JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Lack of Regular Exercise, Depression, and Degree of Apnea are Predictors of Excessive Daytime Sleepiness in Patients with Sleep Apnea: Sex Differences

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Background: Apnea, depression, and metabolic abnormalities are independent predictors of excessive daytime sleepiness (EDS) in patients with sleep apnea. Exercise is beneficial for apnea, depression, and metabolic abnormalities; however, its association with EDS is not known.

Study Objectives: To evaluate the contribution of lack of regular exercise, depression, and apnea severity on daytime sleepiness in patients with sleep apnea.

Participants and Design: One thousand one hundred six consecutive patients (741 men and 365 women) referred to the sleep disorders clinic for symptoms consistent with sleep apnea. Daytime sleepiness was assessed with the Epworth Sleepiness Scale and activity was evaluated with a quantifiable Physical Activity Questionnaire.

Results: Compared with women, men had a higher apnea hypopnea index (AHI) (40.4 ± 1.2 vs 31.0 ± 1.8), lower body mass index (BMI) (35.3 ± 0.3 kg/m^2 vs 39.6 ± 0.5 kg/m^2), and higher rate of regular exercise (39.1% vs 28.8%)($p < 0.05$). Linear regression analysis of the total sample after adjusting for age, BMI, sex, central nervous system medication, and diabetes showed that logAHI, depression, and lack of regular exercise were significant predictors of sleepiness. Predictors of mild or moderate sleepiness for both sexes were depression and logAHI, whereas predictors of severe sleepiness for men were lack of regular exercise, depression, and minimum SaO_2 and, for women, logAHI.

Conclusions: In obese apneic patients, lack of regular exercise (only in men), depression, and degree of apnea are significant predictors of EDS. This association is modified by sex and degree of sleepiness. Assessment and management of depression and physical exercise should be part of a thorough evaluation of patients with sleep apnea.

Keywords: Sleep apnea, excessive daytime sleepiness, depression, exercise, sex differences

Citation: Basta M; Lin HM; Pejovic S; Sarrigiannidis A; Bixler EO; Vgontzas AN. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: sex differences. *J Clin Sleep Med 2008*;4(1):19-25.

Excessive daytime sleepiness (EDS) is very common in modern societies. In the general population, the prevalence of EDS is estimated to range between 5% and 20%.[1-9] EDS and fatigue are the most common complaints of patients referred to the sleep disorders clinic.[10,11] Moreover, they are potential risk factors for cardiovascular disease and mortality,[12,13] are associated with a negative perception of general health and quality of life,[14,15] and raise major public safety concerns.[16]

EDS is commonly assumed to be primarily the result of disturbed or inadequate sleep. Sleep deprivation and sleep apnea are known predictors of EDS. However, in previous studies, the association between EDS and sleep apnea has been found to be significant but rather modest. Two large studies in general population samples demonstrated that, among patients with sleep apnea, approximately 20% to 40% reported EDS.[17,18] On the other hand, it has been found that conditions highly comorbid with sleep apnea, such as obesity, are associated with EDS independent of sleep apnea.[19-21] Furthermore, large population-based epidemiologic studies have shown that the presence of EDS is strongly associated with depression, obesity, and diabetes.[7-9] More recently, physical activity has been suggested as a novel significant factor for sleepiness in the general population after controlling for body mass index (BMI), apnea, age, and other covariates.[8,9] Studies in sleep apneics have found that sleep fragmentation, nocturnal hypoxemia, depression, and age are independent predictors of daytime sleepiness in this group.[22-25] However, to our knowledge, no studies have investigated the effect of exercise on daytime sleepiness in patients with sleep apnea.

The aim of this study was to determine the association between EDS and lack of regular exercise quantified by a standardized questionnaire, as well as depression and severity of apnea, in a large clinical sample of patients with sleep apnea.

Disclosure Statement
This was not an industry supported study. The authors have indicated no financial conflicts of interest.

Submitted for publication July, 2007
Accepted for publication October, 2007
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SUBJECTS AND METHODS

Subjects

Participants for this study were retrospectively selected from the sleep clinic database of the Sleep Disorders Center of Milton S. Hershey Medical Center. Eligible patients were all those who were evaluated in the Sleep Center between September 2001 and July 2005 due to symptoms consistent with sleep apnea, i.e., reported breath cessations, snoring, EDS, and cardiovascular symptoms. Inclusion criteria were (1) age ≥ 18years and (2) sleep apnea defined as an apnea-hypopnea index (AHI) of 5 or more events per hour on the overnight polysomnogram plus the presence of daytime sleepiness and/or cardiovascular symptoms. Exclusion criterion was continuous positive airway pressure treatment during the last year prior to the clinic visit. Of the 2471 patients who had overnight polysomnography in our laboratory, 480 were excluded because they were younger than 18 years old, 740 because their AHI on evaluation was less than 5 events per hour, and 811 because they had already been on continuous positive airway pressure treatment. One thousand one hundred and six individuals (741 men, 365 women) were included in this study.

Medical Evaluation

Patients underwent a thorough medical evaluation including physical examination, medical and sleep history, and an electrocardiogram. 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 5-minute period following 10 minutes of rest in the supine position. Height was measured in centimeters using a stadiometer. Weight was measured in kilograms using an electronic scale. Body mass index (BMI) was calculated from height and weight (kg/m^2). Patients were classified as having depression, diabetes, or cardiovascular disease if they had a current diagnosis of the above disorders on the evaluation.

Sleep Laboratory Recordings

All subjects were evaluated for 1 night for 8 hours (2300-0700) in the sleep laboratory in sound-attenuated, light- and temperature-controlled rooms following the standard polysomnographic procedures.[26] During this evaluation, they were continuously monitored using 16-channel polygraphs (24 analog channel and 10 dc channel TS amplifier using Gamma software, Grass-Telefactor, West Warwick, RI). The 3-channel electroencephalogram, 3-channel electrooculogram, and an electromyogram were recorded. The sleep records were subsequently scored independently, according to standardized criteria.[26] Respiration was monitored throughout the night by thermocouples at the nose and mouth (Protech Thermocouple Airflow Sensor, Protech Services INC, Mukilteo, WA), and nasal pressure (MP45-871 ±2 cm H_2O, Validyne Engineering Corp, North Ridge, CA) and thoracic strain gauges. All-night recordings of hemoglobin oxygen saturation (SaO_2) were obtained with a cardiorespiratory oximeter (Model 8800, Noonin Medical, Plymouth, MN) attached to the finger. An apnea was considered present if a breath cessation exceeded 10 seconds. Each apnea was categorized as obstructive (chest wall movement present) or central (chest wall movement absent). In addition, hypopneas were considered present when a reduction in airflow of approximately 50% was indicated at the nose or mouth and was associated with a reduction of 3% SaO_2.

Assessment of Physical Activity, Sleepiness, and General Health

All patients completed 3 self-assessment questionnaires administered to them the night before polysomnography.

The patient's physical activity level was assessed with a standard questionnaire developed by Wolf et al.[27] The patient was asked to report the average time per week spent doing each of the following 8 activities: walking/hiking, jogging, running, bicycling, calisthenics, tennis/squash/racquetball, lap swimming, and other aerobic activities, such as lawn mowing.[27] These average times per week were multiplied by the typical energy expenditure required for each activity as expressed in metabolic equivalents (METs), where 1 MET is the energy expended by sitting quietly and is equivalent to 3.5 mL of oxygen uptake per kilogram of body weight per minute ($kcal/kg^{-1}/min^{-1}$).[28] The METs were totaled yielding MET hours per week. An activity score of 20 or more MET hours per week was used to denote subjects who practiced regular exercise.[28]

Daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS), a well-validated questionnaire quantifying the self-reported disclosure of the expectation of "dozing" in a variety of situations.[29] The total ESS score ranges from 0 to 24.

Finally, the General Health Questionnaire was used to assess participants' medical conditions, including diabetes, hypertension, hyperlipidemia, cardiovascular disease (heart disease and stroke), allergies, asthma, psychiatric disorders such as depression (including suicidal thoughts and attempts), medications, and sleeping habits. Subjective sleep duration was assessed with the question "How many hours do you usually sleep at night?" In addition, daytime napping was assessed with the question "Do you take naps?" Those who responded "often" or "always" were categorized as "nappers."

Statistical Analyses

The primary objective of the analysis was to evaluate the associations between EDS and regular exercise, depression, and severity of apnea in patients with sleep apnea, after controlling for age, BMI, sex, diabetes, and central nervous system (CNS) medication use. CNS medications included antidepressants, anxiolytics, hypnotics, antipsychotics, stimulants, and antiparkinsonian medication. Because degree of sleepiness has clinical importance in terms of the functional impairment, the sample was further stratified into 3 groups based on the patients' daytime sleepiness as quantified by the ESS score: ESS score of 10 or less (no EDS), an ESS score between 11 and 16 (mild to moderate EDS), and an ESS score of 17 or greater (severe EDS). In this study, women with sleep apnea, as compared with men, were significantly heavier, had a lower AHI, and exercised less frequently. Therefore, the second objective of the analysis

Table 1—Demographic, Sleep and Respiratory Data and Clinical Characteristics: Comparisons Between Men and Women Within Each of the 3 EDS Subgroups and Comparisons Among the 3 EDS Subgroups in Men and Women Separately

	Total Group (N = 1106)		EDS					
			No (n = 528)		Mild/Moderate (n = 385)		Severe (n = 193)	
	Men (n = 741)	Women (n = 365)	Men (n = 364)	Women (n = 164)	Men (n = 255)	Women (n = 130)	Men (n = 122)	Women (n = 71)
Age, y	50.8 ± 0.5	51.3 ± 0.7	52.1 ± 0.7[b]	52.6 ± 0.9	49.5 ± 0.8[b]	50.3 ± 1.2	50.0 ± 1.1	50.1 ± 1.5
AHI	40.4 ± 1.2[a]	31.0 ± 1.8[a]	38.0 ± 1.6[a]	25.1 ± 2.2[a,c]	42.1 ± 2.1[a]	31.5 ± 3.0[a,d]	43.7 ± 3.0	43.9 ± 4.9[c,d]
Lowest SaO_2	79.9 ± 0.3	80.2 ± 0.4	80.7 ± 0.4[c]	81.3 ± 0.5[c]	79.8 ± 0.5[d]	79.5 ± 0.8	77.8 ± 0.9[c,d]	78.8 ± 1.0[c]
BMI , kg/m^2	35.3 ± 0.3[a]	39.6 ± 0.5[a]	34.8 ± 0.4[a,c]	38.7 ± 0.8[a,b]	35.4 ± 0.5[a]	41.7 ± 1.0[a,b]	36.5 ± 0.7[a,c]	39.1 ± 1.1[a]
ESS score	10.8 ± 0.2	11.5 ± 0.3	6.3 ± 0.1[b,c,d]	6.5 ± 0.2[b,c,d]	13.2 ± 0.1[b,c,d]	13.5 ± 0.2[b,c,d]	19.3 ± 0.2[b,c,d]	19.2 ± 0.2[b,c,d]
Activity score	23.9 ± 1.4[a]	18.7 ± 1.6[a]	26.3 ± 2.2[a]	18.7 ± 2.8[a]	22.7 ± 2.2	16.7 ± 2.0	19.3 ± 2.2	22.3 ± 3.4
Regular exercise, %	39.1[a]	28.8[a]	43.7[a,e]	26.8[a]	36.9[a,e]	28.5[a]	30.3[e]	33.8
Blood pressure, mmHg								
Systolic	139.0 ± 0.7	139.9 ± 1.1	138.5 ± 1.0	138.7 ± 1.6	139.6 ± 1.1	141.9 ± 1.8	139.1 ± 1.8	139.1 ± 2.6
Diastolic	81.1 ± 0.4[a]	79.2 ± 0.6[a]	80.7 ± 0.6[c]	80.0 ± 0.9	80.8 ± 0.7[a,d]	78.4 ± 0.9[a]	83.3 ± -0.9[a,c,d]	78.6 ± 1.4[a]
Cardiovascular problems, %	31.4[a]	21.9[a]	33.4[a]	24.7[a]	29.8	20.9	28.9	17.1
Depression, %	18.6[a]	37.4[a]	14.4[a,e]	33.7[a]	22.4[a,e]	42.3[a]	23.3[a,e]	36.6[a]
Insomnia, %	9.8[a]	18.9[a]	10.8[a]	22.4[a]	8.8[a]	17.1[a]	8.4[a]	14.5[a]
Diabetes, %	16.0[a]	21.1[a]	15.8	20.1	16.5	20.0	15.7	25.4
CNS medications, %	29.8[a]	47.8[a]	31.6[a]	47.3[a]	29.8[a]	45.7[a]	24.2[a]	52.2[a]
Sleep stage, %								
1	24.9 ± 0.7[a]	19.2 ± 0.9[a]	24.2 ± 0.9[a]	17.7 ± 1.1[a,c]	25.0 ± 1.3[a]	18.4 ± 1.5[a,d]	26.9 ± 1.8	24.1 ± 2.4[c,d]
REM	9.9 ± 0.3[a]	11.1 ± 0.5[a]	10.2 ± 0.4[a]	11.9 ± 0.7[a]	9.8 ± 0.5	10.6 ± 0.7	9.2 ± 0.8	10.4 ± 1.1
SWS	1.4 ± 0.2[a]	3.6 ± 0.4[a]	1.5 ± 0.2[a,c]	4.3 ± 0.7[a]	1.3 ± 0.2[a]	3.1 ± 0.6[a]	1.5 ± 0.5[e]	3.0 ± 0.8
TST	69.5 ± 0.6	71.2 ± 0.9	68.4 ± 0.9	70.1 ± 1.3	71.6 ± 0.9	72.4 ± 1.5	68.7 ± 1.5	71.3 ± 1.8
Subjective sleep duration, min	406 ± 4	407 ± 6	413 ± 6	401 ± 9	400 ± 7	409 ± 10	400 ± 10	417 ± 13
Napping, %	30.4[a]	37.8[a]	16.7[a,e]	25.0[a,e]	39.6[e]	36.9[e]	52.1[a,e]	69.0[a,e]

Data are expressed as mean ± SEM and percentages. AHI refers to apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; CNS, central nervous system; REM, rapid eye movement; SWS, slow-wave sleep; TST, total sleep time. Cardiovascular problems include heart trouble and stroke.

[a]Comparisons between men and women in the same excessive daytime sleepiness (EDS) group, $p < 0.05$

[b]Comparisons between no EDS vs mild/moderate EDS, $p < 0.05$

[c]Comparisons between no EDS vs severe EDS, $p < 0.05$

[d]Comparisons between mild/moderate EDS vs severe EDS, $p < 0.05$

[e]Comparisons among no EDS vs. mild/moderate EDS vs severe EDS, $p < 0.05$

is to investigate the role of sex in the aforementioned associations.

Sex-stratified descriptive data, reported as means ± SEM and percentage (%), are shown for the entire sample and for the 3 EDS groups (Table 1). Comparisons of continuous variables, including demographic, systolic and diastolic blood pressure, and sleep parameters across the 3 EDS groups were performed for each sex separately using the 1-way analysis of variance. Similarly, comparisons of binary variables, including regular exercise, medical conditions, CNS medication use, napping, and depression, were performed using the χ^2 test. Sex differences on the above variables were assessed within each EDS group by using a 2-sample *t*-test for continuous and χ^2 test for binary variables, respectively.

In the first analysis, sex-, age-, BMI-, diabetes- and CNS medication use-adjusted linear regression was performed using the total ESS score as the outcome variable and regular exercise, depression, and logarithm-transformed AHI (logAHI) as the potential predictors. The backward selection was used to determine which of the 3 variables were specifically predictive for ESS. The AHI was transformed to the logarithmic scale to normalize the distribution and alleviate the necessity of excluding potential outliers from the analysis. Furthermore, interactions of sex with logAHI, depression, and regular exercise were also tested after the main-effects model was examined.

Following the linear regression analysis, 2 logistic regression analyses with backward selection comparing the mild or moderate group versus the no EDS group and the severe EDS group versus the no EDS were performed separately. The independent variables included regular exercise, depression, and logAHI, as well as their respective interactions with sex, after adjusting for sex, age, BMI, diabetes, and CNS medication use. Statistically significant sex interactions in the final step were found in the no versus severe EDS group (logAHI by sex and regular exercise by sex). Therefore, the analysis among these groups was repeated separately for men and women.

Finally, because oxygen saturation (SaO_2) is also commonly used as a surrogate for degree of apnea, we investigated its competing role against AHI in predicting daytime sleepiness in all 3 aforementioned regression analyses by allowing both logAHI and minimum SaO_2 in the initial backward selection process. All statistical analyses were performed using the SAS version 9.1.3 (SAS, Inc., Cary, NC). The significance level for all analyses was 0.05.

RESULTS

Demographic, Sleep and Respiratory Data, and Clinical Characteristics: Sex Differences

Descriptive data of the entire group of women and men, as well as of the 3 subgroups, are shown in Table 1. Comparisons of the total women and men samples revealed significant differences between the two sexes. Mean age was similar between women and men (51.3 ± 0.7 vs 50.8 ± 0.5 years, $p > 0.1$). Women compared with men were significantly heavier (BMI: 39.6 ± 0.5 kg/m^2 vs 35.3 ± 0.3 kg/m^2, $p < 0.05$), and had lower AHI (events/h) (31.0 ± 1.8/h vs 40.4 ± 1.2/h, $p < 0.05$). In terms of sleep stages, men compared with women, had more disturbed sleep with a higher percentage of stage 1 sleep (24.9% ± 0.7% vs 19.2% ± 0.86%, $p < 0.05$), a lower percentage of rapid eye movement sleep (9.9% ± 0.3% vs 11.1% ± 0.5%, $p < 0.05$), and a lower percentage of slow-wave sleep (1.4 ± 0.2 vs 3.6 ± 0.4, $p < 0.05$). There were no differences between men and women in terms of sleep duration, whereas women tended to nap more frequently than men (37.8% vs 30.4% $p < 0.05$). Furthermore, women, compared with men, had a significantly higher prevalence of depression (37.4% vs 18.6%, $p < 0.05$), CNS medication use (47.8% vs 29.8% $p<0.05$), and diabetes (21.1% vs 16.0%, $p < 0.05$). On the contrary, women, compared with men, had significantly lower rate of regular exercise (28.8% vs 39.1%, $p < 0.05$), as well as prevalence of cardiovascular disease (21.9% vs 31.4%, $p < 0.05$).

Differences between men and women within each EDS subgroup are also reported in Table 1. The pattern of the differences between men and women within each EDS subgroup were similar to those in the total group. In terms of differences among the 3 EDS subgroups within each sex, in women, the primary difference was AHI. Specifically, AHI was lower in the no EDS group (25.1 ± 2.2 /h), intermediate in the mild or moderate EDS group (31.5 ± 3.0 /h), and highest in the severe EDS group (43.9 ± 4.9 /h) ($p = 0.041$). In men, among the 3 EDS subgroups, the main differences were observed in exercise and depression. Specifically, regular exercise rate was highest in the no EDS group, intermediate in the mild or moderate EDS group, and lowest in the severe EDS group (43.7% vs 36.9% vs 30.3%, $p < 0.05$). Furthermore, prevalence of depression was lowest in the no EDS group, intermediate in the mild or moderate group, and highest in the severe EDS group (14.4% vs 22.4% vs 23.3%, $p < 0.05$). There was no difference in subjective sleep duration among the 3 EDS groups, whereas patients with more severe sleepiness tended to nap more ($p < 0.05$) (Table 1).

Predictors of EDS

Linear regression analysis of the total sample, after adjusting for age, BMI, sex, CNS medication use, and diabetes showed that regular exercise, depression, and logAHI were all significant predictors of daytime sleepiness. The β coefficients, standard errors, and p values of the linear regression model are presented in Table 2. No significant sex interactions with these predictors were observed.

Binary logistic regression analysis contrasting the mild or moderate EDS group with the no EDS group showed that significant predictors of mild or moderate sleepiness were depression (odds ratio [OR]= 1.69, 95% confidence interval [CI]: 1.15 to 2.49, $p < 0.01$) followed by logAHI, which was close to significant (OR= 1.48, 95% CI: 0.99 to 2.21, $p < 0.1$). Neither regular exercise nor any of the sex interactions was significant.

Table 2—Multiple Regression Model for Epworth Sleepiness Scale Total Score Using Total Sample

Variable	β coefficient	Standard Error	p value
Intercept	11.56	1.459	< 0.001
Age[a]	-0.034	0.014	0.01
BMI[a]	0.019	0.023	0.40
Sex[a]	-0.677	0.398	0.09
CNS Medication[a]	-0.694	0.420	0.10
Diabetes[a]	0.197	0.471	0.67
Regular Exercise	-0.708	0.367	0.05
logAHI	1.421	0.471	0.002
Depression	0.941	0.461	0.04

BMI refers to body mass index; CNS, central nervous system; AHI, apnea-hypopnea index.
[a]Forced in the model.

When the severe EDS group was compared with the no EDS group, depression, as well as the interaction of sex with regular exercise and logAHI, were significant predictors of EDS (both $p < 0.05$). As a result, the analysis was further stratified by sex, forcing age, BMI, depression, CNS medication, and diabetes in the model. Specifically, in the stratified analysis for women with severe sleepiness, the OR of logAHI is 4.36 (95% CI: 2.01 to 9.47, $p < 0.01$), which is considerably larger compared with that for women with mild or moderate sleepiness. In men with severe sleepiness, regular exercise was associated with a reduction of sleepiness by nearly 41% (OR = 0.59, 95% CI: 0.36 to 0.97 $p < 0.05$). The effect of depression in men with severe sleepiness (OR = 2.24, 95% CI: 1.15 to 4.39, $p < 0.1$) is larger than that for women with severe sleepiness (OR = 1.15, 95% CI: 0.56 to 2.37, $p > 0.1$). Finally, the results for men with severe sleepiness remain nearly unchanged even after adjusting for AHI.

AHI vs SaO_2

In the linear regression analysis when both logAHI and SaO_2 were considered in the initial model selection process, both logAHI and minimum SaO_2 were significant. However, there was little gain in the total R-squares (< 1%) by using SaO_2 as the predictor. For the binary logistic regression analysis that compared the mild or moderate EDS group versus the no EDS group, logAHI was a stronger predictor than SaO_2. Unlike log AHI, the effects of SaO_2 were not significant ($p < 0.4$). For the comparison between the severe EDS and the no EDS groups, both logAHI and SaO_2 were individually significantly associated with EDS. But when competing simultaneously during the model selection process, logAHI was a stronger predictor for EDS than was SaO_2. For women, SaO_2 was not significant, whereas logAHI remained significant as before. Interestingly though, for men, SaO_2, but not logAHI, was a significant predictor. Specifically, among apneic men, for every 10% decrease in the minimum SaO_2 level, the odds of having severe EDS increases by 26% (OR = 0.74, 95% CI: 0.55 to 0.99, $p < 0.05$).

DISCUSSION

The primary finding of this study is that, in obese patients with sleep apnea, in addition to degree of apnea, lack of regular exercise and depression are significant independent predictors of EDS after adjusting for age, BMI, sex, diabetes, and CNS medication use. Furthermore, we observed that these associations were modified by sex and degree of sleepiness. Specifically, predictors of mild or moderate sleepiness were degree of apnea and depression for both sexes; in women with severe sleepiness, AHI was a significant predictor of sleepiness, whereas, in men, minimum SaO_2, lack of regular exercise, and depression were significant predictors of sleepiness.

To our knowledge, this is the first study to show that lack of regular exercise, as quantified with a standardized instrument, is an independent predictor of daytime sleepiness in men with sleep apnea. Lack of regular exercise was not a significant predictor of sleepiness in women because, in our study, women tended to exercise significantly less, as compared with men. The mechanism through which exercise improves sleepiness in patients with sleep apnea is not clear. Three small studies that investigated the effect of exercise on respiratory parameters in patients with sleep apnea concluded that exercise decreases the AHI of these patients,[30-32] whereas a large community-based cohort showed that at least 3 hours of vigorous exercise is associated with a decrease in the prevalence of sleep-disordered breathing.[33] Also, in another large study, lack of exercise was associated with increased severity of sleep apnea independently of BMI and other somatometric parameters.[34] However, in our study, the effects of exercise on sleepiness were independent of the degree of apnea. Another possibility is that exercise improves sleepiness by affecting mood.[35] In our study, its beneficial effects were independent of depression. Additionally, exercise improves metabolic factors, such as visceral fat and insulin resistance,[36,37] that have been shown to be independently associated with EDS.[7,38] Further studies are needed to examine this hypothesis. From a clinical standpoint, our study suggests that levels of exercise should be part of the comprehensive clinical assessment of patients with sleep apnea and that regular exercise should be recommended to those patients that exercise less.

Another important finding of this study is that depression is a significant predictor of sleepiness in patients with sleep apnea. Depression was found as a predictor for mild or moderate sleepiness for both sexes, whereas, in severe sleepiness, depression was a predictor only in men. Depression, in the general population, has been shown to be a strong and significant predictor of daytime sleepiness and fatigue.[7,8] Three small studies in patients with sleep apnea report that depression is a significant predictor of sleepiness and fatigue.[39-41] In our large study, depression remained a significant predictor of sleepiness even after adjusting for confounding factors, such as age, AHI, BMI, and physical activity.

In the current study, the prevalence of depression was high among patients with sleep apnea, both in men and women. A higher prevalence of depressive symptoms in patients with sleep apnea, compared to the general population, has been reported since the 1980s. Kales et al first showed that 56% of patients with severe sleep apnea had high scores on the depression scale in the Minnesota Multiple Personality Inventory.[42] They also demonstrated a "somatic-neurotic" type profile in their Minnesota Multiple Personality Inventory, indicating a reactive type of depression in response to a major illness. Since then, most but not all studies have confirmed the increased prevalence of depression and depressive symptomatology among patients with sleep apnea.[43-45] The favorable effect of continuous positive airway pressure treatment on depressive symptoms suggests the reactive nature of these symptoms in some patients with sleep apnea.[46] However, ours and other studies are cross-sectional, and they do not allow us to distinguish whether depression in sleep apnea is primary or secondary. Future longitudinal studies should address this question.

The sex ratio for depression in our study was 2:1 (women: men), consistent with the sex ratio in the general population.[43,47] This finding does not support previous reports that depression is a specific manifestation of sleep apnea in women.[48] However, the high comorbidity of sleep apnea and depression in women suggests that women with 1 of these 2 disorders should be also assessed for the presence of the other. An interesting finding of our study was the increased prevalence of depression in men with sleep apnea and severe sleepiness. This increased prevalence could not be explained by degree of apnea; presence of medical problems, including obesity, type 2 diabetes, and cardiovascular problems (heart problems, stroke); nor level of exercise. It is possible that another factor, e.g., subtle brain pathology, may underlie both severe sleepiness and depression in these apneic men.

Our finding that severity of sleep apnea is a significant predictor of subjective EDS in patients with sleep apnea is consistent with previous studies from clinical samples and general population samples.[18,49] Length of subjective sleep duration did not differ among the 3 EDS subgroups. Daytime napping was more frequent in the groups with more severe EDS and in women compared with men. Previous studies have shown that sleep duration is a significant predictor of objective sleepiness in patients with mild or moderate sleep apnea, whereas daytime napping is reported more frequently by patients with severe sleep apnea and severe sleepiness.[50] These data combined suggest that subjective sleep duration is a risk factor for sleepiness in patients with mild or moderate sleep apnea, whereas daytime napping is associated with severe sleepiness. Finally, cigarette smoking has been shown to be a risk factor for sleepiness.[51] In our study, the role of smoking could not be assessed due to lack of complete data.

In conclusion, in obese patients with sleep apnea, besides degree of apnea, lack of regular exercise (only in men) and depression appear to be significant predictors of daytime sleepiness. This association is modified by sex and degree of sleepiness. The lack of association between exercise and EDS in women may be related to the fact that women exercise less, compared with men. Treatment of sleep apnea with the established methods, i.e., continuous positive airway pressure, remains significant for the management of daytime sleepiness in patients with sleep apnea. However, assessment and management of depression and levels of exercise should always be part of a thorough and comprehensive evaluation and treatment plan in these patients.

ACKNOWLEDGMENTS

This study was partially funded by NIH RO1 64415 grant to ANV. We thank Barbara Green for the overall preparation of the manuscript.

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