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Original Article

Association between sleep disturbance and nocturnal blood pressure profiles by a linear mixed model analysis: the Nagahama study

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ABSTRACT

Objectives: We aimed to analyze associations of sleep disturbance, including sleep disordered breathing, sleep fragmentation, and sleep efficiency, with abnormal nocturnal blood pressure (BP) profiles that may be risk factors for adverse cardiovascular outcomes.
Methods: The study included 5854 community residents with 20,725 multi-day measurements. Sleep fragmentation and efficiency were evaluated using a wrist-worn activity monitor. Sleep disordered breathing was assessed using the 3% oxygen desaturation index corrected for actigraphy-determined sleep duration. A timer-equipped standard cuff-oscillometric device was used for home and sleep BP monitoring.
Results: Mean nocturnal systolic BP (SBP) change was −8.6 ± 9.7% (−11.1 ± 12.6 mmHg), and inter-day correlation coefficient of the nocturnal SBP change was 0.443. Results of a linear mixed model analysis using daily measured values identified lower sleep efficiency (coefficient = −0.130, $p < 0.001$) as a determinant for decreased nocturnal SBP dipping beyond the interday variations of these parameters. Number of nocturnal urinations was another strong determinant (coefficient = 1.191, $p < 0.001$), although the association of sleep efficiency was independent of nocturnal urination, awake SBP, and sleep disordered breathing (coefficient = −0.102, $p < 0.001$). Sleep efficiency was also independently associated with sleep SBP level (coefficient = −0.138, $p < 0.001$). Estimated differences in nocturnal SBP dipping and sleep SBP level as a function of the degree of sleep efficiency (less than 80%) reached 1.63% (1.09–2.17%) and 2.16 mmHg (1.49–2.82%), respectively.
Conclusion: More attention should be paid to sleep efficiency as a factor in maintaining circadian BP rhythm.

1. Introduction

Abnormalities in circadian blood pressure (BP) variation, particularly the disappearance of a nocturnal BP drop and increases in nocturnal BP, have been suggested as independent risk factors for adverse cardiovascular outcomes [1]. Several physiological factors may increase nocturnal BP, salt sensitivity being an important one [2]; its mechanism has been identified via observational [3] and experimental studies [4,5] as an enhancement of natriuresis during sleep. We also previously reported a positive association between circulating B-type natriuretic peptide (BNP) and nocturnal BP [6,7], which might result from excessive body fluid retention due to increased salt sensitivity, in the general population. Ambient

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temperature might be another determinant of circadian BP variation [8], with a higher nocturnal BP and a smaller nocturnal BP drop in hotter seasons.

Sleep disturbance can potentially explain increases in BP during sleep [9]. We previously reported a strong positive association between nocturia and sleep BP [7], and the finding strongly indicates the potential involvement of sleep disturbance in increasing nocturnal BP in addition to salt sensitivity which increases nocturnal urination. However, most studies that have reported an association between sleep disturbance and circadian BP profiles [10] were based on single-day measurements. Results may be somewhat underestimated by not accounting for intra-individual day-to-day variations in sleep characteristics and nocturnal BP [11] whereas the variations have been reported to be non-negligible [8].

Here, we aimed to further clarify the association of sleep disturbance, including sleep disordered breathing (SDB), sleep fragmentation, and sleep efficiency, which are potential factors for increased nocturnal BP [12], with nocturnal BP profiles (ie, nocturnal BP drop and evening-to-morning BP levels). We employed a linear mixed model analysis using a dataset of 5854 community residents with 20,725 multi-day measurements to clarify the association between sleep disturbance and nocturnal BP profiles beyond intra-individual daily variations of these parameters.

2. Methods

2.1. Study participants

We analyzed the second-visit dataset of the Nagahama Prospective Cohort for Comprehensive Human Bioscience study (the Nagahama Study). Participant recruitment details are listed in the Supplementary Material. Briefly, among a total of 9850 s-visit participants, 6249 participants successfully measured home and nocturnal BP change for at least one day, which was an optional activity requested during the second-visit investigation. A total of 5961 participants were considered as potential study participants after excluding 288 participants who met any of the following exclusion criteria: pregnancy, pacemaker implantation, receiving hemodialysis or obstructive sleep apnea therapy, severe renal functional decline [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 or urinary albumin ≥300 mg/day], suspected shift workers, incomplete responses in a health survey questionnaire, and lack of a sleep diary during home BP monitoring. After further excluding participants without a urination record for the measurement days or participants who showed a wide deviation in sleep fragmentation index (FIx), 5854 participants were ultimately included in the analysis. Detailed inclusion criteria are listed in Supplementary Fig. S1.

All study procedures were approved by the ethics committee of the Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board. Written informed consent was obtained from all participants included in the study.

2.2. Self-monitoring at home

During a one-week self-monitoring period, all participants were required to measure pulse oximetry for the first four nights (days 1–4), home BP (morning and evening BP) for seven days, and sleep BP for the last five nights (days 3–7). The participants were also required to use a wrist-worn activity monitor and enter relevant details daily in a sleep diary. The home self-monitoring schedule is schematically presented in Supplementary Table S1. A total of 20,725 measurements were available for the analysis of sleep characteristics and nocturnal BP changes (measurement days: 1 day = 836, 2 days = 865, 3 days = 980, 4 days = 1273, 5 days = 1445, 6 days = 283, 7 days = 172), whereas 10,028 measurements (from 5240 participants) were available for the additional analysis of SDB.

2.3. Calculation of actigraphic sleep parameters

A series of actiwatch (Actiwatch 2 or Actiwatch Spectrum Plus, Philips-Respironics; Murrysville, PA, USA) was used to obtain actigraphs by attaching the device to the participant's non-dominant wrist. Detailed specifications of this device are described in the Supplementary Material. To calculate sleep parameters, bed-in and bed-out times were set on the actigraphs by well-trained investigators after referring to the study participants' sleep diaries, if available, and illuminance data [13]. Next, total sleep duration (sleep onset to awakening) and actual sleep duration [total sleep duration − duration of wake after sleep onset (WASO)] were automatically calculated by the standard factory-default algorithm. When an inaccurate activity recording was found by the investigators, the actigraph was discarded and was no longer used for calculating sleep characteristics. The intraclass correlation coefficient of the determination of actual sleep duration in 48 random samples was over 0.95. Sleep efficiency was calculated as a percent ratio of the actual to the total sleep duration. FIx was calculated as shown in Supplementary Fig. S2.

2.4. Assessment of SDB

Pulse oximetry was measured using a pulse oximeter (PULSOX-Me300; Konica Minolta Inc., Tokyo, Japan) attached to the non-dominant wrist. The sensor probe was fitted to the index or middle finger and secured with tape and a cap by the participant. Mean oxygen saturation (SpO_2) during sleep and 3% oxygen desaturation index (ODI) (ie, the number of times per hour the SpO_2 drops to >3%) were calculated using DS-Me version 2.1.0 software (Konica Minolta Inc., Tokyo, Japan). Sleeping and awakening times were determined according to the actigraphy results to calculate ODI; the actual sleep duration and not the total sleep duration was used for this calculation. SDB data were available for 5240 participants.

2.5. Measurement of home and sleep BP, and calculation of nocturnal BP change

An automatic cuff-oscillometric device (HEM-7080IC; Omron Healthcare, Kyoto, Japan) was provided to all participants for measuring BP at home. The participants were required to measure their morning and evening BP in accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2014 (Supplementary Material) [14]. The participants were also required to measure sleep BP by wearing a cuff on their upper arm. The BP monitor was programed to automatically measure BP at 00:00, 02:00, and 04:00 h. Among the BP values recorded in the built-in device memory, sleep BP was determined using the actigraph, and BP values measured within 1 h after awakening and within 1 h before sleeping were considered morning and evening BP, respectively. In the case of multiple readings in each slot, the mean value was calculated as a representative value. Days for which all evening, sleep, and morning BP measurements were available were included in the analysis.

Percentage decline in sleep systolic BP (SBP) was calculated per day using the following equation: [(sleep BP − awake BP)/awake BP] × 100, where awake BP was calculated as the average of morning and evening BP.

2.6. Frequency of nocturnal urination

Frequency of nocturnal urination was recorded by participants in their sleep diaries.

2.7. Basic clinical parameters

Basic clinical parameters used in this study were obtained from the personal record created at the health survey. Alcohol consumption was calculated by multiplying the amount of alcohol consumed in a single day by the number of drinking days per week and was represented using the Japanese traditional units of alcohol 'Go,' where 1 Go corresponds to 22 g of ethanol. Hypertension was defined as systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or taking antihypertensive drugs. Diabetes was defined as any or all of high glucose levels [fasting ($\geq$4 h): $\geq$126 mg/dl, occasional: $\geq$ 200 mg/dl], HbA1c $\geq$ 6.5%, or taking antihyperglycemic drugs. The eGFR was calculated using the following formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female) [15]. Measurement seasons were defined as follows: summer (July and August), middle (April–June, September, and October), and winter (November–March).

2.8. Statistical analysis

Data were expressed as mean ± standard deviation or frequency. A linear mixed model was used to analyze associations of multi-day measurements of sleep parameters, 3% ODI, home and sleep BPs, and frequency of nocturnal urination with nocturnal BP change. In addition to these variables, age, sex, body mass index, alcohol consumption, antihypertensive medication, eGFR, BNP, and measurement season were further included as fixed-effect factors, whereas individual identifier was included as a random-effect factor. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using JMP Pro 13.2.0 software (SAS Institute Inc., Cary, NC, USA).

3. Results

Clinical characteristics of the study participants are listed in Table 1. Mean nocturnal SBP change and diastolic BP (DBP) change calculated using available values (20,725 readings) were −11.1 ± 12.6 mmHg (−8.6 ± 9.7%) and −7.6 ± 9.1 mmHg (−9.7 ± 11.8%), respectively.

Mean inter-day correlation coefficient of awake and sleep SBP was calculated using day 3–7 measurements (Supplementary Tables S3, S4, and S5) for which a large number of measured values were available (Supplementary Tables S1 and S2) were 0.841 and 0.757, respectively, while that of nocturnal SBP dipping was modest (0.443). Similar results were observed in the analysis of DBP (awaking: 0.817, sleeping: 0.643, dipping: 0.377). Inter-day correlation coefficient of sleep duration (0.570), WASO (0.625), sleep efficiency (0.625), and fragmentation index (0.561) were also modest, thus indicating the need for an analysis using daily measurements rather than a representative value, such as the individual mean of multi-day measurements to precisely evaluate the association between sleep characteristics and nocturnal BP profiles.

Therefore, we adopted a linear mixed model to evaluate the association between the sleep characteristics and nocturnal BP profiles beyond the intra-individual daily variations of these parameters. Table 2 and Supplementary Table S6 summarize the results of the mixed model analysis for nocturnal dipping of SBP and DBP, respectively. Results of an analysis based on a dataset of 5854 participants with 20,725 measurements identified FIx as an independent factor for decreased nocturnal BP dipping (Model 1). The association of sleep disturbance with nocturnal BP dipping was more prominent when WASO (Model 2) or sleep efficiency (Model 3) was used as a representative index of sleep disturbance. When both WASO and sleep duration were included in the same model,

Table 1
Clinical characteristics of the study participants ($N = 5854$).

Age (years)		58.1 ± 11.8		
Sex (men/women)		1819/4035		
BMI (kg/m^2)		22.2 ± 3.3		
Alcohol consumption (Go/week)		3.6 ± 7.4		
Office BP	Systolic (mmHg)	124 ± 18		
	Diastolic (mmHg)	72 ± 11		
	Heart rate (beats/min)	68 ± 10		
	Medication (%)	22.6		
	Hypertension (%)	34.4		
		Evening	Sleeping	Morning
Home BP	Systolic (mmHg)	121 ± 16	112 ± 15	126 ± 18
	Diastolic (mmHg)	71 ± 10	66 ± 9	77 ± 11
	Heart rate (beats/min)	68 ± 9	61 ± 8	66 ± 8
Glycemic traits	Glucose (mg/dL)	87 ± 12		
	HbA1c (%)	5.6 ± 0.5		
	Medication (%)	4.4		
	Diabetes (%)	6.3		
Renal function	Serum creatinine (mg/dL)	0.70 ± 0.15		
	eGFR (mL/min per 1.73 m^2)	76.7 ± 14.0		
BNP (pg/mL)		20.6 ± 20.2		
Nocturnal urination (times)		0.6 ± 0.8		
Sleep characteristics	Sleep duration (min)	359 ± 61		
	Wake after sleep onset (min)	42 ± 24		
	Sleep efficiency (%)	89.7 ± 5.2		
	Fragmentation index	29.3 ± 12.7		
3% ODI with actigraph (times/h)[a]		8.2 ± 7.4		

Values are expressed as mean ± standard deviation of frequency. Alcohol consumption was described in the Japanese traditional unit of alcohol 'Go,' where 1 Go corresponds to 22 g of ethanol. Hypertension was defined as systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or taking antihypertensive drugs. Diabetes was defined as any or all of high glucose level [fasting ($\geq$4 h): $\geq$126 mg/dL, occasional: $\geq$200 mg/dL], HbA1c $\geq$ 6.5%, or taking antihyperglycemic drugs. BMI, body mass index; BNP, B-type natriuretic peptide, BP, blood pressure; eGFR, estimated glomerular filtration rate; ODI, oxygen desaturation index.

[a] Data are available for 5240 participants.

Table 2
Linear mixed model analysis for nocturnal systolic blood pressure (SBP) change.

	Nocturnal SBP dipping (%)									
	Model 1		Model 2		Model 3		Model 4		Model 5[a]	
	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*
Awake SBP (mmHg)	−0.317	<0.001	−0.316	<0.001	−0.317	<0.001	−0.315	<0.001	−0.264	<0.001
Nocturnal urination (*N*)	1.291	<0.001	1.197	<0.001	1.207	<0.001			1.191	<0.001
Fragmentation index	0.027	<0.001	0.010	0.100	0.007	0.312				
WASO (min)			0.015	<0.001						
Sleep efficiency (%)					−0.076	<0.001	−0.130	<0.001	−0.102	<0.001
3% ODI with actigraph (times/h)									0.031	0.050

Individual identifiers were included in the model as random-effects, whereas the following factors were considered as fixed-effects: age, sex, body mass index, alcohol consumption, antihypertensive medication, estimated glomerular filtration rate, B-type natriuretic peptide, and measurement season. Statistical analysis was performed using a dataset of 20,725 measurements of 5854 participants. Coeff, coefficient; ODI, oxygen desaturation index; WASO, wake after sleep onset.
[a] Data are available for 5240 participants (10,028 measurements).

WASO was identified as a positive (coefficient = 0.019, $p < 0.001$) determinant, whereas sleep duration showed an inverse (coefficient = −0.003, $p = 0.001$) association, thus suggesting that sleep efficiency might be an appropriate index of sleep disturbance in the analysis of nocturnal BP profiles. Because the frequency of nocturnal urination was inversely associated with sleep efficiency (age, sex, and body mass index adjusted coefficient = −1.992, $p < 0.001$), the association of sleep efficiency with nocturnal BP dipping was slightly stronger when the frequency of nocturnal urination was excluded from the model (Model 4). In contrast, the 3% ODI showed a moderate association (Model 5).

Similar results were observed in the analysis for sleep SBP (Table 3) and DBP (Supplementary Table S7) levels. The association of sleep efficiency with sleep BP were independent of the awake SBP (Model 2) and 3% ODI (Model 3). In contrast, no significant association was observed with evening SBP (Model 1) and morning SBP (Model 5).

Fig. 1 shows the estimated differences in nocturnal BP and BP dipping levels caused by the degree of sleep efficiency.

4. Discussion

In this cross-sectional study based on a large general population with multi-day measurements, we clarified that lower sleep efficiency was a factor for unfavorable nocturnal BP profiles, namely a smaller nocturnal BP drop and higher sleep BP levels. Nocturnal urination, a factor that may increase sleep fragmentation, was identified as another strong determinant for the BP profiles; however, the inverse association of sleep efficiency was independent of nocturnal urination. To our knowledge, this study is the first to elucidate the association between sleep disturbance and nocturnal BP profiles beyond intra-individual daily variations.

The association between sleep efficiency and nocturnal BP profiles was independent of nocturnal urination. This indicates that sleep efficiency and nocturnal urination might represent different conditions (ie, nocturnal urination triggers awakening and accompanies specific action, whereas sleep efficiency includes restlessness conditions with or without wakefulness) thus showing an independent association. However, regression coefficients of sleep efficiency for both nocturnal BP dipping and BP levels were increased by excluding nocturnal urination from the model, possibly owing to an inverse intercorrelation between the frequency of nocturnal urination and sleep efficiency. This indicates the possibility of an overestimation in previous studies that investigated sleep disturbance and nocturnal BP profiles without considering nocturnal urination as a confounding factor.

We previously reported a lack of association between FIx and nocturnal SBP changes in the same population [7]. Briefly, in a simple linear regression model using individual average values of BPs and FIx, the positive association between FIx and nocturnal SBP changes disappeared after adjustment for measurement season, possibly owing to a larger FIx in the hotter season. A plausible reason for this discrepancy with the present study showing a significant association between FIx and nocturnal BP profiles even after adjustment for measurement season might be the use of a mixed model for analysis. Because a simple regression model cannot consider daily intra-individual variations in the measurements, the previous analysis failed to identify FIx as a determinant for nocturnal BP profiles beyond the confounding of measurement season.

The 3% ODI is a marker for SDB or sleep apnea severity. In a cross-sectional study based on another general population [6], we previously reported that the 3% ODI was a significant determinant for the non-dipping phenomenon; this was independent of plasma BNP levels and carotid hypertrophy. In the present study, as well as in our previous study in the same population [7], the 3% ODI was moderately associated with nocturnal BP change, using either the present mixed model analysis or the previous simple regression

Table 3
Linear mixed model analysis for nocturnal systolic blood pressure (SBP) levels.

	SBP levels (mmHg)							
	Evening		Sleeping				Morning	
	Model 1		Model 2		Model 3[a]		Model 4	
	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*
Awake SBP (mmHg)			0.506	<0.001	0.574	<0.001		
Nocturnal urination (*N*)	1.192	<0.001	1.515	<0.001	1.481	<0.001	0.099	0.475
Sleep efficiency (%)	0.043	0.026	−0.117	<0.001	−0.138	<0.001	−0.023	0.215
3% ODI with actigraph (times/h)					0.043	0.030		

Individual identifiers were included in the model as random-effects, whereas the following factors were considered as fixed-effects: age, sex, body mass index, alcohol consumption, antihypertensive medication, estimated glomerular filtration rate, B-type natriuretic peptide, and measurement season. Statistical analysis was performed using a dataset of 20,725 measurements of 5854 participants. Coeff, coefficient; ODI, oxygen desaturation index.
[a] Data are available for 5240 participants (10,028 measurements).

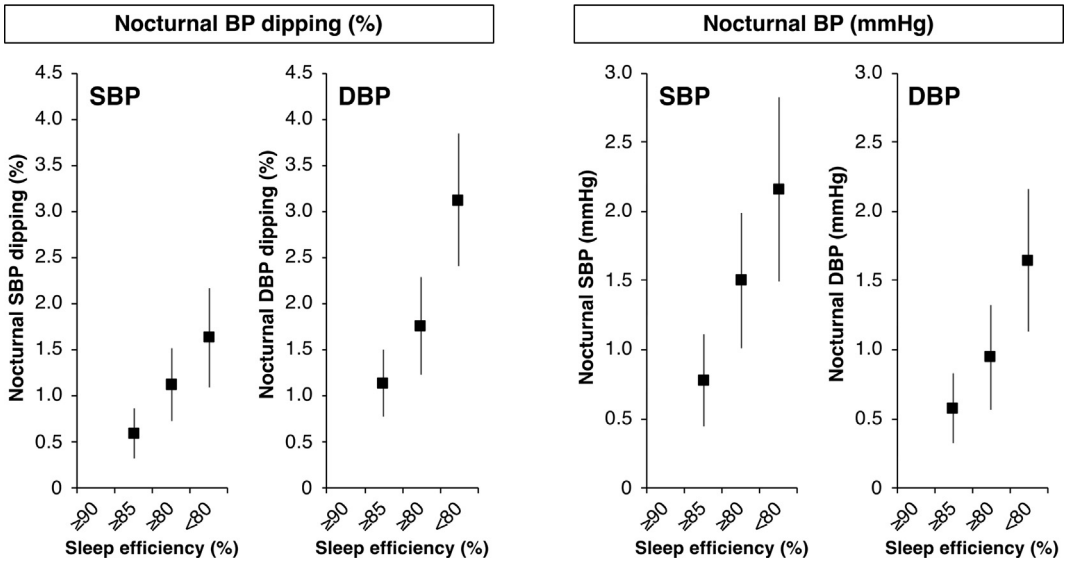

Fig. 1. Estimated differences in nocturnal BP dipping and nocturnal BP levels by the degree of sleep efficiency. Values are estimated as means and 95% confidence intervals calculated by a linear mixed model including age, sex, body mass index, alcohol consumption, awake systolic blood pressure SBP, antihypertensive medication, estimated glomerular filtration rate, B-type natriuretic peptide, and measurement season as fixed-effect factors. DBP, diastolic blood pressure; BP, blood pressure.

analysis [7]. Although SDB and intermittent hypoxia may affect nocturnal BP via various physiological mechanisms, including sleep fragmentation, its effect on mean nocturnal BP levels might not be sufficiently strong to raise it above the awake BP levels because SDB and increases in the sleep BP in response to oxygen desaturation are episodic events [16–18].

The large population size and the availability of the multi-day measurements of objectively measured sleep parameters and home BP, which allowed us to perform a linear mixed model analysis, are strengths of the present study. Furthermore, multi-day measurements made it possible to calculate the daily intra-individual correlation of sleep parameters and nocturnal BP profiles, which resulted in the finding that the intra-individual correlations of these variables were modest. Although several epidemiological studies have indicated enhanced sleep disturbance [19] as well as disappearance of nocturnal BP drop and increases in nocturnal BP [1] as independent risk factors for cardiovascular diseases, the results of the present study underscore the importance of multi-day measurements of these parameters for the precise evaluation of cardiovascular disease risks, not only in epidemiological studies, but also in clinical settings.

The study also has several limitations that warrant mentioning. First, we did not measure 24-h BP using a conventional ambulatory BP monitor to perform multi-day nocturnal BP monitoring. Although the nocturnal BP dipping level in this study might be somewhat smaller than that in previous studies using mean daytime BP as a reference value, there might be no substantial differences in nocturnal BP levels theoretically. Sleep efficiency showed significant association with nocturnal BP dipping level as well as nocturnal BP levels, in addition to a previously reported similar prognostic significance of simply measured night-time BP. Moreover, that of BP measured using an ambulatory BP monitor [20]. Second, although the BNP level varied by day and was positively associated with the frequency of nocturnal urination, we used a single BNP value for analysis [7]. Third, the frequency of nocturnal urination was determined from a self-reported sleep diary. However, misreporting of the urination frequency, if any, would occur independently of the nocturnal BP change and would thus not cause serious bias. Fourth, because our study was cross-sectional, causality between sleep efficiency and sleep BP was uncertain. However, we employed a linear mixed model analysis that included a variety of observations per individual, and the linear relationship between the parameters may partly support a causal relationship between low sleep efficiency and sleep BP.

In conclusion, low sleep efficiency was a strong determinant for increased sleep BP and decreased nocturnal BP drop. More attention should be paid to these conditions so as to maintain the circadian BP rhythm and possibly decrease the potential risk for adverse cardiovascular outcomes.

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Conflict of interest

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The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.049.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.01.049.

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