Neurobiology of Sleep and Circadian Rhythms 10 (2021) 100065

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

journal homepage: www.elsevier.com/locate/

A population-based prospective study on rest-activity rhythm and mild cognitive impairment among Hong Kong healthy community-dwelling older adults

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ARTICLE INFO

Keywords:
Circadian rhythm
Cognition
Actigraphy
Elderly
Cohort studies

ABSTRACT

Background: Relatively few studies investigated the association between rest-activity circadian rhythm and cognitive impairment in population-based study, and the evidence from Asian populations is sparse. We aimed to examine the relationship of actigraphy measured rest-activity circadian rhythm with mild cognitive impairment (MCI) or cognitive impairment in Hong Kong healthy community-dwelling older adults.

Methods: We recruited 174 Hong Kong healthy adults aged ≥65 years (36 male vs. 138 female) during April–September 2018, and followed up them for 12 months. Participants were invited to wear wrist actigraphy for 7 days in both baseline and follow-up study. We used the actigraph data to calculate their midline statistic of rhythm (MESOR), amplitude, acrophase and percent rhythm. Montreal Cognitive Assessment (MoCA) was used to assess their cognitive scores at baseline and follow-up. Multivariate logistic regression model was performed to estimate the association of rest-activity circadian rhythm parameters with MCI; whilst multinomial logistic regression model was used to examine the association between rhythm parameters and changes of cognitive scores (i.e., worsen: <-1, stable: -1 to 1, better cognition: ≥2) after 12-months follow-up respectively.

Results: There was no association between rest-activity circadian rhythm parameters and MCI or cognitive impairment at baseline. Compared to those with an averaged value of acrophase (1:24pm-3:00pm), results of multinominal logistic regression showed that participants with a delayed acrophase (after 3:00pm) were less likely to have better cognition (adjusted odds ratio (AOR) = 0.32, 95% confidence interval (CI) = 0.11–0.88). Upon one year of follow-up, participants who delayed their acrophase for 24 min than their baseline measurements were also less likely to have better cognitive functions (AOR = 0.26, 95%CI = 0.08–0.79).

Conclusions: Results from both the baseline survey and follow-up study consistently confirmed that older adults, especially in light of the majority of participants being the females, with delayed acrophase were less likely to have better cognition in the Asian population.

1. Introduction

Dementia/cognitive impairment is a progressive degenerative brain syndrome of several diseases affecting a person's cognitive abilities and behavior (WHO, 2019a), whilst mild cognitive impairment (MCI) is considered as an intermediate stage between normal stage and dementia (Butterfield et al., 2007). Incidence of dementia and MCI are strongly associated with advanced age. With the aging population grows dramatically around the world, the number of dementia and MCI rises rapidly in the last decade (WHO, 2011). The number of people suffering from dementia is estimated to increase from 50 million in 2017 to 115 million in 2050 (Livingston et al., 2017; WHO, 2019a). Dementia is one of the major causes of disability and dependency among the elderly, and affecting their daily functions including memory, learning capacity, calculation, language and judgement (WHO, 2019a).

Previous epidemiology studies examined that older adult with poor sleep quality such as short/long sleep duration and more sleep disturbance were associated with cognitive impairment (Blackwell et al., 2006; Lim et al., 2013; Potvin et al., 2012; Sterniczuk et al., 2013; Tranah et al., 2011; Yaffe et al., 2014), however, little is known about the association of sleep-wake cycles with MCI or cognitive impairment. Rest-activity circadian rhythm of sleep-wake cycles changing across the

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https://doi.org/10.1016/j.nbscr.2021.100065
Received 7 April 2020; Received in revised form 28 February 2021; Accepted 6 April 2021
Available online 16 April 2021

lifespan and plays a role in learning and memory (Krishnan and Lyons, 2015; Sherman et al., 2015), and relatively few studies examined the association of rest-activity circadian rhythm parameters with cognitive impairment in the general population. Recent evidence from MrOS and MrOS Sleep studies in the United States by following up their participants for 3.4 years found that low amplitude (i.e. levels of peak activity), low midline statistic of rhythm (MESOR) (i.e. means of the rhythm), low rhythm robustness (i.e. rhythm prominence) and advanced acrophase (i.e. time of peak activity) were associated with cognitive impairment in old men (Rogers-Soeder et al., 2018). Another US Osteoporotic Fractures study showed that decreased amplitude, low rhythm robustness, but delayed acrophase, were associated with increased odds of developing dementia and MCI in older women after 4.9 years of follow-up (Tranah et al., 2011).

Circadian rhythm is generated by the anterior hypothalamic suprachiasmatic nucleus (SCN) but also synchronized by the time signal of external cues, known as zeitgebers (Leng et al., 2019). However, the zeitgebers such as intensity and duration of exposure to light at night vary across countries (Li and Zhou, 2017), suggesting there may have cultural differences in rest-activity circadian rhythm between Eastern and Western countries. However, the relevant evidence on the association between circadian rhythm and MCI or cognitive impairment in the Asian population is sparse. The aim of the study was to examine the association of actigraphy rest-activity circadian rhythm parameters with MCI and the change of cognitive scores after one year of follow-up among Hong Kong healthy community-dwelling older adults.

2. Methods

2.1. Study design and subjects

We conducted a population-based prospective cohort study by recruiting baseline participants during April 2018 and September 2018, and following up them for 12 months to obtain the change of cognitive functions. In the baseline survey, 210 eligible subjects were recruited from two non-governmental organizations and four community centers located in different clusters of Hong Kong. To be eligible, participants ought to be Hong Kong Chinese residents aged 65 years old or above, Cantonese speakers, no disease history of dementia diagnosed by physicians and no listening problem. Thirty-six participants were excluded due to incomplete data on cognitive assessment (8 subjects), lack of actigraph data (28 subjects), and finally, 174 participants were retained in the data analysis.

All interviewers received one full-day training session and carried out a face to face interview with each participant using a standardized questionnaire and assessments to obtain information on socioeconomic status, lifestyle habits, physician diagnosed medical history, cognition, depression and physical activity status. We asked our participants to wear the actigraphy on their non-dominant hand continuously for seven days to measure their rest-activity circadian rhythm. All participants signed written informed consensuses at the beginning of the interview and were followed up for 12 months (mean 11.6 months) after the baseline study.

This study was approved by The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC Ref No.:2017.211).

2.2. Exposure: measurement of rest-activity circadian rhythm

We used the GENEActiv Original actigraphy to measure the rest-activity circadian rhythm of the participants. It is a lightweight (16g) and waterproof device (Activinsights, Kimbolton, UK). We placed it on participants' non-dominant wrist for 168 h (seven days), which can gain information on movement and real-time skin temperature. All collected data were downloaded from GENEActiv software (Version 3.1).

The GENEActiv actigraphy detects and records movements in three mutually vertical axes (x, y, and z). Manufacturer's software automatically calculated the gravity-subtracted sum of vector magnitudes (SVM) using the data of these three axes: SVMg s = [(x2 + y2 + z2)½ − 1g] [17], and summarized and converted over 1-min epochs at 100 Hz. To detect the non-wearing time of each participant, we downloaded the data including time, SVM and skin temperature and further processed them using R-program (R Core Team, Vienna, Austria). We applied the open source R package "GGIR" to detect the non-wearing period based on the non-wear scores, which were estimated according to the standard deviation and the range of raw data from each accelerometer axis (Migueles et al., 2019). Since the records of non-wearing periods represent a relatively low and steady SVM reading with abnormal low skin temperature, we then plotted the SVM graphs to examine and identify the abnormal pattern related to the wearing time. For the records with abnormal and steady SVM pattern, we identified and analyzed the SVM data of periods with abnormally low skin temperature from the raw data. The study only included the data of real wearing duration for calculation of rest-activity circadian rhythm, and excluded participants who wore less than 120 h (5/7 of 168 h) in the sum length of wearing time. All eligible participants included in the final data analysis had both the weekdays and weekend actigraph data.

We imported the 'adjusted real wearing time' raw data into R-program, and used R packages "Season" and "Cosinor" to calculate the rest-activity circadian rhythm parameters using the least squares method to fit a sine wave to a time series (Tong, 1976): MESOR, amplitude, acrophase, and percent rhythm. MESOR, refers to the adjusted mean levels of the rhythm; amplitude, refers to the distance between the peak rhythm and the trough of the fitted MESOR; acrophase, refers to the time in the cycle of the daily peak rhythm; and percent rhythm, refers to the percentage of variability accounted by fitted curve.

We classified the baseline levels of MESOR, amplitude and percent rhythm into three subgroups (low, median, and high) according to the tertile category, using the low rhythm as a reference group. According to the tertile distribution of acrophase, we categorized it into 'advanced acrophase' (before 1:24pm) and 'delayed acrophase' (after 3:00pm), using the average acrophase of 1:24pm-3:00pm as the reference group. We further calculated the change of rest-activity circadian rhythm parameters between the baseline and follow-up measures (rest-activity circadian rhythm parameters at follow-up minus rest-activity circadian rhythm parameters at baseline), and classified them into three subgroups according to the cutoff point of tertile: decrease/advanced (Tertile 1), stable (Tertile 2), and increase/delayed (Tertile 3) (Table A1).

2.3. Outcome: cognitive decline

The Hong Kong Cantonese version of Montreal Cognitive Assessment (MoCA) was used to evaluate the MCI and cognitive impairment status of our participants at baseline and follow-up (Yeung et al., 2014). This assessment included a variety of dimensions such as visuospatial and executive functioning, naming, attention, language, abstract reasoning, delayed recall and orientation, and its sensitivity for detecting MCI is 90% (Nasreddine et al., 2005). We categorized MCI and cognitive impairment according to the locally validated MoCA instruction (Wong et al., 2015), which recommended by MoCA test (Nasreddine, 2019). Participants scored ≤7th and ≤2nd percentiles in their age group, stratified by their education years, were classified as MCI and cognitive impairment respectively, whilst participants scored above 7th cutoff

scores in their group were identified as normal cognition, as shown in Table A2 (Wong et al., 2015). As only 16 participants were stated as cognitive impairment, we combined MCI with cognitive impairment in the analysis. We calculated the changes of cognitive scores by using MoCA scores at follow-up minus MoCA scores at baseline, and then categorized the changes of cognitive scores according to the tertile category: lower than -1 (i.e. 33 percentiles) and higher than or equal to 2 (i.e. 66 percentiles) as worsen and better cognitive scores respectively, with stable scores (-1 to 1) as the reference group.

2.4. Covariates

A standardized questionnaire was used to obtain the social demographic information (e.g., age, sex, educational attainment in years, marital status, and recruitment sites), lifestyle habits (e.g. smoking and alcohol drinking history), occupational status, physician diagnosed medical history and medication use (e.g. hypertension and diabetes). We measured participants' anthropometric such as height and weight in their light clothes during the recruitment, and calculated their body mass index (BMI) (<25, ≥25). We used Geriatric Depression Scale (GDS) to measure their depression scores [non-depressed (scored< 8), depressed (scored≥ 8)] (Sheikh and Yesavage, 1986), and Chinese short-version of the International Physical Activity Questionnaire to collect the information on physical activity (Macfarlane et al., 2007). As none of our participants had a regular vigorous-intensity aerobic physical activity habit, we only defined our participants into insufficient moderate-intensity physical activity group (<150 min per week) and sufficient moderate-intensity physical activity (≥150 min per week) according to WHO recommendation for older adults (WHO, 2019b).

2.5. Data analysis

Continuous and categorical variables were expressed as mean-±standard deviation and proportion, respectively. Chi-squared test or Fisher's exact test was used to compare categorical variables. Independent sample *t*-test was performed to compare continuous variables. We used paired *t*-test to test the difference of each participant's cognitive scores and rest-activity circadian rhythm parameters measured between the baseline and follow-up. Unconditional multivariate logistic regress model was performed to assess the odds ratio (OR) and 95% confidence intervals (CI) for the associations of rest-activity circadian rhythm parameters with MCI or cognitive impairment in the baseline. Despite we categorized MCI or cognitive impairment according to their educational levels and age, the range of each category was still big (e.g., the cognitive function of older adults aged 70 may be different from those aged 79). We further adjusted for the age at interview (continuous), sex (female, male), and educational attainment (continuous) that were the statistically significant variables identified from the univariate analysis in the models (Table 1) to minimize the potential residual confounding effects from these variables. We performed this model to examine the association of selected characteristics with MCI or cognitive impairment. We used multinomial logistic regression to examine the association of baseline rest-activity circadian rhythm parameters with the changes of cognitive scores, and the association of change of rhythm parameters with the changes of cognitive scores.

The prior studies have suggested that there may have sex differences in acrophase, in which advanced acrophase was associated with increased risk of cognitive impairment in older men (Rogers-Soeder et al., 2018), while delayed acrophase was associated with increased risk of MCI and dementia in older women (Tranah et al., 2011). We performed stratified analyses according to sex to examine whether the association of baseline circadian rhythm parameters with the changes of cognitive scores; and the association of change of rhythm parameters with the changes of cognitive scores modified by sex.

In addition to the educational attainment, low education levels is a well-known risk factor of cognitive impairment (Livingston et al., 2017), and rest-activity circadian rhythm may differ according to their educational levels (Mitchell et al., 2017). Thus, we used one-way ANOVA to evaluate the interrelationship between rest-activity circadian rhythm parameters and education attainment. We also conducted sensitivity analysis by excluding older adults who were never educated to examine the effect of education levels on the association between baseline circadian rhythm parameters and the changes of cognitive scores, and the association of change of rhythm parameters with the changes of cognitive scores.

We analyzed the data using R-program (R Core Team, Vienna,

Table 1
Distribution of selected characteristics by baseline cognitive status.

Characteristics	Normal cognition n = 123 n(%)	MCI or cognitive impairment [a] n = 51 n(%)	p-value
Age, mean (SD)	74.9 ± 6.8	77.5 ± 7.1	**0.026**
Sex			**0.012**
Male	32 (26.0)	4 (7.8)	
Female	91 (74.0)	47 (92.2)	
Educational attainment			**<0.001**
Never educated	18 (14.6)	23 (45.1)	
Educated	105 (85.4)	38 (54.9)	
Marital status			0.411
Married	68 (55.3)	24 (47.1)	
Single/Divorce/Widow	55 (44.7)	27 (52.9)	
Body mass index			0.616
< 25	84 (70.0)	33 (64.7)	
≥ 25	36 (30.0)	18 (35.3)	
Smoking			1.000
Non-smoker	111 (90.2)	46 (90.2)	
Current/Ex-smoker	12 (9.8)	5 (9.8)	
Habitual alcohol consumption			0.338
No	116 (94.3)	46 (90.2)	
Yes	7 (5.7)	5 (9.8)	
History of hypertension or diabetes			0.995
No	50 (40.7)	20 (39.2)	
Yes	73 (59.3)	31 (60.8)	
Geriatric Depression Scale			1.000
Non depressed (<score 7)	106 (87.6)	44 (86.3)	
Depressed (≥ score 8)	15 (12.4)	7 (13.7)	
Time spend on physical activity (per week)			0.547
<150 min	87 (70.7)	33 (64.7)	
≥150 min	36 (29.3)	18 (35.3)	
Working status			0.963
Part-time/Full-time	5 (4.1)	2 (3.9)	
Retired/Never employed	118 (95.9)	49 (96.1)	
Recruitment cites			0.102
Non-governmental organization	17 (13.8)	13 (25.4)	
Community centers	106 (86.2)	38 (74.5)	

[a] MCI or cognitive impairment were defined as participants' Montreal Cognitive Assessment scored ≤7th.

Austria) version 3.5.1.

3. Results

Among 174 participants with complete actigraph data and cognitive assessment at the baseline, 51 (29.3%) of them were stated as MCI or cognitive impairment. The average age of participants was 75.63 ± 6.94. In general, participants who were older (adjusted OR = 1.04, 95%CI = 0.98–1.10), female (Adjusted OR = 3.52, 95%CI = 1.23–12.74) and never educated (Adjusted OR = 2.65, 95%CI = 1.63–8.35) were more likely to have MCI or cognitive impairment (Table A3). There were no significant differences between normal cognition and MCI regarding BMI, smoking habit, and history of hypertension and diabetes (Table 1). Despite we did not observe any significant difference between alcohol consumption and MCI, we found that more than 42% of alcohol drinkers have MCI in our study, and in contrast only 29% among non-drinkers were defined as MCI (Table 1). The demographic characteristics among participants with actigraph data were similar to those without (Table A4). Regarding the change of rest-activity circadian rhythm parameters between the baseline and follow-up measurement for the same individual, all parameters were weakened after one year, with a significant change for amplitude (mean difference = -8.96) and a marginally significant change for MESOR (mean difference = -8.75) (Table A5).

Table 2
Odds ratio and 95% confidence interval of the association between rest-activity circadian rhythm and prevalent mild cognitive impairment or cognitive impairment at the baseline.

Rest-activity rhythms parameters [c]	Normal cognition n = 123	Mild cognitive impairment or cognitive impairment [a] n = 51		
	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [b]
MESOR				
≤244.26	44 (35.8)	14 (27.5)	1.00	1.00
244.26–315.69	40 (32.5)	17 (33.3)	1.34 (0.59–3.09)	2.16 (0.85–5.70)
>315.69	39 (31.7)	20 (39.2)	1.61 (0.72–3.67)	2.39 (0.93–6.44)
Amplitude				
≤109.60	41 (33.3)	17 (33.3)	1.00	1.00
109.60–168.78	40 (32.5)	17 (33.3)	1.03 (0.46–2.29)	1.37 (0.56–3.41)
>168.78	42 (34.1)	17 (33.3)	0.98 (0.44–2.18)	1.34 (0.53–3.42)
Acrophase				
≤1:24pm	40 (32.5)	19 (37.3)	1.39 (0.62–3.19)	1.40 (0.60–3.34)
1:24pm-3:00pm	41 (33.3)	14 (27.5)	1.00	1.00
>3:00pm	42 (34.1)	18 (35.3)	1.26 (0.55–2.88)	1.65 (0.69–4.06)
Percent rhythm				
≤8.16	38 (30.9)	20 (39.2)	1.00	1.00
8.16–12.28	46 (37.4)	11 (21.6)	0.45 (0.19–1.05)	0.44 (0.17–1.06)
>12.28	39 (31.7)	20 (39.2)	0.97 (0.45–2.10)	1.06 (0.46–2.45)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.

[a] MCI or cognitive impairment were defined as participants' Montreal Cognitive Assessment scored ≤7th

[b] Adjusted for the age at interview, sex, education attainment in years.

[c] All rest-activity rhythms parameters were stratified based on their tertile distribution.

3.1. Change of cognitive scores

Association of rest-activity circadian rhythm parameters with prevalent MCI or cognitive impairment at baseline are shown in Table 2. We did not find any significant difference between normal cognition and MCI or cognitive impairment participants in terms of MESOR, amplitude, acrophase and percent rhythm. Despite no significant difference in their cognitive scores between the baseline (mean = 19.05, SD = 5.62) and follow-up measurements (mean = 19.44, SD = 5.49), participants with delayed acrophase measured at the baseline (i.e. after 3:00pm) were negatively associated with better cognitive scores (Adjusted OR = 0.31, 95%CI = 0.11–0.88) compared to those with an averaged acrophase (i.e. 1:24pm-3:00pm), and the results remained significant after adjustment for age, sex and education attainment (Table 3). After one-year follow-up, participants who had a further delayed acrophase for more than 24 min less likely to get the better cognition (Adjusted OR = 0.26, 95%CI = 0.08–0.79) (Table 4). The event rate of getting better cognitive scores among participants who had a further delayed acrophase for more than 24 min than baseline measure and those with stable or advance acrophase after a year of follow-up was 13% and 32% respectively ("risk" difference = -19%). While the event rate of getting worsen cognitive scores among participants who had a further delayed acrophase for more than 24 min and those with stable or advance acrophase after a year of follow-up was 34% and 20% respectively (risk difference = 14%).

3.2. Analyses according to sex

When we conducted the stratified analysis according to sex, no male participants with delay acrophase at the baseline (after 3:00pm) had better cognitive scores (Table A6). Compared to female participants with averaged acrophase (i.e. 1:24pm-3:00pm), those with delayed acrophase were less likely to have better cognition at follow-up (Adjusted OR = 0.55, 95%CI = 0.18–1.66), albeit not significant (Table A6). Females participants who delayed their acrophase for 24 min than their baseline measure upon one year follow-up were also less likely to have better cognitive function (Adjusted OR = 0.12, 95%CI = 0.03–0.50) (Table A7).

3.3. Sensitivity analyses according to education attainment

In addition to the interrelationship between rest-activity circadian rhythm parameters and education attainment, we found that participants who never educated, seems to have lower MESOR and amplitude levels, and advanced acrophase (Table A8). Educated older adults who have delayed acrophase at baseline was negatively associated with better cognitive function in the follow up study (adjusted OR = 0.22, 95%CI = 0.07–0.71) (Table A9). After one-year follow-up, participants who had a further delayed acrophase for more than 24 min than the baseline measurement were less likely to get the better cognition (Adjusted OR = 0.36, 95%CI = 0.10–1.26) (Table A10), despite it was not significant.

4. Discussion

In this population-based prospective study among Hong Kong community-dwelling older adults, we examined the relationship between rest-activity circadian rhythm and the prevalent MCI or cognitive impairment, and the association with the change of cognitive scores after one-year follow-up. Consistent with the previous studies (Jia et al., 2014; Knopman et al., 2016), the prevalence of MCI and cognitive impairment among our study subjects was around 21% and 9% respectively. Participants who were older and had alcohol consumption habit were more likely to have MCI or cognitive impairment, whilst participants who were female and never educated were associated with a three-fold and two-fold risk of MCI, respectively. We did not observe

Table 3
Odds ratio and 95% confidence interval of the association between baseline rest-activity circadian rhythm and changed cognitive scores during the follow-up.

Rest-activity rhythms parameters [b]	Stable n = 71	Worsen n = 36			Better n = 35		
	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [a]	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [a]
MESOR							
≤244.26	26 (36.6)	11 (30.6)	1.00	1.00	11 (31.4)	1.00	1.00
244.26- 315.69	21 (29.6)	14 (38.9)	1.58 (0.59–4.19)	1.89 (0.67–5.39)	13 (37.1)	1.46 (0.54–3.93)	1.55 (0.55–4.40)
>315.69	24 (33.8)	11 (30.6)	1.08 (0.40–2.95)	1.55 (0.44–4.10)	11 (31.4)	1.08 (0.40–2.95)	1.14 (0.38–3.42)
Amplitude							
≤109.60	22 (31.0)	11 (30.6)	1.00	1.00	14 (40.0)	1.00	1.00
109.60- 168.78	22 (31.0)	14 (38.9)	1.27 (0.47–3.41)	1.42 (0.50–4.05)	12 (34.3)	0.86 (0.32–2.26)	0.80 (0.29–2.23)
>168.78	27 (38.0)	11 (30.6)	0.81 (0.30–2.23)	0.99 (0.32–3.05)	9 (25.7)	0.52 (0.19–1.44)	0.48 (0.16–1.46)
Acrophase							
≤1:24pm	17 (23.9)	12 (33.3)	1.01 (0.38–2.73)	0.98 (0.36–2.67)	15 (42.9)	0.59 (0.21–1.63)	0.58 (0.21–1.60)
1:24pm- 3:00pm	21 (29.6)	15 (41.7)	1.00	1.00	11 (31.4)	1.00	1.00
>3:00pm	33 (46.5)	9 (25.0)	0.39 (0.13–1.10)	0.41 (0.14–1.17)	9 (25.7)	**0.31 (0.11–0.85)**	**0.32 (0.11–0.88)**
Percent rhythm							
≤8.16	24 (33.8)	14 (38.9)	1.00	1.00	11 (31.4)	1.00	1.00
8.16–12.28	20 (28.2)	12 (33.3)	1.03 (0.39–2.72)	1.02 (0.38–2.75)	12 (34.3)	1.31 (0.48–3.60)	1.31 (0.47–3.64)
>12.28	27 (38.0)	10 (27.8)	0.63 (0.24–1.69)	0.68 (0.24–1.86)	12 (34.3)	0.97 (0.36–2.60)	1.00 (0.37–2.75)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[a] Adjusted for the age at interview, sex, education attainment in years.
[b] All rest-activity rhythms parameters were stratified based on their tertile distribution.

Table 4
Odds ratio and 95% confidence interval of the association between changes of rest-activity circadian rhythm and changed cognitive scores between baseline and follow-up measurements.

Changes of rest-activity rhythms parameters [b]	Stable n = 71	Worsen n = 36			Better n = 35		
	N (%)	N (%)	Crude OR (95% CI)	Adjusted OR (95%CI) [a]	N (%)	Crude OR (95% CI)	Adjusted OR (95%CI) [a]
MESOR							
≤-31.62	19 (28.8)	12 (36.4)	1.61 (0.56–4.64)	1.62 (0.56–4.75)	13 (39.41)	1.43 (0.52–3.92)	1.48 (0.53–4.13)
-32.62-15.84	23 (34.8)	9 (27.3)	1.00	1.00	11 (33.3)	1.00	1.00
>15.84	24 (36.4)	12 (36.4)	1.28 (0.45–3.60)	1.29 (0.45–3.68)	9 (27.3)	0.78 (0.27–2.24)	0.78 (0.27–2.24)
Amplitude							
≤-22.84	20 (30.3)	13 (39.4)	1.24 (0.45–3.41)	1.39 (0.49–3.99)	11 (33.3)	1.05 (0.37–2.96)	1.15 (0.39–3.35)
-22.84-5.23	21 (31.8)	11 (33.3)	1.00	1.00	11 (33.3)	1.00	1.00
>5.23	25 (37.9)	9 (27.3)	0.69 (0.24–1.97)	0.77 (0.26–2.31)	11 (33.3)	0.84 (0.30–2.32)	0.93 (0.32–2.67)
Acrophase							
≤-36 min	17 (25.8)	10 (30.3)	0.50 (0.16–1.56)	0.47 (0.14–1.55)	16 (48.5)	0.49 (0.18–1.30)	0.45 (0.16–1.27)
-36-24 min	24 (36.4)	7 (21.2)	1.00	1.00	11 (33.3)	1.00	1.00
>24 min	25 (37.9)	16 (48.5)	1.09 (0.40–2.96)	1.12 (0.41–3.12)	6 (18.2)	**0.26 (0.08–0.78)**	**0.26 (0.08–0.79)**
Percent rhythm							
≤-2.12	23 (34.8)	10 (30.3)	0.56 (0.20–1.55)	0.58 (0.21–1.61)	11 (33.3)	0.78 (0.28–2.21)	0.79 (0.29–2.26)
-2.12-0.74	18 (27.3)	14 (42.4)	1.00	1.00	11 (33.3)	1.00	1.00
>0.74	25 (37.9)	9 (27.3)	0.46 (0.16–1.30)	0.46 (0.16–1.29)	11 (33.3)	0.72 (0.26–2.02)	0.72 (0.25–2.02)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[a] Adjusted for the age at interview, sex, education attainment in years.
[b] All changes of rest-activity rhythms parameters were stratified based on their tertile distribution.

any association between rest-activity circadian rhythm parameters and MCI or cognitive impairment. However, participants with delayed acrophase (after 3:00pm) at the baseline study or a further delayed acrophase for more than 24 min after one year of follow-up were less likely to have better cognitive scores. In addition, we found that old adults' rest-activity circadian rhythm parameters were dampened after a year.

Prior studies showed that older adults with cognitive impairment or dementia had significantly delayed acrophase (Cochrane et al., 2012; Leng et al., 2019). Our study by following up healthy older adults for one year showed that those with delayed acrophase were associated with less likely to get better cognition, compared to those with an averaged acrophase. Results remained consistent after excluding older adults who were never educated. Participants, especially female participants with a further acrophase delayed 24 min measured after one year of follow-up were also negatively associated with better cognitive function compared with those with stable acrophase. One large cohort study followed up 1 282 community-dwelling women for 4.9 years showed that women aged

65 years old or above with delayed acrophase of later than 3:51pm increased the risk of developing MCI (Tranah et al., 2011). However, another cohort study reported that older men with advanced acrophase (<12:28pm) increased 1.8 odds of cognitive decline when compared to those of acrophase between 12:28pm and 4:06pm. As the sample size among male participants was relatively small, we did not observe any male participants with delayed acrophase at the baseline (after 3:00pm) have better cognition at follow-up. Compared to females with an averaged acrophase (i.e. 1:24pm-3:00pm), those with delayed acrophase were also less likely to have better cognitive scores at follow-up, albeit not significant. Female participants who delayed their acrophase for 24 min than their baseline measure upon one year follow-up were also less likely to have better cognitive function. Prior study suggested that circadian rhythm clock genes, such as *CLOCK*, *NPAS2*. *RORA* and *RORB*, contributed to the cognitive declines or aging independently and/or through the interaction with environmental factors such as alcohol consumption and physical activity (Lin et al., 2017). In general, advancing age is linked to phase advanced of circadian rhythm of body temperature, melatonin, and rest-activity cycle as the sensitivity of the light reduces with aging (Duffy et al., 2015; Kondratova and Kondratov, 2012; Musiek et al., 2018), and thus the advance acrophase, but not delayed may be the normal aging progress. Light-dark cycle is the major exogenous time signals that synchronized with neurons in SCN that generated our biological circadian rhythm (Leng et al., 2019). Previous study suggested that the phase delay is not associated with damage of principal neuron in SCN, but may refer to the deranged inputs to the SCN (Wang et al., 2015). For instance, daily rhythms of SCN attenuated by serotonergic inputs that inhibit photic phase-resetting in hamster (Francl et al., 2010), and the pathological changes of serotonergic neurons in dorsal raphe nucleus were also found in early dementia human (Rub et al., 2000). Thus, delayed acrophase may refer to the disturbance of inputs to SCN, and contributed to the dysfunctions of circadian rhythm (Ferrari and Magri, 2008). The circadian dysfunctions also attributed to hippocampal pathology in older adults (Deibel et al., 2015), affecting the older adult's cognitive function and less likely to have better cognition.

Our study demonstrated the association of rest-activity circadian rhythm with MCI or cognitive performance after one year among Hong Kong healthy older adult, which had been less examined in the Asian population. All participants were community-dwelling, good daily functioning and without clinically diagnosed with dementia. We objectively measured their rest-activity circadian rhythm using actigraphy. However, there was a number of limitations should be considered. We had a relatively small sample size and there was no significant difference in their cognitive status between two studies due to the limited follow-up time. Although we have a relatively good follow-up rate (82%), the withdraw rate was high among those with cognitive impairment in the baseline study (follow-up rate = 63%). Potential classification bias may be a concern as we used MoCA to detect MCI and cognitive impairment but not clinically diagnosed, in spite of MoCA is a well-known screening tool for cognitive impairment with good sensitivity for detecting MCI (Nasreddine et al., 2005). Additionally, we used the same version of MoCA at the baseline and follow-up, the observed improvement of MoCA among our study population may be due to the susceptible to the practice effects (Cooley et al., 2015). However, older adults with cognitive impairment were less likely to have practice effects (i.e. improvement) in their overall cognitive scores at follow-up (Machulda et al., 2013). In addition to the selection bias, our study was volunteer-based and the majority of our participants were female, they may relatively concern more about their physical and mental health (Mackenzie et al., 2006). Females tend to have longer lifespans and the selection for health older males in the surviving population may reflect a lower risk for many conditions including cognitive impairment. As the findings in males were not significant due to limited power, the sex difference in the association between acrophase and cognition between males and females among Hong Kong elders should be confirmed by larger studies." Despite around 17% of our participants with missing information on rest-activity circadian rhythm, the demographic characteristics among participants with actigraph data were similar to those without (Table A4).

5. Conclusion

In conclusion, findings from both the baseline survey and follow-up study consistently confirmed that older adults with delayed acrophase were less likely to have better cognition in the Asian population, which indicates that circadian disruption reflected in the delayed acrophase is likely to be involved the etiology of cognitive decline. This study added further evidence that weakened rest-activity circadian rhythm may be involved in the etiology of cognitive function among healthy community-dwelling older adults, especially in light of the majority of the study participants being the females. Future interventions studies targeting on maintaining the timing of peak activity among older adults may have benefits to preserve the robustness of cognitive functions among older population.

CRediT authorship contribution statement

Priscilla Ming Yi Lee: Conceptualization, Methodology, Formal analysis, Writing – original draft, preparation, Reviewing and Editing. **Bonnie Ho Ling Kwok:** Project administration, Reviewing and Editing. **Julie Yuen Ting Ma:** Resources, Reviewing and Editing. **Lap Ah Tse:** Supervision, Reviewing and Editing.

Declaration of competing interest

None.

Table A1
Cutoff scores of changed of rest-activity circadian rhythm parameters after 12 months

Changed of rest-activity circadian rhythm parameters [1]	Decrease/ Advanced	Stable	Increased/ Delayed
MESOR	≤-31.62	-32.62-15.84	>15.84
Amplitude	≤-22.84	-22.84-5.23	>5.23
Acrophase	≤-36 min	-36-24 min	>24 min
Percent rhythm	≤-2.12	-2.12-0.74	>0.74

[1] All changes of rest-activity rhythms parameters were stratified based on their tertile distribution.

Table A2
Cutoff scores of The Hong Kong Cantonese version of Montreal Cognitive Assessment

Age	Education (years)	Cutoff percentile	
		7^{th}	2^{nd}
65–69	0–3	14	9
	4–6	18	13
	7–9	19	16
	10–12	20	17
	>12	23	21
70–79	0–3	14	11
	4–6	15	10
	7–9	18	15
	10–12	19	18
	>12	20	16
≥80	0–6	13	10
	>6	15	13

Wong A, Law LS, Liu W, Wang Z, Lo ES, Lau A, et al. Montreal Cognitive Assessment: One Cutoff Never Fits All. Stroke. 2015;46(12):3547-50.

Table A3
Odds ratio and 95% confidence interval of the association between selective characteristics and prevalent mild cognitive impairment or cognitive impairment at the baseline

Characteristics	Crude OR (95%CI)	Adjusted OR (95%CI) [2]
Age	**1.06 (1.01–1.11)**	1.04 (0.98–1.10)
Sex		
Male	1.00	1.00
Female	**4.13 (1.53–14.48)**	**3.52 (1.23–12.74)**
Educational attainment		
Never educated	**4.79 (2.29–10.23)**	**2.65 (1.63–8.35)**
Educated	1.00	1.00
Marital status		
Married	1.00	1.00
Single/Divorce/Widow	1.39 (0.72–2.69)	0.78 (0.36–1.63)
Body mass index		
< 25	1.00	1.00
≥ 25	1.27 (0.63–2.54)	1.09 (0.50–2.35)
Smoking		
Non-smoker	1.00	1.00
Current/Ex-smoker	1.01 (0.31–2.88)	1.85 (0.46–7.46)
Habitual alcohol consumption		
No	1.00	1.00
Yes	1.80 (0.51–5.93)	2.23 (0.55–8.97)
History of hypertension or diabetes		
No	1.00	1.00
Yes	1.06 (0.55–2.09)	0.86 (0.42–1.78)
Geriatric Depression Scale		
Non depressed (<score 7)	1.00	1.00
Depressed (≥ score 8)	1.12 (0.41–2.86)	0.92 (0.31–2.48)
Time spend on physical activity (per week)		
<150 min	1.00	1.00
≥150 min	1.32 (0.65–2.62)	1.39 (0.66–2.92)
Working status		
Part-time/Full-time	1.00	1.00
Retired/Never employed	1.04 (0.21–7.42)	0.76 (0.12–6.28)
Recruitment cites		
Non-governmental organization	1.00	1.00
Community centers	0.47 (0.21–1.07)	0.76 (0.29–2.05)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[1] MCI or cognitive impairment were defined as participants' Montreal Cognitive Assessment scored $<7^{th}$.
[2] Adjusted for the age at interview, sex, education attainment in years.

Table A4
Distribution of selected characteristics by the availability of actigraph data.

Characteristics	With actigraph data n = 174 n(%)	Without actigraph data n = 28 n(%)	p-value
Age, mean (SD)	75.6 ± 7.1)	76.3 ± 7.5)	0.622
Sex			0.268
Male	36 (32.1)	9 (20.7)	
Female	138 (67.9)	19 (79.3)	
Educational attainment			1.00
Never educated	41 (23.6)	7 (25.0)	
Educated	133 (76.4)	21 (75.0)	
Marital status			0.411
Married	92 (46.4)	13 (46.4)	
Single/Divorce/Widow	82 (53.6)	15 (53.6)	
Body mass index			0.556
< 25	117 (68.4)	17 (60.7)	
≥ 25	54 (31.6)	11 (39.3)	
Smoking			0.743
Non-smoker	157 (90.2)	25 (89.3)	
Current/Ex-smoker	17 (9.8)	3 (10.7)	
Habitual alcohol consumption			0.247
No	162 (93.1)	24 (85.7)	
Yes	12 (6.9)	4 (14.3)	
History of hypertension or diabetes			0.443
No	70 (40.2)	14 (50.0)	
Yes	104 (59.8)	14 (50.0)	
Geriatric Depression Scale			0.540
Non depressed (<score 7)	150 (87.2)	26 (92.9)	
Depressed (≥ score 8)	22 (12.8)	2 (7.1)	
Time spend on physical activity (per week)			0.567
<150 min	120 (69.0)	20 (71.4)	
≥150 min	54 (31.0)	8 (28.6)	
Working status			1.000
Part-time/Full-time	7 (3.6)	1 (4.0)	
Retired/Never employed	167 (96.4)	27 (96.0)	
Recruitment cites			0.598
Non-governmental organization	30 (17.2)	6 (21.4)	
Community centers	144 (82.8)	22 (78.6)	

Table A5
Comparing characteristics of the rest-activity circadian rhythm parameters in baseline and follow-up studies within the same individual

Rest-activity circadian rhythm parameters	Baseline	Follow-up	Mean difference[1]	p-value
MESOR	288.9 ± 78.47	284.83 ± 76.04	-8.75	0.063
Amplitude	146.96 ± 60.98	140.02 ± 58.68	-8.96	0.026
Acrphase	14:14 ± 2:16	14:08 ± 1:57	-0:03	0.636
Percent rhythm	10.72 ± 5.66	10.26 ± 5.28	-0.32	0.422

Abbreviations: MESOR = Midline statistic of rhythm.
[1] Rest-activity circadian rhythm parameters at follow up minus rest-activity circadian rhythm parameters at baseline.

Table A6
Odds ratio and 95% confidence interval of the association between baseline rest-activity circadian rhythm and changed cognitive scores during the follow-up stratified by sex

Male								Female						
Rest-activity rhythms parameters [2]	Stable n = 71	Worsen n = 36			Better n = 35			Stable n = 71	Worsen n = 36			Better n = 35		
	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]
MESOR														
≤244.26	6 (40.0)	1 (14.3)	1.00	1.00	4 (57.1)	1.00	1.00	20 (35.7)	10 (34.5)	1.00	1.00	7 (25.0)	1.00	1.00
244.26- 315.69	4 (26.7)	5 (71.5)	7.50 (0.62–90.65)	21.47 (0.74–62.00)	2 (28.6)	0.75 (0.09–6.23)	2.98 (0.17–50.90)	17 (30.4)	9 (31.0)	1.06 (0.35–3.21)	1.29 (0.40–4.12)	11 (39.3)	1.85 (0.59–5.82)	1.80 (0.55–5.86)
>315.69	5 (33.3)	1 (14.3)	1.20 (0.06–24.47)	3.08 (0.08–12.22)	1 (14.3)	0.30 (0.03–3.63)	1.02 (0.05–21.23)	19 (33.9)	10 (34.5)	1.05 (0.40–2.95)	1.46 (0.43–4.92)	10 (35.7)	1.50 (0.48–4.76)	1.43 (0.41–5.00)
Amplitude														
≤109.60	5 (33.3)	2 (28.6)	1.00	1.00	5 (71.4)	1.00	1.00	17 (30.4)	9 (31.0)	1.00	1.00	9 (32.1)	1.00	1.00
109.60- 168.78	5 (33.3)	3 (42.8)	1.50 (0.17–13.23)	0.36 (0.02–7.59)	0 (0.0)	–	–	17 (30.4)	11 (37.9)	1.22 (0.40–3.70)	1.46 (0.45–4.70)	12 (42.9)	1.33 (0.45–3.99)	1.20 (0.39–3.73)
>168.78	5 (33.3)	2 (28.6)	1.00 (0.01–10.17)	0.87 (0.03–2.19)	2 (28.6)	0.40 (0.05–3.12)	0.92 (0.05–1.82)	22 (39.3)	9 (31.0)	0.77 (0.25–2.37)	1.01 (0.29–3.52)	7 (25.0)	0.60 (0.19–1.94)	0.50 (0.14–1.78)
Acrophase														
≤1:24pm	2 (13.3)	3 (42.9)	1.50 (0.11–21.32)	1.00 (0.05–2.19)	3 (42.9)	0.75 (0.06–8.83)	0.56 (0.03–9.63)	19 (33.9)	12 (41.4)	0.94 (0.32–2.78)	0.95 (0.32–2.82)	8 (28.6)	0.57 (0.18–1.79)	0.57 (0.18–1.79)
1:24pm- 3:00pm	2 (13.3)	2 (28.6)	1.00	1.00	4 (57.1)	1.00	1.00	15 (26.8)	10 (34.5)	1.00	1.00	11 (39.3)	1.00	1.00
>3:00pm	11 (73.3)	2 (27.6)	0.18 (0.02–2.15)	0.11 (0.00–2.98)	0 (0.0)	–	–	22 (39.3)	7 (24.1)	0.48 (0.15–1.53)	0.49 (0.15–1.59)	9 (32.1)	0.56 (0.19–1.67)	0.55 (0.18–1.66)
Percent rhythm														
≤8.16	6 (40.0)	4 (57.1)	1.00	1.00	4 (57.1)	1.00	1.00	18 (32.1)	10 (34.5)	1.00	1.00	7 (25.0)	1.00	1.00
8.16–12.28	3 (20.0)	1 (14.3)	0.50 (0.04–6.69)	0.52 (0.03–9.21)	3 (42.9)	1.50 (0.20–1.15)	2.22 (0.21–2.34)	17 (30.4)	11 (37.9)	1.16 (0.39–3.44)	1.15 (0.39–3.41)	9 (32.1)	1.36 (0.41–4.48)	1.37 (0.42–4.52)
>12.28	6 (40.0)	2 (28.6)	0.50 (0.07–3.85)	0.04 (0.24–5.97)	0 (0.0)	–	–	21 (37.5)	8 (27.6)	0.69 (0.22–2.11)	0.73 (0.23–2.26)	12 (42.9)	1.47 (0.48–4.53)	1.45 (0.47–4.49)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[1] Adjusted for the age at interview and education attainment in years.
[2] All rest-activity rhythms parameters were stratified based on their tertile distribution.

Table A7
Odds ratio and 95% confidence interval of the association between changes of rest-activity circadian rhythm and changed cognitive scores between baseline and follow-up measurements stratified by sex

Male								Female						
Changes of rest-activity rhythms parameters [2]	Stable n = 71	Worsen n = 36			Better n = 35			Stable n = 71	Worsen n = 36			Better n = 35		
	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [2]
MESOR														
≤-31.62	2 (14.3)	4 (57.1)	–	–	3 (42.9)	2.50 (0.25–24.72)	3.25 (0.24–44.41)	17 (32.7)	8 (30.8)	0.94 (0.29–3.00)	1.02 (0.31–3.30)	10 (38.4)	1.32 (0.34–3.30)	1.35 (0.43–4.26)
-32.62-15.84	5 (35.7)	0 (0.0)	–	–	3 (42.9)	1.00	1.00	18 (34.6)	9 (34.6)	1.00	1.00	8 (30.8)	1.00	1.00
>15.84	7 (50.0)	3 (42.9)	–	–	1 (14.2)	0.24 (0.02–3.01)	0.32 (0.02–4.82)	17 (32.7)	9 (34.6)	1.06 (0.42–4.15)	0.98 (0.31–3.10)	8 (30.8)	1.05 (0.32–3.46)	1.03 (0.31–3.42)
Amplitude														
≤-22.84	5 (35.7)	3 (42.9)	1.80 (0.12–26.20)	1.89 (0.08–4.21)	3 (42.9)	1.80 (0.12–26.20)	1.75 (0.10–30.93)	15 (28.8)	10 (38.5)	1.20 (0.39–3.65)	1.26 (0.40–4.03)	8 (30.8)	0.96 (0.30–3.05)	0.93 (0.28–3.09)
-22.84-5.23	3 (21.4)	1 (14.2)	1.00	1.00	1 (14.2)	1.00	1.00	18 (34.6)	10 (38.5)	1.00	1.00	10 (38.4)	1.00	1.00
>5.23	6 (42.9)	3 (42.9)	1.50 (0.12–21.31)	1.96 (0.08–4.55)	3 (42.9)	1.50 (0.12–21.31)	2.19 (0.12–41.70)	19 (36.5)	6 (23.1)	0.57 (0.17–1.89)	0.60 (0.18–2.08)	8 (30.8)	0.76 (0.24–2.35)	0.74 (0.23–2.39)
Acrophase														
≤-36 min	6 (42.9)	1 (14.3)	0.17 (0.01–2.09)	0.23 (0.01–4.10)	3 (42.9)	2.00 (0.15–26.74)	3.77 (0.18–79.49)	18 (34.6)	6 (23.1)	0.72 (0.19–2.75)	0.57 (0.14–2.31)	8 (30.8)	0.39 (0.13–1.18)	0.35 (0.11–1.15)
-36-24 min	4 (28.6)	4 (57.1)	1.00	1.00	1 (14.3)	1.00	1.00	13 (25.0)	6 (23.1)	1.00	1.00	15 (57.7)	1.00	1.00
>24 min	4 (28.6)	2 (28.6)	0.50 (0.06–4.47)	1.21 (0.07–2.01)	3 (42.9)	3.00 (0.21–42.63)	16.93 (0.52–553.16)	21 (40.4)	14 (53.8)	1.44 (0.44–4.70)	1.36 (0.41–4.49)	3 (11.5)	**0.12 (0.03–0.51)**	**0.12 (0.03–0.50)**
Percent rhythm														
≤-2.12	4 (28.6)	2 (28.6)	1.00 (0.09–11.03)	0.82 (0.05–1.46)	2 (28.6)	0.67 (0.07–6.41)	0.37 (0.03–4.79)	19 (36.5)	14 (30.8)	0.49 (0.16–1.52)	0.47 (0.15–1.49)	9 (34.6)	0.83 (0.26–2.69)	0.81 (0.25–2.67)
-2.12-0.74	4 (28.6)	2 (28.6)	1.00	1.00	3 (42.9)	1.00	1.00	14 (26.9)	12 (46.2)	1.00	1.00	8 (30.8)	1.00	1.00
>0.74	6 (42.9)	3 (42.9)	1.00 (0.11–8.95)	0.80 (0.06–1.17)	2 (28.6)	0.44 (0.05–3.98)	0.23 (0.02–3.09)	19 (36.5)	10 (23.1)	0.36 (0.11–1.22)	0.39 (0.16–1.31)	9 (34.6)	0.83 (0.26–2.69)	0.84 (0.26–2.73)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[1] Adjusted for the age at interview, sex, education attainment in years.
[2] All changes of rest-activity rhythms parameters were stratified based on their tertile distribution.

Table A8
Interrelationship between rest-activity circadian rhythm parameters and educational attainment.

Characteristics	MESOR	Amplitude	Acrophase	Percent rhythm
Educational attainment				
Never educated	253.4 ± 68.79	116.1 ± 48.05	13:44 ± 2:31	10.1 ± 6.41
Educated	299.9 ± 78.24	156.5 ± 61.54	14:24 ± 2:10	10.9 ± 5.42
Mean square	67733.00	51174.00	13.97	20.89
F-value	11.68	14.86	2.76	0.65
p-value	<0.01	<0.01	0.10	0.42

Abbreviations: MESOR = Midline statistic of rhythmInterrelationship between rest-activity circadian rhythm parameters and educational attainment was assessed by one-way ANOVA.

Table A9
Odds ratio and 95% confidence interval of the association between baseline rest-activity circadian rhythm and changed cognitive scores during the follow-up stratified by education

Rest-activity rhythms parameters [2]	Stable n = 54	Worsen n = 25			Better n = 27		
	N (%)	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [1]	N (%)	Crude OR (95%CI)	Adjusted OR (95%CI) [1]
MESOR							
≤244.26	15 (27.8)	6 (24.0)	1.00	1.00	9 (33.3)	1.00	1.00
244.26- 315.69	17 (31.5)	12 (48.0)	1.76 (0.53–5.87)	1.79 (0.51–6.29)	10 (37.0)	0.98 (0.31–3.06)	1.04 (0.32–3.44)
>315.69	22 (40.7)	7 (28.0)	0.80 (0.22–2.84)	0.80 (0.20–3.19)	8 (29.6)	0.61 (0.19–1.93)	0.65 (0.18–2.30)
Amplitude							
≤109.60	11 (20.4)	6 (24.0)	1.00	1.00	9 (33.3)	1.00	1.00
109.60- 168.78	18 (33.3)	12 (48.0)	1.22 (0.36–4.20)	1.13 (0.30–4.23)	10 (37.0)	0.68 (0.21–2.19)	0.64 (0.18–2.24)
>168.78	25 (46.3)	7 (28.0)	0.51 (0.14–1.88)	0.46 (0.11–1.98)	8 (29.6)	0.39 (0.11–1.28)	0.38 (0.10–1.44)
Acrophase							
≤1:24pm	16 (29.6)	10 (40.0)	0.86 (0.26–2.87)	0.86 (0.26–2.88)	7 (25.9)	0.37 (0.11–1.23)	0.36 (0.11–1.19)
1:24pm- 3:00pm	11 (20.4)	8 (32.0)	1.00	1.00	13 (48.1)	1.00	1.00
>3:00pm	27 (50.0)	7 (28.0)	0.36 (0.10–1.22)	0.36 (0.10–1.22)	7 (25.9)	**0.22 (0.07–0.70)**	**0.22 (0.07–0.71)**
Percent rhythm							
≤8.16	18 (33.3)	11 (44.0)	1.00	1.00	7 (25.9)	1.00	1.00
8.16–12.28	14 (29.9)	9 (36.0)	1.05 (0.34–3.24)	1.02 (0.33–3.18)	9 (33.3)	1.65 (0.49–5.54)	1.66 (0.49–5.64)
>12.28	22 (40.7)	5 (20.0)	0.37 (0.11–1.27)	0.35 (0.10–1.25)	11 (40.7)	1.29 (0.41–4.00)	1.38 (0.43–4.45)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[1] Adjusted for the age at interview and sex.
[2] All rest-activity rhythms parameters were stratified based on their tertile distribution.

Table A10
Odds ratio and 95% confidence interval of the association between changes of rest-activity circadian rhythm and changed cognitive scores between baseline and follow-up measurements stratified by education.

Changes of rest-activity rhythms parameters [2]	Stable n = 50	Worsen n = 23			Better n = 25		
	N (%)	N (%)	Crude OR (95% CI)	Adjusted OR (95%CI) [1]	N (%)	Crude OR (95% CI)	Adjusted OR (95%CI) [1]
MESOR							
≤-31.62	15 (32.7)	8 (30.8)	1.51 (0.43–5.36)	1.49 (0.41–5.38)	9 (38.4)	1.13 (0.36–3.60)	1.31 (0.40–4.33)
-32.62-15.84	17 (34.6)	6 (34.6)	1.00	1.00	9 (30.8)	1.00	1.00
>15.84	18 (32.7)	9 (34.6)	1.42 (0.42–4.83)	1.42 (0.41–4.87)	7 (30.8)	0.73 (0.22–2.41)	0.75 (0.23–2.51)
Amplitude							
≤-22.84	16 (32.0)	10 (43.5)	1.63 (0.44–5.96)	1.58 (0.42–5.97)	11 (44.0)	1.28 (0.39–4.23)	1.44 (0.42–4.94)
-22.84-5.23	13 (26.0)	5 (21.7)	1.00	1.00	7 (28.0)	1.00	1.00
>5.23	21 (42.0)	8 (34.8)	0.99 (0.27–3.69)	0.95 (0.24–3.76)	7 (28.0)	0.62 (0.18–2.17)	0.74 (0.20–2.73)
Acrophase							
≤-36 min	20 (40.0)	5 (21.7)	0.50 (0.13–2.00)	0.49 (0.12–2.01)	8 (32.0)	0.44 (0.13–1.39)	0.36 (0.11–1.22)
-36-24 min	12 (24.0)	6 (26.1)	1.00	1.00	11 (44.0)	1.00	1.00
>24 min	18 (36.0)	12 (52.2)	1.33 (0.39–4.53)	1.33 (0.39–4.53)	6 (24.0)	0.36 (0.11–1.25)	0.36 (0.10–1.26)
Percent rhythm							
≤-2.12	19 (38.0)	6 (26.1)	0.42 (0.12–1.49)	0.42 (0.12–1.50)	11 (44.0)	0.77 (0.25–2.41)	0.72 (0.23–2.28)
-2.12-0.74	12 (24.0)	9 (39.1)	1.00	1.00	9 (36.0)	1.00	1.00
>0.74	19 (38.0)	8 (34.7)	0.56 (0.17–1.86)	0.56 (0.17–1.87)	5 (20.0)	0.35 (0.09–1.30)	0.33 (0.09–1.25)

Abbreviations: OR, odds ratio; CI, confidence intervals, MESOR = Midline statistic of rhythm.
[1] Adjusted for the age at interview and sex.
[2] All changes of rest-activity rhythms parameters were stratified based on their tertile distribution.

Acknowledgement

The authors would like to thank Hiu Man TSOI and Karina Ka Yin LAM for their assistance in participants' recruitment preparation and data collection. Special thanks to Kitty SIN, Karen YIU, CHAI Man Hon, LO Kin Hei, Dan SHUM, Yue Hon WONG for site arrangement.

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