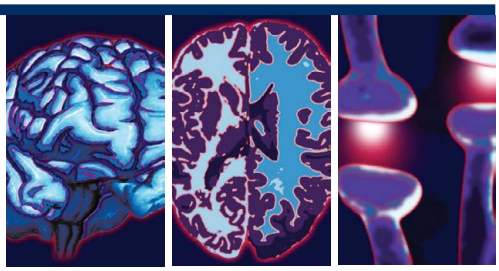

The Association between Earlier Bedtime and Cardiac Vagal Control in Community-Dwelling Older Adults: The Shi-Pai Sleep Study, Taiwan

Shang-Wen Chang [1,2,3], Hsi-Chung Chen [4,†], Pesus Chou[1]

ABSTRACT

Background:

The mechanism underlying the relationship between sleep–wake timing in older adults with poor health remains unclear.

Objective:

This study aimed to examine the relationship between deviant sleep–wake timing and cardiac autonomic function among community-dwelling older adults.

Methods:

A total of 597 randomly selected older adults aged ≥ 65 years and residing in an urban city participated in this study. Cardiac autonomic function was assessed by monitoring heart rate variability.

Results:

There were 58.6% men, and the overall mean age was 77.9 ± 5.2 years. After controlling for various covariates, it was found that the likelihood of poor cardiac vagal function was higher (odds ratio: 1.89, 95% confidence interval 1.20–2.98) for older adults with an earlier bedtime (before 21:59 h).

Conclusions:

This finding suggested that an earlier bedtime in metropolitan older adults may indicate a decline in the health status.

Keywords

Cardiac autonomic function; Community medicine; Heart rate variability; Older adults; Sleep-wake timing

[1]Community Medicine Research Center & Institute of Public Health, National Yang-Ming University, Taipei, Taiwan

[2]Department of Psychiatry, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

[3]School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

[4]Department of Psychiatry & Center of Sleep Disorders, National Taiwan University Hospital, Taipei, Taiwan

[†]Author for correspondence: Hsi-Chung Chen, M.D., Ph.D., Department of Psychiatry and Center of Sleep Disorders, National Taiwan University Hospital, No. 1, Chang-Te St., Zhongzheng District, Taipei City 100, Taiwan, Tel: 886-2-23123456; ext: 66787; Fax: 886-2-23813208; email: hsichungchen@ntu.edu.tw

Introduction

Sleep disorders are prevalent in older adults [1,2]. Various sleep disturbances predict different adverse health outcomes, such as extreme sleep duration [3,4], insomnia disorder [5,6], and disordered-breathing sleep [7]. Several physiological processes have been proposed to mediate the negative impact of sleep disturbances on health, including endocrine dysfunctions in extreme sleep durations [8, 9], systemic inflammation in sleep loss [10], and cardiovascular pathophysiology in insomnia disorder [11]. Specifically, an elevated risk of cardiovascular-related adverse events has consistently been demonstrated in older adults with insomnia [12-14]. Although the circadian timing system has also been considered to influence cardiovascular function [11], it remains unknown whether circadian misalignment affects cardiovascular function in older adults.

According to a broad definition, deviant sleep–wake timing is a subtype of circadian misalignment [15]. Plausible mechanisms that may link circadian misalignment to poor health outcomes include dysregulation of feeding behaviours and changes in appetite-stimulating hormone levels, glucose metabolism and mood [15]. However, most studies on the physiological impact of circadian misalignment have been limited to a younger population [16-18]. With regard to the cardiovascular system, circadian misalignment has been found to have an adverse influence on the cardiovascular system in young adults [11,19]. On the other hand, studies that examined the association between circadian misalignment and cardiovascular function in the older population are few. It has been found that a greater extent of acrophase deviation in rest/activity rhythms was associated with a higher mortality risk in patients with dementia [20]. Specifically, a later acrophase of rest/activity rhythms was associated with peripheral vascular disease [21], while an advanced acrophase was associated an elevated risk of cardiovascular mortality in older adults [22]. These findings suggested a link between cardiovascular morbidities and deviant sleep wake timing in aged individuals; however, the cardiovascular pathophysiology that underlies this association remains unclear.

Heart rate variability (HRV) is an indicator of autonomic control of the cardiovascular system [23,24]. A low HRV implies dysregulation of cardiac autonomic function and has been associated with an increased risk of cardiovascular morbidity [25,26] and mortality [27,28]. Furthermore, HRV diminishes with aging per se [29], and it reflects the self-regulatory capacity and health risk [30]. Therefore, identification of factors that may further impair cardiac autonomic function in older adults is crucial. In the field of sleep research, poor HRV has been reported to correlate with insomnia [31], sleep breathing disorder [32], and extreme sleep duration [33]. However, few studies have examined the relationship between sleep–wake timing and HRV, particularly in the older population.

Therefore, the aim of the present study was to examine the association between deviant sleep–wake timing and HRV in older adults residing in a metropolitan city in Taiwan.

Methods

■ Study design and participants

This study formed a part of a community health study conducted by the Community Medicine Research Center at the National Yang-Ming University, Taiwan. In 2007, 740 older adults (≥ 65 years) living in the Shi-Pai area, an urban community of northern Taipei, were randomly selected to participate in the study. The exclusion criteria were as follows: (1) refusal to undergo HRV measurements (n = 61), (2) significant cardiac arrhythmia (n = 36), (3) unknown medical history (n = 21), (4) inability to complete the Hospital Anxiety and Depression Scale (HADS) (n = 16) and (5) unknown sleep history (n = 9). Finally, 597 of the 740 eligible participants were enrolled.

The participants were interviewed at home or a nearby medical centre by well-trained project assistants. In addition to each participant's body weight and height, demographic data and a self-reported medical history with respect to hypertension, diabetes, cardiac disease, exercise habits and substance exposure was collected. Electrocardiograms were recorded after 20 min of rest and before the interview.

All participants provided written informed consent, and the Ethics Committee of National Yang-Ming University approved this study. All methods were performed in accordance with the relevant guidelines and regulations.

■ Measurement of cardiac autonomic control

The detailed procedures for HRV analysis have been previously reported [34]. In short, a 5-min

electrocardiogram was recorded for all recruited subjects after a quiet rest period of 20 min. HRV was analysed using an analysis software package (SS1C, Enjoy Research, Taipei, Taiwan) with an 8-bit analogue-to-digital converter and a sampling rate of 512 Hz.

HRV parameters, including the high frequency power (HF: 0.15–0.40 Hz), low frequency power (LF: 0.04–0.15 Hz) and LF to HF (LF/HF) ratio, were acquired by analysis using a frequency-domain approach [23]. HF is mediated by parasympathetic activity and considered a good indicator of cardiac vagal control. LF is mediated by both the sympathetic and parasympathetic systems and is considered to reflect baroreflex sensitivity [35]. The LF/HF ratio reflects the comparative balance between the two branches of the autonomic system, with a larger LF/HF ratio inferring a greater predominance of sympathetic activity over cardiac vagal control [23]. In the present study, the lowest quartiles for the total power, HF, LF and the LF/HF ratio were defined as 'unfavourable' HRV parameters. Because HRV is sensitive to environmental conditions [35], the location of HRV collection was included as a potential confounding variable in the analysis.

■ Measurement of sleep parameters

The parameters of sleep patterns were investigated using specific questions and items obtained from the Pittsburgh Sleep Quality Index (PSQI) [36]. Self-reported bedtime was recorded on the basis of a question: 'During the past month, at what time did you go to sleep?' We classified bedtime into three categories using the distribution tertiles: (1) before 21:59 h, (2) 22:00–23:59 h and (3) after 24:00 h. Likewise, the morning arising time was categorized as follows: (1) before 4:59 h, (2) 5:00-6:59 h and (3) after 7:00 h. To allow comprehensive evaluation of the relationship between sleep and HRV, data regarding other sleep-related parameters were also collected, including insomnia, use of hypnotics, morning arising time and sleep onset latency. Insomnia and the use of hypnotics were categorized into two groups depending on participants' complaints about insomnia and their reports on the use of hypnotics in the past 4 weeks, respectively. Habitual snoring was reported by the subjects as 'none', 'mild', 'moderate' or 'severe'. Subjects with mild and moderate snoring were defined as not disturbing snorers, while those with severe snoring were defined as disturbing snorers. The self-reported sleep duration was estimated from answers to the following question: 'During the past month, how many hours of actual sleep did you get at night?' On the basis of the responses, it was then categorized into three groups: (1) <5 h, (2) 5–8 h and (3) ≥9 h.

■ Measurement of depressive and anxiety symptoms

Depression and anxiety symptoms [37] were assessed using the Chinese version of HADS, which has been validated [38]. Depression and anxiety were classified into three categories using the distribution quartiles. Cases falling in the lowest two quartiles were combined into one group because of the relatively small number.

■ Other covariates

We defined an exercise frequency of less than once a week as unhealthy [39]. A body mass index of 25.0 kg/m^2 was used as a cut-off point for defining overweight older adults [40]. With regard to chronic medical morbidities, self-reported information about diabetes mellitus, hypertension, cardiac disease (such as coronary artery disease, rheumatic heart disease and heart failure, among others) and cerebral vascular disease was collected. Medical diseases were recorded as present only for participants who reported both their diagnosis and received treatment.

■ Statistical analysis

All statistical analyses were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). In univariate analysis, the distribution of HRV parameters was examined using the chi-square test. In multivariate analysis, multiple logistic regression analysis with all covariates forced into the models was performed to determine the independent relationship between the sleep–wake timing and unhealthy HRV parameters. All reported p-values are two-tailed and were considered significant when they were <0.05.

■ Data availability

The datasets analysed in the current study can be procured from the corresponding author on reasonable request.

Results

In total, 597 older adults participated in the present study. The mean age was 77.9 ± 5.2 years (73.4% were ≥75 years old), and 58.6%

participants were men. Most data (73.9%) were collected at the participants' homes. The percentage of individuals who slept before 21:59 h was 36.5%, while that of individuals who slept at 22:00–23:59 h and after 24:00 h was 53.3% and 10.2%, respectively. The median bedtime was 22:00 h. Insomnia was a problem faced by 19.6% participants, and 16.6% participants had consumed hypnotics in the past 4 weeks. The mean total sleep duration was 6.7 ± 1.6 h, and 9.2% participants slept for ≥9 h **(Table 1).**

In univariate analysis, the proportion of individuals falling in the lowest quartile for HF was significantly greater than that of individuals falling in the upper three quartiles among participants with a high education level ($p = 0.003$), a low weekly exercise frequency ($p < 0.001$) and HRV parameters that were collected at the hospital ($p < 0.001$). Participants who slept before 21:59 h exhibited a higher likelihood of poor HF (44.0%) compared with those who slept later (22:00–23:59 h; 34%); this difference had a borderline statistical significance ($p = 0.08$). The proportion of individuals falling in the lowest quartile for LF was significantly greater than that of individuals falling in the upper three quartiles among participants with HRV parameters that were collected at the hospital ($p < 0.001$). Older adults aged ≥80 years were significantly more likely to have an LF/HF ratio in the lowest quartile ($p = 0.01$). In contrast, participants reporting a total sleep duration of ≥9 h were less likely to fall in the lowest quartile for this ratio ($p = 0.03$; **Table 2**).

In multivariable analysis, individuals who slept before 21:59 h were found to have poor HF compared with those who slept at 22:00–23:59 h [odds ratio (OR): 1.89, 95% confidence interval (CI): 1.20–2.98]. In contrast, the morning rising time did not correlate with any unhealthy HRV parameters. Moreover, the presence of insomnia, use of hypnotics and sleep onset latency did not correlate with unfavourable HRV parameters. Older adults with a sleep duration of ≥9 h were less likely to fall in the lowest quartile for the LF/HF ratio (OR: 0.36, 95% CI: 0.14–0.92; **Table 3**).

Discussion

The present study used an urban cohort of older adults to investigate the relationship between bedtime and cardiac autonomic control. Our findings suggested that older adults with an earlier bedtime (before 21:59 h) exhibit a higher likelihood of poor HF. Lower HF values indicate poor parasympathetic modulation [23], which suggests an elevated risk of cardiac arrhythmias and cardiovascular death [28,41]. Our findings are robust because the potential confounding effects from various sleep-related variables were well addressed.

Several factors may explain the independent association between an earlier bedtime and low HF values. First, normal aging is accompanied by progressively degenerative functioning of the central nervous system, including the circadian oscillator [42]. An advanced sleep phase syndrome in older adults is a common adverse consequence of a disrupted rest–activity rhythm of the circadian oscillator [42]. Because HF is mainly modulated by cardiac vagal function, which is governed by the central nervous system [43], the phenomena of compromised HF and an advanced bedtime may share a common pathomechanism, considering that both reflect degenerative functioning of the central nervous system.

Second, an advanced bedtime may be a behavioural consequence of a decline in the health status, which is also linked to a compromise in cardiac autonomic function. In the literature, older adults with an earlier bedtime have been reported to exhibit cognitive deficits [42, 44], functional disability [45] , loss of autonomy in activities of daily living [46], and frailty [47]. Interestingly, dysregulation of cardiac autonomic function has also been identified in older adults with cognitive deficits [48], social function impairment [49], and frailty [50]. Because impaired mental and physical function would restrict a person's capacity to engage in social activity and, consequently, lead to an early bedtime, the association between poor cardiac vagal control and an earlier bedtime may represent the link between impaired cardiac autonomic function and the underlying failing health.

The association between bedtime and HRV in older adults has been examined in the Yilan Study, which is another large-scale community-based study in Taiwan [4]. Interestingly, sleep–wake timing did not correlate with HRV in the Yilan Study [4]. The designs of the present study and the Yilan study were similar in general, although they differed in a few aspects, including the sample size, definition of deviant sleep–wake timing, categories of sleep-related covariates and urban–rural distribution of participants. Although the sample size in the Yilan study was

Table 1: Characteristics of the elderly individuals included in the present study (n = 597).	
Age (years) [mean± SD (range)]	77.9 ± 5.2 (65-98)
Sex (n, %)	
Men	350 (58.6%)
Women	247 (41.4%)
Education (n, %)	
Elementary school and below	269 (45.1%)
High school	211 (35.3%)
College and above	117 (19.6%)
Body mass index [mean ± SD (kg/m^2)]	24.8 ± 3.7
Smoking status (n, %)	
Current smoker	51 (8.5%)
Ex-smoker/nonsmoker	546 (91.5%)
Weekly frequency of exercise (n, %)	
<1 session/week	129 (21.6%)
≥1 session/week	468 (78.4%)
Sites of data collection (n, %)	
Hospital	156 (26.1%)
Home	441 (73.9%)
Medical history (n, %)	
Diabetes mellitus	117 (19.6%)
Hypertension	309 (51.8%)
Cardiac disease	221 (37.0%)
Cerebral vascular disease	23 (3.9%)
Snoring	
Absent	247 (41.4%)
Not disturbing	316 (52.9%)
Disturbing	34 (5.7%)
Epworth Sleepiness Scale score ≥ 10	60 (10.1%)
Depression score [median (range)]	4 (0–21)
Lowest two quartiles (0–4; n, %)	335 (56.1%)
Third quartile (5–7) (n, %)	124 (20.8%)
Fourth quartile (≥8) (n, %)	138 (23.1%)
Anxiety score [median (range)]	2 (0–14)
Lowest two quartiles (0–2) (n, %)	309 (51.8%)
Third quartile (3–4) (n, %)	161 (27.0%)
Fourth quartile (≥5) (n, %)	127 (21.3%)
Sleep parameters	
Insomnia in the recent 1 month (n, %)	117 (19.6%)
Use of hypnotics in the recent 1 month (n, %)	99 (16.6%)
Bedtime (24-h format) [median (range)]	22:00 h (18:00-4:00 h)
Before 21:59 h (n, %)	218 (36.5%)
22:00–23:59 h (n, %)	318 (53.3%)
After 24:00 h (n, %)	61 (10.2%)
Morning arising time (24-h format) [median (range)]	6:00 h(0:00 h–12:00 h)
Before 4:59 h (n, %)	95 (15.9%)
5:00–6:59 h (n, %)	372 (62.3%)
After 7:00 h (n, %)	130 (21.8%)
Sleep onset latency (minutes) [mean ±SD (range)]	20.0 ± 20.2 (0–240)
<30	441 (73.9%)
30–59	120 (20.1%)
≥60	36 (6.0%)
Total sleep duration (hours) [mean± SD (range)]	6.7 ± 1.6 (0–13)
<5	37 (6.2%)
5–8	505 (84.6%)
≥9	55 (9.2%)
Heart rate variability parameters (mean ± SD)	
High frequency [Ln(ms^2)]	4.34 ± 1.32
Low frequency [Ln(ms^2)]	5.00 ± 1.31
Low/high frequency [Ln(ratio)]	0.65 ± 1.04

Table 2: Univariate analysis for heart rate variability parameters.

	High frequency			Low frequency			Low frequency/high frequency ratio		
	Lowest quartile	Upper three quartiles	Chi-square test	Lowest quartile	Upper three quartiles	Chi-square test	Lowest quartile	Upper three quartiles	Chi-square test
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Age (years)									
65–74	36 (24.0%)	123 (27.5%)		32 (21.6%)	127 (28.3%)		29 (19.5%)	130 (29.0%)	
75–79	69 (46.0%)	171 (38.3%)	p = 0.25	64 (43.2%)	176 (39.2%)	p = 0.28	57 (38.5%)	183 (40.8%)	p = 0.01
≥80 years	45 (30.0%)	153 (34.2%)		52 (35.1%)	146 (32.5%)		63 (42.3%)	135 (30.1%)	
Sex (Men)	96 (64.0%)	254 (56.8%)	p = 0.12	91 (61.5%)	259 (57.7%)	p = 0.42	84 (56.4%)	266 (59.4%)	p = 0.52
Education									
Elementary school and below	55 (36.7%)	214 (47.9%)		55 (37.2%)	214 (47.7%)		69 (46.3%)	200 (44.6%)	
High school	52 (34.7%)	159 (35.6%)	p = 0.003	59 (39.9%)	152 (33.9%)	p = 0.08	54 (36.2%)	157 (35.0%)	p = 0.75
College and above	43 (28.7%)	74 (16.6%)		34 (23.0%)	83 (18.5%)		26 (17.4%)	91 (20.3%)	
Body mass index (kg/m^2) ≥ 25	62 (41.3%)	200 (44.7%)	p = 0.47	63 (42.6%)	199 (44.3%)	p = 0.71	62 (41.6%)	200 (44.6%)	p = 0.52
Smoking status (Current smoker)	15 (10.0%)	36 (8.1%)	p = 0.46	15 (10.1%)	36 (8.0%)	p = 0.42	11 (7.4%)	40 (8.9%)	p = 0.56
Weekly frequency of exercise, <1 session/week	48 (32.0%)	81 (18.8%)	p < 0.001	40 (27.0%)	89 (19.8%)	p = 0.07	38 (25.5%)	91 (20.3%)	p = 0.18
Sites of data collection (hospital)	66 (44.0%)	90 (20.1%)	p < 0.001	63 (42.6%)	93 (20.7%)	p < 0.001	39 (26.2%)	117 (26.1%)	p = 0.99
Medical history									
Diabetes mellitus (yes)	31 (20.7%)	86 (19.2%)	p = 0.70	29 (19.6%)	88 (19.6%)	p = 0.99	25 (16.8%)	92 (20.5%)	p = 0.32
Hypertension (yes)	78 (52.0%)	231 (51.7%)	p = 0.95	72 (48.6%)	237 (52.8%)	p = 0.38	78 (52.3%)	231 (51.6%)	p = 0.87
Cardiac disease (yes)	56 (37.3%)	165 (36.9%)	p = 0.93	59 (39.9%)	89 (60.1%)	p = 0.41	64 (43.0%)	157 (35.0%)	p = 0.08
Cerebral vascular disease (yes)	3 (2.0%)	20 (4.5%)	p = 0.22	6 (4.1%)	17 (3.8%)	p = 0.88	8 (5.4%)	141 (94.6%)	p = 0.27
Snoring									
Absent	63 (42.0%)	184 (41.2%)		66 (44.6%)	181 (40.3%)		66 (44.3%)	181 (40.4%)	
Not disturbing	79 (52.7%)	237 (53.0%)	p = 0.97	69 (46.6%)	247 (55.0%)	p = 0.07	72 (48.3%)	244 (54.5%)	p = 0.33
Disturbing	8 (5.3%)	26 (5.8%)		13 (8.8%)	21 (4.7%)		11 (7.4%)	23 (5.1%)	
Epworth Sleepiness Scale score ≥ 10	16 (10.7%)	44 (9.8%)	p = 0.77	11 (7.4%)	49 (10.9%)	p = 0.22	15 (10.1%)	45 (10.0%)	p = 0.99
Depression score									
Lowest two quartiles (0–4)	75 (50.0%)	260 (58.2%)		76 (51.4%)	259 (57.7%)		82 (55.0%)	253 (56.5%)	
Third quartile (5–7)	38 (25.3%)	86 (19.2%)	p = 0.17	32 (21.6%)	92 (20.5%)	p = 0.34	28 (18.8%)	96 (21.4%)	p = 0.54
Fourth quartile (≥8)	37 (24.7%)	101 (22.6%)		40 (27.0%)	98 (21.8%)		39 (26.2%)	99 (22.1%)	
Anxiety score									
Lowest two quartiles (0–2)	83 (55.3%)	226 (50.6%)		74 (50.0%)	235 (52.3%)		70 (47.01%)	239 (53.3%)	
Third quartile (3–4)	40 (26.7%)	121 (27.1%)	p = 0.47	43 (29.1%)	118 (26.3%)	p = 0.80	41 (27.5%)	120 (26.8%)	p = 0.28

Fourth quartile (≥5)	27 (18.0%)	100 (22.4%)		31 (20.9%)	96 (21.4%)		38 (25.5%)	89 (19.9%)	
Sleep parameters									
Insomnia in the recent 1 month (yes)	27 (18.0%)	90 (20.1%)	p = 0.57	29 (19.6%)	88 (19.6%)	p = 0.99	29 (19.5%)	88 (19.6%)	p = 0.96
Use of hypnotics in the recent 1 month (yes)	27 (18.0%)	72 (16.1%)	p = 0.59	24 (16.2%)	75 (16.7%)	p = 0.89	25 (16.8%)	74 (16.5%)	p = 0.94
Bedtime (24-h format)									
Before 21:59 h	66 (44.0%)	152 (34.0%)		60 (40.5%)	158 (35.2%)		58 (38.9%)	160 (35.7%)	
22:00–23:59 h	69 (46.0%)	249 (55.7%)	p = 0.08	75 (50.7%)	243 (54.1%)	p = 0.47	78 (52.3%)	240 (53.6%)	p = 0.68
After 24:00 h	15 (10.0%)	46 (10.3%)		13 (8.8%)	48 (10.7%)		13 (8.7%)	48 (10.7%)	
Morning arising time (24-h format)									
Before 4:59 h	25 (16.7%)	70 (15.7%)		24 (16.2%)	71 (15.8%)		28 (18.8%)	67 (62.1%)	
5:00 -6:59 h	96 (64.0%)	276 (61.7%)	p = 0.70	93 (62.8%)	279 (62.1%)	p = 0.96	94 (63.1%)	278 (15.0%)	p = 0.32
After 7:00 h	29 (19.3%)	101 (22.6%)		31 (20.9%)	99 (22.0%)		27 (18.1%)	103 (23.0%)	
Sleep onset latency (min)									
<30	115 (76.7%)	326 (72.9%)		109 (73.6%)	332 (73.9%)		115 (77.2%)	326 (72.8%)	
30–59	28 (18.7%)	92 (20.6%)	p = 0.60	27 (18.2%)	93 (20.7%)	p = 0.42	24 (16.1%)	96 (21.4%)	p = 0.36
≥60	7 (4.7%)	29 (6.5%)		12 (6.0%)	24 (5.3%)		10 (6.7%)	26 (5.8%)	
Total sleep duration (h)									
<5	10 (6.7%)	27 (6.0%)		7 (4.7%)	30 (6.7%)		12 (8.1%)	25 (5.6%)	
5–8	125 (83.3%)	380 (85.0%)	p = 0.89	128 (86.5%)	377 (84.0%)	p = 0.67	131 (87.9%)	374 (83.5%)	p = 0.03
≥9	15 (10.0%)	40 (8.9%)		13 (8.8%)	42 (9.4%)		6 (4.0%)	49 (10.9%)	

Table 3: Logistic regression analyses for factors predicting the lowest quartile for heart rate variability parameters.

	Lowest quartile for high frequency		Lowest quartile for low frequency		Lowest quartile for the low/high frequency ratio	
	Adjusted odds ratio (95% confidence interval)		Adjusted odds ratio (95% confidence interval)		Adjusted odds ratio (95% confidence interval)	
Age (years)						
75–79 *vs.* 65–74	1.38 (0.82–2.31)	p = 0.23	1.47 (0.87–2.47)	p = 0.15	1.53 (0.91–2.58)	p = 0.11
≥80 *vs.* 65–74	1.22 (0.69–2.14)	p = 0.49	1.58 (0.91–2.75)	p = 0.11	2.18 (1.27–3.74)	p = 0.05
Sex						
Men *vs.* women	0.98 (0.59–1.64)	p = 0.95	1.00 (0.61–1.64)	p = 1.00	0.88 (0.54–1.42)	p = 0.59
Education						
High school *vs.* elementary school and below	1.10 (0.67–1.80)	p = 0.71	1.37 (0.85–2.19)	p = 0.20	0.91 (0.50–1.66)	p = 0.75
College and above *vs.* elementary school and below	2.29 (1.26–4.16)	p < 0.01	1.41 (0.77–2.59)	p = 0.27	1.05 (0.67–1.67)	p = 0.82
Body mass index (kg/m^2)						
≥25 *vs.* < 25	0.94 (0.62–1.43)	p = 0.77	1.02 (0.68–1.54)	p = 0.92	0.93 (0.62–1.39)	p = 0.72
Smoking status						
Current smoker *vs.* Ex-smoker/nonsmoker	0.86 (0.42–1.78)	p = 0.68	0.94 (0.46–1.91)	p = 0.87	0.76 (0.36–1.60)	p = 0.47

Weekly frequency of exercise						
<1 session/week *vs.* ≥ 1 session/week	2.84 (1.76–4.60)	p < 0.001	1.58 (0.98–2.55)	p = 0.06	1.26 (0.78–2.02)	p = 0.34
Sites of data collection						
Hospital vs. home	3.74 (2.38–5.87)	p < 0.001	3.23 (2.08–5.01)	p < 0.001	1.21 (0.76–1.91)	p = 0.42
Medical history						
Diabetes mellitus (yes/no)	1.03 (0.62–1.74)	p = 0.89	1.02 (0.61–1.70)	p = 0.94	0.81 (0.48–1.36)	p = 0.42
Hypertension (yes/no)	0.94 (0.61–1.45)	p = 0.77	0.80 (0.53–1.22)	p = 0.30	1.11 (0.73–1.69)	p = 0.61
Cardiac disease (yes/no)	1.13 (0.73–1.75)	p = 0.60	1.30 (0.85–1.98)	p = 0.23	1.41 (0.93–2.13)	p = 0.10
Cerebral vascular disease (yes/no)	0.33 (0.09–1.26)	p = 0.11	1.06 (0.38–2.95)	p = 0.91	1.79 (0.71–4.55)	p = 0.22
Snoring						
Not disturbing *vs.* absent	0.88 (0.58–1.36)	p = 0.58	0.70 (0.46–1.06)	p = 0.09	0.88 (0.58–1.33)	p = 0.54
Disturbing *vs.* absent	0.62 (0.24–1.59)	p = 0.32	1.66 (0.73–3.79)	p = 0.23	1.27 (0.55–2.92)	p = 0.57
Epworth Sleepiness Scale score						
≥10 *vs.* <10	0.90 (0.45–1.77)	p = 0.75	0.60 (0.29–1.25)	p = 0.17	0.97 (0.50–1.86)	p = 0.92
Depression score						
Third quartile (5–7) *vs.* lowest two quartiles (0–4)	2.09 (1.20–3.66)	p < 0.01	1.25 (0.72–2.17)	p = 0.43	0.79 (0.46–1.37)	p = 0.40
Fourth quartile (≥8) *vs.* lowest two quartiles (0–4)	1.72 (0.94–3.13)	p = 0.08	1.33 (0.75–2.37)	p = 0.33	0.78 (0.45–1.36)	p = 0.38
Anxiety score						
Third quartile (3–4) *vs.* lowest two quartiles (0–2)	0.61 (0.35–1.06)	p = 0.08	1.00 (0.59–1.69)	p = 1.00	1.33 (0.79–2.23)	p = 0.28
Fourth quartile (≥5) *vs.* lowest two quartiles (0–2)	0.57 (0.30–1.10)	p = 0.09	0.95 (0.51–1.78)	p = 0.88	1.51 (0.84–2.71)	p = 0.17
Sleep parameters						
Insomnia in the recent 1 month (yes/no)	0.81 (0.40–1.61)	p = 0.54	0.96 (0.48–1.89)	p = 0.90	0.91 (0.46–1.80)	p = 0.79
Use of hypnotics in the recent 1 month (yes/no)	1.49 (0.79–2.81)	p = 0.21	0.95 (0.50–1.79)	p = 0.86	1.20 (0.64–2.23)	p = 0.57
Bedtime (24-h format)						
Before 21:59 h *vs.* 22:00–23:59 h	1.89 (1.20–2.98)	p < 0.01	1.44 (0.92–2.24)	p = 0.11	1.26 (0.82–1.94)	p = 0.29
After 24:00 h *vs.* 22:00–23:59 h	1.53 (0.74–3.16)	p = 0.25	1.00 (0.48–2.06)	p = 0.99	0.78 (0.38–1.58)	p = 0.49
Morning arising time (24-h format)						
Before 4:59 h *vs.* 5:00–6:59 h	1.01 (0.57–1.82)	p = 0.96	1.08 (0.61–1.92)	p = 0.79	1.11 (0.65–1.91)	p = 0.69
After 7:00 h *vs.* 5:00–6:59 h	0.94 (0.53–1.64)	p = 0.81	0.97 (0.56–1.66)	p = 0.90	0.90 (0.52–1.55)	p = 0.70
Sleep onset latency (min)						
30–59 h *vs.* <30 h	0.81 (0.46–1.44)	p = 0.48	0.93 (0.53–1.63)	p = 0.79	0.66 (0.37–1.16)	p = 0.15
≥60 h *vs.* <30 h	0.53 (0.18–1.52)	p = 0.24	1.80 (0.72–4.51)	p = 0.21	0.96 (0.37–2.48)	p = 0.94
Total sleep duration (h)						
<5 *vs.* 5–8	1.50 (0.63–3.57)	p = 0.36	0.69 (0.27–1.75)	p = 0.43	1.65 (0.75–3.64)	p = 0.21
≥9 *vs.* 5–8	1.10 (0.51–2.36)	p = 0.81	1.07 (0.50–2.28)	p = 0.86	0.36 (0.14–0.92)	p = 0.03
Nagelkerke R-square	0.19		0.13		0.08	

nearly three-fold that in the Shih-Pai Sleep Study, the association between an earlier bedtime and poor cardiac vagal control was still noted in the latter. Moreover, a deviant bedtime was defined to be earlier in the Yilan study (lowest quartile, before 20:30 h) than in the Shih-Pai Sleep Study (lowest tertile, before 21:59 h). However, despite a more extreme definition of an earlier bedtime, the Yilan study failed to demonstrate a relationship between an advanced bedtime and cardiac autonomic control.

It is worth noting that sleep onset latency, insomnia, the sleep duration and the use of hypnotics were included as covariates in the present study. In contrast, the Yilan study controlled only for PSQI-defined poor sleep quality, the sleep duration and the use of hypnotics. The inclusion of sleep onset latency and insomnia as covariates excluded the unavoidable confounding effect of maladaptive behaviours on insomnia. In other words, the relationship between an earlier bedtime and poor cardiac vagal control was not influenced by an intentional early bedtime. Intentionally sleeping early is a common dysfunctional coping behaviour among individuals with insomnia, particularly sleep-onset insomnia.

In addition to difference in the included covariates, the urban–rural distribution difference may also serve to explain the inconsistency in findings between the Yilan study and the present study. The present study was conducted in the Shih-Pai area of Taipei city, the most urbanized region in Taiwan. In contrast, the Yilan study was conducted in Yilan city, which is in Yilan county, a rural area with an agricultural economy. In the Yilan study, participants who resided in Yilan city had fewer social zeitgebers to challenge the capacity of entrainment of the internal circadian clock compared to participants living in a metropolitan area. Under these circumstances, the reported sleep–wake timing may simply indicate the local social rhythm. In contrast to Yilan city, the Shih-Pai area is prosperous and economically active. Thus, an earlier bedtime among older adults may indicate an inflexible inner oscillator that drives them to sleep early. Interestingly, cardiac vagal control exerts regulatory control over the attentional and emotional systems as well as behavioural flexibility [51, 52]. Therefore, the present study suggests that an earlier bedtime would be a better indicator of an inflexible behavioural pattern in the urban area than in the rural area.

In the present study, older adults with long sleep duration (≥9 h) were less likely to have a low LF/HF ratio; this was not observed in the Yilan study, where an unfavourable LF/HF ratio was defined as the highest quartile for the LF/HF ratio, thus tending to implicate individuals with high sympathetic predominance. In contrast, the lowest quartile for the LF/HF ratio was defined as the 'case' in the present study. Further studies that use an identical definition of an unfavourable LF/HF ratio and the same set of covariates are necessary to determine the existence of an urban–rural difference.

In fact, recent genomics studies have found the association between deficit of anti-aging gene SIRTUIIN1 (SIRT1), circadian dysrhythmia, and cardiovascular morbidities [53,54]. These genomics studies were more likely revealed a relationship between cardiovascular morbidities with late bedtime [53]. The present study also suggested that deviant sleep–wake timing and poor HRV may share common etiology in the genetic level; however, an association between compromised cardiac autonomic function and advanced bedtime was illustrated instead. Further research is required to determine whether the earlier and late bedtime link to adverse cardiovascular outcomes by similar or different mechanisms.

Our study has some limitations. Because of the cross-sectional design, it was not possible to make causal inferences. The timeframe for recalling bedtime was 4 weeks, and it is unknown whether this recall of sleep–wake timing is capable of delineating profiles over a longer period. A snapshot of the sleep-wake pattern in the past 4 weeks may have introduced recall bias and failed to detect the day-to-day variability in the rest–activity rhythm. Although some factors that may influence day-to-day variability have been controlled for in the present study [55], a more direct recording of the sleep–wake pattern, such as an actigraph or an ecological momentary assessment, is warranted for future work. In addition, the present study may be underpowered to examine the small to modest strength of associations between sleep–wake timing and HRV parameters. Furthermore, residual confounding factors may have biased our findings. First, medications such as beta-blockers may have influenced HRV measurements [56]. In the present study, medical comorbidities were

defined by both self-reported diagnoses and the respective treatments. If the medical morbidities were well-controlled by medications, they may have indirectly served as a proxy in the statistical models to partial out the confounding effects of medications. However, older adults in Taiwan tended to under-report their comorbidities [57], which may still introduce bias. Second, primary sleep disorders were not included as covariates in the present study. However, we included the assessment of insomnia, snoring and daytime sleepiness in the regression models, and this may have reduced their confounding effects to a certain degree. Nevertheless, even though the frequency and intensity of snoring reportedly correlates with the apnea–hypopnea index [58-60], polysomnography is required to confirm disordered-breathing sleep. Third, cognitive function was not evaluated, which may have affected the accuracy of self-reported variables. Because the participants in the present study were interviewed using questionnaires, their cognitive function should be meeting a certain level of cognitive demand. Fourth, we did not control for the time of HRV determination, which may have introduced another bias. Because HRV exhibits circadian variations [61], it would be low if the collection time for older adults with an earlier bedtime was in the afternoon. However, the influence of circadian variations in HRV was ameliorated because adjustments were made for the morning arising time and sleep duration. Finally, potential confounders such as various mental and physical comorbidities were not included in the present study and should be examined in the future.

Conclusion

The results of the present study suggest that poor cardiac vagal control in older adults with an earlier bedtime reflects the failing function of the nervous system. Furthermore, in older adults residing in an urban area, an earlier bedtime may indicate an inflexible behavioural pattern, with an underlying degenerating capacity for entrainment by social zeitgebers. In future, a longitudinal study with a more comprehensive set of covariates should be performed to disentangle the temporal relationship between sleep–wake timing and cardiac autonomic control. Moreover, to consolidate the implications of urban–rural differences in deviant sleep–wake timing, studies using identical study designs and covariates are necessary.

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Author Contributions

S.W.C. drafted the manuscript. P.C. and H.C.C. designed the research and supervised it. All authors participated in revision of the manuscript.

ADDITIONAL INFORMATION

Competing financial interests

The authors declare no competing financial interests.

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