Association of Hypertension and Sleep-Disordered Breathing

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Background: To our knowledge, the association between sleep-disordered breathing (SDB) and hypertension has not been evaluated in subjects from the general population with a wide age range while adjusting for the possible confounding factors of age, body mass index, sex, menopause and use of hormone replacement therapy, race, alcohol use, and smoking.

Methods: In the first phase of this study, we interviewed 4364 men and 12219 women, aged 20 to 100 years. In the second phase of this study, 741 men and 1000 women, previously interviewed, were selected based on the presence of risk factors for SDB (snoring, daytime sleepiness, obesity, hypertension, and, for women, menopause). Each subject selected for the second phase of the study provided a comprehensive history, underwent a physical examination, and was evaluated for 1 night in the sleep laboratory. In terms of severity of SDB, 4 groups were identified: moderate or severe (obstructive apnea/hypopnea index $\geq 15.0$), mild (snoring and an obstructive apnea/hypopnea index of 0.1-14.9), snoring, and no SDB, the control group.

Results: Sleep-disordered breathing was independently associated with hypertension when potential confounders were controlled for in the logistic regression analysis. The strength of this association decreased with age and was proportional to the severity of SDB. In the best-fitted model, neither sex nor menopause changed the relationship between hypertension and SDB.

Conclusions: In the results of this study, SDB, even snoring, was independently associated with hypertension in both men and women. This relationship was strongest in young subjects, especially those of normal weight, a finding that is consistent with previous findings that SDB is more severe in young individuals.

Arch Intern Med. 2000;160:2289-2295

It is generally assumed that sleep-disordered breathing (SDB), especially obstructive apnea, is independently associated with hypertension. However, the 13 cross-sectional epidemiologic studies that assessed this question reported mixed findings. Seven of these studies found a positive association between hypertension and various types of SDB. Closer inspection of these studies indicates that only 6 of the 13 studies actually measured blood pressure and monitored respiration during sleep (either at home or in the sleep laboratory). Most of these studies relied on subjective reports (eg, data from questionnaires). Furthermore, in some of these studies, confounding factors were not adequately controlled for (ie, several factors associated with SDB are also associated with hypertension). Five of the studies that quantified blood pressure and respiration during sleep adjusted for confounding factors of age, sex, and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) and 3 of these 5 studies found a positive association between hypertension and SDB. However, all 5 studies assessed a restricted age range. Thus, they could not adequately identify changes in hypertension and SDB across the full age spectrum in adults. Furthermore, none of these studies controlled for menopause and/or hormone replacement therapy (HRT) use or race.

The purpose of this study was to establish the association between hypertension and SDB in a large random sample of the general population with a wide age range while adjusting for the possible confounding factors of age, BMI, sex, menopause and/or HRT use, race, alcohol use, and smoking.
SUBJECTS AND METHODS

In the first phase of this study, a sample of adult men and women (aged ≥20 years) were randomly selected from households with telephones in 2 counties of southern Pennsylvania (Dauphin and Lebanon). The households with telephones were selected using the Mitofsky-Waksberg 2-stage random-digit dialing procedure. A within-household selection procedure described by Kish was used to select the men and women to be interviewed. Telephone interviews were conducted with 4364 men and 12219 age-eligible women residing in the sample households; the response rate among age-eligible women was 74.1%, which was similar to the response rate of 73.5% previously reported in the age-eligible men. The questionnaire used in this interview included basic demographic information as well as questions assessing the risk factors for SDB (sleep apnea).

In the second phase of this study, a random sample from the 4364 men and the 12219 women previously interviewed by telephone were selected for study in our sleep laboratory to assess for the presence of SDB. This sample was chosen by counting the number of risk factors for SDB (snoring, daytime sleepiness, obesity, hypertension, and, for women, menopause) reported by each interviewed subject. Those subjects with more risk factors were oversampled. The response rate of this phase of the study in women was 65.8% compared with 67.8% in the sample of men, resulting in a total of 741 men and 1000 women who were evaluated in our sleep laboratory. We then compared subjects who were evaluated in the laboratory with those who were selected but not evaluated in the laboratory using the following: age, BMI, prevalence of the risk factors used to select the subjects, sleep disorders, and general health variables. There were no significant differences between these 2 groups in any of these variables.

As previously described, each subject selected for laboratory evaluation provided a comprehensive sleep history and underwent physical examination and a psychometric battery assessing cognitive and other psychological functions. The psychometric data will be reported in a future publication. This study was reviewed by the institutional review board of Pennsylvania State University College of Medicine, Hershey, and signed informed consent was obtained from all subjects.

All subjects were evaluated for 1 night in the sleep laboratory in sound-attenuated and light- and temperature-controlled rooms. During this evaluation, they were continuously monitored for 8 hours using 16-channel polygraphs (model 78d; Grass-Telefactor, West Warwick, RI). The sleep monitoring included the following: electroencephalogram using 3 derivations (C3-A2, C4-A1, and F3-O1); 3-channel electro-oculogram, recorded from the outer canthi of both eyes referred to A1, as well as the 2 eyes referred to each other; and an electromyogram, recorded from the submental muscle. Electrode impedance was established below 5 \( \times 10^3 \) \( \Omega \) and was usually below 3 \( \times 10^3 \) \( \Omega \). The time constant for electroencephalogram and electro-oculogram was 0.1 second and for electromyogram, 0.01 second. The recordings were made at a chart speed of 15 mm/s, which allowed a 2-page scoring epoch of 40 seconds. The sleep records were subsequently scored independently according to standardized criteria. Inter-scorer reliability was monitored and maintained by having each technician independently score a common record weekly. We have consistently maintained approximately 96% to 98% agreement among our scorers.

Respiration was monitored throughout the night by use of thermocouples at the nose and mouth (model TCT; Grass-Telefactor) and thoracic strain gauges. All-night recordings of arterial blood oxygen saturation were obtained with an oximeter (model 8800; Nonin Medical Inc, Plymouth, Minn) attached to the finger. Apnea was considered present if a breath cessation exceeded 10 seconds. Each apnea was categorized in terms of obstructive (chest wall movement present) or central (chest wall movement absent). In addition, hypopnea was considered present when a reduction in airflow of approximately 50% was indicated at the nose or mouth and was associated with a reduction of 4% arterial blood oxygen saturation.

The sampling procedures departed from equal probability selection to improve the efficiency of subject identification and screening. Compensatory weights were developed for the analysis to obtain estimates of prevalence for the original target population of men and women in the 2-county study area. Specifically, 3 weights were created for the men. First, in the telephone sample, 32 of the 963 clusters of phone numbers in the first stage were exhausted before the target sample size was obtained. We computed a compensatory weight to correct this problem. A second weight was computed because the within-household

The subjects included in the sleep laboratory phase of this study were 1000 women and 741 men, with a mean±SD age of 47.4±0.4 years (range, 20-88 years). The mean±SD BMI was 26.7±0.12 (range, 18.2-68.9). Table 1 describes the prevalence of hypertension for each SDB group across sex, age, obesity, and menopausal and/or HRT subgroups. The following results are based on the best-fitted model, which used the entire cohort of men and women across all age (≥20 years) and BMI categories. Table 2 summarizes the SDB variables that reached significance and were included in the final model.

The main effects of the 3 SDB variables on the prevalence of hypertension resulted in approximately a dose-response pattern (ORs, 6.8, 2.3, and 1.6 for moderate or severe SDB [OAHI ≥15], mild SDB, and snoring, respectively). These ORs represent the relative odds of hypertension when compared with the group without SDB for the 3 SDB groups, respectively, for the mean age and BMI of the study cohort. The model indicated that mild SDB and moderate or severe SDB (OAHI ≥15) interact with BMI and age. In other words, the OR of hypertension for these 2 groups changes according to different values of age and BMI. In contrast, the OR for snoring is constant regardless of age and BMI, with one exception: postmenopausal women who received HRT. Furthermore, sex and menopause did not significantly change the relationship between hypertension and the 3 SDB groups.

To help understand how age and BMI interact with mild and moderate or severe SDB, we show, in Figure 1, the estimated ORs of hypertension between the group with
screening deliberately introduced unequal probabilities of selection across the 3 age groups to oversample the middle age group. The final weight for the men was computed to account for the oversampling of subjects for the sleep laboratory study (phase 2); those with more risk factors had substantially higher probability of being selected. For the women, the only weight required was to account for the oversampling of subjects at risk for SDB for the sleep laboratory study (phase 2).

For analysis, we calculated various apnea indexes based on the specific types of apnea per hour of sleep. In this specific analysis, we used an obstructive apnea/hypopnea index (OAHI). The first of 4 mutually exclusive groups of SDB that we defined was moderate or severe SDB (OAHI ≥15.0). A second group had mild SDB, defined as moderate to severe snoring reported during the telephone interview (phase 1), observed snoring in the laboratory (phase 2), and low indexes of SDB (ie, OAHI 0.1-14.9 or breathing-related brief semiarousals). The third group of subjects had snoring, ie, they snored without the presence of any apnea and/or hypopnea (OAHI, 0.0). The final group had no SDB (controls).

Blood pressure was measured in the evening during the physical examination using a pneumoelectric microprocessor-controlled instrument. The recorded blood pressure was the average of 3 consecutive readings during a 3-minute period following 10 minutes of rest in the supine position. Hyper tension was defined as a diastolic blood pressure greater than 90 mm Hg or a systolic blood pressure greater than 140 mm Hg at the time of the sleep laboratory evaluation or the use of antihypertensive medication.

The menopause and/or HRT variable was established by dividing the women into 3 groups: (1) premenopausal, women with regular menstrual cycles and not using any HRT; (2) postmenopausal without HRT, women who had not had regular menstrual cycles in the past 12 months, were older than 40 years, and were not using HRT; and (3) postmenopausal with HRT, women meeting the criteria for menopause above who were using HRT. Hormone replacement therapy was defined as regular use of estrogen alone or estrogen combined with progestrone.

The association between hypertension and SDB was first evaluated using frequencies as a function of subgroups of age, BMI, and menopause and/or HRT, both by themselves (Table 1) and by combining 2 or more factors (data not shown). In these preliminary analyses, we observed a general trend that young, normal-weight individuals with moderate or severe SDB (OAHI ≥15) had a higher risk for hypertension than more obese and older groups. Because of power considerations due to small sample sizes in some categories, logistic regression analysis (SAS statistical software; SAS Institute Inc, Cary, NC) was then used to estimate the effect of SDB on hypertension while using the entire cohort and treating age and BMI as continuous variables.

Because age and BMI have been demonstrated to be significant risk factors for SDB as well as for hypertension,4,5,9,10,11 and age and SDB variables, which is not reported, was also significant. The variable of male sex was also forced into the model to adjust for different probabilities of selection between sex and to deal with the potential for confounding. Secondary variables were included in the initial model but were removed during the model-building processes using backward selection (α = .05). The secondary variables were menopause and/or HRT and all possible interactions between age, log BMI, SDB, and menopause and/or HRT. To reduce the correlation between age and log BMI and their interaction, age and log BMI were centered by subtracting the raw numbers from their respective means. A lower level interaction and the main effect would be added to the model if a higher level interaction was found significant. We also repeated these analyses allowing race, smoking, and alcohol use into the model. Although race (odds ratio [OR], 1.6 [95% confidence limits, 1.0, 2.4]) and an interaction between smoking and log BMI (OR, 8.4 [95% confidence limits, 1.4, 54.8]) were significant risk factors for hypertension, they neither changed the strength of the association between SDB and hypertension nor interacted with any of the SDB variables. Therefore, we limited ourselves to the final model that considered age, BMI, sex, menopause and/or HRT, and the 3 SDB variables.
To assess how well the logistic regression model fits the observed data, we compared the predicted ORs with the observed ORs between the group with moderate or severe SDB and the group without SDB in Table 3. We considered 3 age categories and 3 BMI categories. We calculated the observed ORs based on the 2 \times 2 table for each of the age and BMI combinations. The predicted ORs were generated from the logistic regression model based on the medians of the age and BMI of the range reported in Table 3. The ORs generated by the model closely agreed with the observed ORs.

We also performed several sensitivity analyses, one of which adjusted for smoking, alcohol use, and race. Although smoking and race appeared to be important risk factors of hypertension (not shown here), the ORs concerning the relationship between SDB and hypertension were close to those in Table 2 when these variables were included in the model. Furthermore, there were no interactions between SDB and race, smoking, or alcohol use. Because we previously reported that an intact hormonal system in women may play an important role in protecting them from SDB, we also analyzed our data according to menopause and/or HRT use. The model that included men and postmenopausal women without HRT essentially led to the same conclusions as those observed in the entire cohort. However, for the model that included only premenopausal and postmenopausal women with HRT, we did not find a strong association between hypertension and moderate or severe SDB and mild SDB. In addition, none of the interactions with age and BMI were present.

The findings of this study indicated an independent association between SDB and hypertension in young and middle-aged individuals when adjusting for possible confounders, including age, BMI, sex, menopause and/or HRT use, alcohol use, smoking, and race. The strength of this association varied with the type of SDB, BMI, and age. For mild SDB and moderate or severe SDB, the strength of the association with hypertension was strongest in young individuals, especially those who were normal weight, whereas the association was not significant or in the reverse direction in older individuals. This finding supports our previous finding that the most severe sleep apnea is observed in younger men. These findings support the findings of Young et al, who reported a negative interaction between the apnea/
hypopnea index (AHI) and BMI when assessing the association between SDB and hypertension. In contrast to our findings, Young et al. did not find an interaction between SDB and age, which may have been a reflection of the restricted age range in their sample (30-60 years). This study adjusted for age, BMI, sex, smoking, and alcohol use, but not for race or menopause and/or HRT.

Our data also lend further support to the finding that even subjects with mild SDB (ie, snoring) have an increased risk for hypertension.9,12 Our data showed ORs from 1.6 (snoring) to 6.8 (moderate or severe SDB) in a dose-response manner for the mean age and BMI of the cohort. Snoring, in contrast to the other 2 more severe categories of SDB, did not interact with BMI.

An independent association between SDB and hypertension was found in only 1 cohort, to our knowledge.9,12,13 In the most recent analysis13 of this cohort, the OR for the risk of hypertension was 1.8 in 46-year-old subjects with a BMI of 30 and an AHI of 15 compared with those with an AHI of 0. In our study, the OR for the risk of hypertension was 2.4 in 53-year-old individuals with a BMI of 30 (Table 3). In addition, this OR was based on an OAHI of 15 or higher compared with an AHI of 15, which would have slightly increased the estimate in our study. Young et al.13 did not include simple snoring as a category of SDB in their analysis, which might have slightly decreased the OR, compared with that in the present study, because individuals who snored were included as controls.

Sex does not seem to be a factor in the association between hypertension and SDB. Although women have a lower prevalence of sleep apnea than men,19,20 once SDB is present, the association with hypertension appears to be the same for both sexes. This finding is consistent with the previous report by Young et al.13 However, one exception to this finding is that postmenopausal women who were taking HRT and who snored appeared to be at a reduced risk for hypertension. However, if a postmenopausal woman receiving HRT had more severe SDB (ie, sleep apnea), then the risk for hypertension is the same as for those not receiving HRT. Another sex-related qualification was that, unlike young men, normal-weight premenopausal and postmenopausal women receiving HRT did not have moderate or severe SDB. There were no normal-weight young women with moderate or severe SDB (OAHI ≥15); in other words, moderate or severe SDB in young women occurred only in those who were obese. Thus, the power to detect sex differences in this age and BMI range may have been reduced. However, the relationship between SDB and hypertension in postmenopausal women who were not receiving HRT was similar to that in men.

Race and the use of alcohol and tobacco products were not included in the final model. Although race and smoking were significantly associated with hypertension, they did not interact with the association between SDB and hypertension and did not confound the strength of this association.

The finding that the association of SDB with hypertension decreases with age is consistent with the findings in studies evaluating the association between SDB and mortality. Of the studies23-28 that evaluated this question, a positive association was reported in only 3 studies,23,25,28 with a mixed association in a fourth (positive for women and negative for men)24 and no association in 4 studies.21,22,26,27 The 3 studies23,25,28 that reported a positive association included young subjects, while the remaining studies only included older subjects.
An association between SDB and hypertension that decreases with age could be accounted for by a "ceiling" effect. In other words, because the outcome (mortality or hypertension) becomes more common in older individuals, it would take a large sample to detect a difference. This reason probably does not account for the relationship because a similar relationship has been observed between BMI and mortality. Two recent studies demonstrated that the risk for mortality associated with BMI decreases with age. Both of these studies examined large samples: one studied 324,135 subjects from the general population, and the other, 6,193 obese subjects. Thus, in these studies, the ceiling effect cannot be used as an explanation. Because BMI and SDB are strongly related, the ceiling effect probably does not account for the association between SDB and hypertension either.

Because the data reported in this study are cross-sectional, a selection bias could account for the findings of a negative relationship with age. In other words, young subjects could have a more severe form of SDB. We previously reported that obstructive sleep apnea in younger men is more severe than in older men. This finding is consistent with the observation that sleep apnea may have a genetic predisposition. Another possibility is that the older subjects in our study constitute a survivor group who are more resistant to the stress of SDB. For example, in the present study, an older normal-weight individual with SDB might have a lower risk for hypertension than an older normal-weight individual without SDB. This latter possibility could also be explained by age-related changes in the physiological characteristics of older individuals, which might make them less likely to react to sleep apnea with a hypertensive response.

We found an independent association between SDB and hypertension even though the blood pressure readings were obtained in the evening. Imai et al demonstrated that measures of blood pressure are higher in the morning than in the evening. Furthermore, the difference between morning and evening blood pressure measures is related to the magnitude of the evening blood pressure; in other words, the greatest difference between morning and evening blood pressure is expected in those with hypertension. It has also been suggested that the treatment of hypertension may reduce the frequency of SDB. Thus, it is possible that the effects of the treatment of hyperten-

Figure 2. The probability of hypertension across age and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) in men based on the best-fitted logistic regression model. The surface plots represent 1 of 4 groups of men: without sleep-disordered breathing (SDB) (A), snoring (B), mild SDB (C), and moderate or severe SDB (D). Because the absolute prevalences were higher for the men, the differences are easier to visualize. However, the shape of the distribution of the prevalence of hypertension in women alone or in men and women combined was almost identical to the distribution of the men alone.
tion on SDB might have reduced our estimate of the strength of the association between SDB and hypertension.

Finally, the guidelines for the management of hypertension published in 1999 do not mention any type of SDB, even as a potential risk factor for hypertension. The findings of this study add further support to the hypothesis that SDB, including snoring, is an independent risk factor for hypertension, even when potential confounders are controlled for. Thus, a physician should consider the possibility of hypertension whenever any type of SDB is present and conversely should consider the possibility of SDB whenever hypertension is present.

Accepted for publication February 28, 2000.

This study was supported by grants HL40916 and HL51931 from the National Institutes of Health, Bethesda, Md. We gratefully acknowledge J. Richard Landis, PhD, for assisting with the study design. In addition, James M. Lepkowski, PhD, contributed expert guidance for the sampling strategy, as well as for the establishment of the sample weights.

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Table 3. Comparison of Subjects With an Obstructive Apnea/Hypopnea Index of 15.0 or Higher With Those Without Sleep-Disordered Breathing*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>BMI</th>
<th>OR (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>71</td>
<td>2.50 (0.54, 11.69)</td>
</tr>
<tr>
<td>28-32</td>
<td>24.28</td>
<td>2.48 (0.73, 8.09)</td>
</tr>
<tr>
<td>32-36</td>
<td>29.75</td>
<td>2.90 (0.89, 9.12)</td>
</tr>
<tr>
<td>36-40</td>
<td>34.70</td>
<td>3.03 (0.95, 9.50)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>39.30</td>
<td>3.01 (0.94, 9.38)</td>
</tr>
</tbody>
</table>

* BMI indicates body mass index (calculated as weight in kilograms divided by the square of height in meters); OR, odds ratio; and CL, confidence limits. The ages and BMIs for the predicted data are the median values of the ranges in the observed data.