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Sleep duration and risk of cardiovascular events: The SAVE study

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Abstract

Background and aim: Controversy exists regarding cardiovascular risk in relation to sleep duration. We determined sleep duration and major recurrent cardiovascular event associations in patients with obstructive sleep apnoea and established cardiovascular disease.

Methods: Secondary analyses of the international, multicenter, Sleep Apnea Cardiovascular Endpoints trial. Sleep duration was estimated from overnight home oximetry (ApneaLink monitor) used for obstructive sleep apnoea diagnosis. Cox proportional hazards models were used to determine associations of categorized sleep duration (<6 h, 6–8 h (reference), and >8 h) and major cardiovascular outcomes: primary composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and any hospitalization for unstable angina, heart failure, or transient ischemic attack; secondary composite of cardiac and cerebral (stroke/transient ischemic attack) events.

Results: Oximetry-derived sleep duration estimates were available in 2687 participants (mean 61.2 years, 80.9% males) who experienced a total of 436 cardiovascular events over a mean follow-up of 3.7 years. Compared to the reference category, sleep duration was not associated with risk of the primary composite cardiovascular outcome (adjusted hazard ratio (HR) 1.00, 95% confidence interval 0.76–1.33, and HR 1.22, 95% confidence interval 0.98–1.52, for sleep duration <6 and >8 h, respectively). However, long sleep was associated with increased cerebral events (HR 1.67, 95% confidence interval 1.17–2.39; $P = 0.005$) and stroke alone (HR 1.79, 95% confidence interval 1.22–2.63; $P = 0.003$).

Conclusions: Long sleep duration is associated with an increased risk of stroke but not cardiac events in obstructive sleep apnoea patients with existing cardiovascular disease.

Clinical trial registration: The trial is registered at ClinicalTrials.gov (NCT00738179).

Keywords

Sleep duration, obstructive sleep apnoea, cardiovascular disease, stroke

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Introduction

Accumulating evidence indicates that sleep quantity is related to the risk of cardiovascular (CV) disease. A recently published study involving 116,632 adults in 21 countries showed a J-shaped relationship of sleep duration and serious CV events and death,[1] supporting findings of earlier systematic reviews.[2,3] However, an important limitation of many epidemiologic studies on this topic is the evaluation of self-reported sleep profile by questionnaire or interview, which only correlates moderately well with objective measures and is prone to recall bias.[4,5] While sleep duration has been shown to be associated with preclinical markers of CV disease, stroke patients may suffer subsequent sleep-related problems that lead to longer time in bed.[6] As such, the relationship between sleep duration and risk of future CV events may differ according to the presence of CV and obstructive sleep apnoea (OSA). A recent study found a positive association of short sleep ($\leq$6 h) duration and risk of coronary heart disease that was higher in those with greater sleep disturbance.[7]

OSA is a common sleep-related breathing disorder characterized by intermittent hypoxia and sleep fragmentation, which is associated with increased risk of CV disease. There is persistent uncertainty over the strength of relationship between sleep duration and CV disease, and of the influence of sleep duration on abnormal serum lipids,[8] low mean oxygen saturation,[9] insulin resistance,[10] visceral obesity,[11] and hypertension.[12] Herein, we report our efforts to determine the relationship of sleep duration and risk of recurrent CV events in OSA patients with co-occurring CV disease who participated in the international, Sleep Apnea Cardiovascular Endpoints (SAVE) trial.[13] Our approach was to estimate sleep duration based on data derived from participant use of the ApneaLink device as part of the diagnostic inclusion procedures.

Methods

Study design

The SAVE study was an international, multicenter, prospective randomized, open, blinded endpoint assessed trial undertaken to determine the effects of continuous positive airway pressure (CPAP) treatment for prevention of recurrent CV disease events.[13] In brief, a total of 2717 eligible adults (age 45–75 years) were recruited from 89 clinical centers in seven countries between December 2008 and November 2013, with 2687 included in the primary analysis. Inclusion criteria were a diagnosis of moderate to severe OSA diagnosed by an overnight home recording on the ApneaLink (ResMed) cardiorespiratory monitor showing an oxygen desaturation index of $\geq$12 of $\geq$4% oxygen desaturation events per hour and a history of coronary or cerebrovascular CV disease. Those excluded reported severe daytime sleepiness (Epworth sleepiness scale score >15), a previous "fall asleep" traffic accident, very severe hypoxemia (oxygen saturation SpO_2 $\leq$80% for >10% of recording time, or resting awake $SpO_2 \leq 90\%$), or a predominant pattern of Cheyne–Stokes respiration on the nasal pressure recording. After a one-week run-in period of sham CPAP, those remaining eligible and adherent were randomly assigned to receive CPAP treatment plus usual care or usual care alone. Additional details of the study are provided in Supplementary Material. Local institutional review boards or independent ethics committees at recruiting sites approved the protocol, and all participants provided written informed consent. The trial is registered at ClinicalTrials.gov (NCT00738179).

Outcomes and exposure variables

Baseline information included patient demographics, anthropomorphic measurements, OSA severity, and medical and medication history. Sleep duration at baseline was estimated from the recording of oximetry on the ApneaLink on registration visit (Day 9), where the algorithm excluded periods of loss of signal or artifacts on the raw recording. ApneaLink recording time was used an objective measure of sleep duration, noting that participants were instructed not to deviate from their usual sleep habits, to start the recording when the light was switched off with the intention of falling asleep, and to terminate the recording after final wake up/lights on.

The primary outcome in the study was a composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina, heart failure, or transient ischemic attack (TIA). For these analyses, two secondary composite outcomes of cardiac (any MI, hospitalization for unstable angina, or heart failure, including fatal events) and cerebral (any stroke or hospitalization for TIA, including fatal events) events were assessed. All CV events were confirmed according to standard definitions by an adjudication committee whose members were blind to the study-group assignments.

Statistical analysis

Continuous data were described using mean (standard deviation) or median (interquartile range) when non-normally distributed and categorical data as frequencies and percentages. We compared baseline characteristics of participants according to sleep duration (<6 h ("short"), 6–8 h ("reference"/"normal"), and >8 h ("long")) using a trend test from a generalized

linear model for continuous variables and Cochran–Armitage trend test for discrete variables. The categories of sleep duration were chosen according to cut-offs used in earlier studies to allow for comparability.[1,3] Associations of sleep duration with CV outcomes were analyzed in Cox proportional hazards regression models. For the main analyses, sleep duration was assessed both as a categorical and continuous variable. Kaplan–Meier plots for the cumulative incidence of cerebral events by categories of sleep duration. Data were reported with hazard ratios (HRs) and 95% confidence intervals (CIs). Two-sided P values < 0.05 were considered significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Data sharing

Individual participant data used in these analyses can be shared by formal request with protocol from any qualified investigator to the Research Manager, Adelaide Institute for Sleep Health, South Australia.

Results

Oximetry-derived estimates of sleep duration were available for all 2687 participants, where the estimated mean sleep duration was 7.3 ± 1.5 h (Supplemental Figure I). Sleep duration from the ApneaLink showed moderate correlation with total sleep time from polysomnogram but better than from questionnaire data as used in our pilot study (Supplemental Figure II). A total of 436 (16.2%) primary CV events occurred during the follow-up period. Table 1 shows that increasing sleep duration was associated with older age, female sex, cerebrovascular disease history, higher heart rate, and greater frequency of depression symptoms at baseline. Other baseline variables were comparable between sleep duration categories (Table 1; Supplemental Table I).

There was no association between sleep duration and the primary composite CV endpoint, nor of the secondary composite of cardiac events in multivariable analyses. Compared to the reference category, long sleep duration was significantly associated with any cerebrovascular event (HR 1.67, 95% CI 1.17–2.39; $P = 0.005$) and stroke (HR 1.79, 95% CI 1.22–2.63; $P = 0.003$) (Figure 1; Table 2). Sleep duration was not associated with individual outcomes of CV death, MI, and hospitalization for unstable angina, heart failure, or TIA (Supplemental Table V). Sensitivity analyses restricted to patients with 6–10 h of sleep, using 7–8 h as the reference group and having sleep duration as a continuous variable, showed results similar to the main analyses (Supplemental Table III and VI). Non-linear trend tests for CV events and stroke were not significant ($P = 0.123$ and 0.180, respectively).

Discussion

Our study of approximately 2700 patients with co-occurring OSA and CV disease who were prospectively followed up over several years has shown no association of sleep duration and a composite serious CV events or cardiac events alone. However, long sleep (>8 h) was associated with higher risks of stroke and TIA.

Our finding of a potential harmful association of long sleep duration and stroke but not cardiac events in OSA patients contrasts with studies of the general population.[14,15] This may reflect the underlying mechanism of CV diseases and OSA, where a study has shown untreated severe OSA to be an independent risk factor for stroke but not coronary heart disease in elderly patients,[16] and two meta-analyses reporting much stronger associations of OSA and stroke rather than cardiac events.[17,18] One explanation is an apparent differential link in that acute or long-term intermittent hypoxia may impact differently on the brain compared to the heart in relation to variable collateral vasculature.[19,20] Another is that nocturnal biochemical and physiological disturbances (e.g. acute post-apneic blood pressure surges) may have greater adverse effects on cerebral than coronary endothelium. Superimposed upon an increased propensity for stroke in those with OSA, increased sleep duration might by itself, or from greater exposure to apnea events, promote inflammatory[21] and atherosclerotic[22] mediators of extra- and intra-cranial atherosclerosis, atrial fibrillation, cerebral small-vessel disease, and left ventricular hypertrophy, all of which might further increase the risk of cerebrovascular events.[23] We recognize, however, that it is also possible that some patients have longer sleep duration due to pre-existing cerebrovascular injury or neurological disability[24] and may not therefore benefit from voluntarily reducing their length of sleep.

Prolonged sleep has been identified as a risk factor for stroke in a primary care population[14] and in those with diabetes mellitus,[25] findings which have been confirmed in a large meta-analysis of 16 prospective cohort studies involving over half a million subjects.[23] Conversely, evidence exists for increasing numbers of people curtailing sleep in favor of lifestyle pursuits or entertainment.[15] In particular, a prospective study has shown that income and education are strongly related to short sleep duration,[26] raising concerns over short sleep and poor health. Thus, while our findings add to the literature indicating that long sleep duration increases the risk of stroke in OSA patients, we have also shown no clear harms of short sleep on CV events. The potential that longer sleep duration may increase exposure to OSA-related hypoxia is supported by an animal study using chronic intermittent hypoxia as a model of OSA, to show that excessive hypoxia caused

Table 1. Baseline characteristics by sleep duration

Variable	Overall	Sleep duration (h)			
		<6	6–8	≥8	*P* trend[a]
Patients	2687 (100)	491 (18.3)	1381 (51.4)	815 (30.3)	
Sleep duration, h	7.3 ± 1.5	5.2 ± 0.6	7.1 ± 0.6	9.0 ± 0.8	<0.001
Demography					
Age, years	61.2 ± 7.8	60.3 ± 7.6	61.2 ± 7.9	62.0 ± 7.7	<0.001
Male	2174 (80.9)	407 (82.9)	1144 (82.8)	623 (76.4)	0.001
Asian	1700 (63.3)	306 (62.3)	869 (62.9)	525 (64.5)	0.396
Medical history					
Cardiovascular disease type					
Coronary artery disease	1363 (50.7)	260 (53.0)	731 (52.9)	372 (45.6)	0.003
Cerebrovascular disease[b]	1324 (49.3)	231 (47.1)	650 (47.1)	443 (54.4)	0.003
Both	108 (4.0)	23 (4.7)	43 (3.1)	42 (5.2)	0.393
Hypertension	2103 (78.4)	389 (79.7)	1087 (78.8)	627 (77.1)	0.246
Diabetes mellitus	798 (29.8)	152 (31.2)	388 (28.1)	258 (31.7)	0.568
Angina	989 (36.9)	188 (38.5)	508 (36.8)	293 (36.0)	0.385
Myocardial infarction	81 (3.0)	14 (2.9)	42 (3.0)	25 (3.1)	0.840
Heart failure	51 (1.9)	6 (1.2)	25 (1.8)	20 (2.5)	0.107
Current smoker	407 (15.2)	71 (14.6)	216 (15.7)	120 (14.8)	0.979
Current drinker	683 (25.5)	135 (27.7)	359 (26.0)	189 (23.3)	0.063
Exercise score[c]	7 (4–14)	7 (4–14)	7 (4–14)	7 (3–14)	0.643
Snoring almost every day[d]	2140 (82.5)	372 (78.8)	1092 (82.2)	676 (85.3)	<0.001
Clinical assessment					
BMI, kg/m^2	28.6 ± 4.5	28.8 ± 4.8	28.5 ± 4.3	28.8 ± 4.6	0.999
Systolic BP, mmHg	131 ± 16	131 ± 16	131 ± 16	132 ± 17	0.260
Diastolic BP, mmHg	80 ± 11	80 ± 11	79 ± 11	80 ± 11	0.596
Heart rate, bpm	71 ± 11	70 ± 11	71 ± 11	73 ± 12	<0.001
Waist:hip ratio	0.96 ± 0.08	0.95 ± 0.07	0.96 ± 0.08	0.96 ± 0.08	0.098
ODI[e]	24 (17–37)	23 (16–35)	24 (17–37)	24 (16–38)	0.090
AHI[f]	25 (16–40)	24 (15–38)	25 (17–38)	26 (16–42)	0.048
ESS[g]	7 (5–10)	7 (5–10)	7 (5–10)	7 (5–10)	0.757
Mood–HADS[h]					
Anxiety	4 (2–7)	4 (2–7)	4 (2–7)	4 (2–7)	0.034

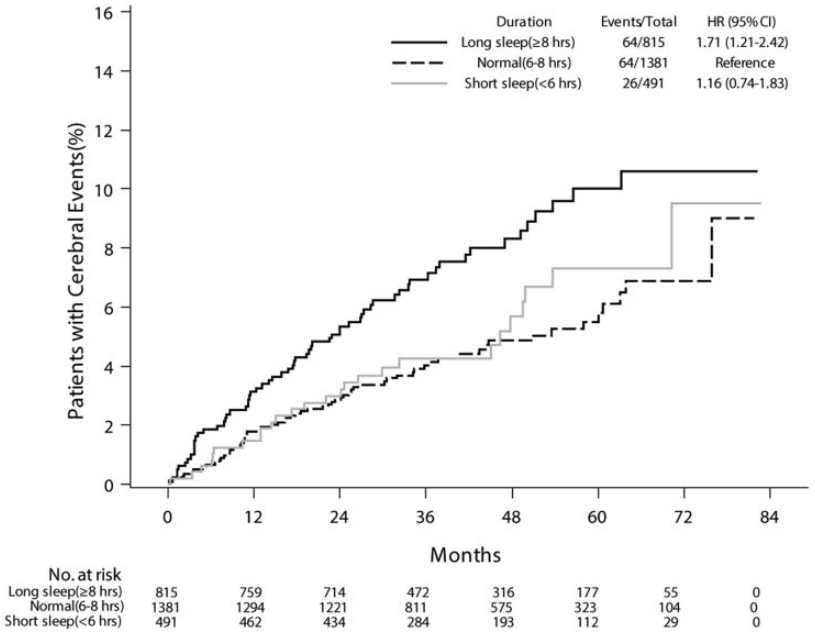
(continued)

Table 1. Continued

Variable	Overall	Sleep duration (h)			
		<6	6–8	≥8	*P* trend[a]
Depression	5 (2–8)	4 (2–7)	4 (2–7)	5 (2–8)	0.001
Total	9 (5–14)	8 (4–13)	9 (5–13)	10 (5–14)	0.002

Note: Data are n (%), mean (standard deviation), and median (interquartile range).
AHI: apnea–hypopnea index; BMI: body mass index; BP: blood pressure; ESS: Epworth sleepiness scale score; HADS: Hospital Anxiety Depression Scale; ODI: oxygen desaturation index.
[a]Trend test from generalized linear model for continuous variables, and Cochran–Armitage trend test for discrete variables.
[b]25 (0.9%) cases of transient ischemic attack.
[c]Exercise (number of ≥15-min sessions or more of "mild," "moderate," and "vigorous" exercise per week) – weighted to obtain a continuous score; mild × 1 + moderate × 2 + vigorous × 3.
[d]Snoring is collected by questionnaire.
[e]ODI is the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by at least four percentage points from baseline.
[f]AHI is the number of apnea and hypopnea events per hour of recording.
[g]ESS ranges from 0 to 24, with higher scores indicating greater sleepiness; a score higher than 10 indicates pathologic sleepiness.
[h]Scores on the HADS anxiety and depression subscales range from 0 to 21, with higher scores indicating greater symptoms.

Figure 1. Cumulative event curve of cerebral events by categories of sleep duration. HR from unadjusted analysis. CI: confidence interval; HR: hazard ratio.



ischemic brain injury.[27] Our results are also consistent with prior literature showing that long sleep duration is associated with higher risk of cerebral events in women than men, which may reflect greater underlying risk and/or susceptibility to CV risk factors.[28,29] However, the association between long sleep duration and cerebral events in those with less snoring is confusing and may simply be a chance finding. Although short sleep duration is associated with more severely impaired vascular and metabolic health,[10–12] it was not associated with cerebral events in our study patients possibly due to inadequate statistical power and residual confounding by CPAP treatment.

Our study was strengthened by the inclusion of a large number and broad range of well-characterized OSA patients with co-occurring CV disease who were

Table 2. Relationship between sleep duration and cardiovascular outcomes

	Events/total	Unadjusted		Model I[a]		Model II[b]	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary outcome[c]			0.104[d]		0.097[d]		0.120[d]
Short sleep (<6 h)	73/491	0.96 (0.73–1.25)	0.745	0.94 (0.72–1.24)	0.672	1.00 (0.76–1.33)	0.976
Reference (6–8 h)	215/1381	–		–		–	
Long sleep (≥8 h)	148/815	1.18 (0.96–1.45)	0.127	1.18 (0.95–1.46)	0.138	1.22 (0.98–1.52)	0.076
Per 1 h increase	436/2687	1.05 (0.99–1.12)	0.129	1.05 (0.98–1.12)	0.157	1.05 (0.98–1.13)	0.167
Cardiac events[e]			0.887[d]		0.990[d]		0.654[d]
Short sleep (<6 h)	53/491	0.85 (0.62–1.15)	0.290	0.83 (0.61–1.15)	0.264	0.88 (0.64–1.23)	0.463
Reference (6–8 h)	176/1381	–		–		–	
Long sleep (≥8 h)	95/815	0.90 (0.70–1.16)	0.421	0.88 (0.68–1.14)	0.316	0.98 (0.75–1.28)	0.879
Per 1 h increase	324/2687	1.01 (0.94–1.09)	0.829	1.00 (0.93–1.08)	0.981	1.03 (0.94–1.11)	0.549
Cerebral events[f]			0.022[d]		0.021[d]		0.055[d]
Short sleep (<6 h)	26/491	1.16 (0.74–1.83)	0.526	1.15 (0.73–1.81)	0.560	1.21 (0.76–1.93)	0.427
Reference (6–8 h)	64/1381	–		–		–	
Long sleep (≥8 h)	64/815	1.71 (1.21–2.42)	**0.002**	1.74 (1.22–2.48)	**0.002**	1.67 (1.17–2.39)	**0.005**
Per 1 h increase	154/2687	1.14 (1.02–1.27)	0.017	1.13 (1.01–1.26)	0.027	1.11 (0.99–1.24)	0.073
Stroke			0.010[d]		0.010[d]		0.029[d]
Short sleep (<6 h)	22/491	1.16 (0.71–1.91)	0.557	1.13 (0.69–1.86)	0.625	1.20 (0.72–2.00)	0.479
Reference (6–8 h)	54/1381	–		–		–	
Long sleep (≥8 h)	59/815	1.87 (1.29–2.70)	**0.001**	1.87 (1.28–2.72)	**0.001**	1.79 (1.22–2.63)	**0.003**
Per 1 h increase	135/2687	1.17 (1.04–1.31)	0.008	1.15 (1.03–1.29)	0.016	1.13 (1.00–1.27)	0.046
TIA			0.408[d]		0.350[d]		0.378[d]
Short sleep (<6 h)	4/491	1.04 (0.33–3.28)	0.941	1.11 (0.35–3.53)	0.866	1.13 (0.35–3.60)	0.842
Reference (6–8 h)	11/1381	–		–		–	
Long sleep (≥8 h)	10/815	1.53 (0.65–3.60)	0.330	1.69 (0.70–4.08)	0.242	1.67 (0.69–4.04)	0.254
Per 1 h increase	25/2687	1.20 (0.92–1.56)	0.175	1.23 (0.94–1.62)	0.131	1.22 (0.93,1.61)	0.149

Note: CI: confidence interval; HR: hazard ratio; TIA: transient ischemic attack.
[a]Model I adjusted for age, sex, and continuous positive airway pressure adherence.
[b]Model II adjusted for all variables included in model I plus disease type (cardiac or cerebral), baseline snore frequency, Epworth sleepiness scale score, Hospital Anxiety Depression Scale depression subscale score, and apnea–hypopnea index.
[c]A composite of death from a cardiovascular cause, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for unstable angina, heart failure, or a TIA.
[d]Trend test.
[e]Cardiac events includes any fatal/non-fatal MI, or hospitalization for unstable angina, atrial fibrillation or heart failure.
[f]Cerebral events, consisting of any stroke or hospitalization for TIA.
Bold indicates significant difference between groups ($P < 0.05$).

systematically followed up over several years according to a standardized protocol. However, there are several limitations, in particular inferred sleep duration from oximetry data which is subject to measurement error. However, duration of oximetry recording time from the ApneaLink provides a reasonably accurate representation of patients' habitual time spent in bed, and overall sleep duration was similar to previous reports.[3] Measurement by polysomnography to confirm sleep by electroencephalography and actigraphy would have been technically demanding to apply across large multicenter studies and would arguably have been less representative of participants' usual habits. Moreover, since any measurement error for sleep duration is likely to be non-differential between those with and without events, the association of longer sleep and stroke is likely to be an under-estimation of the true effect. Although our study had a large sample, there were still low numbers of individual CV events, and we were unable to distinguish between ischemic and hemorrhagic stroke which have different pathological mechanisms pertaining to large- and small-vessel CV disease and sleep. Moreover, as in all observational studies, rather than increased sleep duration being a direct cause of stroke, it could simply be a marker of ill health, lifestyle choices, or co-morbid conditions that predispose to stroke, and which were not adequately captured by the covariate adjustments made in the models. Finally, as the present analyses were conducted in OSA patients with pre-existing cardio- or cerebrovascular disease, there may be limitations to generalizing our finding to other populations.

Conclusions

In summary, our study shows that prolonged sleep duration beyond 8 h in OSA patients with existing CV disease is associated with increased risk of stroke and TIA. Further studies in larger populations with objective measures of sleep duration are required to confirm these findings, while intensive management of underlying health issues may be indicated rather than necessarily reducing the opportunity for sleep.

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Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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