSQI, Pittsburgh Sleep Quality Index; STOP, questionnaire for obstructive sleep apnea; RBDSQ, REM sleep behavior disorder screening questionnaire; CH-RLSq, Cambridge-Hopkins questionnaire for restless leg syndrome), and APOE ε4 positivity; df1 = 1, df2 = 127.
[c] Significantly different from CN+ at $p < 0.05$.
[d] Significantly different from MCI+ at $p < 0.05$.
[e] Significantly different from ADD at $p < 0.05$.

with and without Aβ. Age-related earlier timing of circadian phase appeared at a relatively younger age (early-old age) in older CN+ adults, compared with CN− participants, and the RAR pattern robustness decreased in older CN+ adults, although those associations were not statistically significant (RA [F {1, 57} = 3.761, p = 0.057]; Fig. 2).

3.4. Influences of clinical progression of Alzheimer's disease on sleep and RAR

Table 3 shows the effects of cognitive status of AD (CN, MCI, and ADD) on sleep and RAR among individuals with cerebral Aβ deposition. After adjustment for covariates, some circadian timing variables (bed time, wake-up time, and acrophase) and sleep duration (TST) differed in accordance with the participants' cognitive status. Post hoc analyses revealed that MCI had later circadian timing than preclinical AD, but a further delayed pattern was not observed in participants with ADD. By contrast, TST was significantly increased in patients with ADD (Table 3).

4. Discussion

The present study revealed that older age was associated with an earlier timing of circadian phase and higher consistency and robustness of daily activity rhythm in cognitively healthy individuals without cerebral Aβ deposition. Sleep quantity and quality were mostly unaffected by age without AD. Independent of age, the presence of Aβ in CN participants was associated with earlier circadian phase; otherwise sleep and activity variables were not affected by AD in adults with normal cognition. Among overall Aβ+ individuals, MCI was related to later timing of daily rhythm, whereas dementia led to increased TST compared with CN.

An earlier timing of circadian rhythm in older adults is consistent with previous studies, although most of these investigated mixed populations undergoing healthy or pathologic aging (Duffy et al., 2015; Ohayon et al., 2004). Based on our analyses including only a cognitively healthy population without Aβ pathology, an earlier timing in response to older age itself is better supported. Although the mechanisms underlying phase advance are unclear, a reduction in circadian arousal signals against the homeostatic sleep drive has been suggested to lead to earlier timing in older adults; this phase desynchrony might be caused by age-related physiological changes in the intrinsic clock system (Hofman and Swaab, 2006; Skeldon et al., 2016; Van Someren and Riemersma-Van Der Lek, 2007).

The presence of Aβ deposition was related to an earlier wake-up time in CN adults. Only a few studies have examined the associations between preclinical Aβ deposition with sleep and RAR in living humans. A previous report from our study group also showed phase advance in preclinical AD, but only in apolipoprotein ε4 noncarriers (Hwang et al., 2018), whereas another report did not show phase-related findings but noted increased IS and intradaily variability (Musiek et al., 2018). We showed that an earlier circadian phase was associated with both older age and preclinical AD, independently of each other. In addition, there were interaction effects between age and amyloid pathology on bed time and acrophase. These findings indicate that age-related earlier circadian phase is more prominent in older adults during the course of AD, compared with older adults undergoing physiological aging. Although the underlying mechanisms that connect prominent earlier phase in older adults with Aβ pathology are unclear, age-related circadian rhythm differences may be accentuated by Alzheimer's pathology in aged brain (Musiek et al., 2018).

The higher consistent RAR, measured by IS, in healthy older adults is similar with a recent report (Musiek et al., 2018), and Van Someren (Van Someren and Riemersma-Van Der Lek, 2007) suggested that maintaining a regular rhythm is a compensatory behavior to adhere to a stricter 24-h zeitgeber against the vulnerable circadian timing system in the older population. As older adults are less flexible to environmental challenges than younger adults, they might try to adapt to circadian misalignments by more regular physical activity, mealtimes, and social behavior (Monk et al., 2006). The higher RA in older age could also be explained by the relationship with IS: older adults can adhere to a natural light-dark cycle more effectively by increasing their activity during the daytime and decreasing activity at nighttime (higher robustness) (Van Someren and Riemersma-Van Der Lek, 2007). On the other hand, the age-related increasing tendencies of IS and RA were no longer apparent in late-old−aged individuals. Similarly, some previous studies reported that age-related changes in sleep parameters tended to end near the age of 80 years (Ohayon et al., 2004) and suggested that environmental factors such as retirement might cause these different patterns in late-old adults. Although the present study showed that this nonlinear pattern remained after the inclusion of employment status as a covariate, the adjustment to re-establish daily rhythms after retirement might lead to the disappearance of increasing patterns of IS and RA at this age.

Among older adults with cerebral Aβ pathology, higher IS and RA were not observed in older age; in contrast, those parameters showed decreasing tendencies. This finding is in line with a previous longitudinal study which reported that decreased robustness of circadian rhythm was associated with increased risk of developing cognitive impairment (Tranah et al., 2011). Although this previous study did not define pathological status of the samples, it is possible that decreased robustness of RAR might have been shown in participants having preclinical Aβ pathology. Dysfunction of a circadian pacemaker in AD has been repeatedly reported in previous studies (Cronin et al., 2017; Zhou et al., 1995). Disappearance of the age-dependent increase in IS and RA (in contrast with healthy older adults) might be related with impaired clock function in AD; behavioral compensation against age-related circadian dysregulation might become difficult because of homeostatic overload in individuals with Alzheimer's pathology. Alternatively, less adherence to daily routine in older adults with Alzheimer's pathology might reflect their less involvement in regular activities or subtle impairment in daily function (Skeldon et al., 2016).

The objective measures of sleep quantity and quality generally did not change with age in our participants. This is inconsistent with previous studies, which reported decreased sleep duration and poorer quality of sleep in older adults (Huang et al., 2002; Ohayon et al., 2004). These discrepancies may be related to the participants' characteristics. Unlike previous studies, we only included individuals without pathological cerebral Aβ. A meta-analysis reported that the average TST and WASO at 70 years were 6 hours 15 minutes and 60 minutes, respectively (Ohayon et al., 2004), whereas the current early-old participants (65−74 years) had better sleep profiles with TST and WASO of 6 hours 30 minutes and 50 minutes, respectively. Furthermore, relatively small numbers of participants in our study, compared with those in the previous community-based studies, might have contributed to those discrepancies.

Later circadian timing was evident in individuals with symptomatic AD. A phase delay in AD has been reported frequently (Coogan et al., 2013), and some studies showed the same phenomenon in participants with MCI (Tranah et al., 2011). This finding contradicts the advanced timing in preclinical AD; thus, a phase delay can be caused by further neurodegeneration in addition to Aβ pathology during the course of AD (Coogan et al., 2013). In addition, the increased TST observed in ADD may be explained by additional

degenerative changes in AD progression. The associated brain regions involved in circadian timing system, such as tauopathy in the brainstem (Satoh and Iijima, 2017), should be investigated further. In addition, the environmental influences from caregivers or family members who provide assistance with activities of daily living to individuals with ADD should be considered.

Several strengths of this study should be mentioned. First, our cohort included a wide range of participants aged 20–90 years, all of whom received comprehensive clinical assessments, objective sleep and RAR measurements by actigraphy monitoring, and neuroimaging evaluations. Second, we investigated both interactive and independent effects of age and AD pathology on sleep and activity variables. Moreover, regarding the influences of clinical AD on sleep, we included only patients with MCI and ADD with amyloid deposition to minimize the confounding effect of non-AD MCI or ADD phenocopy cases: 47% of patients with MCI and 12% of patients with probable AD do not have Aβ deposition in their brain.(Jansen et al., 2015; Ossenkoppele et al., 2015). Finally, we evaluated and adjusted for various external and internal factors, particularly sleep problems common in older adults including OSA, RBD, and RLS, in our analyses.

This study also had some potential limitations that should be discussed. First, we attempted to assess the effects of age itself on sleep and circadian rhythms by excluding the effects of Aβ pathology. Nevertheless, age-related nonamyloid brain pathologies may have affected our results, even though we excluded individuals with serious neurological disorders or brain lesions on MRI and adjusted for vascular risk factors and the WMH volume in the analyses. Second, a relatively small sample size of CN participants with Aβ pathology might have affected the negative findings in terms of the influences of preclinical AD on sleep and RAR. Third, multiple comparisons might increase the possibility of false positive discovery even though all the significant findings regarding age-related differences in sleep and circadian parameters remained significant after Bonferroni correction for multiple comparisons ($p < 0.008$). Fourth, we did not count the numbers of work days and free days during the period monitored by actigraphy. Although we included employment status in the analyses as an indicator of schedule differences between participants, working days that could impose environmental constraints on sleep and RAR should be assessed in future studies. Finally, because our results are based on cross-sectional observations, age-related differences in sleep and RAR are not necessarily indicative of age-related changes within each individual. There is also a possibility that generation effects due to rapid social changes in Korea affected the results of our study. Future studies with longitudinal designs are needed to confirm the present findings.

5. Conclusions

In conclusion, the findings from our study suggest that older age itself does not affect sleep duration but is associated with earlier timing of sleep phase and more regular daily activity rhythm. In terms of the AD effect, while preclinical AD relates with age-related earlier timing more prominently, clinical AD instead links to later circadian timing and longer sleep duration.

Disclosure statement

The authors have no competing interests to declare.

CRediT authorship contribution statement

Jee Eun Park: Data curation, Writing - original draft, Writing - review & editing. **Yu Jin Lee:** Methodology, Investigation, Data curation. **Min Soo Byun:** Investigation, Data curation. **Dahyun Yi:** Investigation, Data curation. **Jun Ho Lee:** Investigation. **So Yeon Jeon:** Investigation. **Jeong Yeon Hwang:** Formal analysis. **Heenam Yoon:** Formal analysis. **Young Min Choe:** Investigation. **Yu Kyeong Kim:** Methodology, Investigation, Data curation. **Seong A. Shin:** Methodology, Investigation, Data curation. **Hye Won Suk:** Formal analysis. **Dong Young Lee:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary data

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