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Objective short sleep duration modifies the relationship between hypertension and all-cause mortality

Julio Fernandez-Mendoza^a, Fan He^b, Alexandros N. Vgontzas^a, Duanping Liao^b, Edward O. Bixler^a

^aSleep Research & Treatment Center, Penn State Milton S. Hershey Medical Center

^bDepartment of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA

Abstract

Objective: Short sleep duration has been associated with cardiovascular morbidity and mortality. However, previous studies were limited by using subjective sleep measures and treating sleep duration as a sole, independent predictor. Therefore, the role of sleep duration in predicting mortality is still not well understood. We posit that objective sleep duration is an effect modifier of the relationship between hypertension and all-cause mortality.

Methods: We addressed this question in the Penn State Adult Cohort, a random, general population sample of 1741 men and women (48.7 ± 13.5 years) who were studied in the sleep laboratory and followed up for 15.5 ± 4.1 years. Hypertension was defined on the basis of SBP and DBP ($140/90$ mmHg) or use of antihypertensive medication. Polysomnographic sleep duration was classified into three clinically meaningful categories.

Results: We tested the interaction between hypertension and polysomnographic sleep duration on all-cause mortality using multiple logistic regression while controlling for several potential confounders (P value = 0.03). The odds (95% confidence interval) of all-cause mortality associated with hypertension were 1.77 (1.07–2.92), 2.78 (1.47–5.24), and 3.93 (2.22–6.95) for individuals who slept at least 6, 5–6, and 5 h or less, respectively.

Conclusion: The risk of mortality associated with hypertension increases in a dose–response manner as a function of shorter sleep duration. Short sleep in hypertensive individuals may be a marker of the degree of central autonomic dysfunction. Future epidemiological studies should examine this effect modification using cause-specific mortality, whereas future clinical trials should examine whether lengthening sleep improves the prognosis of individuals with hypertension.

Keywords

hypertension; mortality; sleep

Correspondence to Julio Fernandez-Mendoza, PhD, Sleep Research & Treatment Center, Penn State Milton S. Hershey Medical Center, Penn State University College of Medicine, 500 University Drive H073, Hershey, PA 17033, USA. Tel: +1 717 531 6385; fax: +1 717 531 6491; jfernandezmendoza@hmc.psu.edu.

Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Approximately 30% of the United States population has hypertension, which is associated with significant cardiovascular morbidity, great economic healthcare cost, and increased mortality [1]. A large amount of literature has linked sleep disorders, particularly sleep-disordered breathing (SDB), to hypertension [2-4] and mortality [5-7]. Furthermore, sleep duration has been recently shown to be associated with hypertension [8,9], other cardiovascular risk factors [10-14], and mortality [15-17]; however, these previous studies have reported modest and inconsistent effects [10,17,18]. This has led to the understanding that measures of impaired sleep, such as sleep duration, may not yet be useful in predicting adverse health outcomes, such as probability of death, in the context of cardiovascular risk.

An important limitation of previous studies is that they relied typically on subjective measures of sleep duration and, thus, the role of polysomnographic sleep duration was not examined, and the potential confounder of SDB not controlled for. Most importantly, these previous studies focused on the sole, independent association of sleep duration with morbidity and mortality [18], and none conceptualized objective sleep duration as an effect modifier of the association of cardiovascular risk with mortality. Support for a potential role of objective sleep duration as an effect modifier of cardiovascular risk comes from previous studies showing that objective short sleep duration modifies the association of insomnia, the most prevalent sleep disorder, with cardiometabolic morbidity [19-25] and its underlying biological mechanisms [26-41]. Thus, to test the novel hypothesis that objective sleep duration may likely modify the increased risk of mortality associated with hypertension, we examined the effect modification of objective sleep duration on the risk of all-cause mortality associated with hypertension in a large, random, general population sample. We hypothesized that the association between hypertension and all-cause mortality was stronger in individuals with shorter objective sleep duration.

METHODS

Participants

The data presented here were collected as part of a population-based study of sleep disorders, which used a two-phase protocol to recruit participants from various age groups [19-21,24,25,42-44]. In the first phase of the study, telephone interviews were conducted with 4364 age-eligible men and 12 219 age-eligible women residing in the sample households, for a total sample of 16 583 with response rates of 73.5 and 74.1%, respectively. In the second phase of this study, a subsample of 741 men and 1000 women, selected randomly from the first phase, were studied in our sleep laboratory, with response rates of 67.8 and 65.8%, respectively. These baseline data were collected between January 1990 and March 1999 [42,43]. After giving a complete description of the study to the participants, written informed consent was obtained. The study protocol was approved by the Institutional Review Board at the Pennsylvania State University College of Medicine.

Mortality follow-up

Death certificates for deceased individuals as of 31 December 2011 in this cohort were retrieved from the U.S. Center for Disease Control and Prevention (CDC). Participants were linked by CDC to death records from the National Death Index for the years 1992–2011, and vital status was determined through a rigorous process of probabilistic matching and death certificate review based on participant social security number, full name, date and state of birth, sex, race/ethnicity, state of residence, and marital status [45,46]. Of the 1741 participants, a total of 1361 participants were alive at follow-up, whereas 380 were deceased. Duration of follow-up was calculated from the time of the baseline evaluation to the date of death for those deceased or to 31 December 2011 for those alive. The average follow-up duration was 15.5 ± 4.1 years. Our primary outcome was all-cause mortality.

Hypertension

Blood pressure (BP) was measured in the evening, about 2 h before the start of the sleep recording, using a pneumoelectric microprocessor-controlled instrument with the appropriately sized cuffs (Welch Allyn; Skaneateles Falls, New York, USA) used for routine clinical care at our hospital at the time of the baseline examination. The accuracy of this monitor is reported to be ± 3 mmHg; in addition, internal calibration was performed before each use, and the machine was checked against a mercury sphygmomanometer at least annually; if required, devices were sent to clinical engineering for repair. The recorded BP was the average of three consecutive readings during a 5-min period following 10 min of rest in the supine position. BP levels at the time of the sleep laboratory evaluation were categorized as normal (i.e. SBP < 120 mmHg and DBP < 80 mmHg), prehypertensive (i.e. SBP 120–139 mmHg or DBP 80–89 mmHg), and hypertensive (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg). Our primary exposure was hypertension defined by the presence of hypertensive BP levels or use of antihypertensive medication, as compared with individuals with SBP less than 140 mmHg and DBP less than 90 mmHg and who did not use antihypertensive medication [19,20,44].

Sleep laboratory evaluation

All participants were evaluated for one night in the sleep laboratory in sound-attenuated, light-controlled, and temperature-controlled rooms. During this evaluation, each participant was continuously monitored for 8 h (fixed time period) using 16-channel polysomnography (PSG) including electroencephalogram, electrooculogram, and electromyogram. Bedtimes were adjusted to conform to participants' usual bedtimes, and participants were recorded between 2200–2300 h and 0600–0700 h. The sleep recordings were subsequently scored independently, according to Rechtschaffen and Kales [47] criteria. Respiration was monitored throughout the night by use of thermocouples at the nose and mouth and thoracic strain gauges. All night recordings of hemoglobin oxygen saturation were obtained with an oximeter attached to the finger. In this study, the presence of SDB was defined as an obstructive apnea/hypopnea index (AHI) at least 5 [19,20]. According to distribution of polysomnographic sleep duration, we categorized the entire study sample into three ordinal groups: at least 50th percentile (i.e. ≥ 6 h), 25–50th percentile (i.e. 5–6 h), and 25th

percentile or less (i.e. ≤ 5 h). This cutoff point of 6 h of sleep has been shown in previous studies to be predictive of significant medical morbidity and mortality [14,17,19-21,24,25].

Other measurements

BMI was based on measured height (cm) and weight (kg) during the participants' sleep laboratory visit. As part of the standardized questionnaire, we also assessed the presence of all sleep disorders. The presence of sleep difficulty was established on three levels of severity: insomnia was defined by a complaint of insomnia with a duration of at least 1 year, poor sleep was defined as a moderate-to-severe complaint (based on a mild-to-severe scale) of difficulty falling asleep, difficulty staying asleep, early final awakening, or unrefreshing sleep, whereas normal sleeping was defined as the absence of either of these two categories [19-25,44]. Additional information obtained from the standardized questionnaire included assessing other physical health conditions, depression, and substance use. The presence of diabetes at baseline was defined as a self-report of receiving treatment for diabetes or having a fasting blood sugar at least 126mg/dl from blood drawn the morning after the participant's PSG [21]. From this blood drawn, we also ascertained total cholesterol (TC) levels. Baseline information regarding the participant's history of heart disease, stroke, and depression, including a history of suicidal thoughts or attempts, were also obtained [44]. Participants' daily consumption of caffeine (number of cups/day), tobacco (number of cigarettes/day), and alcohol (number of drinks/day) was also assessed at baseline.

Statistical analyses

The design of this study included oversampling of those at higher risk for SDB and women with markedly higher BMI to increase the precision of the risk estimates. Because of this sampling strategy, numeric sampling weights were developed for the analysis so that the estimates could be inferred to the original target population [42,43,48-50]. We adjusted for the sampling weight in all of our statistical analyses, including those estimating the rate of all-cause mortality.

Multivariable adjusted logistic regression models were used to assess the association between hypertension and all-cause mortality, and the potential effect modification of objective sleep duration in the association. Sex, age, race, BMI, smoking, sleep apnea, sleep difficulty, heart disease, stroke, TC level, and depression were treated as major covariates and adjusted in the models. Sleep duration was adjusted when investigating the overall effect of hypertension on all-cause mortality in the entire sample. To assess the potential effect modification of objective sleep duration in the association between hypertension and all-cause mortality, the significance of the interaction term between hypertension and objective sleep duration was examined. The association between hypertension and mortality was then evaluated in each objective sleep duration stratum (i.e. ≥ 6 , 5–6, and ≤ 5 h), without assuming common variance in covariables. The results are presented as the multivariable-adjusted odds ratios (ORs) with their 95% confidence intervals (CIs). To further plot and interpret the risk of all-cause mortality associated with hypertension, we compared the projected mortality rates between hypertensive and normotensive participants across objective sleep duration groups, under the average demographic and clinical characteristics of the sample (i.e. aged 48.8 years; 47.8% men; 90.1% white; 27.6 kg/m² BMI; 211.5 mg/dl cholesterol;

23% smoker; 14% diabetic; 10% with a history of heart disease; 1.7% with a history of stroke; 10.7% SDB; 7.5% insomnia; and 17.3% depression). More specifically, the log odds of mortality rates were estimated by applying these values, along with objective sleep duration stratum and hypertension status, to the fitted logistic regression model. The inverse logit function was then applied to transform log odds to mortality probabilities. Finally, to examine whether the effect modification by objective short sleep duration on all-cause mortality applied to hypertensive groups regardless of their treatment status, we split the hypertensive participants into clinically meaningful subgroups based on both their treatment status and BP management. Controlled hypertension was defined as receiving treatment for high BP and BP levels less than 140/90mmHg, untreated hypertension as not receiving treatment for high BP and BP levels at least 140/90 mmHg, and uncontrolled hypertension as receiving treatment for high BP and BP levels at least 140/90mmHg. As sample size across these four groups did not permit using the three-level objective sleep duration variable to examine effect modification, we used the cutoff of 6 h (i.e. ≥ 6 vs. <6 h) to stratify the data; this cutoff has previously shown to be associated with significant cardiometabolic morbidity and mortality [14,17,19-21,24,25]. A P value of 0.05 or less was used to determine the significance for all analyses. All analyses were conducted with SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

The average demographic characteristics of the study population are presented in Table 1. The mean (SD) age was 48.8 (13.6) years, 47.8% were men and 90% whites, with an overall mortality rate of 19.6%. Overall, participants with hypertension showed a three times higher crude mortality rate than normotensive participants (35.5 vs. 11%, $P < 0.01$). The mean (SD) objective sleep duration for the entire sample was 5.9 (1.2) h. On average, participants with hypertension slept 0.6 h less than those without hypertension. As anticipated, the hypertensive group showed significantly higher BMI, AHI, and other cardiometabolic risk factors (all $P < 0.01$).

The interaction between hypertension and objective sleep duration was statistically significant ($P = 0.03$); therefore, the association between hypertension and mortality was evaluated for each objective sleep duration stratum. Overall, hypertensive participants showed a 2.54 (95% CI = 1.81–3.57, $P < 0.01$) times higher odds of dying compared with normotensive participants after adjusting for major covariables. When we examined the OR for different objective sleep duration groups, we observed that the strength of the association between hypertension and mortality increased in a dose–response manner. Specifically, the odds of all-cause mortality associated with hypertension was 1.77 (95% CI = 1.07–2.92, $P = 0.03$), 2.78 (95% CI = 1.47–5.24, $P < 0.01$), and 3.93 (95% CI = 2.22–6.95, $P < 0.01$) for participants who slept at least 6, 5–6, and 5 h or less, respectively. These data indicated that objective sleep duration is an effect modifier of the association between hypertension and all-cause mortality already at the less than 6 h of sleep threshold, with the strongest association found in the 5 h or less of sleep group.

To graphically illustrate the effect modification of objective sleep duration in the association between hypertension and all-cause mortality, we projected the mortality rates in

hypertensive participants vs. normotensive participants across objective sleep duration subgroups with equal demographic and clinical characteristics ('Methods' section). As shown in Fig. 1, the expected mortality rate for normotensive participants who slept at least 6 and 5–6 h was 14.0%, whereas the expected mortality rates for hypertensive participants who slept at least 6 and 5–6 h were 22.4 and 31.2%, respectively (P for comparisons <0.05 and <0.01 , respectively). Among participants who slept 5 h or less, hypertension showed a significantly larger impact; the expected mortality rate for normotensive participants who slept 5 h or less was 19.4%, whereas the expected mortality rate for hypertensive participants who slept 5 h or less was 49.7% ($P < 0.01$). The substantial differences with respect to the effect of hypertension on all-cause mortality rates across the three objective sleep duration groups with identical demographic and clinical characteristics shown in Fig. 1 were commensurate with the multivariable-adjusted ORs reported above. It should be noted that the ratio of these expected mortality rates can provide a closer estimate of associated risk than the ORs reported above; specifically, we could estimate a 1.6 (22.4 vs. 14.0%), 2.2 (31.2 vs. 14.0%), and 2.6 times (49.7 vs. 19.4%) higher risk of mortality in hypertensive participants than normotensive participants among those who slept at least 6, 5–6, and 5 h or less, respectively.

Furthermore, we examined other clinically meaningful hypertensive groups based on both their treatment status and BP management. Overall, the odds of all-cause mortality associated with controlled, untreated, and uncontrolled hypertension followed a dose–response pattern (Table 2). We found that the interaction between hypertensive treatment status groups and objective sleep duration on all-cause mortality was also statistically significant ($P < 0.05$). As shown in Table 2, the odds of all-cause mortality associated with controlled, untreated, and uncontrolled hypertension were significantly elevated among participants who slept less than 6 h, that is, 1.90, 2.21, and 3.06, respectively. In contrast, the odds of all-cause mortality associated with these three hypertensive treatment status groups were not significantly elevated among participants who slept at least 6 h. These data further indicated that the observed dose–response pattern of controlled, untreated, and uncontrolled hypertension was present specifically among participants who slept less than 6 h.

In secondary analyses, we also tested the association of the three-level BP variable with all-cause mortality and its interaction with objective sleep duration. As compared with normotensive participants, the odds of all-cause mortality were significantly increased in hypertensive participants (OR = 2.49, 95% CI = 1.40–4.46, $P < 0.01$) but not in prehypertensive participants (OR = 1.27, 95% CI = 0.75–2.12, $P = 0.36$), and the interaction between the three-level BP variable and objective sleep duration was not statistically significant ($P = 0.84$). These data indicated that the observed effect modification applied to individuals with clinical hypertension, which is significantly associated with all-cause mortality.

DISCUSSION

The current study is the first one to demonstrate that objectively measured short sleep duration modifies the increased odds of all-cause mortality associated with hypertension. This increased odds follows a dose–response pattern, with the largest magnitude of

association observed in those who slept 5 h or less, and is independent of other factors frequently associated with hypertension, mortality, or objective sleep duration (e.g. sex, age, race, smoking, obesity, diabetes, SDB, or depression). Objective short sleep duration in persons with hypertension may be biologically driven (e.g. genetics), behaviorally induced (e.g. self-infringed sleep deprivation), or, most likely, a marker of the degree of central autonomic dysfunction (e.g. sleep/arousal mechanisms and sympathetic nervous system dysregulation). Future epidemiological studies should examine whether this effect modification is stronger when cause-specific mortality is ascertained [i.e. cardiovascular disease (CVD) and stroke], whereas future clinical studies should examine whether improving/lengthening sleep reduces the odds of mortality in individuals with hypertension.

Consistent with previous studies, individuals with hypertension were associated with a significant risk of all-cause mortality [1]. When we stratified this risk by objectively measured short sleep duration, we showed a strong and significant dose-response on the association of hypertension with all-cause mortality. Among individuals who slept at least 6 h, hypertensive participants were associated with a significant 1.8-fold odds of all-cause mortality compared with normotensive participants. In contrast, among individuals who slept 5–6 and 5 h or less, hypertensive participants were associated with an increased 2.8 and 3.9-fold odds of all-cause mortality, respectively. Thus, objective short sleep duration had a strong modifying effect in the association between hypertension and all-cause mortality.

In the present study, we did not only calculate the odds of mortality associated with hypertension as modified by objective sleep duration while adjusting for multiple potential confounders, but we also pinpointed the expected mortality rate in this effect modification for populations with equal demographic (e.g. age, sex, and race) and clinical characteristics (e.g. prevalence of smoking, obesity, SDB, diabetes, and depression). The data presented in Fig. 1 can, therefore, be extrapolated to other populations with similar characteristics to our cohort of middle-aged men and women. Furthermore, these findings support the additional consideration of objective short sleep duration to increase the accuracy in estimating the risk of mortality associated with hypertension.

The vast majority of previous studies have focused on examining the independent association of sleep duration, typically subjectively measured, with hypertension, other morbidity and mortality, and the results have been inconsistent and modest [8–18]. In most of those studies, no PSG measures were obtained, and therefore the potential confounder of SDB was not controlled for, and the role of objective short sleep duration not examined. Most importantly, none of the previous studies conceptualized sleep duration as an effect modifier. The strong effect modification presented herein raises the question of what does objective short sleep duration mean in the context of cardiovascular risk.

There are, at least, three potential mechanistic explanations. Objective short sleep duration in persons with hypertension may be behaviorally induced – for example, individuals with short sleep duration in the sleep laboratory may be demonstrating self-infringed sleep deprivation. However, this is unlikely given that individuals were given enough in-lab conditions to satiate any accumulated sleep debt. Alternatively, objective short sleep duration in persons with hypertension may be biologically driven – for example, it may be a

genetically determined trait that is unlikely to be subjected to modification. However, short sleep duration on the absence of high BP was not associated with significantly increased mortality rates, as shown in Fig. 1. That objective short sleep duration modified the odds of all-cause mortality in persons with hypertension suggests that objective short sleep is rather a biological marker of the degree of central autonomic dysfunction (e.g. sympathetic nervous system dysregulation), a mechanism that is well known to be associated both with BP and sleep regulation. This view is consistent with recent studies that showed that objective short sleep duration modifies in a similar manner the association of insomnia with significant morbidity, including hypertension [19,20], diabetes and poor glucose regulation [21-23], neurocognitive deficits [24], and mortality [25]. Notably, insomnia with objective short sleep duration has been associated with increased cortisol levels [26-30], catecholaminergic activity [31,32], 24-h metabolic rate [33], daytime alertness [34-36], and heart rate (HR) as well as impaired HR variability [37-39] and faster cardiac preejection period [40] suggesting that objective short sleep duration, as measured by PSG, may be a marker of the biological severity of the disorder [41]. Thus, the results of the present study further expand the proposal that objective short sleep duration in the context of conditions associated with sympathetic nervous system activation (i.e. hypertension and insomnia) is an index of their biological severity and a premorbid, modifiable risk factor for cardiovascular morbidity and mortality.

Future experimental studies should examine the central and peripheral mechanisms that may differentiate individuals with hypertension who sleep at least 6 h vs. those who sleep less than 6 h, given the strong effect modification on all-cause mortality found in this study. Moreover, future epidemiological studies should examine whether the effect modification found herein is stronger when CVD and stroke mortality is ascertained. Furthermore, future clinical trials should examine whether lengthening sleep improves the prognosis of individuals with hypertension.

Some limitations should be taken into account when interpreting our results. First, the objective sleep duration in this study was based on one night of PSG, which may be affected by the ‘first night effect’. However, we and others have recently shown that measures of sleep continuity, such as objective sleep duration based on three consecutive nights or two single-night recordings separated by several years, are stable and reflect a person’s habitual sleep and that a single night in the laboratory is useful for reliably classifying individuals as short sleepers [51,52]. Nevertheless, future studies should explore the association between hypertension, sleep duration, and mortality using multiple night recordings. Second, we only measured BP in the evening, and we did not have morning levels available, which would have provided a more in-depth assessment of hypertension throughout the 24 h. Third, we examined all-cause mortality. As we are currently following up the Penn State Adult Cohort for cause of death, we will explore in the near future the role of objective sleep duration using cause-specific mortality, when sample size permits. Finally, the OR reported herein should be cautiously interpreted and differentiated from relative risk (RR). As mentioned above, the expected mortality rates and their ratio may provide a closer estimate of the RR.

In summary, the odds of all-cause mortality associated with hypertension increases as a function of objective short sleep duration in a dose–response manner, with the greatest odds

observed in hypertensive participants who sleep 5 h or less. Given the high prevalence of hypertension in the general population and the need to more accurately predict its prognosis, the introduction of novel, modifiable biological markers should become the target of public health policy. Individuals with hypertension who demonstrate objective short sleep duration may suffer from more severe central autonomic dysregulation and be at greater risk of all-cause mortality. Finally, because PSG measures of sleep are inconvenient and expensive, there is a need for validation of practical, easy to use, and inexpensive methods to measure sleep duration outside of the sleep lab. Meanwhile, our findings indicate that individuals with hypertension should undergo a sleep study, particularly those reporting symptoms of SDB or insomnia.

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Abbreviations:

95% CI	95% confidence interval
AHI	apnea/hypopnea index
BP	blood pressure
CDC	U.S. Center for Disease Control and Prevention
CVD	cardiovascular disease
NDI	National Death Index
OR	odds ratio
PSG	polysomnography
SDB	sleep-disordered breathing
SpO₂	hemoglobin oxygen saturation

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FIGURE 1.

Expected mortality rates associated with hypertension across objective sleep duration groups. Figure depicts the expected probability of death associated with hypertension (HTN) across objective sleep duration groups with identical demographic (e.g. age, sex, and race) and clinical (e.g., prevalence of smoking, obesity, sleep-disordered breathing, diabetes, and depression) characteristics.

TABLE 1.

Demographic and clinical characteristics of the study population

	Hypertension			P value
	Overall	No	Yes	
N	1741	783	958	
Age (years)	48.8 (13.6)	44.7 (14.1)	56.4 (10.4)	<0.01
Male (%)	47.8	45.4	52.1	<0.01
White (%)	90.1	91.6	87.4	<0.01
BMI (kg/m ²)	27.6 (5.7)	26.5 (6.0)	29.5 (5.0)	<0.01
Diabetes (%)	14.0	7.8	25.4	<0.01
Cholesterol (mg/dl)	211.5 (73.7)	204.7 (52.1)	224.2 (86.6)	<0.01
Heart disease (%)	10.0	6.0	17.2	<0.01
Stroke (%)	1.7	1.2	2.6	0.03
AHI (events/h)	2.4 (7.6)	1.6 (7.4)	3.8 (7.7)	<0.01
Insomnia (%)	7.5	5.2	11.8	<0.01
Depression (%)	17.3	15.6	20.4	0.01
Smoker (%)	23.0	25.2	18.9	<0.01
Objective sleep duration (h)	5.9 (1.2)	6.1 (1.3)	5.5 (1.0)	<0.01

All data are adjusted for sampling weight. AHI, apnea/hypopnea index.

TABLE 2.
Odds ratio (95% confidence interval) associating hypertension status and all-cause mortality

Hypertension	Overall	6 h	<6 h
No	1.00	1.00	1.00
Controlled	1.60 (0.85–3.01)	1.22 (0.47–3.18)	1.90 (0.94–3.85)
Untreated	1.88 (1.25–2.84)	1.49 (0.79–2.84)	2.21 (1.30–3.77)
Uncontrolled	2.28 (1.40–3.72)	1.58 (0.72–3.45)	3.06 (1.74–5.38)

Adjusted for age, race, sex, BMI, smoking, SDB, sleep difficulty, heart disease, stroke, cholesterol, depression, and sampling weight.

*P*value for the interaction between hypertension and objective sleep duration <0.05.