Population-Based Study of Sleep-Disordered Breathing as a Risk Factor for Hypertension

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Background: Clinical observations have linked sleep-disordered breathing, a condition of repeated apneas and hypopneas during sleep, with hypertension but evidence for an independent association has been lacking. Understanding this relationship is important because the prevalence of sleep-disordered breathing is high in adults.

Objective: To test the hypothesis that sleep-disordered breathing is related to elevated blood pressure independent of confounding factors.

Methods: The sample included 1060 employed women and men aged 30 through 60 years who had completed an overnight protocol as part of the Wisconsin Sleep Cohort Study. In-laboratory polysomnography was used to determine sleep-disordered breathing status, quantified as the number of apneas and hypopneas per hour of sleep (apnea-hypopnea index). Blood pressure was measured on the night polysomnography was performed.

Results: Blood pressure increased linearly with increasing apnea-hypopnea index ($P=.003$ for systolic, $P=.01$ for diastolic, adjusted for confounding factors). The magnitude of the linear association increased with decreasing obesity. At a body mass index (weight in kilograms divided by the square of the height in meters) of 30 kg/m^2, an apnea-hypopnea index of 15 (vs 0) was associated with blood pressure increases of 3.6 mm Hg for systolic (95% confidence interval, 1.3-6.0) and 1.8 mm Hg for diastolic (95% confidence interval, 0.3-3.3). The odds ratio for hypertension associated with an apnea-hypopnea index of 15 (vs 0) was 1.8 (95% confidence interval, 1.3-2.4).

Conclusions: There is a dose-response relationship between sleep-disordered breathing and blood pressure, independent of known confounding factors. If causal, the high prevalence of sleep-disordered breathing could account for hypertension in a substantial number of adults in the United States.

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THE REPEATED episodes of apnea and hypopnea in sleep-disordered breathing are known to cause transient elevations in blood pressure (BP) during sleep, and it has been hypothesized that these episodes result in elevated daytime BP as well.[1] Because the prevalence of untreated sleep-disordered breathing, ranging from mild to severe, is high in both women and men (9% and 24%, respectively), quantifying the role of this condition in the development of hypertension is particularly important.[2] Even a modest role for sleep-disordered breathing in BP elevation would place a large number of people at increased risk for cardiovascular morbidity and mortality.

A causal role of sleep-disordered breathing in hypertension is supported by strong biological plausibility and some experimental evidence. The acute physiological consequences of apnea and hypopnea, including hypoxemia, hypercapnia, arousals from sleep, and large negative intrathoracic pressures, may affect BP regulation through both neural and humoral mechanisms. Although a causal mechanism has not been established, there is some evidence that patients with sleep-disordered breathing have increased sympathetic nerve activity,[3] decreased baroreceptor sensitivity,[4] accentuated vascular responsiveness,[5] and abnormal salt and water metabolism,[6] all of which could contribute to hypertension. A few studies[7-10] have shown BP to decrease in patients with sleep-disordered breathing after successful treatment by tracheostomy or by the most commonly used therapy of nasal continuous positive air pressure.

Widely cited clinical observations[11-13] that 50% to 90% of patients with sleep-disordered breathing have hypertension add support to the hypothesis. However, inconsistent findings have re-

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summary measure of sleep-disordered breathing. For descriptive analyses, AHI cutoff points at 5, 15, and 30 were used.

Blood pressure was measured by conventional standard mercury sphygmomanometer according to the American Heart Association recommendations[31] in the early evening, following orientation and acclimation to the bedroom. Measurements were made using the left arm with an appropriate-sized cuff, after participants had been seated for 15 minutes. Three readings at 5-minute intervals of systolic and diastolic (phase 5) BPs were recorded.

Body habitus measures, including height and weight without shoes and waist, neck, and hip girths, were measured using standard procedures [32] Body mass index was calculated from the height and weight. Use of antihypertensive medication was determined by interview. Participants who reported current use of α- and β-blockers, calcium channel blockers, diuretics, or angiotensin-converting enzyme inhibitors for treatment of hypertension were coded as positive for medication use. Information on medical history, smoking, alcohol use, education, age, and other sociodemographic factors were also obtained as part of the interview.

DATA ANALYSIS

Data were analyzed with SAS statistical software[33] and SUDAAN[34] software modules for descriptive statistics, contingency tables, multiple linear regression, and logistic regression. To account for the stratified sampling of the sleep cohort, all analyses were weighted to give unbiased estimates. The SUDAAN software was used to compute appropriate SEs for the weighted analyses.

The association between sleep-disordered breathing and BP adjusted for confounding factors was quantified by multiple regression techniques. Apnea-hypopnea index, the primary independent variable, was used in all models as a continuous variable.

Multiple linear regression was used to estimate the change in BP associated with increases in the AHI. Although linear regression has the advantage of modeling BP as a continuous variable, the ability to estimate the true relationship is hampered by the influence of antihypertensive medication on BP. To account for this, we fit models with an interaction term, allowing associations between sleep-disordered breathing and BP to be estimated for those using and not using antihypertensive medication. Since, as expected, there was no linear association between AHI and BP for those receiving medication, only the regression results for those not using medication are presented. (The results were the same as those obtained from performing regression on the sample after medication users are excluded.) This strategy is commonly used in linear regression analyses of BP as the outcome, but it has been shown that this leads to underestimation of associations.[35] Use of multiple logistic regression modeling with hypertension as the outcome variable avoids the analytic problem due to data with BPs influenced by medication. This approach allows both people with BPs above specified cutoff points and people with treated hypertension, regardless of BP level, to be coded as having hypertension. For the logistic modeling, 3 hypertension variables were created: (1) systolic BP of 140 mm Hg or more or antihypertensive medication use, (2) diastolic BP of 90 mm Hg or more or antihypertensive medication use, and (3) systolic BP of 140 mm Hg or more or diastolic BP of 90 mm Hg or more or antihypertensive medication use.

Age, gender, body habitus (height, weight, BMI, skinfolds, and waist, hip, and neck circumferences), smoking (current, former, or never status and amount in pack-years), alcohol use (usual weekly consumption and amount consumed 24 hours before the sleep study), education, and physical activity were investigated as confounding factors. Confounding was assessed by the standard method of comparing the association of interest before and after addition of each potential confounding factor.[36] When adjustment changed the regression coefficient for AHI by 15% or more, the covariate was retained in the final model. In addition, interactions between the covariates and AHI with respect to BP were tested for statistical significance. The statistical significance of linear regression coefficients was assessed by t tests and that of logistic regression coefficients was assessed by Wald χ^2 tests. Two-tailed P values of less than .05 were considered to indicate statistical significance. Standard regression diagnostics were performed to assess model fit and adequacy of compliance with the modeling assumptions.

lighting the need to account for these factors that are also correlates of hypertension.

Multiple linear regression modeling, adjusting for age, sex, and several indicators of body habitus (BMI, waist-hip ratio, neck girth, and skinfolds thickness), showed that sleep-disordered breathing, measured by AHI, was significantly related to systolic and diastolic BPs. The body habitus variables were all significant in the regression models and reduced the coefficient for AHI to the same degree. Use of combinations of the body habitus variables produced the same results. Body mass index has been most widely used, so this measure of body habitus was adopted. There was no interaction of AHI and age or sex, indicating that the relationship between AHI and BP did not vary by age or sex. There was, however, a significant negative interaction of AHI and BMI, indicating the association of AHI and BP decreases with increasing BMI. Although the decrease is small, to correctly estimate the association of AHI and BP, it is necessary to specify a BMI level. Final models of systolic and diastolic BPs, centered at a BMI of 30 kg/m^2 for individuals not using antihypertensive medication, are given in **Table 2**. Under the conditions of the model, the β coefficient for AHI indicates an increase of 0.24 and 0.12 mm Hg in systolic and diastolic BPs, respectively, for each additional apnea or hypopnea per hour of sleep. The model predicts, for example, that BPs will be 3.6 mm Hg (systolic) and 1.2 mm Hg (diastolic) higher for mild sleep-disordered breathing (AHI, 15) vs no sleep-disordered breathing (AHI, 0). To illustrate the decrease in this effect with increasing obesity, predicted BP increases associated with mild to moderate sleep-disordered breathing over 3 BMI levels are given in **Figure 1**.

The final multiple logistic regression model of sleep-disordered breathing and hypertension, with terms for AHI, sex, age, BMI, and an interaction term for BMI and

and accurate assessment of the AHI. Furthermore, our use of standard polysomnography means that our findings are expressed with the same metrics used to describe the spectrum of sleep-disordered breathing in sleep medicine. A shortcoming of our analysis is the lack of exploration of other physiological parameters of sleep-disordered breathing. The AHI, as a measure of the frequency of apneas and hypopneas, is the most commonly used measure of sleep-disordered breathing occurrence and severity, but it is possible that variables based on the underlying physiological effects, such as level of oxygen desaturation and cortical arousals, better describe severity in relation to BP. The BP measures, conducted by trained technicians, were taken under similar conditions for all subjects and the average BPs for the total sample are comparable with those for the adult US population.[37]

This study was designed to analyze the effect of hypothesized and established factors that would be capable of confounding the findings. Extensive investigation with statistical modeling indicated that there was an independent association between sleep-disordered breathing and BP. However, it is possible that an unknown risk factor for both sleep-disordered breathing and hypertension exists that may have biased the findings. Furthermore, although we used variables based on commonly used measures of potential confounding factors, it is not possible to know with certainty that these factors were fully accounted for. Obesity, because of its strong association with both sleep-disordered breathing and BP, is of special concern. It is unlikely that variables derived from the simple parameters of weight, height, circumferences, and skinfolds truly capture the aspect of obesity that contributes to both sleep-disordered breathing and elevated BP. The consistent results from using several body habitus variables singly and in combination, however, is reassuring.

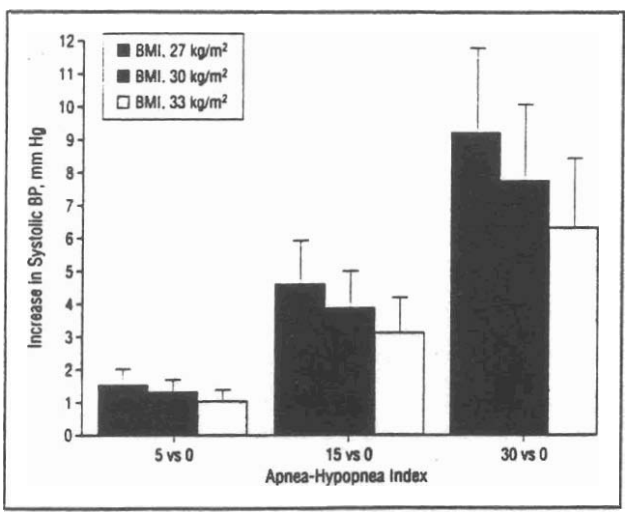

Figure 1. *Predicted increase in systolic blood pressure (BP) associated with sleep-disordered breathing at 3 body mass index (BMI, a measure of weight in kilograms divided by the square of the height in meters) levels. Increases are based on linear regression after exclusion from the sample of individuals receiving antihypertensive medication and are adjusted for age, sex, and BMI.*

The major limitation of our study is the cross-sectional nature of the data. The temporal direction of the association cannot be discerned because the onset dates of sleep-disordered breathing and hypertension are not known. Research has been focused mostly on the physiological sequence of events following apneas and hypopneas, with sleep-disordered breathing hypothesized as the causal factor. However, the reverse pathway cannot be dismissed and, although little relevant research has been conducted, there is also evidence in support of a causal role of hypertension in breathing instability during sleep. Treatment of hypertension with β-blockers or angiotensin-converting enzyme inhibitors has been shown to reduce the frequency of the apneas and hypopneas in patients with sleep-disordered breathing.[38] Some studies suggest that hypertension augments peripheral chemoreceptor responsiveness,[39] an effect that has been shown to cause breathing instability during sleep at high altitude.[40] Evidence that one causal direction exists, however, does not disallow the other and the possibility of synergistic effects cannot be dismissed.

Our findings in support of an independent association between sleep-disordered breathing and elevated BP are in agreement with those of only a few clinic-based

Table 3. Odds Ratios for Sleep-Disordered Breathing and Hypertension: Sleep Cohort Study*

Independent Variable	Systolic BP ≥140 mm Hg or the Use of Antihypertensive Medication		Diastolic BP ≥90 mm Hg or the Use of Antihypertensive Medication		Systolic BP ≥140 mm Hg or Diastolic BP ≥90 mm Hg or the Use of Antihypertensive Medication	
	OR	95% CI	OR	95% CI	OR	95% CI
AHI						
5 vs 0	1.21	1.10-1.34	1.18	1.07-1.30	1.21	1.09-1.34
15 vs 0	1.78	1.32-2.38	1.64	1.22-2.21	1.75	1.28-2.40
30 vs 0	3.15	1.75-5.67	2.68	1.48-4.86	3.07	1.65-1.74

**N=1069. The formulas to calculate odds ratios (ORs) for each definition of hypertension associated with other apnea-hypopnea index (AHI)–body mass index (BMI, a measure of weight in kilograms divided by the square of the height in meters) combinations are as follows: for the logistic regression models, the OR for hypertension defined as systolic blood pressure (BP) ≥140 mm Hg or the use of antihypertensive medication associated with any AHI-BMI combination can be calculated as* $OR_{HTN}=e^{[0.038+(BMI-30)\times(-0.00198)]\times AHI}$. *The OR for hypertension defined as diastolic BP ≥90 mm Hg or the use of antihypertensive medication associated with any AHI-BMI combination can be calculated as* $OR_{HTN}=e^{[0.033+(BMI-30)\times(-0.0021)]\times AHI}$. *The OR for hypertension defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or the use of antihypertensive medication associated with any AHI-BMI combination can be calculated as* $OR_{HTN}=e^{[0.037+(BMI-30)\times(-0.0022)]\times AHI}$. *HTN indicates hypertension. Body mass index centered at 30 kg/m².*

sociated with AHI and BMI midpoints of the 2 AHI categories (1.3 for the 5-15 category for both men and women, and 2.0 and 2.1 for the >15 category for men and women, respectively). Under the assumption that there is a causal association between sleep-disordered breathing and hypertension, we estimate from these data that among adults in their most productive years, sleep-disordered breathing would contribute to hypertension in approximately 400 000 women and 2 million men.

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