

Association of Sleep-Disordered Breathing, Sleep Apnea, and Hypertension in a Large Community-Based Study

F. Javier Nieto, MD, PhD

Terry B. Young, PhD

Bonnie K. Lind, MS

Eyal Shahar, MD, MPH

Jonathan M. Samet, MD, MS

Susan Redline, MD, MPH

Ralph B. D'Agostino, PhD

Anne B. Newman, MD, MPH

Michael D. Lebowitz, PhD

Thomas G. Pickering, MD

for the Sleep Heart Health Study

SLEEP-DISORDERED BREATHING (SDB) and the related clinical syndrome, sleep apnea, have been associated with hypertension in clinical reports since the early 1980s.¹⁻⁴ Earlier studies of this association used self-reported history of "snoring" as a surrogate for the presence of sleep apnea. Although some of these studies showed an independent association between snoring and hypertension,⁵⁻⁷ others found that this relationship may be explained by confounding effects of age, sex, or obesity.⁸⁻¹¹ Two recent studies have demonstrated that self-reported history of snoring is associated with increased incidence of self-reported hypertension in middle-aged men¹² and women.¹³ Other studies have used polysomnography (PSG), a more objective measure of SDB. Most of these studies,¹⁴⁻¹⁹ but not all,^{20,21}

For editorial comment see p 1880.

Context Sleep-disordered breathing (SDB) and sleep apnea have been linked to hypertension in previous studies, but most of these studies used surrogate information to define SDB (eg, snoring) and were based on small clinic populations, or both.

Objective To assess the association between SDB and hypertension in a large cohort of middle-aged and older persons.

Design and Setting Cross-sectional analyses of participants in the Sleep Heart Health Study, a community-based multicenter study conducted between November 1995 and January 1998.

Participants A total of 6132 subjects recruited from ongoing population-based studies (aged ≥ 40 years; 52.8% female).

Main Outcome Measures Apnea-hypopnea index (AHI, the average number of apneas plus hypopneas per hour of sleep, with *apnea* defined as a cessation of airflow and *hypopnea* defined as a $\geq 30\%$ reduction in airflow or thoracoabdominal excursion both of which are accompanied by a $\geq 4\%$ drop in oxyhemoglobin saturation), obtained by unattended home polysomnography. Other measures include arousal index; percentage of sleep time below 90% oxygen saturation; history of snoring; and presence of hypertension, defined as resting blood pressure of at least 140/90 mm Hg or use of antihypertensive medication.

Results Mean systolic and diastolic blood pressure and prevalence of hypertension increased significantly with increasing SDB measures, although some of this association was explained by body mass index (BMI). After adjusting for demographics and anthropometric variables (including BMI, neck circumference, and waist-to-hip ratio), as well as for alcohol intake and smoking, the odds ratio for hypertension, comparing the highest category of AHI (≥ 30 per hour) with the lowest category (< 1.5 per hour), was 1.37 (95% confidence interval [CI], 1.03-1.83; P for trend = .005). The corresponding estimate comparing the highest and lowest categories of percentage of sleep time below 90% oxygen saturation ($\geq 12\%$ vs $< 0.05\%$) was 1.46 (95% CI, 1.12-1.88; P for trend $< .001$). In stratified analyses, associations of hypertension with either measure of SDB were seen in both sexes, older and younger ages, all ethnic groups, and among normal-weight and overweight individuals. Weaker and nonsignificant associations were observed for the arousal index or self-reported history of habitual snoring.

Conclusion Our findings from the largest cross-sectional study to date indicate that SDB is associated with systemic hypertension in middle-aged and older individuals of different sexes and ethnic backgrounds.

JAMA. 2000;283:1829-1836

www.jama.com

found an association between sleep apnea and hypertension, independent of age, sex, body weight, and other potential confounders. With the excep-

Author Affiliations, the SHHS Investigators and Parents Cohorts are listed at the end of this article.

Corresponding Author and Reprints: F. Javier Nieto, MD, PhD, Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, 615 N Wolfe St, Room W6009, Baltimore, MD 21205.

tion of the reports from the Wisconsin Sleep Cohort Study of middle-aged employed persons,^{15,18} most previous studies were based on a small number of patients in clinical settings.²²

Given the strong association between SDB and obesity and adiposity measures,²³ some researchers have cautioned that even in studies controlling for body mass index (BMI), there is a potential for residual confounding, since fat distribution may be the strongest confounding component of obesity.²⁴

This study is based on baseline cross-sectional data from the Sleep Heart Health Study (SHHS), a multicenter study of the cardiovascular consequences of sleep apnea in participants recruited from ongoing population-based cohort studies.²⁵ Our results represent the largest cross-sectional study to date of the association between SDB and hypertension in apparently healthy middle-aged and older adults. We assessed SDB in the subjects' homes using a portable PSG monitor. Its association with blood pressure and hypertension is examined while controlling for the potential confounding effects of demographic variables, body weight, and measures of body fat distribution.

METHODS

Parent Cohorts and Study Sample

The specific aims and design of the SHHS have been previously reported^{25,26} (also available at: <http://www.jhsph.edu/shhs>). In brief, SHHS subjects were recruited from participants in ongoing cohort studies of cardiovascular or respiratory disease. From these parent cohorts, a sample meeting inclusion criteria (aged 40 years or older; no history of treatment of sleep apnea with continuous positive airway pressure; no tracheostomy; no current home oxygen therapy) were invited to participate in the initial examination of the SHHS. Selection and recruitment procedures varied by study site according to logistical considerations and participants' characteristics. Some were recruited at the time of their periodic parent study's clinic examination; others were recruited by mail or by telephone.^{25,26} Since the sam-

pling frame for the study already constitutes a somewhat selected group investigators made no effort to obtain a random sample. To optimize statistical power by increasing the prevalence of sleep-disordered breathing in the younger participants, an attempt to oversample persons with a history of snoring was made in sites recruiting individuals younger than 65 years.

Among 11 053 participants in the parent cohorts identified as potentially eligible, 3394 (30.7%) refused to participate in the SHHS, while 818 (7.4%) could not be located or were unable to participate due to illness. The remaining 6841 participants (62%) were enrolled for the SHHS baseline sleep study conducted in the homes of the participants between November 1995 and January 1998.

Baseline SHHS Examination

A self-administered sleep habits questionnaire on snoring history, sleep apnea awareness and treatment, and sleepiness was administered prior to the baseline home visit. The home visit included a brief health interview, assessment of current medication use,²⁷ blood pressure and anthropometric measurements, and a full unattended PSG.

Resting blood pressure was measured in the right arm after a 5-minute rest using a conventional mercury sphygmomanometer. The first and last Korotkoff sounds were used to determine systolic and diastolic blood pressure, respectively. The average of the second and third of 3 consecutive measurements was used as the blood pressure value in this report. Weight was measured in light clothes on a portable scale. Neck circumference was measured just below the laryngeal prominence using standard methods.²⁸

Polysomnography was conducted using a Compumedics PS-2 system (Compumedics Pty Ltd, Abbotsford, Australia) with the following montage: central electroencephalogram, electrooculogram, chin electromyogram, single bipolar electrocardiogram, finger pulse oximetry, chest and abdominal excursion by respiratory inductance plethys-

mography, and airflow by oronasal thermocouples, body position, and ambient light.²⁹ Sensors were placed and equipment calibrated during the evening home visit by centrally trained and certified technicians.²⁶ Data were stored in real time on PCMCIA cards. The equipment was retrieved the next morning.

Of the 6841 home PSG studies attempted, 401 (5.9%) failed (sensor losses or <4 hours of recorded data of sufficient quality), leaving 6440 PSG studies scored at the SHHS Reading Center (Case Western Reserve University, Cleveland, Ohio). Detailed protocol for central scoring of sleep stages, arousals, and respiratory events has been described.²⁹

Study Variables

Following standard recommendations,^{30,31} hypertension was defined as blood pressure of at least 140/90 mm Hg, or current treatment with antihypertensive medications.

Sleep-disordered breathing was assessed using the *apnea-hypopnea index* (AHI), defined as the average number of apneic plus hypopneic episodes per hour of sleep. *Apnea* was defined as a complete or an almost complete cessation of airflow and *hypopnea* as a decrease in airflow or thoracoabdominal excursion of at least 30% of baseline for 10 seconds or more. Both apnea and hypopnea must be accompanied by a 4% or more decrease in oxygen saturation. Other indices of SDB included arousal index (average number of arousals per hour of sleep, with arousals identified following modified American Sleep Disorders Association criteria),³² percentage of sleep time with oxygen saturation below 90%, and snoring history (self-report of snoring ≥ 3 nights a week). The AHI and the arousal index scoring reliability have been reported.³³ The AHI as defined herein showed high interscorer reliability (intraclass correlation coefficient [ICC], 0.99), whereas the reliability of scoring for the arousal index was moderate (ICC range, 0.54-0.72) depending on the quality of sleep recording and experience of the scorer.

Smoking history was obtained from the health interview questionnaire. Usual alcohol intake, waist and hip circumferences, and height were obtained from the parent studies. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Overweight and obesity categories were defined according to current recommendations (TABLE 1).³⁴

Statistical Analyses

Among the 6440 SHHS participants, this report is based on 6132 individuals with complete information on demographics, weight, height, hypertension status, and AHI. For arousal index, analyses were restricted to the 5112 participants with electroencephalogram and electromyogram data of sufficient quality for sleep staging.

Means and proportions were compared using analysis of variance and χ^2 tests, respectively. The relationship be-

tween the SDB variables and blood pressure values was analyzed using multiple linear regression. Due to the skewed distribution of SDB measures and to prevent undue influence of observations with extreme values, these variables were log-transformed (natural log $[x+0.1]$).

Logistic regression was used to calculate the odds ratio (OR) of hypertension comparing SDB categories, while adjusting for possible confounders.³⁵ In these analyses, AHI was categorized according to the observed distribution as well as by commonly used clinical cutoff points. The reference category was an AHI of less than 1.5 per hour (approximately the bottom quartile of the AHI distribution); other cutoff values were AHIs equal to 5, 15, and 30 per hour, resulting in 5 categories. Criteria for the categorical definitions of the other SDB variables were chosen so that the categories would divide the study

population into groups of approximately the same size as for the AHI criteria.

To assess the impact of using arbitrary cutoff points, the OR of hypertension in relationship to SDB variables was also estimated using nonparametric logistic regression.^{36,37} With this method, the dose-response relationship between a putative risk factor (eg, AHI) and an outcome (eg, hypertension) can be estimated without parametric assumptions about the risk trend and without the need to categorize the continuous exposure variable. As a result of the high prevalence of hypertension, the ORs presented herein should not be interpreted as risk ratios.³⁸

Nonparametric logistic regression used the generalized additive models, as implemented by the GAM function in S-PLUS software.³⁹ All other statistical analyses were conducted using SAS software (SAS Institute, Cary, NC).

Table 1. Distributions of Selected Characteristics of the Study Population, Sleep Heart Health Study, 1995-1998*

Characteristics	Overall (N = 6132)†	Apnea-Hypopnea Index Category					P Value
		<1.5 (n = 1691)	1.5-4.9 (n = 1598)	5-14.9 (n = 1751)	15-29.9 (n = 719)	≥30 (n = 373)	
Men, %	47.2	30.6	44.5	53.8	64.3	71.0	.001
Age ≥65 y, %	46.7	35.4	46.8	54.0	52.8	52.0	.001
Ethnicity, %							
White	77.0	76.0	79.2	77.0	76.4	73.7	.001
Black	7.7	9.1	7.3	6.7	7.2	9.1	
American Indian	9.8	7.5	8.7	11.3	12.4	12.9	
Other	5.4	7.3	4.8	5.0	4.0	4.3	
Smoking, %							
Never	46.0	48.4	47.6	43.6	44.6	41.9	.001
Former	42.6	35.6	41.0	47.6	45.8	51.9	
Current	11.4	16.0	11.4	8.8	9.6	6.2	
Alcohol intake, %‡							
None	54.0	54.8	53.1	54.1	54.4	53.3	.001
1-2 drinks per week	16.9	20.0	16.8	15.2	15.1	14.3	
3-7 drinks per week	16.3	15.4	16.9	16.2	15.9	18.4	
>7 drinks per week	12.8	9.8	13.2	14.6	14.6	14.0	
Body weight, %§							
Normal	26.5	44.0	25.9	17.9	15.9	10.2	.001
Overweight	40.8	39.9	46.4	41.5	34.8	28.7	
Obese	32.8	16.1	27.7	40.6	49.4	61.1	
BMI, kg/m ² , mean	28.5	26.1	27.9	29.6	30.7	32.2	<.001
Neck circumference, cm, mean	38.0	35.8	37.5	38.9	40.2	41.4	<.001
Waist-to-hip ratio, mean	0.92	0.88	0.92	0.95	0.96	0.97	<.001

*Includes all participants, unadjusted. Apnea-hypopnea index (AHI) is defined as the average number of apneic episodes plus hypopnea episodes per hours of sleep, and hypopnea defined as a 30% or more reduction in airflow or thoracoabdominal excursion accompanied by a 4% or more drop in oxyhemoglobin.

†Includes participants with information on sex, age, ethnicity, systolic and diastolic blood pressure, antihypertensive medications, body mass index (BMI), and AHI.

‡Analysis excludes 725 participants with missing alcohol intake information.

§Normal weight is defined as having a BMI between 18 and 24.9 kg/m²; overweight, between 25 and 29.9 kg/m²; obese, BMI more than 30 kg/m².

Table 2. Prevalence of Snoring, Mean Levels of Sleep-Disordered Breathing Indicators, and Mean Blood Pressures, by Apnea-Hypopnea Index (AHI) Category, Sleep Heart Health Study, 1995-1998*

Variables	Overall	AHI Category					P Value (Trend)
		<1.5	1.5-4.9	5-14.9	15-29.9	≥30	
All Participants, Unadjusted							
No. of subjects	6132	1691	1598	1751	719	373	
Snoring, %							
No	37.5	48.3	40.5	32.7	27.1	18.5] <.001
Yes	33.9	20.2	29.8	39.4	47.5	61.7	
Unknown	28.6	31.5	29.7	27.9	25.4	19.8	
AHI per hour, mean	8.8	0.6	3.0	9.0	20.6	46.9	
Arousal index per hour, mean†	19.0	15.3	17.0	19.3	24.0	35.6	<.001
Percentage of sleep time <90% of oxygen saturation	3.7	0.8	1.8	3.5	7.7	18.2	<.001
Participants Not Taking Antihypertensive Medications, Adjusted for Demographic Characteristics‡							
No. of subjects	3670	1142	1011	966	384	167	
Systolic blood pressure, mm Hg, mean	126.7	124.3	127.1	128.1	128.4	130.1	<.001
Diastolic blood pressure, mm Hg, mean	74.6	72.9	75.0	75.4	75.6	76.3	<.001

*For a definition of AHI, see Table 1.

†For arousal index analysis, the number of subjects were 5112. The remaining observations were excluded because of unreliable sleep staging data.

‡Adjusted for age (continuous variable), sex, ethnicity, and center.

Table 3. Linear Regression Analyses of Blood Pressure on Measures of Sleep-Disordered Breathing, Participants Not Taking Antihypertensive Medications (n = 3670), Sleep Heart Health Study, 1995-1998*

Variables	Systolic Blood Pressure, mm Hg		Diastolic Blood Pressure, mm Hg	
	β (SE)†	P Value	β (SE)†	P Value
Apnea-hypopnea index (log transformed)				
Demographics adjusted	1.21 (0.20)	<.001	0.78 (0.11)	<.001
Demographics and BMI-adjusted	0.57 (0.21)	.008	0.49 (0.12)	<.001
Arousal index (log transformed)				
Demographics adjusted	1.28 (0.56)	.02	0.83 (0.33)	.01
Demographics and BMI-adjusted	1.05 (0.56)	.06	0.71 (0.33)	.03
Percentage of sleep time <90% oxygen saturation (log transformed)				
Demographics adjusted	0.66 (0.17)	<.001	0.41 (0.10)	<.001
Demographics and BMI-adjusted	0.10 (0.18)	.59	0.14 (0.01)	.18

*BMI indicates body mass index. For a definition of apnea-hypopnea index, see Table 1.

†Estimate of the linear regression coefficient (SE).

RESULTS

Descriptive characteristics of the study population are presented in Table 1 and TABLE 2, both overall and by AHI categories. Compared with those with lower AHI values, participants with higher levels of SDB (AHI ≥15 per hour) included a larger proportion of men, persons aged 65 years or older, American Indians, former smokers, and being obese (Table 1). Neck circumference and waist-to-hip ratio were also significantly higher in participants with high AHI values. The results shown in Table 1 should be interpreted with caution because they are unadjusted. With regard to ethnicity, for example, the increased prevalence of SDB

among American Indians seems to be entirely explained by differences in age and the higher prevalence of obesity in this ethnic group. The unadjusted mean AHI for each ethnic group was 8.7 for whites; 9.0 for blacks; 10.7 for American Indians; and 7.2 for others ($P<.001$); after adjusting for age and BMI, these values were 8.8, 8.3, 8.7, and 8.9, respectively ($P=.81$).

As expected, AHI was strongly associated with self-reported history of snoring as well as with other measures of SDB, including arousal index and sleep time below 90% oxygen saturation (Table 2).

Excluding participants taking antihypertensive medications, AHI was lin-

early associated with blood pressure values (Table 2). However, multiple linear regression analyses (TABLE 3) showed that these associations were partially explained by BMI, although a statistically significant linear association between AHI and blood pressure persisted even after adjustment for BMI. Arousal index was also associated with blood pressure, while the associations between sleep time below 90% oxygen saturation and both systolic and diastolic blood pressure became nonsignificant after BMI adjustment (Table 3).

To use data from the entire cohort, including those in treatment, the remaining analyses were based on hypertension status. In unadjusted analyses, the prevalence rates of hypertension in increasing AHI categories were 43% (<1.5 per hour), 53% (1.5-4.9 per hour), 59% (5-14.9 per hour), 62% (15-29.9 per hour), and 67% (≥30 per hour). Adjustment for age and demographic characteristics showed that the odds of hypertension increased with escalating AHI categories in a graded-dose response fashion (TABLE 4); the OR of hypertension comparing participants with high AHI (≥30 per hour) to participants in the lowest AHI category (<1.5 per hour) was 2.27 (95% confidence interval [CI], 1.76-2.92). Similarly strong associations were present for sleep time below 90% oxygen

saturation, whereas weaker associations were seen for the arousal index and snoring. Adjustment for BMI reduced these estimates, although statistically significant elevated ORs were still present for the highest categories of AHI and sleep time below 90% oxygen saturation (OR range, 1.5-1.6). Further adjustment for other anthropometric measurements (neck circumference and waist-to-hip ratio) reduced these estimates only slightly. The latter model showed no significant associations with arousal index.

Adding cigarette smoking and alcohol intake to the model had very little impact on the estimates (slightly reducing and slightly increasing the point estimates for AHI and sleep

time below 90% oxygen saturation, respectively).

The associations between the top and bottom categories of AHI, sleep time below 90% oxygen saturation, and snoring with hypertension in subgroups defined according to demographic variables and body weight categories are shown in TABLE 5. Associations between these SDB measures and hypertension were present in all subgroups, although estimates vary in part due to small sample sizes in these subgroup analyses. The associations between AHI and hypertension among women were markedly weakened in the fully adjusted model (including BMI, neck circumference, and waist-to-hip ratio); on the other hand, the association be-

tween sleep time below 90% oxygen saturation and hypertension was still present after full adjustment in both women and men (OR, 1.3). Similarly, although the association between AHI and hypertension seemed stronger among those who were younger than 65 years, the opposite was observed for sleep time below 90% oxygen saturation after full adjustment. Associations for either SDB measure were present in all 3 major ethnic groups in the SHHS cohort (white, black, American Indians), although some of the CIs overlap 1 due to relatively small sample sizes. Likewise, associations were present in all 3 relative weight categories in this population, although slightly stronger in the high-body weight groups.

Table 4. Adjusted Odds Ratio (OR) and 95% Confidence Intervals (CIs) of Hypertension by Sleep-Disordered Breathing Measures, Sleep Heart Health Study, 1995-1998*

Variables	No. of Subjects	Adjusted for Demographics†	OR Adjusted for Demographics‡		
			BMI OR (95% CI)	BMI, Neck, Waist-to-Hip Ratio OR (95% CI)	BMI, Neck, Waist-to-Hip Ratio, Alcohol Use, Smoking OR (95% CI)
Apnea-hypopnea index per hour					
<1.5	1691	1.00	1.00	1.00	1.00
1.5-4.9	1598	1.25 (1.08-1.44)	1.12 (0.96-1.30)	1.11 (0.95-1.29)	1.07 (0.91-1.26)
5-14.9	1751	1.57 (1.35-1.81)	1.28 (1.09-1.48)	1.24 (1.06-1.45)	1.20 (1.01-1.42)
15-29.9	719	1.73 (1.43-2.10)	1.32 (1.08-1.61)	1.26 (1.03-1.55)	1.25 (1.00-1.56)
≥30	373	2.27 (1.76-2.92)	1.60 (1.23-2.08)	1.47 (1.12-1.92)	1.37 (1.03-1.83)
P (trend)		.0001	.0001	.0008	.005
Arousal index per hour§					
<12	1260	1.00	1.00	1.00	1.00
12-16.9	1335	0.92 (0.78-1.09)	0.91 (0.77-1.07)	0.93 (0.78-1.10)	0.94 (0.78-1.12)
17-22.9	1145	1.06 (0.89-1.25)	1.03 (0.87-1.23)	1.04 (0.87-1.24)	1.04 (0.86-1.26)
23-29.9	745	1.18 (0.97-1.43)	1.14 (0.93-1.38)	1.11 (0.91-1.36)	1.12 (0.90-1.39)
≥30	627	1.30 (1.05-1.60)	1.20 (0.97-1.49)	1.19 (0.96-1.48)	1.15 (0.91-1.45)
P (trend)		.002	.02	.04	.003
Percentage of sleep time <90% of oxygen saturation					
<0.05	2005	1.00	1.00	1.00	1.00
0.05-0.49	1542	1.24 (1.07-1.42)	1.13 (0.98-1.30)	1.12 (0.96-1.29)	1.10 (0.94-1.29)
0.50-3.9	1498	1.56 (1.35-1.91)	1.30 (1.12-1.51)	1.25 (1.08-1.46)	1.24 (1.05-1.46)
4.0-11.9	594	1.55 (1.27-1.89)	1.18 (0.96-1.45)	1.10 (0.89-1.35)	1.13 (0.90-1.42)
≥12	493	2.03 (1.62-2.53)	1.49 (1.18-1.88)	1.39 (1.10-1.75)	1.45 (1.12-1.88)
P (trend)		.0001	.0002	.005	.0003
Snoring					
No	2273	1.00	1.00	1.00	1.00
Yes	2058	1.21 (1.07-1.38)	1.05 (0.92-1.20)	1.02 (0.89-1.16)	1.01 (0.88-1.17)
Unknown	1732	1.27 (1.11-1.46)	1.24 (1.08-1.42)	1.25 (1.08-1.43)	1.26 (1.08-1.46)

*For definition apnea-hypopnea index, see Table 1. Hypertension is defined as resting blood pressure of at least 140/90 mm Hg or use of antihypertensive medication. BMI indicates body mass index.

†Adjusted for age (continuous variable), sex, and ethnicity.

‡Models include demographics and variables listed in column headings.

§For arousal index analysis, the number of subjects were 5112. The remaining observations were excluded because of unreliable sleep staging data.

Table 5. Demographic and Fully Adjusted Odds Ratio (OR) and 95% Confidence Intervals (CIs) of Hypertension by Sleep-Disordered Breathing Measures, Sleep Heart Health Study, 1995-1998*

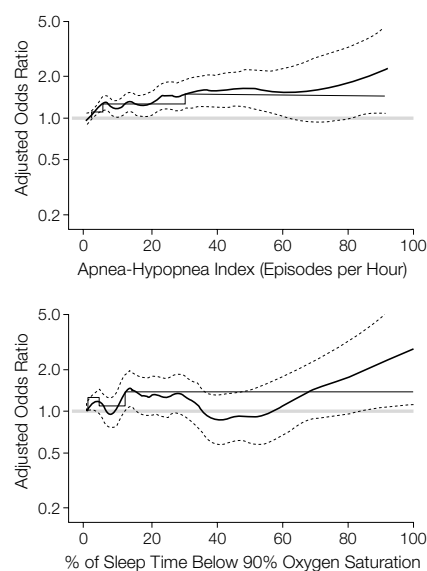
Characteristics	No. of Subjects	AHI per Hour, ≥30 vs <1.5 (Reference)		Percentage of Sleep Time <90% Oxygen Saturation, ≥12 vs <0.05 (Reference)		Snoring, Yes vs No	
		Demographic† OR	Fully Adjusted‡ OR (95% CI)	Demographic† OR	Fully Adjusted‡ OR (95% CI)	Demographic† OR	Fully Adjusted‡ OR (95% CI)
Sex							
Men	2897	2.14	1.49 (1.06-2.12)	1.85	1.32 (0.97-1.81)	1.00	0.89 (0.74-1.07)
Women	3235	2.03	1.17 (0.74-1.86)	2.04	1.33 (0.92-1.93)	1.46	1.16 (0.95-1.42)
Age, y							
<65	3267	2.72	1.64 (1.14-2.36)	2.00	1.26 (0.89-1.78)	1.23	0.99 (0.83-1.18)
≥65	2865	1.69	1.23 (0.83-1.83)	1.90	1.44 (1.03-2.00)	1.16	1.04 (0.84-1.28)
Ethnicity							
White	4724	2.08	1.36 (1.00-1.85)	2.06	1.42 (1.08-1.85)	1.18	1.01 (0.87-1.18)
Black	473	2.71	1.87 (0.65-5.43)	2.38	1.47 (0.52-4.17)	1.02	0.79 (0.44-1.42)
American Indian	601	3.48	2.15 (0.99-4.67)	1.89	1.28 (0.67-2.48)	1.54	1.27 (0.82-1.97)
Other	334	2.03	1.04 (0.30-3.69)	1.92	1.04 (0.31-3.49)	1.24	0.85 (0.45-1.60)
Body weight§							
Normal	1622	1.75	1.48 (0.69-3.16)	1.29	1.11 (0.62-1.96)	1.10	1.10 (0.82-1.47)
Overweight	2500	1.66	1.53 (0.95-2.46)	1.97	1.93 (1.25-2.96)	1.02	0.96 (0.78-1.17)
Obese	2010	2.08	1.54 (1.02-2.31)	1.83	1.36 (0.95-1.95)	1.14	1.06 (0.84-1.34)

*AHI indicates apnea-hypopnea. For definitions of AHI, see Table 1. For definition of hypertension, see Table 4.

†Adjusted for age (continuous), sex, and ethnicity.

‡Adjusted for age, body mass index (BMI), neck circumference, and waist-to-hip ratio (all continuous variables), sex, ethnicity, cigarette smoking, and alcohol intake. Age-stratified analyses includes age as a continuous covariate in the model; similarly, body weight-stratified analyses also includes BMI as a continuous variable.

§Normal weight is defined as BMI of 18 to 24.9 kg/m², overweight, between 25 and 29.9 kg/m²; and obese, 30 kg/m² or more.

Figure. Adjusted Odds Ratio of Hypertension According to Apnea-Hypopnea Index and Sleep Time Below 90% Oxygen Saturation

Solid thick line represents estimates from nonparametric logistic regression; dashed lines, 95% confidence limits for the nonparametric logistic regression estimates; solid thin line, adjusted odds ratio estimated from conventional logistic regression using the categories shown in Table 4. Odds ratios adjusted for demographics, body mass index, neck circumference, and waist-to-hip ratio. Hypertension is defined in Table 4.

As shown in the FIGURE, nonparametric logistic regression analyses confirmed the dose-response relationship between AHI or sleep time below 90% oxygen saturation and the odds of hypertension. The data suggest that, although with some fluctuations probably stemming from random variability, the adjusted odds of hypertension increase steadily with AHI from values of about 15 or 20 per hour, reaching ORs greater than 2 for the very high AHI values. For sleep time below 90% oxygen saturation, a steady increase in the fully adjusted OR is only observed for values higher than 50%.

COMMENT

This large cross-sectional study in healthy middle-aged and older adults shows that SDB is associated with prevalent hypertension. After controlling for the main potential confounders (age, sex, BMI, and other measures of adiposity), as well as for other potentially relevant variables (alcohol intake, smoking), high levels of AHI or sleep time below 90% oxygen saturation were associated with greater odds of hypertension in a dose-response fashion (Table 4 and Figure). In contrast, with these ob-

jective measures of SDB, self-reported snoring showed little or no association with hypertension. This contrast may be due to misclassification errors resulting from the limited validity of self-reported snoring information^{40,41} and could explain the inconsistencies in previous studies that use snoring as an indicator of SDB.⁵⁻¹⁰ The weak associations for arousal index and AHI may be explained by the dilution effect, which stems from the exclusion of 1011 participants from the arousal index analyses because of unreliable electroencephalogram and electrocardiogram data. This group may include a large proportion of persons with SDB who because of movement associated with poor sleep quality may be more prone to sensor loss than those who do not have SDB. The median AHI of 4.2 per hour among those with and 5.3 per hour among those without arousal index data supports the latter hypothesis.

The large sample size allowed us to conduct analyses stratified according to potential effect modifiers (Table 5). Studies have reported stronger association between SDB and hypertension among younger persons than older persons,^{8,42} an effect that is apparent for

AHI but not for sleep time below 90% oxygen saturation in our study. Associations between SDB measures and hypertension were seen in both sexes and in all ethnic groups and were slightly stronger among those who were overweight or obese.

Unlike previous studies that did not adequately control for potential confounding variables,^{10,22,24,43} we attempted to account for all of the most important potential confounders, including measures of overweight and fat distribution. As expected, controlling for BMI diminished the strength of the association between estimates of SDB and hypertension (Table 3 and Table 4). Additionally, controlling for neck circumference and waist-to-hip ratio changed these estimates only slightly, thus providing little support to criticisms that previous studies that only controlled for BMI alone may have been subject to residual confounding due to obesity.²⁴

Our results support the common conceptualization of overweight as a possible confounder of the putative association between SDB and hypertension. However, these observations are also consistent with an alternative model, whereby sleep apnea is one of the intermediary mechanisms by which overweight is causally related to hypertension. Under this alternative model, the BMI-adjusted estimates presented in Table 4, Table 5, and the Figure may be subject to overadjustment. Indeed, since AHI is measured with error because of night-to-night variability,²⁴ adjusting for BMI, which is more precisely measured and is strongly correlated with the true level of SDB, may be equivalent to adjusting for this true underlying level of the very condition that the observed AHI is trying to measure. Thus, the true level of association between SDB and hypertension may lie between the unadjusted estimates (subject to confounding) and the BMI-adjusted estimates (partially subject to overadjustment).

Nonetheless, given the observational nature of this study, the possibility of residual confounding due to un-

measured or unknown confounders cannot be ruled out. Moreover, if confounding variables were measured with error, adjustment may be incomplete leading to a residual overestimate of the associations.^{44(p328)} Potential problems derived from the somewhat arbitrary AHI definition (highly dependent on the definition used for hypopnea identification)⁴⁵ were addressed by using alternative definitions of SDB in addition to AHI (Table 4 and Table 5) and by using nonparametric logistic regression analyses that are not dependent on arbitrary cutoff points (Figure).

The possibility of selection biases due to the volunteer character of the sample (participants in ongoing cohort studies who agreed to undertake home PSG) needs to be considered as well. However, we consider it unlikely that these biases will affect the internal validity of the main results (ie, the association between SDB and hypertension), particularly because of the internal consistency in stratified analyses (Table 5). In any event, we consider that this study will be less prone to these biases than previous studies in patient populations.

Finally, the cross-sectional nature of the study precludes definitive causal inferences. The temporal relationship between SDB and hypertension cannot be firmly established. In addition, prevalence-incidence (duration) bias may also be affecting these cross-sectional results. If sleep apnea is related to increased mortality, as suggested in previous studies,⁴⁶⁻⁴⁸ the survival of a hypertensive person with sleep apnea would tend to be shorter than that of a hypertensive person without sleep apnea. Under these assumptions, the cross-sectional estimates from this and similar studies will tend to underestimate the true relative risk.^{44(p155),49}

The hypothesis of a causal association between sleep apnea and hypertension is supported by evidence from intervention trials, showing that successful treatment of sleep apnea by means other than weight loss (eg, continuous positive airway pressure) is accompanied by significant decreases in both daytime and nighttime blood pressure.⁵⁰⁻⁵² The mechanisms un-

derlying the association between SDB and hypertension are not entirely clear. Several have been proposed,^{10,52-54} including hemodynamic disturbances resulting from intermittent negative intrathoracic pressure during apneic episodes, recurrent episodes of hypoxemia and hypercapnia resulting in abnormal activation of arterial chemoreceptors and increased sympathetic activity, and increased sympathetic activity associated with repeated arousals during sleep.

In summary, this study suggests an independent association between sleep apnea and hypertension, particularly among the middle-aged participants. However, because of the observational and cross-sectional nature of the study, these results should be interpreted with caution. Further prospective studies on the longitudinal association between SDB in relationship to changes in blood pressure and hypertension incidence will help elucidate the true nature and magnitude of the association.

Author Affiliations: Departments of Epidemiology, Johns Hopkins School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Md (Drs Nieto and Samet); Preventive Medicine, University of Wisconsin, Madison (Dr Young); Biostatistics, University of Washington, Seattle (Ms Lind); Epidemiology, University of Minnesota, Minneapolis (Dr Shahar); Division of Clinical Epidemiology, University Hospital-Rainbow Babies & Children's Hospital, Cleveland, Ohio (Dr Redline); Mathematics Department, Boston University, Boston, Mass (Dr D'Agostino); Division of Geriatric Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa (Dr Newman); Respiratory Sciences Center, University of Arizona College of Medicine, Tucson (Dr Lebowitz); and Cardiovascular Center, New York-Cornell Medical Center, Cornell University, New York, NY (Dr Pickering).

SHHS Investigators: *Arizona:* Stuart F. Quan, Michael D. Lebowitz, Paul L. Enright, Richard R. Bootzin, Anthony E. Camilli, Bruce M. Coull, Russell R. Dodge, Gordon A. Ewy, Steven R. Knoper, and Linda S. Snyder, Strong Heart Study, University of Arizona, Tucson, and Barbara V. Howard, Medlantic Research Institute-Phoenix Strong Heart, Phoenix; *California:* John A. Robbins, William H. Bonekate, University of California Davis, Sacramento; *Maryland:* F. Javier Nieto, Jonathan M. Samet, Joel G. Hill, Alan R. Schwartz, Philip L. Smith, and Moyses Szklo, The Johns Hopkins University, Baltimore, and James P. Kiley, Teri A. Manolio, and Richard R. Fabsitz, Project Office, National Heart, Lung, and Blood Institute, Bethesda; *Massachusetts:* George T. O'Connor, Sanford H. Auerback, Emelia J. Benjamin, Ralph B. D'Agostino, Rachel J. Givelber, Daniel J. Gottlieb, and Philip A. Wols, Boston University, Boston; *Minnesota:* Eyal Shahar, Conrad Iber, Mark W. Mahowald, Paul G. McGovern, and Lori L. Bolland, University of Minnesota, Minneapolis; *New York:* Velvie A. Pogue and Charles K. Francis, Harlem Hospital, Columbia University, Thomas G. Pickering and Gary D. James, New York Hospital-Cornell University Medical Center, New York, David M. Rapoport and Joyce A. Walsleben, New York Uni-

versity, and Joseph E. Schwartz, State University of New York, Stonybrook; *Ohio*: Susan Redline, Carl E. Rosenberg, and Kingman P. Strohl, Sleep Reading Center, Case Western Reserve University, Cleveland; *Oklahoma*: Elisa T. Lee and J. L. Yeh, University of Oklahoma-Oklahoma Strong Heart, Oklahoma City; *Pennsylvania*: Anne B. Newman and Mark Sanders, University of Pittsburgh; *Washington*: Patricia W. Wahl, Bonnie K. Lind, Coralyn W. Whitney, Richard A. Kronmal, Bruce M. Psaty, and David S. Siscovick, Coordinating Center, University of Washington, Seattle; *Wisconsin*: Terry B. Young, University of Wisconsin, Madison; and *South Dakota*: Thomas K. Welty, Missouri Breaks Research Institute-Dakotas Strong Heart, Rapid City.

Funding/Support: This work was supported by National Heart, Lung, and Blood Institute cooperative agreements U01HL53940, University of Washington, Seattle; U01HL53938, University of Arizona, Tucson; U01HL53931, New York University, New York; U01HL53941, Boston University, Boston, Mass; U01HL53937, Johns Hopkins University, Baltimore, Md; U01HL53916, University of California, Davis; U01HL53934, University of Minnesota, Minneapolis.

Acknowledgment: The Sleep Heart Health Study (SHHS) acknowledges the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, the Cornell Worksites and Hy-

pertension Studies, The Strong Heart Study, the Tucson Epidemiology Study of Airways Obstructive Diseases, and the Tucson Health and Environment for allowing their cohort members to be part of this project. We thank the many participants in the SHHS cohort who so willingly participated and the technical staff of the clinical sites whose patience, conscientiousness, and creativity made this study successful. We thank Eliseo Guallar, MD, and Roberto Pastor, PhD, for their statistical advice and for providing the macros to obtain the nonparametric logistic regression function, Jingzhong Ding, MD, and Jon Schildcrout for their help in programming and statistical analyses, and Compumedics for modifying equipment for use by the SHHS.

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RESEARCH LETTER

Cellulitis and Sepsis Due to *Sphingobacterium*

To the Editor: Cellulitis-associated sepsis is usually due to gram-positive organisms such as group A streptococci or *Staphylococcus aureus*. This report describes the case of an elderly man with cellulitis and sepsis due to *Sphingobacterium spiritivorum* the patient most likely acquired from walking barefoot in his back yard.

Report of a Case. A 72-year-old man with Parkinson disease presented with acute onset of fever, chills, leg redness, and confusion. Vital signs were: temperature, 38.8°C; pulse, 90/min; respirations, 40/min; and blood pressure, 95/57 mm Hg. Physical examination revealed marked erythema and warmth of the entire right leg without crepitus, discharge, or bullae. There was evidence of chronic venous stasis, onychomycosis, and intertriginous cracking of the toes. The white blood cell count was 26 100 cells/mm³ with 66% neutrophils and 33% band forms. Computed tomography of the leg revealed evidence of cellulitis without abscess, myositis, or fasciitis.

The patient was recuscitated with saline and received 1.5 g of cefazolin every 8 hours and 3 g ampicillin-sulbactam every 6 hours after blood cultures were obtained. Over the next 48 hours, the patient's mental status, vital signs, and leukocyte count returned to normal levels. By the third day, the leg erythema had almost resolved. Two sets of blood cultures yielded *S spiritivorum*, which was resistant to amikacin, gentamicin, tobramycin, and aztreonam; the organism was susceptible to ceftriaxone, imipenem, piperacillin, trimethoprim-sulfamethoxazole, and ciprofloxacin.

Further questioning revealed that the patient commonly walked barefoot in his back yard, often in the garden area, which had been moist due to recent heavy rainfall. At discharge, the patient was prescribed 500 mg of oral ciprofloxacin twice daily for 10 days and advised to always wear shoes when going outside.

Comment. *S spiritivorum*, a former member of the *Flavobacterium* genus,¹ has not been reported, to my knowledge, as a cause of community-acquired sepsis in an immunocompetent person. Previously reported cases of infection due to *Sphingobacterium* species have been nosocomially acquired or have involved immunocompromised hosts (eg, those having human immunodeficiency virus infection or receiving hemodialysis).¹⁻⁴ Community-acquired soft-tissue infection due to this organism may be overlooked, and hence underestimated, if blood and tissue or wound cultures are not performed in patients with cellulitis.

Sphingobacteria are ubiquitous gram-negative organisms containing large amounts of sphingophospholipids and are naturally present in soil, plant material, and water.^{1,2,5} This patient had dry, cracked skin with evidence of tinea pedis and onychomycosis, which likely served as portals of entry for the bacteria as he walked barefoot in his yard and garden. The use of footwear when walking outdoors, especially if there is any breach in skin integrity of the feet, may help to prevent cellulitis and resulting sepsis.

Mark A. Marinella, MD
Wright State University School of Medicine
Dayton, Ohio

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CORRECTION

Incorrect Wording: In the Original Contribution entitled "Association of Sleep-Disordered Breathing, Sleep Apnea, and Hypertension in a Large Community-Based Study," published in the April 12, 2000, issue of THE JOURNAL (2000;283:1829-1836), there was incorrect wording in the abstract and in the "Methods" section. On page 1829 in the "Main Outcome Measures" section the sentence that read "(AHI, the average number of apneas plus hypopneas per hour of sleep, with hypopnea defined as a $\geq 30\%$ reduction in airflow or thoracoabdominal excursion accompanied by a $\geq 4\%$ drop in oxyhemoglobin saturation)," should have read "(AHI, the average number of apneas plus hypopneas per hour of sleep, with apnea defined as a cessation of airflow and hypopnea defined as a $\geq 30\%$ reduction in airflow or thoracoabdominal excursion, both of which are accompanied by a $\geq 4\%$ drop in oxyhemoglobin saturation)."

On page 1830, in the "Study Variables" section, the sentence that read, "Sleep-disordered breathing was assessed using the apnea-hypopnea index (AHI), defined as the average number of apneic plus hypopneic episodes per hour of sleep. Apnea was defined as a complete or an almost complete cessation of airflow and hypopnea as a decrease in airflow or thoracoabdominal excursion of at least 30% of baseline for 10 seconds or more, accompanied by a 4% or more decrease in oxygen saturation" should have read, "Sleep-disordered breathing was assessed using the apnea-hypopnea index (AHI), defined as the average number of apneic plus hypopneic episodes per hour of sleep. Apnea was defined as a complete or an almost complete cessation of airflow and hypopnea as a decrease in airflow or thoracoabdominal excursion of at least 30% of baseline for 10 seconds or more. Both apnea and hypopnea must be accompanied by a 4% or more decrease in oxygen saturation."

On page 1831 in the Alcohol intake section of Table 1, the number of drinks consumed should be by the week and not by the day.

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