Decreased Slow Wave Sleep Increases Risk of Developing Hypertension in Elderly Men

Maple M. Fung, Katherine Peters, Susan Redline, Michael G. Ziegler, Sonia Ancoli-Israel, Elizabeth Barrett-Connor, Katie L. Stone, for the Osteoporotic Fractures in Men Research Group

Abstract—The importance of sleep to health and cardiovascular disease has become increasingly apparent. Sleep-disordered breathing, sleep duration, and sleep architecture may all influence metabolism and neurohormonal systems, yet no previous study has evaluated these sleep characteristics concurrently in relation to incident hypertension. Our objective was to determine whether incident hypertension is associated with polysomnography measures of sleep-disordered breathing, sleep duration, and sleep architecture in older men. Participants were 784 community-dwelling, ambulatory men ≥65 years of age (mean age: 75.1±4.9 years) from the Outcomes of Sleep Disorders in Older Men Study who did not have hypertension at the time of their in-home polysomnography sleep studies (2003–2005) and who returned for follow-up (2007–2009). Of 784 older men included in this report, 243 met criteria for incident hypertension after a mean follow-up of 3.4 years. In unadjusted analyses, incident hypertension was associated with increased hypoxemia, increased sleep stages N1 and N2, and decreased stage N3 (slow wave sleep [SWS]). After adjustment for age, nonwhite race, study site, and body mass index, the only sleep index to remain significantly associated with incident hypertension was SWS percentage (odds ratio for lowest to highest quartile of SWS: 1.83 [95% CI: 1.18 to 2.85]). No attenuation of this association was seen after accounting for sleep duration, sleep fragmentation, and indices of sleep-disordered breathing. Percentage time in SWS was inversely associated with incident hypertension, independent of sleep duration and fragmentation, and sleep-disordered breathing. Selective deprivation of SWS may contribute to adverse blood pressure in older men. (Hypertension. 2011;58:596-603.) ● Online Data Supplement

Key Words: hypertension ■ slow wave sleep ■ respiratory disturbance index ■ elderly ■ polysomnography

The importance of sleep to health, including hypertension (HTN) and cardiovascular disease, continues to be elucidated. HTN is present in >30% of the US adult population, with a much higher risk in the elderly: >65% of Americans age >60 years have been diagnosed with HTN.1 Sleep disturbances and disorders are also exceedingly common in older adults. Sleep disorders such as sleep-disordered breathing (SDB), sleep duration, and sleep architecture may affect neurohormonal axes, including the sympathetic nervous system, which contribute to elevated blood pressure and HTN. To our knowledge, a comprehensive evaluation of sleep characteristics and incident HTN in an elderly cohort has not been reported.

SDB, which includes obstructive sleep apnea, is strongly associated with HTN.2 In a study of veterans, 60% of obstructive sleep apnea patients had HTN,3 which is often refractory to treatment.4 Conversely, OSA may be present in ≥30% of adults with HTN.5 Previous studies have suggested that SDB, as determined by the respiratory disturbance index (RDI; number of respiratory events per hour of sleep), precedes incident HTN,6 although these associations may be partly attributable to obesity.7

Epidemiological studies of self-reported sleep have also found that sleep deprivation and/or short sleep duration are associated with both prevalent and incident HTN8,9 and that such associations may be most pronounced among premenopausal women.10 A case-control polysomnographic study showed that severity of HTN was associated with short sleep duration, lower sleep efficiency, and less rapid eye movement (REM) sleep.11 Sleep disruption may also lead to increased blood pressure.12

Human sleep is divided into REM and non-REM (NREM) sleep. NREM is further divided into the stages of N1 (previously called stage 1), N2 (previously stage 2), and N3 (previously stage 3 and 4; also called slow wave sleep [SWS]).13 Both NREM and REM sleep are assessed by the brain wave activity (frequency and amplitude) recorded with polysomnography (PSG). SWS is considered to be "restor-
ative” and is the sleep stage associated with the highest arousal threshold. The importance of SWS continues to be elucidated; it has been implicated in memory and overnight improvements in perceptual and visuomotor performance and learning. SWS has also been associated with transplant metabolic, hormonal, and physiological changes, which affect glucose metabolism, and is associated with decreased sympathetic nervous activity and increased vagal tone. These, in turn, are associated with decreased heart rate and blood pressure, which may influence nocturnal blood pressure profiles. The disappearance of a nocturnal “dipping” blood pressure pattern is known to increase the risk of HTN and cardiovascular disease.

We recently reported from the Outcomes of Sleep Disorders in Older Men Study (Osteoporotic Fractures in Men [MrOS] Sleep Study) that decreased percentage of time in SWS assessed by PSG was related to increased odds of obesity. Obesity and high blood pressure are very highly associated conditions with important public health consequences as major risk factors for both cardiovascular disease and death. To our knowledge, assessment of the association between SWS or other markers of sleep architecture with HTN has not yet been reported in prospective epidemiological studies.

The aim of the present study was to determine whether sleep characteristics, including SDB, determined by RDI or hypoxemia, decreased sleep duration, or indices of sleep architecture (which include overall arousal index, time in each sleep stage, sleep efficiency, or sleep fragmentation), predict incident HTN among elderly community-dwelling men.

Methods

Study Subjects

Study subjects were participants in the MrOS Sleep Study conducted in 2003–2005, an ancillary study of the parent MrOS study, a cohort of 5994 community-dwelling men, aged ≥65 years, described previously. A total of 3135 participants in the MrOS Sleep Study had full in-home PSG. See the online Data Supplement at http://hyper.ahajournals.org for details of MrOS participants who were enrolled and excluded.

For the present study, 2911 older men had PSG data, of whom 1986 (68.2%) had a history of HTN, were taking antihypertensive medications, or had an elevated systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg at the initial sleep visit and were excluded from the current analyses; 49 participants had missing data for either history of HTN or SWS and were also excluded. Of the 876 remaining, 784 participants attended the follow-up visit (2007–2009) and had complete HTN data (blood pressure measurements, response to questionnaires, and antihypertensive medication data) and are included in this report. In general, older men who regularly used mechanical sleep devices were excluded from the MrOS Sleep Study. However, our analysis sample included 1 man who reported intermittent use of a sleep device (but did not use the device on the night of the PSG measurement). The mean follow-up time was 3.40 years (SD 0.45 years). All of the protocols were approved by the institutional review boards at the respective enrollment sites, and participants signed informed consent to participate in the MrOS Sleep Study.

Classification and Measurement of HTN

As noted, HTN was defined as those who self-reported HTN (by affirmative answer to the question, “Have you ever had hyperten-

sion?”) or use of antihypertensive medications or who had measured SBP ≥140 mm Hg or DBP ≥90 mm Hg. Pre-HTN was classified as an SBP 120 to <140 mm Hg or DBP 80 to <90 mm Hg. Two seated resting blood pressure measurements were performed at the time of the initial sleep study using a conventional mercury sphygmomanometer on the right arm and an appropriate cuff size. Participants rested with their feet flat on the floor for ≥5 minutes before measurements, which were averaged. SBP was determined by phase I and diastolic as phase V Korotkoff values. At the follow-up visit, seated blood pressures were measured using the same protocol, but a BP Tru automated blood pressure monitor (model BMP-300) was used because of prohibition of mercury sphygmomanometers for safety reasons.

Other Measures

Self-administered questionnaires to assess participant demographics, including race; lifestyle factors such as physical activity, depression, and alcohol and smoking; and classification of medication use are described in the online Data Supplement. Height (in centimeters) was measured on regularly calibrated Harpenden stadiometers and weight (in kilograms) on calibrated standard balance beam or digital scales (body mass index [BMI] was calculated as kilograms per meter squared. Waist, hip, and neck circumferences were measured using a tape measure and standard techniques.

Polysomnography

In-home, single-night sleep studies using unattended PSG (Safiro, Compumedics, Inc, Melbourne, Australia) were performed. See the online Data Supplement for more details. Sleep stages (REM and stages 1 to 4 NREM, now N1 to N3) were scored using the standard criteria at the time of the studies. SWS was defined as the total sleep time scored as stage 3 plus stage 4, now N3, and expressed as percentage of total sleep time. RDI, an indication of the severity of SDB, was defined as the number of apneas and hypopneas (based on the Sleep Heart Health Study criteria) per hour of sleep, each associated with an oxygen desaturation of ≥4%. Hypoxemia was determined by sleep time spent with oxygen desaturation to <80% (PaO2 <80%). Central apnea index was defined as the number of apneas per hour of sleep with no displacement of either chest or abdominal inductance channels, regardless of oxygen desaturation. Total sleep duration at night and sleep efficiency, defined as the percentage of the sleep period (time in bed) spent asleep, were also obtained from PSG. Overall arousal index was determined as number of arousals per hour of sleep. Wake after sleep onset (the minutes awake after having been asleep) was used as a marker of sleep fragmentation.

Statistical Analyses

Initial associations of sleep variables with incident HTN were examined using ANOVA, Kruskal-Wallis, or χ² tests. Sleep variables considered included indices of SDB (by RDI and percentage of sleep time with oxygen saturation <80%), nighttime sleep duration, and sleep architecture (sleep stage distributions, wake after sleep onset, sleep efficiency, and overall arousal index). Descriptive and inferential statistics were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). To account for multiple end points that are highly correlated, we used the Dubey and Armitage-Parmar procedure. Potential confounders were identified a priori. Summary statistics for variables believed to be related to the polysomnographic variables and/or incident HTN were performed. ANOVA, Kruskal-Wallis, or χ² tests were used to examine associations with the sleep characteristics and incident HTN for normal, nonparametric, and categorized variables, respectively. Variables that were significant at P<0.10 for both outcomes were included in a multivariable model. A list of potential confounders and sleep variables considered are shown in Tables 1 and 2, respectively.

To account for nonlinear associations, sleep variables were categorized as quartiles. Parameters with a high number of 0 values (central apnea index and hypoxemia [percentage of time with PaO2 <80%]) were expressed as present or absent. Logistic regression was
The 784 men included in this report had a mean age of 75.1 years (SD 4.9 years) and mean BMI of 26.4 kg/m² (SD 3.4 kg/m²); ≈90% were white. Demographic characteristics are shown in Table 1. The mean baseline SBP was 121.0 mm Hg (SD 10.6 mm Hg) and DBP was 67.5 mm Hg (SD 7.7 mm Hg). A majority of the participants (61%) were prehypertensive, classified as a SBP 120 to <140 mm Hg or DBP 80 to <90 mm Hg; 19.7% reported a history of cardiovascular disease, and 5.7% reported a history of diabetes mellitus. Almost all (92.3%) rated their health as “excellent” or “good.”

At baseline, participants had a mean RDI of 10.0 (SD 12.0; median of 5.7), but 54.0% of men had an RDI >5, indicating at least mild SDB, shown with other sleep characteristics in Table 2. On average, the total sleep duration was 364 minutes (SD 66.4 minutes) or 6.1 hours. Average percentage of time in REM was 20.2% (SD 6.2%), stage 1 (N1) 6.5% (SD 4.2%), stage 2 (N2) 62.0% (SD 9.2%), and SWS (stages 3 and 4, N3) 11.2% (SD 8.5%).

### Incident HTN Was Associated With Sleep Architecture

Over the 3.4-year follow-up interval, 243 men developed incident HTN; 59 (24.3%) were diagnosed by blood pressure criteria alone, 9 (3.7%) by self-report of HTN alone, 5 (2.1%) had both self-reported HTN and met blood pressure criteria, and 170 (70%) were taking ≥1 antihypertensive medication. Those with incident HTN were older (75.7 versus 74.9 years; \( P=0.04 \)) and more likely to report cardiovascular disease (24.1% versus 17.7%; \( P=0.04 \)), shown in Table 1. There was a nonsignificant trend toward higher mean RDI with incident HTN, shown in Table 2. Percentage of time in
sleep stages (N1), 2 (N2), and SWS (N3) were associated with incident HTN, shown in Table 2. Those with incident HTN had poorer sleep architecture, as evidenced by significantly less SWS (mean: 9.8% versus 11.2%; P = 0.001) and correspondingly more stage 1 (N1) and stage 2 (N2) sleep (P = 0.013 and P = 0.033, respectively). After adjusting for age, race, BMI, and study site, only the association between SWS and incident HTN remained statistically significant (Table S1, available in the online Data Supplement).

SWS and Incident HTN

To further explore the associations between SWS and incident HTN, we first assessed the associations of covariates and other sleep variables with quartiles of time in SWS (Table 3). The lowest quartile of percentage of sleep time in SWS (<4.1%) was associated with increasing age (P < 0.001), BMI (P = 0.015), and neck circumference (P = 0.012) but not baseline SBP and DBP. In those in the lowest quartile of SWS, we observed a higher mean RDI (P < 0.001), a higher mean overall arousal index (P < 0.001), lower mean total sleep duration (P = 0.009), and lower mean sleep efficiency (P < 0.001). Those in the lowest quartile of percentage of sleep time in SWS were also more likely to have any SDB (RDI ≥5) or moderate-severe SDB (RDI ≥15; P = 0.048 and P = 0.0005, respectively). Central apnea index was not associated with quartile of SWS. Men taking either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at follow-up (9.6% total) were more likely to be in the lowest quartile of SWS (P = 0.034).

In unadjusted analyses, 41% of those in quartile 1 of SWS (Q1; least SWS) developed incident HTN compared with <30% in each of the other quartiles (Figure). We further examined the association of SWS and incident HTN in multivariate models (Table 4). After adjusting for age and BMI, those in Q1 of SWS experienced an >80% increase in risk of incident HTN as compared with those in Q4 (odds ratio: 1.81 [95% CI: 1.18 to 2.80]). These results were unchanged after further adjustment for study site, race, history of cardiovascular disease, the polysomnographic sleep variables of overall arousal index, sleep time with PaO2 <80% saturation, RDI, sleep efficiency, total sleep duration, and smoking history and alcohol use. After adjusting for multiple correlated comparisons using the Dubey and Armitage-Parmar procedure,27 results were not significantly changed. In addition, substituting height and weight, waist circumference, hip circumference, or hip:waist ratio for BMI did not significantly change the results.

Subgroup analysis of sleep architecture in normotensive men who progressed to pre-HTN or HTN, described in the online Data Supplement and Figure S1, revealed an association with decreased percentage of time in SWS (P < 0.004) and percentage of increased time in stage 2 (N2; P = 0.042) sleep as subjects either stayed normotensive or progressed to pre-HTN or HTN.

Discussion

Sleep disturbances are exceedingly common in older adults and may contribute to a number of adverse health outcomes, including HTN and cardiovascular disease through perturbations in a number of physiological systems. Most previous research on the relationship between incident HTN and sleep disturbances has focused on SDB, with some studies also addressing sleep duration. To our knowledge, this is the first large-scale analysis of comprehensive PSG data that assesses the association of indices of 3 key sleep domains, SDB, sleep duration, and sleep architecture, to incident HTN in an elderly cohort. In these community-dwelling older men, we found

Table 2. Sleep Characteristics of Study Cohort: Overall and by Follow-Up HTN Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 784)</th>
<th>Incident HTN (N = 243)</th>
<th>No Incident HTN (N = 541)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-disordered breathing, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDI</td>
<td>10.0 ± 12.0</td>
<td>10.8 ± 13.5</td>
<td>9.7 ± 11.3</td>
<td>0.256*</td>
</tr>
<tr>
<td>Hypoxemia (% sleep time PaO2 &lt;80%)</td>
<td>0.05 ± 0.3</td>
<td>0.09 ± 0.4</td>
<td>0.03 ± 0.2</td>
<td>0.025†</td>
</tr>
<tr>
<td>Central apnea index</td>
<td>1.5 ± 4.5</td>
<td>1.7 ± 5.6</td>
<td>1.4 ± 4.0</td>
<td>0.835*</td>
</tr>
<tr>
<td>RDI ≥15, n (%)</td>
<td>164 (20.9)</td>
<td>51 (21.0)</td>
<td>113 (20.9)</td>
<td>0.975</td>
</tr>
<tr>
<td>RDI ≥5, n (%)</td>
<td>423 (54.0)</td>
<td>133 (54.7)</td>
<td>290 (53.6)</td>
<td>0.770</td>
</tr>
<tr>
<td>Sleep duration, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep duration, min</td>
<td>364.1 ± 66.4</td>
<td>365.5 ± 72.3</td>
<td>363.5 ± 63.7</td>
<td>0.715</td>
</tr>
<tr>
<td>Sleep architecture, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall arousal index</td>
<td>22.9 ± 11.3</td>
<td>23.1 ± 12.3</td>
<td>22.8 ± 10.8</td>
<td>0.724*</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>75.9 ± 11.7</td>
<td>74.9 ± 12.8</td>
<td>76.4 ± 11.2</td>
<td>0.116</td>
</tr>
<tr>
<td>Wake after sleep onset, min</td>
<td>106.3 ± 63.0</td>
<td>112.2 ± 63.7</td>
<td>103.6 ± 62.6</td>
<td>0.079</td>
</tr>
<tr>
<td>% time in stage 1 (N1) sleep</td>
<td>6.5 ± 4.2</td>
<td>7.2 ± 5.3</td>
<td>6.2 ± 3.6</td>
<td>0.013†</td>
</tr>
<tr>
<td>% time in stage 2 (N2) sleep</td>
<td>62.0 ± 9.2</td>
<td>63.1 ± 9.2</td>
<td>61.6 ± 9.2</td>
<td>0.033†</td>
</tr>
<tr>
<td>% time in slow wave (N3) sleep</td>
<td>11.7 ± 8.5</td>
<td>9.8 ± 8.1</td>
<td>11.8 ± 8.5</td>
<td>0.002†</td>
</tr>
<tr>
<td>% time in REM</td>
<td>20.2 ± 6.2</td>
<td>20.0 ± 6.4</td>
<td>20.3 ± 6.1</td>
<td>0.479</td>
</tr>
</tbody>
</table>

RDI indicates respiratory disturbance index; HTN, hypertension; REM, rapid eye movement sleep.

*Data show the use of Kruskal-Wallis statistic because of nonnormal distributions.
†P < 0.05
that men with SWS in the lowest quartile had an \( \approx 1.8 \) fold increased incidence of HTN compared with men with the highest levels of SWS. This association persisted after adjusting for several covariates and after considering other sleep exposures, such as RDI, the overall arousal index, and total sleep duration. This study adds to the growing important body of literature regarding sleep and cardiovascular risks. Rather than noting associations alone, it describes more detailed associations of incident disease with sleep in particular stages.

Decreased SWS is increasingly recognized as a marker, possibly etiologically associated with several adverse health outcomes. Sleep architecture, particularly SWS, has been implicated in neurocognition and, more recently, in influencing endocrine function. Human metabolism is affected by changes in circadian rhythm, which includes the sleep-wake cycle. Low sleep quality and reduced SWS have been associated with insulin resistance and associated with the presence of diabetes mellitus, findings that may relate to the close interactions between the hypothalamic-pituitary-adrenal axis and sleep homeostasis. SWS may potentially be associated with the metabolic syndrome, a notion consistent with our previous observations of an inverse association of SWS with obesity in this cohort. The findings in this study provide new evidence that decreased SWS is associated with the development of HTN. Whether decreased SWS is also associated with altered glucose metabolism or with other components of metabolic syndrome could not be assessed because of the unavailability of biochemical measures.

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**Table 3. Baseline Demographic Characteristics of Cohort, Overall and by Percent Time in Slow Wave Sleep (SWS) Quartiles (Q1–Q4)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N=784)</th>
<th>Q1: &lt;4.1 (N=195)</th>
<th>Q2: 4.1 to 10.2 (N=197)</th>
<th>Q3: 10.2 to 16.9 (N=192)</th>
<th>Q4: &gt;16.9 (N=200)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>75.1±4.9</td>
<td>76.5±5.5</td>
<td>74.6±4.9</td>
<td>74.6±4.3</td>
<td>74.8±4.5</td>
<td>0.0001†</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4±3.4</td>
<td>27.0±3.7</td>
<td>26.3±3.0</td>
<td>26.5±3.6</td>
<td>25.9±3.3</td>
<td>0.015†</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>97.3±10.0</td>
<td>98.8±10.3</td>
<td>97.1±8.7</td>
<td>97.0±10.4</td>
<td>96.4±10.2</td>
<td>0.096</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>101.9±8.3</td>
<td>102.9±7.9</td>
<td>101.6±7.2</td>
<td>101.9±10.2</td>
<td>101.1±7.5</td>
<td>0.162</td>
</tr>
<tr>
<td>Baseline SBP, mm Hg</td>
<td>121.0±10.6</td>
<td>121.8±10.5</td>
<td>120.9±10.1</td>
<td>120.9±10.9</td>
<td>120.3±10.9</td>
<td>0.569</td>
</tr>
</tbody>
</table>

**BMI** indicates body mass index; PASE, physical activity score in the elderly; REM, rapid eye movement sleep; SBP, systolic blood pressure; DBP, diastolic blood pressure; RDI, respiratory disturbance index; GDS, geriatric depression scale; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

†Data show the use of Kruskal-Wallis statistic because of nonnormal distributions.

‡\( P<0.05 \).
limitation of this study is the lack of fasting glucose or insulin or hemoglobin A1C measurements to investigate these relationships further. However, this sample included only a few diabetics (5.7%), and adjusting for diabetes mellitus history did not attenuate the association.

Our results are consistent with a positive effect of SWS on blood pressure regulation. Studies of cardiac hemodynamics during sleep have noted decreased blood pressure and heart rate during NREM, particularly SWS, suggesting that the decline in blood pressure is attributable to a decline in cardiac output, because peripheral vascular resistance and stroke volume are unaffected. These adaptations are primarily mediated by the autonomic nervous system with decreased sympathetic nervous system activity and increased parasympathetic activity. Sympathetic nervous system activity continuously decreases with the deepening of NREM toward SWS, coinciding with the increase of the sympathovagal baroreflex. This baroreflex may account for the benefits of “dipping” of blood pressure on cardiovascular disease, which is impaired in hypertensive subjects who have increased sympathetic nervous system activity. This “nondipping” nocturnal blood pressure is a better predictor of all-cause and cardiovascular mortality, coronary heart disease, and stroke than daytime pressure. Experimental SWS deprivation in healthy subjects resulted in an attenuation of the dipping of blood pressure during SWS. Several studies have demonstrated that SWS is lower in older men than women and declines with age. Our data suggest that reduced SWS with aging may contribute to the high rates of HTN in older men. Our study found no independent associations between incident HTN and RDI (as a marker of SDB), arousal index (a marker for both SDB and disturbed sleep), and total sleep duration.

Two previous studies have evaluated whether SDB predicts incident HTN. First, the Wisconsin Sleep Cohort Study, with a younger mean age of 47 years, reported a dose-response association between SDB at baseline and incident HTN 4 years later, which was independent of known confounding factors. The Sleep Heart Health Study, with a mean age of 60 years, found that much of the longitudinal association was accounted for by obesity. The disparate results may be because of the difference in mean ages or exclusions, given that the incidence of HTN increases with age, and at our baseline sleep visit, 68% of the subjects were excluded at baseline because of prevalent HTN.

Consistent with some previous studies, total sleep duration measured by PSG was not associated with incident HTN in this older cohort. The literature on incident HTN and sleep duration examined this association in younger populations or with use of self-reported sleep duration. Our study suggests differences across the age span in the associations between sleep characteristics and health outcomes.

Poor sleep quality may be measured by several different metrics, including an increased arousal index and increased wake after sleep onset, decreased sleep efficiency, and increased stages 1 and 2 (N1 and N2) sleep. Previous studies have focused on the arousal index as a metric for increased sympathetic activation and as a potential predictor of HTN. Our study suggests that a specific reduction of SWS, rather than nonspecific sleep disruption, may be a more critical factor that influences blood pressure.

The strengths of this study include the use of PSG for objectively measuring sleep characteristics and assessment in a large community-dwelling cohort of older men. However, given that the parent study (MrOS) was originally designed to

Table 4. Adjusted Odds Ratios for Incident Hypertension by Slow Wave Sleep Quartile

<table>
<thead>
<tr>
<th>Adjusted Characteristics</th>
<th>SWS Quartile 1</th>
<th>SWS Quartile 2</th>
<th>SWS Quartile 3</th>
<th>SWS Quartile 4</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and BMI</td>
<td>1.81 (1.18 to 2.80)</td>
<td>1.09 (0.70 to 1.70)</td>
<td>1.15 (0.74 to 1.80)</td>
<td>1.0 (reference)</td>
<td>0.012</td>
</tr>
<tr>
<td>+Race, study site</td>
<td>1.83 (1.18 to 2.85)</td>
<td>1.14 (0.73 to 1.78)</td>
<td>1.18 (0.75 to 1.85)</td>
<td>1.0</td>
<td>0.012</td>
</tr>
<tr>
<td>+History of CVD</td>
<td>1.84 (1.18 to 2.87)</td>
<td>1.14 (0.73 to 1.79)</td>
<td>1.17 (0.75 to 1.84)</td>
<td>1.0</td>
<td>0.012</td>
</tr>
<tr>
<td>+RDI</td>
<td>1.86 (1.19 to 2.91)</td>
<td>1.14 (0.73 to 1.80)</td>
<td>1.18 (0.75 to 1.85)</td>
<td>1.0</td>
<td>0.011</td>
</tr>
<tr>
<td>+Total sleep duration, % sleep time, PaO2 &lt;80%, overall arousal index and sleep efficiency</td>
<td>1.87 (1.18 to 2.95)</td>
<td>1.12 (0.71 to 1.77)</td>
<td>1.15 (0.73 to 1.82)</td>
<td>1.0</td>
<td>0.013</td>
</tr>
<tr>
<td>+Alcohol use* and current smoking</td>
<td>1.82 (1.15 to 2.88)</td>
<td>1.11 (0.70 to 1.75)</td>
<td>1.15 (0.73 to 1.82)</td>
<td>1.0</td>
<td>0.019</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SWS, slow wave sleep; CVD, cardiovascular disease; RDI, respiratory disturbance index (No. of apneas and hypopneas per h of sleep, each associated with an oxygen desaturation of ≤4%).

*Alcohol use denotes ≥1 drink per wk. Further categorization of alcoholic drinks per week 0, <1, 1 to 2, 3 to 5, 6 to 13, or ≥14 did not significantly change results.
evaluate the risks of fractures in older men, this study must be considered exploratory in nature. We acknowledge that this observational study is challenged by many factors that influence both blood pressure and sleep, which also change over time. Additional study to confirm this association is necessary to determine the direction of the association after longer follow-up. Other limitations include the lack of 24-hour ambulatory blood pressure monitoring for HTN and the precise time of the blood pressure readings. Almost a quarter of those with incident HTN (24.3%) were classified based on a single blood pressure measurement; however, sensitivity analysis that excluded these participants showed similar results (data not shown).

In an exploratory study, we evaluated 11 sleep variables (Table s1) that raise questions about multiple comparisons. Because many of these indices are highly correlated (Pearson coefficients range from −0.86 to 0.64), we used the Dubey and Armitage-Parmar procedure27 to address the influence of the data in the study and take responsibility for the integrity of the results (data not shown).

Disclosures
M.M.F. discloses previous grant support from Forest Laboratories and currently owns stock and is employed by Amgen. S.A.I. is a consultant for Ferring Pharmaceuticals, Inc, GlaxoSmithKline, Johnson & Johnson, Merck, NeuroVigil, Inc, Pfizer, Philips, Purdue Pharma LP, sanofi-aventis, and Somaxon.

References

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Decreased Slow Wave Sleep Increases Risk of Developing Hypertension in Elderly Men
Maple M. Fung, Katherine Peters, Susan Redline, Michael G. Ziegler, Sonia Ancoli-Israel, Elizabeth Barrett-Connor, Katie L. Stone and for the Osteoporotic Fractures in Men Research Group

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DECREASED SLOW WAVE SLEEP INCREASES RISK OF DEVELOPING HYPERTENSION IN ELDERLY MEN

Authors: Maple M. Fung, MD\textsuperscript{1,2}, Katherine Peters\textsuperscript{3}, Susan Redline, MD\textsuperscript{4}, Michael G. Ziegler, MD\textsuperscript{2}, Sonia Ancoli-Israel, PhD\textsuperscript{5}, Elizabeth Barrett-Connor, MD\textsuperscript{6}, and Katie L. Stone, PhD\textsuperscript{3} for the Osteoporotic Fractures in Men (MrOS) Research Group

\textsuperscript{1}San Diego Veterans Affairs Healthcare System, Medicine Service.
\textsuperscript{2}University of California, San Diego, Department of Medicine
\textsuperscript{3}San Francisco Coordinating Center and California Pacific Medical Center Research Institute
\textsuperscript{4}Brigham and Women’s Hospital and Beth Israel Deaconess Medical School, Harvard Medical School, Department of Medicine
\textsuperscript{5}University of California, San Diego, Department of Psychiatry
\textsuperscript{6}University of California, San Diego, Department of Family and Preventive Medicine
Online supplemental methods.

Study participants.

2,860 participants from the original cohort did not participate in the sleep study as they were unwilling (1997), not screened because recruitment goals were met (332), death before the sleep study visit (334), ineligible due to exclusion criteria such as use of mechanical devices during sleep, including positive airway pressure devices, oral appliances for snoring or sleep apnea, or oxygen therapy (150), and quitting the MrOS study before the sleep study was offered (37). Among the 49 men who reported use of one of the sleep devices, 17 men were able to forego use of their sleep devices during the night of the in-home PSG study and had sleep studies performed. Of the 3,135 enrolled participants, 2,911 had valid PSG data. Of these, sleep staging could not be performed on 39 studies (due to poor EEG quality), and in 132 records there was difficulty differentiating stage 2 and SWS due to artifact; 5 people fell into both categories.

Other measures. Self-administered questionnaires were used at the time of the sleep study to ascerene participant demographic and lifestyle information and their personal and family medical history, including self-reported HTN, diabetes, and cardiovascular disease (which included history of myocardial infarction, angina, congestive heart failure, coronary bypass surgery, transient ischemic attack, stroke, or rheumatic heart disease). Race/ethnicity was self-reported using a questionnaire with a choice of 5 categories (Caucasian/White, African American/Black, Asian, Hispanic, and Other). Due to the small percentiles of non-Caucasian participants (<10% total) and no difference by SWS or incident hypertension, they were then simplified to Caucasian and Non-Caucasian. Interviews and examinations by trained study staff members included measures of functional status and anthropometric data. Physical activity was assessed by using the physical activity scale for the elderly (PASE)1. Depressed mood was assessed using the Geriatric Depression Scale (GDS), a 15 point scale of yes or no questions, and a standard cut point of >6 was used to define depressed mood2. Participants also reported tobacco use (current, past, or never) and alcohol use (drinks per week). Alcohol use was assessed by <1 or >1 drink per week and also by 0, <1, 1-2, 3-5, 6-13, or 14+ drinks per week. Participants were asked to bring in all current medications used within the preceding 30 days. All prescription and nonprescription medications were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA)3. They were also asked whether each medication was used for sleep, and if so, the subject was considered to have “Use of Sleep Medication.” Zolpidem, diphenhydramine, acetaminophen, trazadone, and melatonin were the most common medications reported for this purpose.

Sleep studies.

The recording montage consisted of C3/A2 and C4/A1 electroencephalograms, bilateral electroculograms, electrocardiogram, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (using nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Trained certified staff members performed home visits for setup of the sleep study units. After sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality, replacing electrodes if impedances were > 5000 ohms, using approaches similar to those in the Sleep Health Heart Study4. After studies were downloaded, they were transferred to the Case Western Reserve University Reading Center (Cleveland, OH) for centralized scoring by a trained technician using standard criteria5,6. PSG data quality was excellent, with > 70% of studies graded as being of excellent or outstanding quality and a failure rate < 4%. Quality codes for signals and studies were graded using previously described approaches, including coding of the duration of artifact-free data per channel and overall study quality (reflecting the combination of grades for each channel)6.

The inter-scorer reliability of percent time in SWS was high (intraclass correlation coefficient [ICC] = 0.958, 95% CI = 0.921-0.982). The intra-scorer reliability was also high, with the ICC ranging from 0.964-0.998.
Pre-hypertension subgroup analysis. In a subgroup analysis, determined whether the association between SWS and incident HTN persisted after excluding men who were pre-hypertensive at baseline. The normotensive participants were further divided into normotensive, pre-hypertensive or hypertensive groups at follow-up. ANOVA, Kruskal-Wallis and chi square tests were analyzed for significant differences in SWS and the other sleep stages in this subset.

Results.

Subgroup analysis of sleep architecture in normotensive subjects.

In evaluating only normotensive subjects at the start of the study (without blood pressure medication or other evidence of pre-hypertension), there was an association with decreased percent time in SWS (P=0.004) and percent increased time in stage 2 (N2; P=0.042) sleep as subjects either stayed normotensive, or progressed to pre-hypertension or HTN, shown in Online Supplemental Figure S1. There was no difference in percent time in REM sleep or stage 1 (N1) sleep and HTN progression. These results were unchanged after adjustment for age and covariates.
References:

Table S1. Adjusted odds ratios of incident hypertension (HTN) in the lowest quartile compared to the highest quartile in sleep characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio of lowest quartile to highest quartile</th>
<th>95% CI</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep disordered breathing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory disturbance index (RDI)</td>
<td>0.89</td>
<td>0.56, 1.42</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypoxemia (% sleep time Pao2 &lt;80%)</td>
<td>0.62*</td>
<td>0.31, 1.24</td>
<td>0.18</td>
</tr>
<tr>
<td>Central apnea index</td>
<td>1.00*</td>
<td>0.73, 1.38</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Sleep duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep duration (minutes)</td>
<td>0.68</td>
<td>0.44, 1.06</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>Sleep architecture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall arousal index</td>
<td>1.26</td>
<td>0.82, 1.94</td>
<td>0.26</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>0.93</td>
<td>0.59, 1.47</td>
<td>0.81</td>
</tr>
<tr>
<td>Wake after sleep onset (minutes)</td>
<td>0.89</td>
<td>0.56, 1.40</td>
<td>0.57</td>
</tr>
<tr>
<td>% time in stage 1 (N1) sleep</td>
<td>0.69</td>
<td>0.44, 1.08</td>
<td>0.075</td>
</tr>
<tr>
<td>% time in stage 2 (N2) sleep</td>
<td>0.77</td>
<td>0.50, 1.19</td>
<td>0.068</td>
</tr>
<tr>
<td>% time in slow wave (N3) sleep</td>
<td>1.83</td>
<td>1.18, 2.85</td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>% time in REM</td>
<td>0.97</td>
<td>0.62, 1.52</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*Denotes variables dichotomized as zero or greater than zero rather than quartiles due to distributions not suitable for quartiles. Models are adjusted for age, non-white race, study site, and body mass index. (Models are not significantly changed when additionally adjusting for alcohol use or smoking).
Online Supplemental Figure S1 Legend

Sleep architecture of normotensive subjects at baseline based on hypertension progression ~3.4 years later. In subset analysis of participants who were normotensive at baseline (not pre-hypertensive but with SBP<120 mmHg and DBP <80 mmHg; N=307), we found an association with percent time in slow wave sleep (SWS; P=0.004) and stage 2 sleep (P=0.042) as subjects progressed to pre-hypertension or hypertension. There was no difference in percent time in REM sleep or stage 1 sleep.