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Relation of Sleep-disordered Breathing to Cardiovascular Disease Risk Factors

The Sleep Heart Health Study

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Associations between sleep-disordered breathing and cardiovascular disease (CVD) may be mediated by higher cardiovascular risk factor levels in those with sleep-disordered breathing. The authors examined these relations in the Sleep Heart Health Study, a multiethnic cohort of 6,440 men and women over age 40 years conducted from October 1995 to February 1998 and characterized by home polysomnography. In 4,991 participants who were free of self-reported CVD at the time of the sleep study, moderate levels of sleep-disordered breathing were common, with a median Respiratory Disturbance Index (RDI) of 4.0 (interquartile range, 1.25–10.7). The level of RDI was associated cross-sectionally with age, body mass index, waist-to-hip ratio, hypertension, diabetes, and lipid levels. These relations were more pronounced in those under age 65 years than in those over age 65. Women under age 65 years with RDI in the higher quartiles were more obese than men with similar RDI. Although the pattern of associations was consistent with greater obesity in those with higher RDI, higher body mass index did not explain all of these associations. If sleep-disordered breathing is shown in future follow-up to increase the risk for incident CVD events, part of the risk is likely to be due to the higher cardiovascular risk factors in those with higher RDI. *Am J Epidemiol* 2001;154:50–9.

cardiovascular diseases; respiration; sleep apnea syndromes; sleep disorders

Sleep apnea is hypothesized to increase the risk of developing cardiovascular disease (CVD) and hypertension. Initial support for this hypothesis came from several population studies of snoring and CVD outcomes, suggesting that those who snore are more likely to develop hypertension, myocardial infarction, and stroke (1–3). Studies of CVD risk factors in patient populations with obstructive sleep apnea syndrome suggest that these persons have a higher than expected prevalence and incidence of CVD (4) but that the strength of these associations is decreased after accounting for confounding by higher weight and age in those with sleep apnea. None of these studies, however, has had detailed information regarding the presence of other CVD risk factors in those with sleep apnea. Patients with CVD have a higher prevalence of sleep-disordered breathing by polysomnography (5–9), but it is unclear whether sleep-disordered breathing preceded CVD or was its consequence.

The prevalence of sleep-disordered breathing has been documented in population-based studies to be quite substantial: 24 percent in men and 9 percent in women (10). These persons, most of whom are asymptomatic with respect to daytime sleepiness, clearly have a higher BMI and blood pressure than do those without sleep-disordered breathing. However, most of these samples have not been characterized in detail regarding other CVD risk factors and future outcomes. Thus, neither studies of obstructive sleep apnea patients nor population studies of sleep-disordered breathing have adequately evaluated the intrinsic host factors that increase the risk of CVD in relation to sleep-disordered breathing or fully assessed its interactions with intrinsic CVD risk factors. The hypothesized pathway between sleep-disordered breathing and CVD events is complex and may be bidirectional. For example, some factors, such as obesity, may worsen breathing during sleep. Other factors, such as hypertension, are potentially worsened by sleep-disordered breathing, yet hypertension has also been postulated to influence the severity of sleep-disordered breathing. A detailed analysis of these relations is needed to refine hypotheses of the possible causal mechanisms underlying

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Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL, high density lipoprotein; RDI, Respiratory Disturbance Index; SHHS, Sleep Heart Health Study.

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the potential relation between sleep-disordered breathing and CVD.

The Sleep Heart Health Study (SHHS) was designed to measure sleep-disordered breathing and its consequences in cohorts that have previously been well-characterized regarding CVD risk factors. In these cross-sectional analyses, we evaluated the relation of CVD risk factors to sleep-disordered breathing in the subgroup of SHHS participants at risk for incident CVD. We hypothesized that participants found to have higher levels of sleep-disordered breathing would also have higher levels of most traditional CVD risk factors and that these relations would vary by age and gender.

MATERIALS AND METHODS

Population

The SHHS is a longitudinal study established to determine the presence of sleep-disordered breathing in participants in several ongoing cohort studies of cardiovascular and respiratory disease. Analyses were conducted on 5,978 participants whose sleep studies were read as of January 4, 1999. Those with a self-report of any prevalent CVD as defined below (n = 878) were excluded. "Unsure" responses (n = 109) were classified as missing, leaving 4,991 for this analysis.

The SHHS cohort (n = 6,440) was assembled from more than 23,000 participants in several ongoing, population-based studies in diverse populations in the United States. The parent cohort studies participating in the SHHS include the Minneapolis, Minnesota, and Washington County, Maryland, cohorts of the Atherosclerosis Risk in Communities Study; the Pittsburgh, Pennsylvania, the Sacramento, California, and the Washington County, Maryland, cohorts of the Cardiovascular Health Study; the Framingham Heart Study; three New York City, New York, cohorts recruited as part of a program project to assess the effect of psychosocial factors on the risk of CVD; the Strong Heart Study cohorts recruited from American Indian tribes in Arizona, Oklahoma, North Dakota, and South Dakota; and two cohorts from Tucson, Arizona: the Tucson Epidemiologic Study of Airway Obstructive Diseases and the Tucson Health and Environment cohort. Persons from these cohorts were recruited by mail or at the clinic visit that occurred during the SHHS recruitment period. The design of the study has been described in detail (11).

Polysomnography

Polysomnography was performed by using a portable, unattended monitor set up in the home (Compumedics P Series system, Abbotsville, Victoria, Australia). Multiple channels were recorded, including electroencephalogram, electrooculogram (bilateral), electrocardiogram, Chin electromyogram, abdominal and thoracic excursions (by impedance plethysmography), oxyhemoglobin saturation (finger pulse oximetry; Nonin, Minneapolis, Minnesota), airflow (oral-nasal thermistor; Protec, Woodsville, Washington), body position (by mercury gauge), and ambient light. These leads were connected to a small monitor worn in a vest pocket, allowing the participant to be fully ambulatory while awake. Sleep-disordered breathing was defined for this analysis by using the Respiratory Disturbance Index (RDI). A respiratory event was defined as a decrease in airflow or chest wall movement to an amplitude of less than 25 percent (apnea) or 70 percent (hypopnea) of the baseline breathing signal. A qualifying event was defined as one that lasted at least 10 seconds in association with an oxyhemaglobin desaturation of 4 percent or greater.

Demographic characteristics and CVD risk factors

Age, gender, and ethnicity were obtained from data collected by the parent studies. To update prevalent CVD, its prevalence was established by interview at the time of the sleep study. Those with prevalent CVD (self-report of myocardial infarction, angina, coronary artery bypass, angioplasty, stroke, or congestive heart failure) were excluded. Weight and blood pressure were measured in the home by using standard protocols. All other CVD risk factors were assessed within 5 years of the home sleep study by the parent study. CVD risk factors evaluated in this analysis included height, body mass index (BMI) (weight (kg)/height (m^2), waist/hip ratio, self-reported hypertension, self-reported diabetes, lipids (total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides, all measured as mg/dl), current or past smoking status, pack-years of smoking, and presence of left ventricular hypertrophy or major abnormalities on electrocardiogram. All electrocardiograms were read by the parent studies. Left ventricular hypertrophy and major electrocardiographic abnormalities (major Q waves or minor Q waves with major ST-T wave changes) were defined by using Minnesota codes (12) as follows: ventricular conduction defect = codes 7–1 (left bundle branch block), 7–2 (right bundle branch block), 7–4 (intraventricular block on indeterminate type with QRS ≥ 120 ms); major Q/QS-wave abnormalities (Q/QS) = codes 1–1 to 1–2, except 2–1–8; left ventricular hypertrophy (high-amplitude R waves with major or minor ST-T wave abnormalities) = codes 3–1 and 3–3 and 4–1 to 4–3 or 5–1 to 5–3; isolated major ST-T wave abnormalities = codes 4–1, 4–2, 5–1, and 5–2 without 3–1, 3–3, 1–1 to 1–3; and atrial fibrillation = code 8–3.

Data analysis

The distribution of the RDI was skewed toward lower values. We evaluated the RDI distribution in quartiles and subsequently further divided the upper quartile into equal subdivisions (subquartiles) to evaluate whether associations with CVD risk factors were linear into the tail of the distribution. The range of the RDI was 0–115.6. The midpoints of the quartiles and upper subquartiles correspond to RDIs of 0.49, 2.42, 6.80, 12.33, 16.26, 23.26, and 46.41. Bivariate analyses were stratified by age (<65, ≥65 years) and gender. Within each stratum, significant differences across RDI quartiles were evaluated by overall chi-square or analysis of variance, as well as a test for trend. Gender-specific general linear models were constructed to evaluate the relation of

TABLE 1. Demographics of SHHS* participants at risk for incident CVD* (*n* = 5,978), United States, October 1995 to February 1998

	Full cohort (*n* = 5,978)	Subgroup without CVD at baseline (*n* = 4,991)
With prior CVD	878	
Missing prior CVD variable	109	
Age (years) (mean, minimum, maximum)	63.0 (40, 100)	62.1 (40, 99)
Women‡ (no. (%))	3,156 (52.8)	2,708 (54.3)
Ethnicity (no. (%))		
Caucasian	4,527 (75.7)	3,860 (77.3)
African American	486 (8.1)	345 (6.9)
American Indian	603 (10.1)	453 (9.1)
Other	362 (6.1)	333 (6.7)
Education (years) (no. (%))		
Missing	548	481
<9	316 (5.8)	225 (5.0)
9–11	445 (8.2)	332 (7.4)
12	1,603 (29.5)	1,352 (30.0)
13–16	1,738 (32.0)	1,432 (31.8)
17–18	718 (13.2)	622 (13.8)
>18	610 (11.2)	547 (12.1)

* SHHS, Sleep Heart Health Study; CVD, cardiovascular disease.

each risk factor to the RDI, adjusted first for age, then for age and BMI, and then using forward stepwise multivariate models. For these models, the RDI was log transformed (log(1 + RDI)).

RESULTS

Of the 5,978 SHHS participants with available data, 4,991 (83.5 percent) were free of CVD at the time of the baseline sleep study (table 1). These persons are currently being followed for incident CVD. The mean age was 62.1 years. A total of 54.3 percent were women, and 77.3 percent were Caucasian, with less than 10 percent each of African Americans, American Indians, or other races. Most (88 percent) had a high school education, 42 percent had a post-high school education, and 12.1 percent had a postgraduate education.

The distribution of the RDI was skewed, with a median of 4.0 events per hour of sleep and an interquartile range of 1.25–10.7. We determined the distribution of demographic factors and CVD risk factors across quartiles of the RDI. Table 2 shows the demographic distributions by RDI quartile. The mean age was higher in each succeeding quartile, ranging from 59.2 to 64.1 years (p for association and p for

TABLE 2. Demographics by RDI* quartile and subquartile among SHHS* participants, United States, October 1995 to February 1998

	RDI					*p* value	
	0–<1.25 (*n* = 1,258)	1.25–<4.0 (*n* = 1,245)	4.0–<10.7 (*n* = 1,244)	≥10.7–115.6 (*n* = 1,244)	Overall (*n* = 4,991)	Association	Trend
Age (mean (SD*))	59.2 (10.8)	61.8 (10.9)	63.5 (10.7)	64.1 (10.3)	62.1 (10.8)	<0.0001	<0.0001
Age ≥ 65 years (%)	30.8	40.3	47.1	47.9	41.5	<0.001	<0.001
Women (%)	72.1	59.6	49.2	35.9	54.3	<0.001	<0.001
Ethnicity (no. (%))							
Caucasian	76.8	77.7	77.6	77.3	77.3	0.939	0.809
African American	7.6	6.9	5.9	7.2	6.9	0.407	0.455
American Indian	6.8	8.8	10.1	10.6	9.1	0.005	<0.001
Other	8.7	6.6	6.4	5.0	6.7	0.002	<0.001

* RDI, Respiratory Disturbance Index; SHHS, Sleep Hearth Health Study; SD, standard deviation.

trend both < 0.0001). This trend was also apparent in gender-stratified analyses, in which the proportion of participants age 65 years or more was higher in each quartile. Those in the lower quartiles were much more likely to be women (72.1 percent in the first quartile, compared with 35.9 percent in the highest quartile ($p < 0.001$ for both trend and association)). American Indians were overrepresented in the highest quartile, while the proportion of "other" (mostly Hispanics) was lower in the highest quartile of RDI (p for trend < 0.001). The proportion of African Americans and Caucasians did not vary significantly across quartiles of RDI.

Tables 3–5 show the distribution of several important CVD risk factors by RDI in each subgroup. The mean levels or proportions of these CVD risk factors were examined within strata by age and gender (men age <65 or ≥65 years and women age <65 or ≥65 years).

There were strong associations between of measures of obesity and RDI quartile (table 3). All subgroups in the first RDI quartile had similar BMIs of 25.8–25.9, which is in the normal range. The mean BMI was higher with higher RDI quartile in all subgroups (p for trend < 0.0001). Of note, this relation appeared to be stronger in the younger than in the older participants, in that the younger participants, and especially the younger women, appeared to have a steeper increase in mean BMI across higher RDI quartiles. In younger men, the mean BMI ranged from 25.9 to 31.4, while it ranged from 25.9 to 29.2 in the older men. In women, the mean BMI in the younger women ranged from 25.8 to 35.3, while in the older women, it ranged from 25.9 to 30.0. Waist and waist-to-hip ratio (table 3) were also associated with higher RDI in a similar fashion in all age-gender groups.

Hypertension and diabetes were more common in the older than in the younger participants, yet both conditions were more strongly associated with higher RDI in the younger men (p for trend < 0.001) and women (p for trend < 0.001) than in the older participants (table 4). The prevalence of hypertension in men and women in the highest quartile of RDI approached the prevalence of the older adults in the lowest quartile of RDI. Diabetes was also more strongly related to the RDI level in the younger than in the older participants. For younger men, the prevalence of diabetes ranged from 3.8 to 12.4 percent, and for younger women, it ranged from 5.8 to 17.5 percent (both p for trend < 0.0001). There was also a trend of greater prevalence of diabetes with higher RDI in the older women, but not in the older men.

Current smoking was less prevalent in all groups as the RDI level increased. The trend was stronger in the younger men ($p < 0.001$) and women ($p = 0.003$), but the pattern was similar in all subgroups. However, we found that the number of pack-years of smoking in those who had ever smoked did not vary significantly in subgroups across RDI quartiles, except for women aged 65 years, for whom the number of pack-years of smoking was lower in the highest quartile of RDI, although of borderline significance (p for trend = 0.05).

Total cholesterol level did not vary across quartiles of RDI, although in the men less than age 65 years there was a slight trend of a modestly higher cholesterol in those with higher RDI (table 5). The mean total cholesterol ranged from 197 to 206 mg/dl (p for trend = 0.0078) in the younger men as the RDI level increased. The HDL cholesterol levels were more clearly and inversely related to the RDI level in women and in men less than age 65 years, but not in men aged 65 or more. For men less than age 65 years, the mean HDL cholesterol level varied from 46.7 to 41.0 mg/dl (p for trend < 0.001), and for women aged less than age 65, it varied from 57.7 to 49.0 mg/dl ($p < 0.0001$). Triglyceride levels were associated with the level of RDI only in the younger men and women.

Abnormalities on resting electrocardiogram were also evaluated as cardiovascular risk factors, although these find-

TABLE 3. Body mass index and waist-to-hip ratio by quartiles of RDI* in SHHS* participants at risk for incident CVD* (n = 4,991), United States, October 1995 to February 1998

	RDI					p value	
	0–<1.25	1.25–<4.0	4.0–<10.7	≥10.7–115.6	Overall	F test (general)	Trend
Body mass index (kg/m²; mean (SD*))							
Men							
<65 years	25.9 (3.8)	27.6 (3.7)	29.7 (4.5)	31.4 (5.0)	29.1 (4.8)	<0.0001	<0.0001
≥65 years	25.9 (3.2)	26.8 (3.3)	27.8 (3.8)	29.2 (4.5)	27.9 (4.1)	<0.0001	<0.0001
Women							
<65 years	25.8 (4.8)	28.1 (4.7)	30.9 (6.0)	35.3 (7.5)	28.7 (6.3)	<0.0001	<0.0001
≥65 years	25.9 (4.2)	27.4 (4.8)	28.3 (4.9)	30.0 (6.4)	27.8 (5.3)	<0.0001	<0.0001
Waist-to-hip ratio (mean (SD))							
Men							
<65 years	0.93 (0.06)	0.94 (0.06)	0.96 (0.06)	0.98 (0.07)	0.96 (0.06)	<0.0001	<0.0001
≥65 years	0.94 (0.08)	0.96 (0.08)	0.97 (0.06)	0.98 (0.06)	0.97 (0.07)	<0.0001	<0.0001
Women							
<65 years	0.84 (0.08)	0.86 (0.08)	0.89 (0.08)	0.91 (0.08)	0.86 (0.09)	<0.0001	<0.0001
≥65 years	0.89 (0.10)	0.90 (0.09)	0.91 (0.09)	0.92 (0.09)	0.90 (0.09)	0.0011	<0.0001

* RDI, Respiratory Disturbance Index; SHHS, Sleep Heart Health Study; CVD, cardiovascular disease; SD, standard deviation.

TABLE 4. Hypertension, diabetes, and smoking (current and pack-year) by quartiles of RDI* in SHHS* participants at risk for incident CVD* (*n* = 4,991), United States, October 1995 to February 1998

	RDI					χ^2: *p* value	
	0–<1.25	1.25–<4.0	4.0–<10.7	≥10.7–115.6	Overall	Association	Trend
Hypertension (%)							
Men							
<65 years	23.3	20.5	30.2	39.0	29.5	0.001	0.001
≥65 years	47.1	43.5	50.0	50.3	48.5	0.448	0.232
Women							
<65 years	24.0	26.9	31.8	41.8	28.6	0.001	0.001
≥65 years	46.8	50.0	50.8	60.6	51.6	0.016	0.004
Self-reported diabetes (%)							
Men							
<65 years	3.8	4.8	6.4	12.4	7.5	0.001	0.001
≥65 years	6.0	13.4	12.6	11.2	11.4	0.221	0.410
Women							
<65 years	5.8	7.4	10.8	17.5	8.8	0.001	0.001
≥65 years	6.8	8.8	9.6	14.3	9.7	0.037	0.006
Currently smoking (%)							
Men							
<65 years	22.5	17.9	6.2	12.0	16.3	0.005	<0.001
≥65 years	10.2	7.6	6.2	5.2	6.6	0.275	0.055
Women							
<65 years	16.7	11.3	10.4	10.3	13.2	0.009	0.003
≥65 years	8.6	9.4	5.5	4.7	7.2	0.085	0.027
	(*n* = 629)	(*n* = 624)	(*n* = 669)	(*n* = 690)			
Pack-years in current or past smokers (mean (SD*))							
Men							
<65 years	22.2 (21.6)	22.6 (20.0)	20.9 (19.6)	25.6 (24.9)	23.1 (22.0)	0.117	0.131
≥65 years	31.0 (34.2)	29.0 (23.7)	32.0 (28.6)	30.5 (27.3)	30.8 (28.1)	0.858	0.893
Women							
<65 years	18.5 (17.9)	17.5 (18.5)	18.8 (19.1)	19.1 (17.6)	18.4 (18.2)	0.892	0.773
≥ 65 years	29.8 (24.2)	25.4 (22.6)	28.4 (29.0)	20.5 (18.9)	26.3 (24.5)	0.057	0.050

* RDI, Respiratory Disturbance Index; SHHS, Sleep Heart Health Study; CVD, cardiovascular disease; SD, standard deviation.

ings are more accurately defined as markers of subclinical CVD. In this subgroup with no history of CVD, major electrocardiogram abnormalities were present in less than 5 percent of those in each of the subgroups and were not related to the quartile of RDI. Left ventricular hypertrophy by electrocardiogram was also present in less than 5 percent of those in each subgroup and was related to the RDI, with borderline significance in only the subgroup of women aged 65 years or less.

For each risk factor, we also evaluated the prevalence or mean levels in the upper subquartiles of the distribution of the RDI. This was done to examine whether risk factor levels might be higher in a nonlinear fashion in those with the more extreme levels of RDI. Continued trends for higher BMI were apparent and statistically significant in all subgroups (figure 1). The slope of the relation appeared to be steeper in the women than in the men in this upper tail of the distribution of RDI. A similar pattern was seen with waist-to-hip ratio. There was also a continued strong association with hypertension in the men and women, in which the steepness of the relation between the prevalence of hypertension and the RDI was greatest in the upper subquartiles. This was more prominent in men and women aged 65 years or less.

It appeared from these analyses that many of these CVD risk factor relations could be due to the higher prevalence of obesity in those with higher RDIs. In separate analyses for men and women, we evaluated the relation of each risk factor to the RDI as a continuous variable, transformed to log (1 + RDI), adjusted first for age and then for age and BMI (table 6 for men and table 7 for women).

The first models were constructed to evaluate the relation between each risk factor and RDI, adjusted for age alone, and shown for men and women separately. For men, BMI, waist-to-hip ratio, hypertension, diabetes, American Indian ethnicity, total cholesterol, lower HDL cholesterol, and higher triglyceride level were each associated with the RDI, while current smoking was inversely associated with RDI.

TABLE 5. Cholesterol, HDL* cholesterol, and triglycerides by quartiles of RDI* in SHHS* participants at risk for incident CVD* (*n* = 4,991), United States, October 1995 to February 1998

	RDI					*p* value	
	0–<1.25	1.25–<4.0	4.0–<10.7	≥10.7–115.6	Overall	*F* test (general)	Trend
Cholesterol (mg/;dl; mean (SD*))							
Men							
<65 years	197.2 (37.2)	202.8 (39.3)	204.9 (40.3)	206.0 (37.8)	203.4 (38.8)	0.043	0.0078
≥65 years	196.3 (32.4)	194.4 (36.0)	198.3 (39.7)	200.4 (35.1)	198.1 (36.4)	0.312	0.0984
Women							
<65 years	203.8 (40.9)	209.3 (39.3)	210.6 (38.8)	205.8 (37.4)	206.8 (39.6)	0.052	0.1272
≥65 years	214.0 (38.3)	217.9 (35.9)	215.8 (39.2)	211.6 (32.3)	215.1 (36.7)	0.239	0.397
HDL cholesterol (mg/dl; mean (SD))							
Men							
<65 years	46.7 (14.5)	42.8 (11.9)	42.7 (12.6)	41.0 (12.3)	42.8 (12.8)	<0.0001	<0.0001
≥65 years	47.0 (14.0)	44.6 (11.2)	44.9 (11.4)	45.3 (13.2)	45.3 (12.4)	0.4544	0.5425
Women							
<65 years	57.7 (16.8)	55.1 (15.8)	51.2 (15.4)	49.0 (16.7)	54.6 (16.6)	<0.0001	<0.0001
≥65 years	60.0 (17.1)	57.5 (15.9)	55.6 (14.7)	54.4 (14.8)	56.9 (15.8)	0.0006	<0.0001
Triglycerides (mg/dl; mean (SD))							
Men	135.6 (130.4)	158.8 (114.9)	166.2 (160.4)	178.9 (131.2)	163.4 (136.6)	0.0023	0.0002
<65 years	125.1 (65.5)	146.5 (85.5)	137.5 (72.5)	144.5 (88.2)	140.5 (81.0)	0.1068	0.1424
≥65 years							
Women	128.5 (83.9)	136.1 (76.8)	163.1 (125.4)	164.9 (95.6)	142.2 (94.4)	<0.0001	0.0001
<65 years	136.3 (69.1)	147.6 (88.2)	152.0 (100.2)	152.9 (88.6)	147.2 (87.8)	0.1325	0.0305
≥65 years							

* HDL, high density lipoprotein; RDI, Respiratory Disturbance Index; SHHS, Sleep Heart Health Study; CVD, cardiovascular disease; SD, standard deviation.

Results were similar in women, except that cholesterol was not associated with RDI and American Indian ethnicity was. The next set of models included adjustment for age and BMI. In these models, in men, only waist-to-hip ratio, hypertension, and total cholesterol level remained associated with RDI, with an inverse association with current

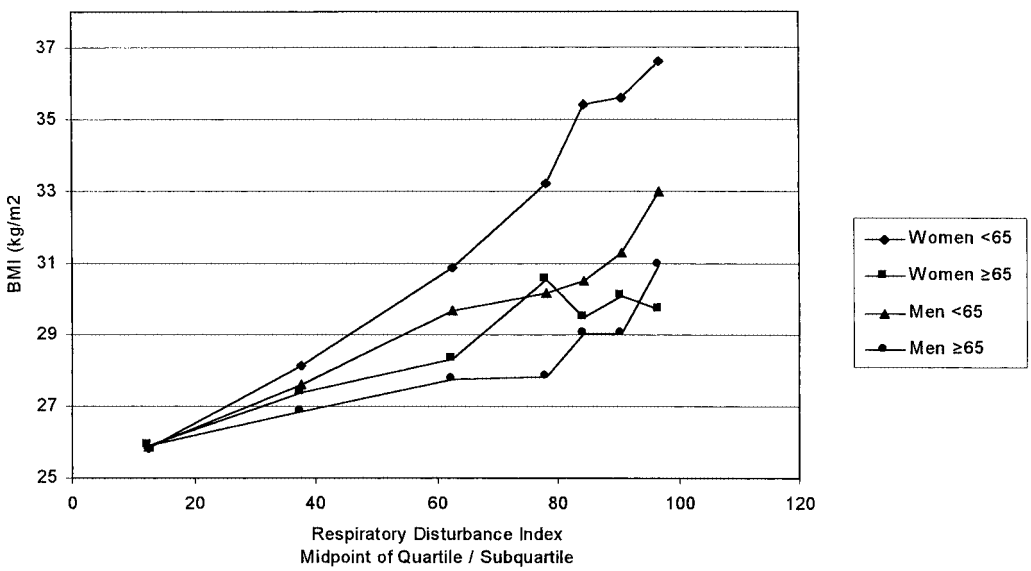

FIGURE 1. Mean body mass index in quartiles and subquartiles of the RDI, stratified by age and gender groups for SHHS participants, United States, October 1995 to February 1998

TABLE 6. Multivariate models: CVD† risk factor associations with log(1 + RDI)† for men only, United States, October 1995 to February 1998

	Adjusted for age: β (SE (β))†	Adjusted for age and BMI†: β (SE (β))	Stepwise model
Age (5 years)			0.074 (0.0148)***
BMI†	0.119 (0.0059)***		0.109 (0.0073)***
Waist-to-hip ratio	4.654 (0.4348)***	1.272 (0.4598)**	1.465 (0.5071)**
Hypertension	0.300 (0.606)***	0.176 (0.0571)**	0.196 (0.0610)**
Diabetes	0.323 (0.1028)**	0.040 (0.0961)	
Smoking			
Current	–0.314 (0.946)***	–0.256 (0.0887)**	–0.310 (0.0903)***
Past	0.042 (0.0623)	–0.032 (0.0585)	
Pack-years (10 years)	0.009 (0.0126)	–0.006 (0.0117)	
Ethnicity			
African American	–0.015 (0.1165)	–0.023 (0.1109)	
American Indian	0.247 (0.1055)*	0.036 (0.0981)	
Other	–0.040 (0.1206)	0.088 (0.1167)	
Cholesterol (25 mg/dl)	0.058 (0.0192)**	0.0065 (0.0179)***	0.065 (0.0196)***
HDL† cholesterol (5 mg/dl)	–0.062 (0.0117)***	–0.004 (0.0114)	
Triglycerides (25 mg/dl)	0.028 (0.0064)***	0.009 (0.0061)	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
† CVD, cardiovascular disease; RDI, Respiratory Disturbance Index; SE, standard error; BMI, body mass index; HDL, high density lipoprotein.

smoking. In women, three factors were inversely associated—African-American ethnicity, HDL cholesterol, and current smoking, while triglyceride level was positively associated with the RDI. Forward stepwise models yielded consistent results in that the same factors of age, BMI, waist-to-hip ratio, total cholesterol, hypertension, and not currently smoking were independently associated with the RDI in men. In women, age and BMI were positively and independently associated with RDI, with current smoking, African-American ethnicity, and higher HDL cholesterol being protective.

DISCUSSION

Participants in the SHHS, including many persons with undiagnosed, mild-to-moderate degrees of sleep-disordered breathing, had elevated cardiovascular risk factors at the time of the baseline sleep study. There was a 5-year difference in mean age from the lowest quartile of RDI to the highest, and the proportion of men increased about twofold from the lowest to the highest quartile, consistent with previous clinical and population studies (13). Across age and gender categories, all participants with a higher RDI had a higher mean BMI, a higher mean waist-to-hip ratio, and a greater prevalence of hypertension and diabetes. Participants less than age 65 years were more likely to have a significant inverse trend in the levels of HDL cholesterol and triglycerides as the level of RDI increased. Total cholesterol was not related to the level of RDI.

Current smoking was inversely proportional to the level of RDI, although pack-years of exposure did not differ, suggesting that those with higher RDIs might have quit smoking in relation to the severity of their sleep-disordered breathing. This relation is opposite of that seen in the Wisconsin Sleep Study cohort, in which current smokers had an increased risk of snoring as well as mild-to-severe apnea as measured by home polysomnography (14). The lower prevalence of current smoking with increasing RDI in this study should decrease risk of future acute events. Smoking had been reported to be used as a method of weight control in some persons (15). More detailed study of the relation of smoking habits and attempted weight control to the degree of sleep-disordered breathing in this multiethnic cohort would be useful and might explain the inverse relation between RDI and current smoking.

The risk factor pattern of hypertension, diabetes, and hypertriglyceridemia is commonly seen those who are obese (16). The multivariate models in this study suggest that the degree of obesity associated with the degree of sleep-disordered breathing, along with age and gender, explains most of the elevation in the other CVD risk factors, with the exception of hypertension in men. Thus, a thorough evaluation of weight

TABLE 7. Multivariate models: CVD† risk factor associations with log(1 + RDI)† for women only, United States, October 1995 to February 1998

	Adjusted for age: β (SE (β))†	Adjusted for age and BMI†: β (SE (β))	Stepwise model
Age (5 years)			0.200 (0.0134)**
BMI	0.104 (0.0043)**		0.101 (0.0051)**
Waist-to-hip ratio	3.253 (0.3184)**	0.601 (0.322)	
Hypertension	0.259 (0.0594)**	0.069 (0.0553)	
Diabetes	0.551 (0.098)**	0.128 (0.0919)	
Smoking			
Current	–0.356 (0.0933)**	–0.283 (0.0861)**	–0.349 (0.0922)**
Past	0.052 (0.0612)	–0.005 (0.0567)	
Pack-years (10 years)	–0.0200 (0.0166)	–0.024 (0.0151)	
Ethnicity			–0.364 (0.1094)**
African American	–0.126 (0.1079)	–0.374 (0.1009)**	
American Indian	0.511 (0.0947)**	0.003 (0.0889)	
Other	–0.070 (0.1155)	–0.164 (0.1075)	
Cholesterol (25 mg/dl)	0.015 (0.0187)	0.023 (0.0170)	
HDL† cholesterol (5 mg/dl)	–0.082 (0.0088)**	–0.027 (0.0086)*	–0.028 (0.0092)*
Triglycerides (25 mg/dl)	0.050 (0.0079)**	0.020 (0.0073)*	

* $p < 0.01$; ** $p < 0.001$.
† CVD, cardiovascular disease; RDI, Respiratory Disturbance Index; SE, standard error; BMI, body mass index; HDL, high density lipoprotein.

history may help to determine to what degree obesity is antecedent to the development and progression of sleep-disordered breathing. Many of the participants in this study have prior weight data that will be examined retrospectively.

The pattern of fat distribution was independently associated with a higher RDI in men, but not in women, in these analyses. There is growing consensus that the intraabdominal or visceral depot of fat may relate more strongly than weight to the risk of CVD because it is highly metabolically active and is associated with elevated levels of coagulation factors and markers of inflammation (17). Although the waist-to-hip ratio was not independently associated with a high RDI in women, the risk factor pattern seen in this cohort of a greater risk of diabetes and higher triglycerides with higher RDI suggests that those with higher RDIs could have a more central distribution of body fat. These relations must be explored within the subgroups of similar BMI. In the Wisconsin Sleep Study, the gender relation was minimal when adjusted for BMI and body fat distribution, suggesting that the more central body fat distribution of men may explain the gender difference in the prevalence of sleep-disordered breathing (18). More recently, a study of visceral fat quantified by computed tomography scan in obese and apneic patients found that those with apneas had a higher proportion of visceral fat (19).

CVD risk factors were more likely to be elevated in the younger (aged <65 years) than the older (age ≥65 years) participants. This is consistent with the known decrease in the predictive value of CVD risk factors in older adults, which is due in part to the effects of survivorship and disease (20). We excluded those with established clinical CVD to avoid this as a confounder of the relations between risk factors and RDI. Furthermore, we assessed the presence of markers of subclinical disease by examining the electrocardiogram and found no relation with major abnormalities and little with left ventricular hypertrophy. Thus, these relations do not appear to be confounded by the presence of subclinical CVD in older participants.

Adjustment for age did not negate the relation of most of the risk factors studies with the RDI, and age remained associated with a higher RDI after multivariate adjustment. Overall, its effect was relatively small, in that there was only a 5-year difference in the mean age of those with the highest RDI compared with the lowest. Others have reported that the RDI increases with age, but these studies have not excluded those with established CVD (21).

At each level of RDI, the expected difference in CVD risk factors due to gender is quite apparent, yet the within-gender relations between risk factors and RDI are similar, especially in those under age 65 years. For example, HDL cholesterol levels are higher in women at every level of

RDI, yet the relation between HDL cholesterol and RDI in the younger men and women is similar. Of note, for each level of RDI above the first quartile, women tend to have a higher BMI than do men. In addition, women less than age 65 years appeared to have the steepest rise in BMI with increasing RDI. The relation of RDI to BMI and gender is similar to that reported in the Wisconsin Sleep Study cohort. In that study, women had a higher BMI than men did at each level of RDI. Women with an RDI of 15 or more had a mean of 41.4 compared with 33.3 in men (22). Thus, women with a given elevated level of RDI are heavier than men. This suggests that the level of obesity needed to precipitate apnea is greater in women than in men; conversely, men appear to be more susceptible to apnea at lower BMI than do women.

Although American Indians were more likely to be in the two highest quartiles, there was a weaker relation of the RDI with ethnicity than might have been expected with multivariate adjustment in gender-specific models. This may be due in part to sample size, as American Indian ethnicity was associated with RDI in age-adjusted, gender-specific models. Of note, this relation disappeared with additional adjustment for BMI. In addition, when we initially excluded those with prevalent CVD from the analysis, we eliminated relatively more African Americans and American Indians than Caucasians, and this may have further minimized the relation between either ethnicity or RDI. Others have found that the adjusted prevalence of sleep apnea is higher in African-American children (23) and young adults (24) than in Caucasians. The exclusions as well as participation bias could effect both apparent associations or lack of associations with ethnicity. Because these are volunteers from larger cohort studies, these data cannot be used as prevalence estimates for the source populations.

If the level of RDI proves to be related independently to future incident CVD in this cohort in a dose-dependent fashion, several causal pathways are possible. Higher BMI may be antecedent in the causal pathway. If so, the association of RDI with BMI in this moderate range implies that prevention of weight gain would be central to public health efforts to prevent sleep-disordered breathing as well as other consequences of obesity. The lack of a strong relation of the RDI with total cholesterol, but a strong association with lower HDL cholesterol, suggests that increased low density lipoprotein cholesterol is not in the causal pathway. Similarly, the inverse association with current cigarette smoking suggests that it is not a confounder of a potential relation between RDI and CVD. The presence of an independent association of the RDI level with hypertension, although significant only in men, suggests that it may be in the causal pathway or may be related to a correlate of both, such as obesity. Because of the acute and profound effects of sleep-disordered breathing on vascular tone, hypertension is thought to be a major mechanism by which sleep-disordered breathing might influence future CVD risk (25).

There were apparent departures from linearity in the upper tail of the distribution for obesity and hypertension. This could lead to a higher estimate of the overall linear association of these factors with RDI than actually exists in the midrange of RDI. We did not formally test for a difference in the slope between the subquartiles of the fourth and the first three quartiles. However, the pattern of these relations suggests that if RDI proves to predict CVD and if the mechanism is via its association with other CVD risk factors and obesity, one might anticipate that the risk would be most apparent for those within the fourth quartile of RDI.

Several important limitations must be considered in evaluating these findings. First, the observational nature of the study does not allow any conclusions to be drawn regarding the causal pathway of these associations. Furthermore, residual confounding due to measurement error or to unknown confounders may have resulted in incomplete adjustment or overestimation of these associations. However, in combining data sets across the studies, variations in risk factor assessment across time and with slight protocol variations could also have decreased the power to detect associations. The use of self-reported data for CVD, hypertension, and diabetes is suboptimal because of underestimation and misclassification, further limiting these analyses. As noted, these participants are volunteers from larger cohort studies. These data should not be used for population prevalence estimates, although this should not affect the internal validity of the study. Finally, the sample size was relatively low in some subgroups, especially in the younger women, limiting power to detect associations in the upper tail of RDI.

Evaluation of the role of sleep-disordered breathing as an independent risk factor for CVD in this cohort will require careful adjustment for multiple CVD risk factors, especially BMI. If sleep-disordered breathing proves in future follow-up to be a risk factor for CVD events, it is likely that part of this association would be mediated by the presence of higher CVD risk factors in those with higher RDI.

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