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THIS WEEK IN THE JOURNAL 1377

ORIGINAL ARTICLES

Prospective Study of the Association between
Sleep-Disordered Breathing
and Hypertension 1378

P.E. PEPPARD, T. YOUNG, M. PALTA,
AND J. SKATRUD

Effects of Physiologic Pacing versus Ventricular
Pacing on the Risk of Stroke and Death
Due to Cardiovascular Causes 1385

S.J. CONNOLLY AND OTHERS

Beneficial Effects of High Dietary Fiber Intake
in Patients with Type 2 Diabetes Mellitus 1392

M. CHANDALIA AND OTHERS

Mortality from Pneumonia in Children
in the United States, 1939 through 1996 1399

S.F. DOWELL, B.A. KUPRONIS, E.R. ZELL,
AND D.K. SHAY

IMAGES IN CLINICAL MEDICINE

Upper-Airway Resistance Syndrome 1408

M.S. BADR AND B.R. ZAHN

SPECIAL ARTICLE

The Effect of Longevity on Spending for Acute
and Long-Term Care 1409

B.C. SPILLMAN AND J. LUBITZ

REVIEW ARTICLE

Drug Therapy: Prophylaxis against
Opportunistic Infections in Patients
with Human Immunodeficiency Virus
Infection 1416

L.A. KOVACS AND H. MASUR

CASE RECORDS OF THE
MASSACHUSETTS GENERAL HOSPITAL

A 60-Year-Old Farm Worker
with Bilateral Pneumonia 1430

D.S. SHAPIRO AND E.J. MARK

EDITORIALS

A New Feature — This Week in the *Journal* 1430

M. ANGELL

Dietary Treatment of Diabetes Mellitus 1440

M. RENDELL

SOUNDING BOARD

Fortification of Foods with Folic Acid
— How Much Is Enough? 1442

J.L. MILLS

INFORMATION FOR AUTHORS 1446

CORRESPONDENCE

Coronary-Artery Stenting in Acute Myocardial
Infarction 1447

Improved Clinical Outcome after Widespread Use
of Coronary-Artery Stenting in Canada 1448

Idiopathic Chronic Pericardial Effusion 1449

Transient Enhanced Uptake of ¹²³I-Metaiodobenzyl-
guanidine in the Contralateral Adrenal Region
after Resection of an Adrenal Pheochromocytoma 1450

Domestic Violence 1450

The Scope of Practice in Primary Care 1453

Making the Diagnosis of Subarachnoid Hemorrhage 1454

BOOK REVIEWS 1457

BOOKS RECEIVED 1459

CORRECTION

Case Records of the Massachusetts General Hospital
(Case 1-2000) 1460

PROSPECTIVE STUDY OF THE ASSOCIATION BETWEEN SLEEP-DISORDERED BREATHING AND HYPERTENSION

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ABSTRACT

Background Sleep-disordered breathing is prevalent in the general population and has been linked to chronically elevated blood pressure in cross-sectional epidemiologic studies. We performed a prospective, population-based study of the association between objectively measured sleep-disordered breathing and hypertension (defined as a laboratory-measured blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications).

Methods We analyzed data on sleep-disordered breathing, blood pressure, habitus, and health history at base line and after four years of follow-up in 709 participants of the Wisconsin Sleep Cohort Study (and after eight years of follow-up in the case of 184 of these participants). Participants were assessed overnight by 18-channel polysomnography for sleep-disordered breathing, as defined by the apnea-hypopnea index (the number of episodes of apnea and hypopnea per hour of sleep). The odds ratios for the presence of hypertension at the four-year follow-up study according to the apnea-hypopnea index at base line were estimated after adjustment for base-line hypertension status, body-mass index, neck and waist circumference, age, sex, and weekly use of alcohol and cigarettes.

Results Relative to the reference category of an apnea-hypopnea index of 0 events per hour at base line, the odds ratios for the presence of hypertension at follow-up were 1.42 (95 percent confidence interval, 1.13 to 1.78) with an apnea-hypopnea index of 0.1 to 4.9 events per hour at base line as compared with none, 2.03 (95 percent confidence interval, 1.29 to 3.17) with an apnea-hypopnea index of 5.0 to 14.9 events per hour, and 2.89 (95 percent confidence interval, 1.46 to 5.64) with an apnea-hypopnea index of 15.0 or more events per hour.

Conclusions We found a dose-response association between sleep-disordered breathing at base line and the presence of hypertension four years later that was independent of known confounding factors. The findings suggest that sleep-disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population. (N Engl J Med 2000;342:1378-84.)

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SCREENING studies in the United States, Europe, and Australia have shown that a substantial proportion of the adult population has mild-to-moderate sleep-disordered breathing, a condition characterized by repeated episodes of apnea and hypopnea during sleep.¹⁻⁶ Apnea and hypopnea cause temporary elevations in blood pressure in association with blood oxygen desaturation, arousal, and sympathetic activation and may cause elevated blood pressure during the daytime and, ultimately, sustained hypertension.⁷ Recent reviews judged the epidemiologic evidence relating sleep-disordered breathing to hypertension to be inconclusive, but they noted that study designs were inappropriate, that there was inadequate control for confounding factors such as obesity, and that there was a dearth of prospective studies.^{8,9} Since sleep-disordered breathing is prevalent and treatable and the morbidity and costs of hypertension are profound, a rigorous assessment of the relation between the two conditions remains a priority.

We assessed the association between sleep-disordered breathing and hypertension in a prospective analysis of data from the Wisconsin Sleep Cohort Study. The Sleep Cohort Study is a population-based, longitudinal study of the natural history of sleep-disordered breathing in adults. Participants complete overnight sleep studies at four-year intervals. These studies include assessment of sleep-disordered breathing (by monitored polysomnography), blood pressure, and many potential confounding factors.

METHODS

Overview

The protocols for the Wisconsin Sleep Cohort Study and informed-consent documents were approved by the institutional review board of the University of Wisconsin Medical School. In

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1989, a subgroup of employees of four Wisconsin state agencies was mailed a four-page questionnaire on sleep habits, health history, and demographic information. A stratified random sample of respondents was invited to participate in the study. Participants completed a base-line overnight protocol that included assessments of the physiologic characteristics of sleep by polysomnography, blood pressure, habitus, health history, and other information. Approximately every four years thereafter, participants have been invited for follow-up studies.

Exclusion criteria included pregnancy, unstable or decompensated cardiopulmonary disease, airway cancers, and recent surgery of the upper respiratory tract. For this report, participants were also excluded if they had sleep studies with unusable physiologic measurements, an inadequate period of sleep (less than four hours), no episodes of rapid-eye-movement sleep, or a history of physician-diagnosed stroke or cardiovascular disease, or if they were receiving medical treatment for sleep-disordered breathing.

Participants

As of September 1999, a total of 1189 participants had completed a base-line sleep study and 957 of these participants had been invited for four-year follow-up studies. Of those invited, 709 (74 percent) participated in a follow-up study, 233 (24 percent) declined, and 15 (2 percent) could not be contacted (because they had moved or died). Of the 709 who completed four-year follow-up studies, 219 had been invited for eight-year follow-up studies at the time of our analysis. Of these, 184 (84 percent) completed the second follow-up study, 30 (14 percent) declined, and 5 (2 percent) could not be contacted. Table 1 compares key base-line variables among the participants who completed the base-line sleep study, those who completed the four-year follow-up study, and those who completed the eight-year follow-up study. There were no substantial differences among the three groups, although the percentage of female participants was slightly lower in the subgroup that completed the eight-year follow-up study.

Collection of Data

The overnight sleep studies were conducted at the University of Wisconsin General Clinical Research Center in rooms resembling typical bedrooms. Participants arrived in the early evening. Sleep technicians obtained written informed consent and administered health-history and lifestyle questionnaires. The use of antihypertensive medication was determined on the basis of participants' answers to questions concerning the current use of α -adrenergic antagonists, beta-blockers, calcium-channel blockers, diuretics, and angiotensin-converting-enzyme inhibitors for the treatment of hypertension. After administration of the questionnaires and after participants had been seated for at least 15 minutes, two or three

readings of systolic and diastolic (phase V) blood pressure were obtained at 5-minute intervals with the use of conventional mercury sphygmomanometry according to the recommendations of the American Society of Hypertension.¹⁰ Habitus was assessed with the use of standard procedures¹¹ and included measurements of height (in meters) and weight (in kilograms); waist, hip, and neck circumference (in centimeters); skin-fold thickness (in millimeters) of the biceps, triceps, and subscapular and supriliac areas with use of a caliper; and body-mass index, which was calculated as the weight in kilograms divided by the square of the height in meters.

After the assessment of blood pressure and habitus, technicians affixed polysomnography leads to each participant and performed calibrations. An 18-channel polysomnographic recording system (model 78, Grass Instruments, Quincy, Mass.) was used to assess sleep state and respiratory and cardiac variables. Sleep state was measured with electroencephalography, electrooculography, and chin electromyography. These signals were used to determine the sleep stage for each 30-second interval of the polysomnographic record, according to conventional criteria.¹² Arterial oxyhemoglobin saturation, oral and nasal airflow, nasal air pressure, and rib-cage and abdominal respiratory motion were used to assess episodes of sleep-disordered breathing. Oxyhemoglobin saturation was continuously recorded with a pulse oximeter (model 3740, Ohmeda, Englewood, Colo.). Stalk-mounted thermocouples (Pro-Tec, Hendersonville, Tenn.) detected oral and nasal airflow. A pressure transducer (Validyne Engineering, Northridge, Calif.) measured air pressure at the nares. Respiratory inductance plethysmography (Respirace, Ambulatory Monitoring, Ardsley, N.Y.) recorded rib-cage and abdominal excursions. Sleep stage and respiratory events were assessed by trained sleep technicians and reviewed by an expert polysomnographer. Each 30-second interval of the polysomnographic record was inspected visually for episodes of abnormal breathing. Cessation of airflow for at least 10 seconds was defined as an episode of apnea. A discernible reduction in the sum amplitude of the rib-cage plus the abdominal excursions on respiratory inductance plethysmography that lasted at least 10 seconds and that was associated with a reduction in the oxyhemoglobin saturation of at least 4 percent was defined as an episode of hypopnea. The apnea-hypopnea index was defined as the average number of episodes of apnea and hypopnea per hour of objectively measured sleep and was the summary measurement of the occurrence of sleep-disordered breathing.

Statistical Analysis

The primary goal of the study was to estimate the association of sleep-disordered breathing at base line with the presence of hypertension four years later. With this approach, an interpretation of a positive association might be that greater initial degrees of sleep-disordered breathing accelerate the development of hypertension. Actual changes in blood-pressure levels were not modeled, because the prevalent use of antihypertensive medication in the cohort obscures underlying blood-pressure levels in those who use medications, possibly biasing associations.¹³ Participants whose blood pressure exceeded a specified cutoff point or who used antihypertensive medication at the time of their studies were classified as being hypertensive. In defining hypertension, we examined cutoff points for blood pressure ranging from 130/85 to 180/110 mm Hg. The cutoff point of primary interest was 140/90 mm Hg, which was defined as stage 1 hypertension by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹⁴ Other cutoff points were also examined to determine whether the associations depended on the choice of cutoff point.

Among 709 participants who completed base-line and four-year follow-up sleep studies, 184 also completed eight-year follow-up studies, yielding data on 893 sets of four-year sleep studies for analysis. We used logistic-regression analysis with the SAS GENMOD procedure¹⁵ to estimate the odds ratios for the presence of hypertension at follow-up according to the level of sleep-disordered

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PARTICIPANTS WHO COMPLETED THE BASE-LINE SLEEP STUDY, THE FOUR-YEAR FOLLOW-UP STUDY, AND THE EIGHT-YEAR FOLLOW-UP STUDY. *

CHARACTERISTIC AT BASE LINE	BASE-LINE STUDY (N=1189)	FOUR-YEAR FOLLOW-UP STUDY (N=709)	EIGHT-YEAR FOLLOW-UP STUDY (N=184)
Apnea-hypopnea index (events/hr)	4 ± 10	4 ± 9	4 ± 9
Stage 1 or worse hypertension	28	27	27
Female sex (%)	45	45	40
Age (yr)	46 ± 8	46 ± 7	46 ± 8
Body-mass index	29 ± 7	29 ± 6	29 ± 5

* Plus-minus values are means ± SD. The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

breathing at base line. We used the generalized-estimating-equations approach^{16,17} to incorporate correlations between observations resulting from the inclusion of the 184 participants assessed at all three times. The significance of logistic-regression coefficients was determined with two-sided P values with use of an α level of 0.05 for main effects and of 0.01 for interactions between the covariates and the apnea-hypopnea index.

The degree of sleep-disordered breathing was characterized by the apnea-hypopnea index. We examined whether untransformed values for the apnea-hypopnea index at base line, log-transformed values (apnea-hypopnea index + 1), the square of the values, and categorization of values (0, 0.1 to 4.9, 5.0 to 14.9, and 15.0 or more events per hour) were predictors of the presence of hypertension at follow-up. The category of 0 events per hour was included because a substantial proportion of the participants had no episodes of apnea or hypopnea at base line. The cutoff points of 5.0 and 15.0 events per hour have been used in previous epidemiologic studies of sleep-disordered breathing. Further subdivision of the highest category was impractical because few participants had more than 15.0 events per hour.

Because of variability within subjects and measurement error in assessing blood pressure, some misclassification of hypertension status was inevitable. Thus, we could not precisely identify a cohort of participants who were free of hypertension at base line to follow for a determination of the incidence of hypertension. Instead, in all models, we controlled for hypertension status at base line. This approach allowed us simultaneously to examine the association between sleep-disordered breathing at base line and hypertension at follow-up in participants classified as normotensive at base line and the association between sleep-disordered breathing and persistent hypertension in participants classified as hypertensive at base line. We used an interaction term to assess whether these two associations were different. As a check for a possible bias resulting from the misclassification of hypertension, we performed Monte Carlo simulations in which a random error was added to the measurement of participants' blood pressure. Using conservative (larger than likely) estimates of the error in blood-pressure measurements calculated from the variability between participants' base-line and follow-up measurements, we determined that the misclassification of hypertension might lead to slight underestimates of the odds ratios for the likelihood of hypertension at follow-up.

We examined the following base-line variables as covariates: age, sex, body-mass index, neck circumference, waist circumference, waist-to-hip ratio, skin-fold measurements, smoking status (current smoker, former smoker, or no history of smoking; the number of pack-years; and the current number of packs smoked per week), extent of alcohol use (based on the participant's usual weekly consumption), hours of regular exercise per week, and menopausal status. Base-line covariates that substantially altered regression coefficients for the apnea-hypopnea index at base line were included in the final models. Interactions between the covariates and the apnea-hypopnea index were tested for statistical significance.

RESULTS

Table 2 presents key characteristics at base line and follow-up according to the apnea-hypopnea index at base line. When data on all 893 follow-up studies were analyzed, there was a decrease in mean blood pressure from base line to follow-up (from 125/82 mm Hg to 123/79 mm Hg) and an increase in the prevalence of stage 1 or worse hypertension (from 28 percent to 31 percent). These changes were due, in part, to a net increase in the use of antihypertensive medications (from 10 percent to 17 percent).

Odds ratios for the presence of hypertension at follow-up according to the apnea-hypopnea index at base line are given in Table 3. Results from four

models are presented. The first model adjusted for hypertension status at base line, the second controlled for this variable as well as for age and sex (nonmodifiable risk factors), the third controlled for all these variables as well as for habitus, and the fourth controlled for all the preceding variables as well as for weekly alcohol consumption and cigarette use. Within each model there was a linear increase in the logarithm of the odds ratios for successively higher strata of the apnea-hypopnea index. These models fit better than alternative models that used continuous measures of the apnea-hypopnea index. No higher-order terms (e.g., linear squared or cubed) for the strata of the apnea-hypopnea index were statistically significant.

Table 3 reveals that age and sex minimally confounded the association between sleep-disordered breathing and hypertension: the odds ratios remained essentially unchanged after adjustment for age and sex. Adjustment for habitus variables did reduce the odds ratios, but further adjustment for alcohol and cigarette use did not. Other variables examined did not appreciably alter the odds ratios. No interaction terms for sleep-disordered breathing and the covariates examined, including base-line hypertension status, were significant.

Odds ratios obtained with the use of a more conservative definition of hypertension (blood pressure of at least 160/100 mm Hg or the use of antihypertensive medications) were similar to those in Table 3. After adjustment for base-line hypertension status, age, sex, body-mass index, waist and neck circumference, and weekly alcohol and cigarette use, the odds ratio associated with an apnea-hypopnea index of 0.1 to 4.9 events per hour as compared with none was 1.39 (95 percent confidence interval, 1.04 to 1.84), the odds ratio associated with an apnea-hypopnea index of 5.0 to 14.9 events per hour was 1.92 (95 percent confidence interval, 1.09 to 3.39), and the odds ratio associated with an apnea-hypopnea index of 15.0 or more events per hour was 2.66 (95 percent confidence interval, 1.13 to 6.25). Odds ratios based on other cutoff points for blood pressure (ranging from 130/85 to 180/110 mm Hg) were similar.

As a check for possible bias resulting from the dropout of participants from the study, we analyzed data after excluding all eight-year follow-up data and adjusting for base-line hypertension status, age, sex, body-mass index, waist and neck circumference, and weekly alcohol and cigarette use. The resulting odds ratios for the presence of hypertension at the four-year follow-up study were 1.40 (95 percent confidence interval, 1.09 to 1.81) with an apnea-hypopnea index of 0.1 to 4.9 events per hour at base line, 1.97 (95 percent confidence interval, 1.19 to 3.27) with an apnea-hypopnea index of 5.0 to 14.9 events per hour at base line, and 2.77 (95 percent confidence interval, 1.30 to 5.92) with an apnea-hypopnea in-

TABLE 2. CHARACTERISTICS OF THE PARTICIPANTS WHO COMPLETED ONE OR BOTH FOLLOW-UP SLEEP STUDIES, ACCORDING TO THE APNEA-HYPOPNEA INDEX AT BASE LINE.*

CHARACTERISTIC	BASE-LINE APNEA-HYPOPNEA INDEX				ENTIRE GROUP (N=893)
	0 (N=187)	0.1-4.9 (N=507)	5.0-14.9 (N=132)	≥15.0 (N=67)	
Sex — no. (%)					
Female	107 (57)	226 (45)	41 (31)	15 (22)	389 (44)
Male	80 (43)	281 (55)	91 (69)	52 (78)	504 (56)
Age — yr					
At base line	45±7	46±8	50±8	49±8	47±8
At follow-up	49±7	50±8	54±8	53±8	51±8
Apnea-hypopnea index — events/hr					
At base line	0	2±1	9±3	31±16	5±9
At follow-up	2±4	4±6	12±15	27±22	6±12
Median value at base line	0	1.1	8.1	24.6	1.2
Median value at follow-up	0.3	1.6	8.4	23.5	1.9
Systolic blood pressure — mm Hg					
At base line	120±14	124±14	130±14	135±16	125±15
At follow-up	118±15	123±15	131±18	129±16	123±16
Diastolic blood pressure — mm Hg					
At base line	79±9	82±9	84±9	88±11	82±10
At follow-up	75±10	79±11	82±11	81±10	79±11
Use of antihypertensive medications — no. (%)					
At base line	12 (6)	38 (7)	23 (17)	15 (22)	88 (10)
At follow-up	18 (10)	72 (14)	33 (25)	30 (45)	153 (17)
Stage 1 or worse hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medications) — no. (%)					
At base line	34 (18)	121 (24)	59 (45)	40 (60)	254 (28)
At follow-up	32 (17)	142 (28)	64 (48)	40 (60)	278 (31)
Stage 2 or worse hypertension (blood pressure ≥160/100 mm Hg or use of antihypertensive medications) — no. (%)					
At base line	13 (7)	52 (10)	31 (23)	24 (36)	120 (13)
At follow-up	19 (10)	87 (17)	37 (28)	33 (49)	176 (20)
Body-mass index					
At base line	27±5	29±5	32±6	35±7	29±6
At follow-up	29±6	30±6	33±7	36±8	30±7
Alcoholic drinks — no. of drinks/wk					
At base line	3±5	4±7	4±6	5±8	4±6
At follow-up	3±4	4±5	4±5	4±6	4±5
Current cigarette smoker — no. (%)					
At base line	34 (18)	88 (17)	23 (17)	8 (12)	153 (17)
At follow-up	32 (17)	76 (15)	18 (14)	8 (12)	134 (15)

*Data are from 893 follow-up sleep studies: 709 participants completed the four-year follow-up study, and 184 also completed the eight-year follow-up study. For the 184 participants who completed both the four-year and the eight-year follow-up studies, four-year follow-up data were used to calculate the base-line values and eight-year follow-up data were used to calculate the follow-up values. Plus-minus values are means ±SD.

dex of 15.0 or more events per hour at base line. In each case the reference category was an apnea-hypopnea index of 0 events per hour. These odds ratios were similar to those in Table 3.

DISCUSSION

We found a relation between sleep-disordered breathing and hypertension, measured over a four-year period, after adjustment for habitus, age, sex, and cigarette and alcohol use. Persons with few episodes of apnea or hypopnea (0.1 to 4.9 events per hour) at base line had 42 percent greater odds of having hypertension at follow-up than did persons with no episodes. Persons with mild sleep-disordered breathing (as defined by an apnea-hypopnea index

of 5.0 to 14.9 events per hour) and those with more severe sleep-disordered breathing (as defined by an apnea-hypopnea index of 15.0 or more events per hour) had approximately two and three times, respectively, the odds of having hypertension at follow-up of those with no episodes of apnea or hypopnea. Our findings, if accurate and reflective of a causal relation, are particularly important because of the high prevalences of sleep-disordered breathing and hypertension.

Dropout of participants, the possibility of confounding, and error in assessing key study factors are important features of our study that may be relevant to the accuracy of our results. Among the participants who were invited for the four-year and eight-

TABLE 3. ADJUSTED ODDS RATIOS FOR HYPERTENSION AT A FOLLOW-UP SLEEP STUDY, ACCORDING TO THE APNEA-HYPOPNEA INDEX AT BASE LINE.*

BASE-LINE APNEA-HYPOPNEA INDEX	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS AND NONMODIFIABLE RISK FACTORS (AGE AND SEX)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, AND HABITUS (BMI AND WAIST AND NECK CIRCUMFERENCE)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, HABITUS, AND WEEKLY ALCOHOL AND CIGARETTE USE
odds ratio (95% confidence interval)				
0 events/hr†	1.0	1.0	1.0	1.0
0.1–4.9 events/hr	1.66 (1.35–2.03)	1.65 (1.33–2.04)	1.42 (1.14–1.78)	1.42 (1.13–1.78)
5.0–14.9 events/hr	2.74 (1.82–4.12)	2.71 (1.78–4.14)	2.03 (1.29–3.19)	2.03 (1.29–3.17)
≥15.0 events/hr	4.54 (2.46–8.36)	4.47 (2.37–8.43)	2.89 (1.47–5.69)	2.89 (1.46–5.64)
P for trend‡	<0.001	<0.001	0.002	0.002

*Hypertension was defined as a blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications. Data on 893 follow-up sleep studies from 709 participants were analyzed. The odds ratios and confidence intervals were adjusted for the fact that 184 participants completed two follow-up sleep studies. BMI denotes body-mass index.

†This category served as the reference group.

‡P values are for the linear trend of the logistic-regression coefficients (log_e of the odds ratios).

year follow-up studies, 74 percent and 84 percent, respectively, completed the studies. The odds ratios for hypertension at follow-up that were calculated from base-line and all follow-up data were similar to those that excluded eight-year follow-up data, indicating that factors influencing participation in the eight-year follow-up studies did not lead to biased associations. If similar factors influenced participation in the four-year follow-up studies, then it would be unlikely that an important bias related to dropout affected the findings.

The associations between sleep-disordered breathing and hypertension may be confounded by variables that cause both sleep-disordered breathing and hypertension. We measured and controlled for established confounding factors (age, sex, and habitus) as well as several additional variables. In our sample, measures of habitus, but not age or sex, were strong confounding variables. Previous cross-sectional studies of sleep-disordered breathing and hypertension have been faulted for not adjusting for smoking or alcohol use.⁸ We found no evidence that these factors were important confounders.

Measurement error in assessing sleep-disordered breathing, blood pressure, or other covariates may have reduced the accuracy of our findings. Random error in measuring sleep-disordered breathing is likely to produce a bias toward the absence of an association.¹⁸ Our Monte Carlo simulations indicated that a random error in blood-pressure measurement might also produce a bias toward a reduced association. If the accuracy of the classification of hypertension was related to the degree of sleep-disordered breathing or to important covariates such as obesity, then under-

estimates or overestimates of association could occur. Incomplete control of confounding due to, for example, measurement error in assessing habitus may produce a bias toward an overestimate of associations between sleep-disordered breathing and hypertension.¹⁸

The fact that our study was prospective lends support to the evidence of a causal role of sleep-disordered breathing in hypertension. We found that the presence of sleep-disordered breathing was predictive of the presence of hypertension four years later. This finding may indicate that sleep-disordered breathing accelerates the progression of blood-pressure levels commonly present in middle-aged adults in the United States. However, our findings do not offer comprehensive insight into the natural history of the association. Sleep-disordered breathing changes blood pressures acutely.^{19–22} Nocturnal exposure to sleep-disordered breathing may lead to elevations in blood pressure that last throughout the morning or the entire day.²³ A daytime pressor response that outlasts experimentally induced nocturnal hypoxia has been demonstrated in humans.²⁴ It has also been hypothesized that sleep-disordered breathing could cause permanent changes in blood pressure by remodeling the systemic vasculature.²⁵

We did not have data that could be used to model the dynamic relation between sleep-disordered breathing, habitus, and hypertension. For example, although there have been few relevant studies, there has been speculation that sleep-disordered breathing has a causal role in obesity.²⁶ If this is the case, then our efforts to control for confounding by including measures of obesity in our models may have led to a partial overadjustment of the association between sleep-

disordered breathing and hypertension and thus to an underestimate of the association.

We found no evidence of a threshold of the apnea-hypopnea index below which hypertension was not related to sleep-disordered breathing. Even persons with minimal sleep-disordered breathing (as defined by an apnea-hypopnea index of 0.1 to 4.9 events per hour) had higher odds of hypertension than those with no episodes of sleep-disordered breathing. If even those with minimal sleep-disordered breathing are at higher risk for hypertension, then the proportion of cases of hypertension that are attributable to this factor may be substantial.

Previous epidemiologic studies of sleep-disordered breathing and hypertension that focused on subjects from the general population and patients from sleep-disorders clinics have reached conflicting conclusions, although none have precluded the existence of a moderate association.⁹ Studies that involved cross-sectional samples from sleep-disorders clinics²⁶⁻³⁴ have typically used high-quality methods to assess sleep-disordered breathing (multichannel polysomnography). However, unknown factors that influence referral to a sleep-disorders clinic may have made these studies incapable of accurately assessing the relations. Conversely, most cross-sectional population-based studies^{5,35-43} have used samples that were epidemiologically more rigorous but used instruments with poor or unknown validity to assess sleep-disordered breathing. Two recent population-based cross-sectional analyses from the Wisconsin Sleep Cohort Study⁴⁴ and the Sleep Heart Health Study,⁴⁵ which used polysomnography to assess sleep-disordered breathing, reported moderate, statistically significant associations between sleep-disordered breathing and hypertension. In a recent prospective study, Hu and colleagues⁴⁶ assessed a large number of normotensive women and found that snoring, a cardinal (but nonspecific) symptom of sleep-disordered breathing, significantly increased the risk of hypertension. As compared with the risk in nonsnorers, the risk of hypertension was increased by 29 percent in occasional snorers and by 55 percent in those who snored regularly.

As evidence builds of a causal role of sleep-disordered breathing in hypertension and other health outcomes, there is a growing need to understand the natural history of and risk factors for sleep-disordered breathing. Continued development and refinement of medical treatments for sleep-disordered breathing are also priorities. Available treatments, such as continuous positive airway pressure, can be effective. However, these therapies may be overly burdensome for the treatment of mild cases of asymptomatic sleep-disordered breathing. Little is known about the effectiveness of risk-factor intervention for mild-to-moderate sleep-disordered breathing, and this is an important area for future research.

In this prospective analysis, we found an association

between laboratory-assessed sleep-disordered breathing and hypertension. Important elevations in the odds of hypertension were observed even in participants with mild-to-moderate sleep-disordered breathing. Because sleep-disordered breathing is highly prevalent, afflicting as many as 9 percent of women and 24 percent of men in the United States,¹ a causal association could be responsible for a substantial number of cases of hypertension and its sequelae, such as cardiovascular and cerebrovascular morbidity and mortality.

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Treating Obstructive Sleep Apnea Improves Essential Hypertension and Quality of Life

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About one half of patients who have essential hypertension have obstructive sleep apnea, and about one half of patients who have obstructive sleep apnea have essential hypertension. A growing body of evidence suggests that obstructive sleep apnea is a major contributing factor in the development of essential hypertension. Despite many patients with obstructive sleep apnea having clear symptoms of the disorder, an estimated 80 to 90 percent of cases are undiagnosed. When physicians routinely seek the diagnosis of obstructive sleep apnea by asking patients (especially those with hypertension) three basic sleep-related questions about snoring, excessive daytime sleepiness and reports of witnessed apneic events, the number of cases diagnosed and treated increases by about eightfold. Eliminating snoring and occurrences of apneic-hypopneic episodes will dramatically improve patients' quality of sleep and eliminate excessive daytime sleepiness, which has a detrimental effect on general functioning. Increased alertness will reduce the likelihood that patients will be involved in motor vehicle crashes. In most studies in which blood pressure was measured following treatment for obstructive sleep apnea, daytime and nighttime blood pressure levels were found to decrease significantly. This decrease in blood pressure may also reduce the likelihood of cardiovascular complications. The key to the diagnosis of obstructive sleep apnea is physician knowledge about the disorder. The dramatic improvement in quality of life that occurs when patients are successfully treated for obstructive sleep apnea makes detecting and treating this disorder imperative. (Am Fam Physician 2002;65:229-36. Copyright© 2002 American Academy of Family Physicians.)

● A patient information handout on snoring, obstructive sleep apnea, and high blood pressure, written by the authors of this article, is provided on the AFP Web site.

O bstructive sleep apnea (OSA), defined as an average of at least 10 apneic and hypopneic episodes per sleep hour, is a common sleep-related breathing disorder that leads to excessive daytime sleepiness because of marked fragmentation of sleep. Patients are frequently not diagnosed despite years of being symptomatic (especially with hypersomnolence), because physicians do not routinely look for the disorder. Additionally, the role of OSA in the production of essential hypertension (EH) is frequently not appreciated.¹⁻⁴ The purpose of this article is to demonstrate how commonly OSA occurs, how the quality of patients' lives can improve with successful treatment, and how the disorder is related to EH.

OSA is characterized by a repetitive partial (hypopnea) or complete (apnea) closing of

the pharynx during sleep. By definition, apneas or hypopneas that last a minimum of 10 seconds are considered clinically significant, although they usually last from 20 to 30 seconds and can last more than one minute. Most of these episodes end when the patient wakes up slightly, almost always without being aware of it. This "arousal response" causes the airway to reopen. In severe cases, the cycle of opening and closing of the pharynx can recur 400 to 600 times a night.

The apnea-hypopnea index (AHI), also called the respiratory disturbance index, is the average number of apneas and hypopneas that occur per sleep hour. Although different thresholds exist for defining OSA, it is often defined as an AHI of 10 or more. The prevalence of OSA depends on how it is defined. When using the definition of an AHI of 10 or more, about 10 percent of persons 30 to 60 years of age (5 percent of women and 15 percent of men) have OSA.⁵ However, if OSA is defined as an AHI of

See editorial on page 182.

Obstructive sleep apnea is a very common sleep disorder with major clinical and social consequences, yet it is often neglected, underdiagnosed and undertreated.

five or more and the primary symptom of hypersomnolence is present, OSA is present in 2 percent of women and 4 percent of men between 30 and 60 years of age.⁵ A patient with an AHI of 40 or more is generally considered to have severe OSA.

Diagnosing OSA

The first question to ask patients suspected of having OSA is if they snore and, if so, whether they snore loudly or quietly, frequently or infrequently, and only when lying on their back or when lying on their side. In most cases, patients cannot hear their own snoring. Even if they admit to being told that they snore, patients often have a tendency to underestimate the loudness and frequency of their snoring. Snoring marked by frequent changes in loudness and frequency (as opposed to quiet and steady snoring) is highly suggestive of OSA. A bed partner or person in

the household may be needed to give an accurate description of the patient's snoring. If the patient lives alone, a tape recorder can be placed near the bed and used to record hours of sleep to assess snoring.

The second question related to OSA is if patients have excessive daytime sleepiness. Patients may have difficulty describing their sleepiness and may call it "tiredness" or "fatigue." Physicians should ask patients exactly what they mean, and they may have to ask directly, "Do you mean you are sleepy most of the time?" Patients may then volunteer that they wake up feeling sleepy and remain uncontrollably sleepy throughout the day, especially when engaging in passive activities (e.g., reading, watching television, or even driving an automobile).

A patient's spouse or bed partner can usually describe the sleep behavior much better than the patient. It is *crucial*, therefore, that a bed partner be present during the interview. While patients may report being "a little sleepy," persons who live with patients may describe them as being very sleepy. If asked, patients may admit to having had one or more motor vehicle crashes or near crashes because of lack of attentiveness or falling asleep while driving. Patients who have OSA have a significantly greater chance of having a motor vehicle crash when compared with persons who do not have OSA.⁶ Excessive daytime sleepiness may also manifest as difficulty concentrating, remembering things, or thinking clearly. Other causes of sleepiness such as sleep deprivation, shift work, depression, hypothyroidism, or use of sleeping pills, sedatives, or excessive alcohol should be eliminated. Other sleep disorders, such as narcolepsy, should be ruled out.

Successful treatment of OSA will eliminate apneic and hypopneic breathing episodes, snoring, and the arousal responses caused by these respiratory events. Patients usually regain restful, uninterrupted sleep, which should dramatically improve their alertness during daytime hours. Also, patients' chances

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of being involved in motor vehicle crashes will be greatly reduced.⁶

The third question to ask (which should be directed to the bed partner, if possible) is whether the patient has episodes during sleep when breathing stops. The bed partner may describe periods of loud snoring by the patient followed by silence or a total absence of breathing lasting a few seconds up to one minute or longer. At the moment patients arouse from the apneic episode and the airway is opened, they usually take several deep, loud, gasping breaths that may be accompanied by gross body movements. The noise and body movements may awaken the bed partner.

Besides asking the three preceding questions, another useful question to ask is if the patient has a dry mouth on waking during the night or in the morning. Most heavy snorers and patients with OSA have a dry mouth because they usually breathe through their mouth when they sleep.

Another factor in the presence of OSA is nocturia, which is present in about one third of patients. Apneic episodes cause an increase in secretion of atrial natriuretic factor, which causes diuresis throughout the night. What may appear to be a prostatic problem may actually be diuresis caused by OSA. The nocturia may disappear with successful treatment of OSA.⁷

Hypertension is another major indicator of the presence of OSA because about one half of patients with EH have OSA, and about one half of all patients with OSA have EH.¹⁻⁴ In fact, in the last two years, seven major studies⁸⁻¹⁴ have shown that OSA is an independent risk factor for hypertension and, generally, the more severe the OSA, the more prevalent and severe the hypertension. In addition, many studies,¹⁻⁴ including four that have been recently published,¹⁵⁻¹⁸ have shown that successful treatment of OSA is associated with a significant reduction in blood pressure levels, although two other studies^{19,20} did not report similar findings. A recent long-term study²¹

also showed that normotensive patients with OSA are far more likely to develop hypertension over a four-year period than those without OSA.

If ambulatory blood pressure monitoring indicates that a patient is a "nondipper" (i.e., blood pressure during sleep fails to fall, or "dip," by at least 10 percent as it normally does when compared with the mean awake blood pressure level), then the chances that the patient has OSA are increased.²²

Obesity is a major indicator of the presence of OSA. Many patients with OSA may report a recent weight gain along with an increase in snoring and sleepiness. The risk of OSA is particularly high in patients who are obese and who have a large neck circumference and central obesity (i.e., a large waist-to-hip ratio). Although about 70 percent of patients with OSA are obese, thin people also can have OSA.

OSA can be worsened by sleep deprivation, alcohol intake, smoking, use of central nervous system depressants, and chronic nasal congestion.

Missed Diagnosis

Eighty to 90 percent of patients with OSA are undiagnosed, despite having clear signs and symptoms.^{23,24} When patients are finally diagnosed with OSA, they have had obvious symptoms of the disorder for an average of seven years, during which time they report having seen a family physician about 17 times and a subspecialist about nine times.²⁵ The most likely reason for missed diagnosis is that physicians simply do not suspect sleep apnea. Studies have shown that when physicians are informed about the disorder, their index of suspicion is high and they routinely ask their patients about OSA symptoms,²⁶ which increases the numbers of patients diagnosed and treated in their practices by about eightfold.²⁷

OSA As a Major Contributing Factor in EH

Evidence that OSA can cause elevated blood pressure levels during sleep and during the

day is very strong (Table 1).^{1-4,8-23,28-33} Not only are OSA and EH clinically similar but also, as shown in Table 2,¹⁻⁴ the physiologic, biochemical and hematologic characteristics that contribute to the persistence of hypertension are similar. Therefore, in many cases, OSA and EH appear to be the same condition.¹

Some evidence suggests that OSA may also be an important contributor in the development of coronary heart disease, stroke, cardiac

TABLE 1
Evidence That OSA Causes Hypertension and Contributes to Essential Hypertension

About 50% (range 30 to 80%) of patients with EH have OSA.
About 50% of patients with OSA have EH.
In patients with OSA, mean blood pressure during sleep often fails to fall as it normally does during sleep, but remains at a level similar to the awake blood pressure. This "non-dipping" is caused by frequent apneic/hypopneic episodes (up to 600 per night) ending with arousals that are associated with marked spikes in blood pressure that last for several seconds.
One third of patients with EH have blood pressure levels during sleep that fail to fall normally (i.e., they are non-dippers). Ninety percent of these patients have been found to have OSA.
Multiple studies have shown that OSA is an independent risk factor for the presence of EH even when considering age, gender, and degree of obesity.
Patients who are normotensive and who have OSA are much more likely to develop EH during the next few years than those without OSA.
The more severe the OSA, the higher the blood pressure levels and the greater the prevalence of EH.
Numerous studies have shown that treatment of OSA by CPAP or position therapy lowers the awake and 24-hour blood pressure levels.
In persons successfully treated with CPAP, cessation of treatment causes blood pressure levels to increase, while restarting treatment causes blood pressure levels to fall again.
The more severe the OSA, the more difficult it becomes to control blood pressure levels with medications.
In animal studies, the production of OSA causes sleeping and awake systemic hypertension to develop within a few weeks, and the cessation of OSA causes blood pressure levels to return to normal within a few weeks.
Some evidence exists that habitual snoring, especially loud frequent snoring, even without OSA is associated with elevated blood pressure levels during the night and day, and that treatment with CPAP can lower blood pressure levels.

OSA = obstructive sleep apnea; EH = essential hypertension; CPAP = continuous positive airway pressure.

Information from references 1 through 4, 8 through 23 and 28 through 33.

TABLE 2
Similarities Between Obstructive Sleep Apnea and Essential Hypertension

Epidemiologic findings

Increased prevalence of obesity and central obesity
More common in middle-aged men than women
More common in older than younger women
More common in blacks than whites
More common in persons who abuse alcohol (Alcohol is an important cause of hypertension and can worsen OSA and snoring.)

Genetic characteristics

A similar hereditary pattern is present in OSA and EH

Clinical findings

Improve with weight loss
Increased prevalence of snoring, cardiovascular complications, renal damage, cognitive dysfunction, headaches, impotence, non-dipping blood pressure levels during sleep, increased blood pressure variability, diabetes and insulin resistance

Hematologic and biochemical findings

Elevated hematocrit
Hyperuricemia
Reduced renin levels during sleep
Increased sympathetic activity
Elevated atrial natriuretic factor
Elevated ratio of vasoconstrictor to vasodilator prostaglandins
Reduced testosterone levels in men
Reduced endothelium dependent relaxation factor (nitric oxide)
Reduced blood fibrinolytic activity
Increased platelet activation and aggregation
Elevated erythropoietin levels
Elevated plasma fibrinogen levels
Elevated endothelin
Elevated leptin levels
Elevated von Willebrand factor

Physiologic responses

Increased chemoreceptor sensitivity as seen by exaggerated pressor response and ventilation response to hypoxia
Reduced baroreceptor sensitivity

Information from references 1 through 4.

arrhythmia, and congestive heart failure,³⁴ because about one half of all patients with coronary heart disease,³⁵ stroke,³⁶ and congestive heart failure³⁷ have OSA. Additionally, retrospective studies have shown that successful treatment of OSA is associated with a marked reduction in hospitalization³⁸ and mortality,³⁹ and prospective studies have shown that successful treatment of OSA improves nocturnal angina,⁴⁰ nocturnal cardiac arrhythmia,⁴¹ and congestive heart failure.⁴²

The Role of OSA in Secondary Hypertension

Some evidence suggests that OSA may also contribute to hypertension associated with hypothyroidism, acromegaly, alcohol abuse, and chronic renal failure.¹

Diagnostic Evaluation of OSA

Several reviews^{43,44} have been published about the diagnosis and physical examination of patients with OSA. The common physical findings in OSA are listed in *Table 3*.^{43,44} Because many patients with OSA have an upper airway abnormality, an ear, nose and throat evaluation is essential in the diagnostic workup.

The gold standard for an accurate diagnosis of OSA is a polysomnography evaluation performed in a sleep disorders unit. During this overnight evaluation, the number of apneas and hypopneas can be quantified, their duration measured, their relationship to body position and sleep stages determined, the level of oxygen desaturation measured and the existence of arrhythmic episodes can be quantified. This information determines the severity of the disorder and helps determine the treatment choice. Other tests often performed to objectively evaluate daytime sleepiness include the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test.

Treatment of OSA

Treatment of OSA includes nonsurgical and surgical approaches.⁴⁵⁻⁵⁴ No successful

The gold standard for accurate diagnosis of obstructive sleep apnea is a polysomnography examination in a sleep disorders unit.

pharmacologic treatment currently exists for snoring or OSA.

NONSURGICAL PROCEDURES

Weight Loss. Weight loss should always be strongly encouraged in patients with OSA who are obese (about 70 percent of all patients who have OSA are obese). Weight loss can produce good results and even small reductions in weight can produce major improvements in OSA.^{46,47} Because compliance with this treatment is usually poor,⁴⁶ physicians should not delay initiating other

TABLE 3
Common Physical Findings in OSA

Obesity
Primarily central obesity as assessed by an increased waist-to-hip ratio
Short neck and increased neck circumference
On oral examination
No clear abnormalities present in some cases
Crowded mouth with low-extending soft palate sometimes present
Large uvula
Generalized erythema and swelling of all tissues including the pharyngeal pillars
Large tonsils and adenoids may be present, especially in children
Large tongue (macroglossia)
High, arched and narrow hard palate (causes a narrow and crowded mouth)
Overbite of upper teeth
Retrognathia or micrognathia
Obstructed nasal passages
Evidence of hypothyroidism and acromegaly

Information from references 43 and 44.

Nasal continuous positive airway pressure is the treatment of choice for most patients with moderate to severe cases of obstructive sleep apnea.

forms of therapy unless patients are making serious attempts to reduce their weight.

Continuous Positive Airway Pressure (CPAP). During sleep, room air is continuously applied by a small, quiet air compressor that delivers positive pressure through a nasal mask. The CPAP system acts as a physical pressure splint to prevent partial or complete collapse of the upper airway during sleep. CPAP is the treatment of choice for patients with moderate to severe OSA, but it is also used to treat patients with mild OSA and those with loud and continuous snoring.

While CPAP is an extremely effective form of therapy, there are two pitfalls in its use. It is not a permanent cure; when patients stop treatment, OSA returns within a few days. Secondly, because patients may be reluctant to attempt CPAP or persist in using it, family physicians should encourage and closely follow patients because the beneficial effects on quality of life can be great.^{45,48}

Position Therapy (Avoiding the Supine Position). A large study⁴⁹ of patients with OSA who were diagnosed in a sleep disorders unit recently demonstrated that "positional patients" (those who have more than twice as many abnormal breathing episodes when sleeping in the supine position than when sleeping in the lateral position) represent more than one half of patients with OSA. These patients, in most cases, were found to have mild OSA. These results were not surprising because, when lying in the lateral position, patients have significantly fewer breathing abnormalities than when lying in the supine position. In some instances, a total absence of breathing disturbances was observed when patients were lying in the lateral position. For these patients and those

who had an AHI of 10 or less while lying in the lateral position, position therapy represented a valuable and effective therapy.

Results from another study⁵⁰ showed that patients with OSA who were hypertensive and normotensive and who avoided sleeping in the supine position for one month by using the tennis ball technique, a simple and inexpensive behavioral method, had a significant reduction in 24-hour blood pressure values and blood pressure variability. (In the tennis ball technique, a wide cloth belt with a pocket that a tennis ball is placed into is worn around the chest so that the pocket with the ball is positioned in the middle of the back. When the patient rolls onto his or her back, the pressure of the tennis ball causes the patient to roll onto their side again.) If these preliminary results are confirmed in larger studies, avoiding the supine position during sleep could become a new nonpharmacologic treatment for many hypertensive patients.

Oral Devices. Oral devices placed in the mouth at bedtime to keep the mandible and tongue in a forward position during sleep can prevent upper airway obstruction during sleep. This therapy has been shown to be useful primarily in patients with simple snoring and in patients with mild to moderate OSA.⁵¹

SURGICAL PROCEDURES

A wide variety of surgical procedures are currently used to treat OSA and, of these, uvulopalatopharyngoplasty is the most common. This procedure can be performed using conventional or laser techniques. Unfortunately, only about 40 to 60 percent of patients who have OSA show an improvement in symptoms following the procedure, and it is impossible to predict which patients will benefit from surgery and which will not. Other surgical procedures include relief of nasal obstruction, tonsillectomy, adenoidectomy, mandibular-maxillary surgery, and, most recently, somnoplasty, in which radiofrequency energy is used to shrink part of the tongue and soft palate.⁵²⁻⁵⁴

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Chronic Insomnia With Short Sleep Duration Is Significant Risk Factor For Hypertension

ScienceDaily (Apr. 1, 2009) — A study in the April 1 issue of the journal *SLEEP* is the first to demonstrate that chronic insomnia with objectively measured short sleep time is an independent and clinically significant risk factor for hypertension.

Results indicate that participants with insomnia and an objectively measured, severely short sleep duration of less than five hours had a risk for hypertension that was 500 percent higher than participants without insomnia who slept more than six hours. People with insomnia and a moderately short sleep duration of five to six hours had a risk for hypertension that was 350 percent higher than normal sleepers.

In contrast, neither insomnia with a normal sleep duration of more than six hours nor a short sleep duration without a sleep complaint was associated with a significant risk for hypertension. This suggests that there is an additive or synergistic effect on hypertension risk when insomnia occurs in combination with a short sleep duration.

According to lead author Alexandros N. Vgontzas, MD, director of the Sleep Research and Treatment Center at the Penn State College of Medicine in Hershey, Pa., one of the study's strengths is that sleep duration was measured objectively by overnight polysomnography.

"It should be emphasized that many times the amount that we feel we slept is different from the actual amount," said Vgontzas. "Thus self-reported sleep duration cannot replace measured sleep duration."

The study involved a random sample of 1,741 men and women in central Pennsylvania with an average age of 49 years. Eight percent were classified as having chronic insomnia with symptoms persisting for at least one year; 22 percent were poor sleepers with a moderate to severe complaint of difficulty falling asleep, staying asleep, early final awakening or unrefreshing sleep; and 70 percent were normal sleepers. Twenty-one percent had a severely short sleep duration of less than five hours; 23 percent had a moderately short sleep duration of five to six hours; and 56 percent had a normal sleep duration of more than six hours.

Although the cross-sectional nature of the study did not allow for causality to be determined, the authors note that large amounts of clinical and research data indicate that it is most likely that insomnia leads to hypertension. Previous reports have shown that insomnia with short sleep duration is associated with the hypersecretion of cortisol, increased catecholaminergic activity, increased heart rate and 24-hour metabolic rate, and impaired heart rate variability. All of these conditions may lead to hypertension and other cardiovascular events.

Because the study sample is representative of the general population, the authors estimate that eight percent to 10 percent of the U.S. population may be at risk for hypertension and other significant

medical complications related to chronic insomnia.

According to Vgontzas, the study indicates that people with insomnia should seek evaluation and treatment from their medical provider. Although the results suggest that people with insomnia have a lower risk for physical problems if their sleep duration is normal, they still are at risk for depression and may suffer from the behavioral effects of insomnia.

Journal reference:

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