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Predictors of moderate to severe obstructive sleep apnea: identification of sex differences

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Abstract

Purpose Home sleep apnea tests are recommended only for patients at high risk of moderate to severe obstructive sleep apnea (OSA, apnea-hypopnea index [AHI] ≥ 15/h). We evaluated 14 factors known to be associated with OSA and identified sex differences in predictors of moderate to severe OSA.

Methods Retrospective analysis was done on 545 subjects who completed sleep questionnaires and underwent diagnostic polysomnogram at a tertiary sleep center. Univariate and multivariate analysis was conducted separately in males and females to determine which variables were independent predictors of moderate to severe OSA.

Results Overall, physical traits were stronger predictors in both males and females. For each sex, only 3 variables were found to be independently predictive of moderate to severe OSA. In order of predictive strength, this included body mass index (BMI) ≥ 38 kg/m^2 (aOR 5.80, $p < 0.001$), neck circumference (NC) ≥ 17 in. (aOR 2.52, $p = 0.002$), and Epworth sleepiness scale (ESS) ≥ 13 (aOR 2.22, $p = 0.015$) for males and age ≥ 50 years (aOR 4.19, $p < 0.001$), NC ≥ 14.5 in. (aOR 3.13, $p = 0.003$), and report of morning headaches (aOR 2.00, $p = 0.039$) for females. Applying the Bonferroni correction, BMI and NC remained significant for males, and age and NC remained significant for females.

Conclusions In a subject population referred for sleep evaluation at a tertiary care center only a few variables are independently predictive of moderate to severe OSA, and these variables differed between males and females. Only BMI, NC, and a high ESS were independently predictive of moderate to severe OSA in males, whereas age, NC, and morning headaches were independently predictive in females.

Keywords Obstructive sleep apnea · Predictors · Sex · Body mass index · Neck circumference · Symptoms

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent condition, ranging from 9 to 38% in the general population [1], and is associated with numerous health consequences, including cardiovascular disease, hypertension, diabetes, mood disorders, sexual dysfunction, and cognitive dysfunction [2–6]. OSA of at least moderate severity (apnea-hypopnea index [AHI] ≥ 15/h) in particular carries long-term cardiovascular risk [6]. Due to increasing recognition of the risks and medical costs associated with untreated OSA, there is growing need to identify these undiagnosed individuals.

While polysomnography is the gold standard for the diagnosis of OSA, a home sleep apnea test (HSAT) is a cost-effective alternative. However, HSAT may underestimate the severity of OSA and potentially yield false-negative results [7]. Thus, the guidelines published by the American Academy of Sleep Medicine (AASM) recommend HSAT only be used for medically uncomplicated patients at increased risk for moderate to severe OSA, defined as "the presence of excessive daytime sleepiness and at least two of the following three criteria: habitual loud snoring; witnessed apnea or gasping or choking; or diagnosed hypertension [8]. These criteria, however, might not be equivalently predictive for males and females.

Factors known to be associated with the presence of OSA include older age, male sex, anthropometric variables (e.g., body mass index [BMI] and neck circumference [NC]),

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symptoms of OSA itself (e.g., loud snoring, witnessed apneas, awaken gasping), and symptoms of sleepiness [9–20]. Though several studies have evaluated the predictive value of these factors and of currently available sleep questionnaires in diagnosing OSA of at least moderate severity [12–19], some have done so in very specific patient populations, such as bariatric surgery candidates [17, 18] or patients with insomnia [19]. To our knowledge none has evaluated sex-specific predictors of moderate to severe OSA, aside from identification of sex-specific cutoffs for anthropometric indices in a Korean population [20]. We therefore evaluated OSA predictors separately in males and females in an adult subject population referred to a tertiary care center for polysomnography in order to determine sex differences in the prediction of moderate to severe OSA.

Methods

Subjects

Institutional Review Board approval was granted for retrospective chart review of 850 consecutive subjects who were referred for sleep study evaluation at a tertiary sleep center over a two-year interval from August 1, 2013 to July 31, 2015. Subjects were excluded if they underwent home sleep testing (298 subjects), were < 18 years old (1 polysomnogram subject), had total sleep time less than 60 min on diagnostic polysomnogram (5 subjects), and had predominantly central sleep apnea on diagnostic polysomnogram (i.e., central apneas comprising > 50% of total respiratory events with overall AHI of at least 5/h; 1 subject). The remaining 545 subjects who underwent diagnostic laboratory polysomnography were included in analysis. All subjects completed a sleep questionnaire prior to undergoing polysomnogram.

Polysomnography

All subjects included in analysis underwent overnight polysomnography at an AASM-accredited sleep center affiliated with Duke University Hospital. Polysomnographic variables monitored included electroencephalogram, electrooculogram, chin and leg electromyogram, electrocardiogram, oronasal air flow by thermistor and pressure transducer, snoring microphone, chest and abdominal wall excursion by piezoelectric belts, body position monitors, and oxygen saturation by continuous pulse oximetry. All studies were monitored by qualified sleep technicians during the entire recording. Recordings were scored manually and interpreted by a board-certified sleep physician according to established guidelines [21]. An apnea was defined as ≥ 90% reduction of oronasal airflow signal compared to pre-event baseline for ≥ 10 s. A hypopnea was defined as a ≥ 30% reduction in nasal pressure signal compared to pre-event baseline for ≥ 10 s associated with either a ≥ 3% desaturation or an arousal. In some cases, subjects were scored according to Centers for Medicare & Medicaid Services (CMS) guidelines, which use the same definition for apnea, but define a hypopnea as a ≥ 30% reduction in nasal pressure signal compared to pre-event baseline for ≥ 10 s associated with a ≥ 4% desaturation. The AHI was defined as total apneas and hypopneas per hour of sleep. Diagnosis of OSA is defined as AHI ≥ 5/h, mild OSA as 5–14.9/h, moderate OSA as 15–29.9/h, severe OSA as ≥ 30/h, and moderate to severe OSA as ≥ 15/h.

Statistical analysis

Statistical analysis was performed using JMP® Pro 13.1.0 software (SAS Institute Inc.). Fourteen variables were analyzed, including 2 demographic variables (sex and age), 2 anthropometric variables (BMI [kg/m^2] and NC [in inches]), 1 sleepiness measure (Epworth sleepiness scale [ESS]), 5 symptoms of obstructive sleep apnea (loud snoring, witnessed apneas, awaken gasping, snorting awake, and morning headaches), 3 symptoms of sleepiness (daytime sleepiness, intentional napping, and MVA or near-MVA due to drowsiness), and 1 comorbid diagnosis (hypertension). Continuous data (e.g., AHI, age, BMI, NC, and ESS) are reported as mean ± standard deviation and categorical data (e.g., sex and "yes"/"no" questions) are reported as percentages of the total population. Comparisons between groups were performed with two-tailed Student's *t* test for continuous variables and Fisher's exact test for dichotomous variables. Receiver operating characteristic (ROC) curves were created for continuous variables (age, BMI, NC, and ESS) to determine optimal cutoff points maximizing sensitivity and specificity for AHI ≥ 15/h (i.e., maximal Youden index). Odds ratios (ORs) for AHI ≥ 15/h were calculated for each dichotomous variable and each continuous variable at the cutoff determined by ROC analysis. ORs were reported with 95% confidence intervals and analyzed for statistical significance with Fisher's exact test. Variables identified by univariate analysis as potentially significant predictors ($p < 0.15$) were included in multiple logistic regression to obtain adjusted ORs (aORs). This analysis was performed separately for all subjects, males only, and females only. A final model was created for each group that included only significant independent predictors ($p < 0.05$ by multivariate analysis) or possible confounders. A variable was considered a confounder if it had an unadjusted OR with $p < 0.05$ by univariate analysis. A p value < 0.05 was considered significant. Multivariate analysis was then repeated while modifying statistical significance using the Bonferroni correction considering 14 variables analyzed, which reduced p value of significance to $p < 0.004$.

Results

Clinical and polysomnographic characteristics of the 545 subjects included in the study are shown in Table 1 and compared by both AHI (< 15/h to ≥ 15/h) and sex. The mean age was 51.6 ± 14.7 years and 47.0% were male. The overall prevalence of OSA was 64.6% and the prevalence of moderate to severe OSA was 34.7%. Compared to subjects with AHI < 15/h, subjects with moderate to severe OSA were more likely to be males ($p < 0.001$), have higher BMI ($p < 0.001$) and neck circumference ($p < 0.001$), and were more likely to report witnessed apneas ($p = 0.003$) and awaken gasping ($p =$

Table 1 Patient characteristics overall and compared by AHI and sex

Characteristic	Total ($n = 545$)	AHI < 15/h ($n = 356$)	AHI ≥ 15/h ($n = 189$)	p value	Males ($n = 256$)	Females ($n = 289$)	p value
Clinical variables							
Male sex	256 (47.0)	356 (40.2)	189 (59.8)	< 0.001	N/A	N/A	N/A
Age (years)	51.6 ± 14.7	50.9 ± 15.5	52.8 ± 12.9	0.151	52.2 ± 15.1	51.0 ± 14.3	0.356
BMI (kg/m^2)	34.9 ± 8.4	33.6 ± 7.9	37.2 ± 8.6	< 0.001	33.4 ± 7.0	36.1 ± 9.2	< 0.001
NC (inches)	15.8 ± 1.9	15.3 ± 1.7	16.7 ± 1.9	< 0.001	16.9 ± 1.6	14.8 ± 1.5	< 0.001
ESS	9.9 ± 5.1	9.7 ± 5.0	10.4 ± 5.2	0.117	9.9 ± 4.8	10.0 ± 5.3	0.910
Loud snoring	431 (79.1)	275 (77.2)	156 (82.5)	0.149	219 (85.5)	212 (73.4)	< 0.001
Witnessed apneas	241 (44.2)	141 (39.6)	100 (52.9)	0.003	134 (52.3)	107 (37.0)	< 0.001
Awaken gasping	229 (42.0)	136 (38.2)	93 (49.2)	0.014	105 (41.0)	124 (42.9)	0.655
Snort awake	278 (51.0)	175 (49.2)	103 (54.5)	0.236	133 (52.0)	145 (50.2)	0.678
Morning headache	291 (53.4)	191 (53.7)	100 (52.9)	0.869	110 (43.0)	181 (62.6)	< 0.001
Daytime sleepiness	338 (62.0)	228 (64.0)	110 (58.2)	0.181	149 (58.2)	189 (65.4)	0.085
Intentional naps	268 (49.2)	171 (48.0)	97 (51.3)	0.465	125 (48.8)	143 (49.5)	0.879
MVA/near MVA[a]	107 (19.6)	65 (18.3)	42 (22.2)	0.268	60 (23.4)	47 (16.3)	0.036
Hypertension	296 (54.3)	184 (51.7)	112 (59.3)	0.092	132 (51.6)	164 (56.7)	0.226
Other comorbidities							
Diabetes mellitus	130 (23.9)	80 (22.5)	50 (26.5)	0.300	49 (19.1)	81 (28.0)	0.016
Hyperlipidemia	174 (31.9)	117 (32.9)	57 (30.2)	0.519	85 (33.2)	89 (30.8)	0.548
Depression	179 (32.8)	119 (33.4)	60 (31.7)	0.691	60 (23.4)	119 (41.2)	< 0.001
Headaches	269 (49.4)	179 (50.3)	90 (47.6)	0.554	86 (33.6)	183 (63.3)	< 0.001
Asthma	137 (25.1)	90 (25.3)	47 (24.9)	0.916	38 (14.8)	99 (34.3)	< 0.001
COPD	17 (3.1)	12 (3.4)	5 (2.6)	0.644	4 (1.6)	13 (4.5)	0.060
Myocardial infarction	25 (4.6)	18 (5.1)	7 (3.7)	0.474	18 (7.0)	7 (2.4)	0.014
Stroke	33 (6.1)	22 (6.2)	11 (5.8)	0.867	21 (8.2)	12 (4.2)	0.052
Polysomnographic data							
OSA[b]	352 (64.6)	N/A	N/A	N/A	193 (75.4)	159 (55.0)	< 0.001
Mild OSA	163 (29.9)	N/A	N/A	N/A	80 (31.3)	83 (28.7)	0.520
Moderate OSA	91 (16.7)	N/A	N/A	N/A	41 (16.0)	50 (17.3)	0.688
Moderate to severe OSA	189 (34.7)	N/A	N/A	N/A	113 (44.1)	76 (26.3)	< 0.001
Severe OSA	98 (18.0)	N/A	N/A	N/A	72 (28.1)	26 (9.0)	< 0.001
Total sleep time (min)	283.9 ± 106.1	323.5 ± 78.9	209.3 ± 110.1	< 0.001	264.9 ± 112.3	300.7 ± 97.0	< 0.001
Sleep efficiency (%)	79.5 ± 15.2	81.4 ± 14.2	75.8 ± 16.3	< 0.001	79.0 ± 15.3	79.9 ± 15.1	0.458
Sleep latency (min)	26.0 ± 30.2	28.8 ± 32.3	20.7 ± 24.9	0.003	23.4 ± 31.7	28.3 ± 28.6	0.063
AHI (events/h)	17.5 ± 23.4	5.1 ± 4.4	40.8 ± 26.5	< 0.001	23.6 ± 26.3	12.0 ± 18.8	< 0.001
Apnea index (events/h)	3.2 ± 9.1	0.8 ± 1.5	7.7 ± 14.3	< 0.001	5.0 ± 12.3	1.6 ± 4.1	< 0.001
Hypopnea index (events/h)	14.3 ± 19.7	4.3 ± 3.8	33.1 ± 23.3	< 0.001	18.6 ± 21.5	10.4 ± 17.0	< 0.001
Central apnea index (events/h)	0.3 ± 1.4	0.2 ± 0.8	0.6 ± 2.1	0.001	0.5 ± 1.7	0.2 ± 1.0	0.021
SpO_2 nadir (%)	84.2 ± 15.9	86.9 ± 17.3	79.0 ± 11.0	< 0.001	83.9 ± 21.3	84.4 ± 8.5	0.688

BMI, body mass index; NC, neck circumference; ESS, Epworth sleepiness scale; MVA, motor vehicle accident; COPD, chronic obstructive pulmonary disease; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; N/A, not applicable. Data are reported as mean ± SD or N (%). [a] Report of MVA or near MVA due to sleepiness. [b] OSA is defined as AHI ≥ 5/h, mild OSA as AHI 5–14.9/h, moderate OSA as AHI 15–29.9/h, moderate to severe OSA as AHI ≥ 15/h, and severe OSA as AHI ≥ 30/h

0.014). There was a trend towards a greater prevalence of hypertension in subjects with moderate to severe OSA ($p = 0.092$). No differences were observed in other comorbidities.

The degree of OSA was more severe in males compared to females ($p < 0.001$) and OSA was more prevalent in males ($p < 0.001$), as was moderate to severe OSA ($p < 0.001$). Males demonstrated a significantly lower BMI ($p < 0.001$) and larger neck circumference ($p < 0.001$), were more likely to report loud snoring ($p < 0.001$), witnessed apneas ($p < 0.001$), and MVA or near-MVA due to sleepiness ($p = 0.036$), and were less likely to report morning headaches ($p < 0.001$) compared to females. In terms of comorbidities, males had a lower prevalence of diabetes mellitus ($p = 0.016$), depression ($p < 0.001$), headaches ($p < 0.001$), and asthma ($p < 0.001$), and a greater prevalence of myocardial infarction ($p = 0.014$) compared to females.

Receiver operator characteristic (ROC) curves for age, BMI, NC, and ESS are shown in Fig. 1 with area under the curve (AUC) values and optimal cutoff points for the diagnosis of moderate to severe OSA shown in Table 2. These cutoff values were used in univariate analysis to determine ORs for these variables. Table 3 shows unadjusted ORs in all subjects, males, and females for the 14 variables evaluated (13 variables in males and females). Table 4 shows the aORs from multivariate analysis, which included only independently predictive variables ($p < 0.05$ in multivariate analysis) or possible confounders ($p < 0.05$ in univariate analysis). Even though age was not a significant predictor of moderate to severe OSA in males, it was included as a continuous variable in the multivariate model to ensure age was adjusted for. The AUC for each of the ROC curves generated by the multivariate analysis was 0.738, 0.755, and 0.745 for all subjects, males, and females, respectively. For all subjects, only 5 of the 14 variables were found to be significant independent predictors of moderate to severe OSA. In order of strength of predictive value, these included BMI ≥ 38 kg/m^2 ($p < 0.001$), NC ≥ 17 in. ($p < 0.001$), age ≥ 49 years ($p < 0.001$), males sex ($p = 0.006$), and report of awaken gasping ($p = 0.027$). For males, only 3 variables were significant independent predictors, BMI ≥ 38 kg/m^2 ($p < 0.001$), NC ≥ 17 in. ($p = 0.002$), and ESS ≥ 13 ($p = 0.015$). For females, again only 3 variables were significant independent predictors, age ≥ 50 years ($p < 0.001$), NC ≥ 14.5 in. ($p = 0.003$), and report of morning headaches ($p = 0.039$).

Table 2 AUC values and optimal cutoff points determined by ROC curve analysis

	Total		Males		Females	
	AUC	Cutoff	AUC	Cutoff	AUC	Cutoff
NC (inches)	0.701	≥17	0.700	≥17	0.646	≥14.5
BMI (kg/m^2)	0.624	≥38	0.681	≥38	0.616	≥35
Age (years)	0.542	≥49	0.502	≤63	0.585	≥50
ESS	0.539	≥12	0.584	≥13	0.509	≤4

BMI, body mass index; NC, neck circumference; ESS, Epworth sleepiness scale; AUC, area under the curve

When the Bonferroni correction is applied, which includes only independently predictive variables ($p < 0.004$ in multivariate analysis) or possible confounders ($p < 0.004$ in univariate analysis) the AUC for each of the ROC curves generated by the multivariate analysis was 0.728, 0.755, and 0.706 for all subjects, males, and females, respectively. Using this method, 3 of the 14 variables were found to be significant independent predictors of moderate to severe OSA for all subjects. In order of strength of predictive value, these included BMI ≥ 38 kg/m^2 ($p < 0.001$), NC ≥ 17 in. ($p < 0.001$), and age ≥ 49 years ($p < 0.001$). There was a trend towards male sex ($p = 0.008$) and report of witnessed apneas ($p = 0.028$) to predict moderate to severe OSA. For males, only 2 variables were significant independent predictors, BMI ≥ 38 kg/m^2 ($p < 0.001$) and NC ≥ 17 in. ($p = 0.002$). There was a trend towards ESS ≥ 13 ($p = 0.015$) to predict moderate to severe OSA. For females, 2 variables were significant independent predictors, age ≥ 50 years ($p < 0.001$) and NC ≥ 14.5 in. ($p = 0.003$). Although there was a trend for report of witnessed

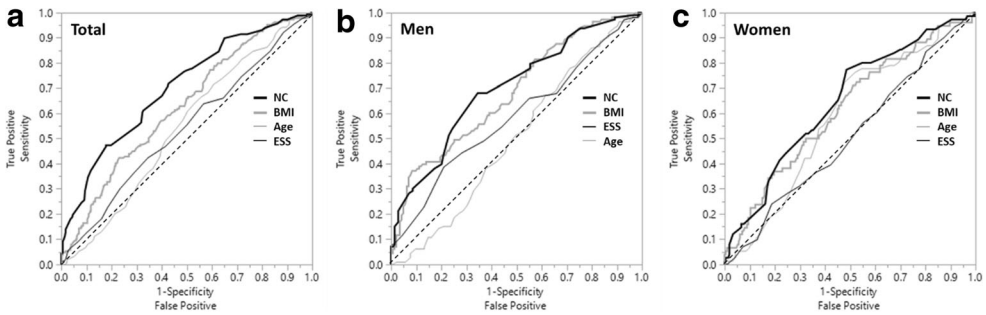

Fig. 1 ROC curve analysis for each continuous variable in all subjects, males, and females. Receiver operator characteristic (ROC) curves for the prediction of moderate to severe obstructive sleep apnea (apnea hypopnea index ≥ 15/h). The continuous variables neck circumference (NC, thick black line), body mass index (BMI, thick gray line), age (thin gray line), and Epworth sleepiness scale (ESS, thin black line) are shown for the total subject population (**a**), males (**b**), and females (**c**). The dashed line indicates predictive value no better than chance. NC and BMI are both predictive in males and females, while ESS is predictive in males but not females, and age is predictive in females but not males

Table 3 Unadjusted odds ratios of having moderate to severe OSA for each variable

Variable	Total		Males		Females	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Male sex	2.21 (1.55–3.17)	< 0.001	N/A	N/A	N/A	N/A
Age[a]	1.57 (1.09–2.26)	0.015	1.41 (0.80–2.51)	0.235	2.85 (1.61–5.04)	< 0.001
BMI[a]	2.38 (1.63–3.47)	< 0.001	6.46 (3.20–13.05)	< 0.001	2.18 (1.26–3.77)	0.005
NC[a]	4.07 (2.74–6.06)	< 0.001	4.05 (2.39–6.88)	< 0.001	3.30 (1.76–6.19)	< 0.001
ESS[a]	1.40 (0.96–2.04)	0.079	2.37 (1.35–4.18)	0.003	1.36 (0.71–2.63)	0.352
Loud snoring	1.39 (0.89–1.44)	0.149	0.71 (0.35–1.43)	0.341	1.86 (0.97–3.56)	0.061
Witnessed apneas	1.71 (1.20–2.45)	0.003	1.36 (0.83–2.24)	0.222	1.80 (1.06–3.07)	0.031
Awaken gasping	1.57 (1.10–2.24)	0.014	1.45 (0.88–2.39)	0.149	1.83 (1.08–3.11)	0.024
Snort awake	1.24 (0.87–1.76)	0.236	1.23 (0.75–2.02)	0.407	1.23 (0.73–2.08)	0.444
Morning headache	0.97 (0.68–1.38)	0.869	0.85 (0.51–1.40)	0.516	1.66 (0.94–2.93)	0.079
Daytime sleepiness	0.78 (0.54–1.12)	0.181	0.89 (0.54–1.47)	0.652	0.75 (0.44–1.29)	0.299
Intentional naps	1.14 (0.80–1.62)	0.465	1.12 (0.69–1.84)	0.646	1.19 (0.70–2.00)	0.522
MVA/near MVA[b]	1.28 (0.83–1.98)	0.268	1.25 (0.70–2.23)	0.455	1.09 (0.54–2.19)	0.817
Hypertension	1.36 (0.95–1.94)	0.092	1.44 (0.88–2.37)	0.149	1.43 (0.84–2.460	0.190

OR, odds ratio; CI, confidence interval; BMI, body mass index; NC, neck circumference; ESS, Epworth sleepiness scale; MVA, motor vehicle accident; N/A, not applicable. [a] ORs were calculated at optimal cutoff points for these variables determined by receiver operator characteristic curve analysis as shown in Fig. 1 and reported in Table 2. [b] Report of MVA or near MVA due to sleepiness

apneas ($p = 0.031$) and awaken gasping ($p = 0.024$) to predict moderate to severe OSA in univariate analysis, these variables did not reach statistical significance in multivariate analysis. Of note, with or without Bonferroni correction, BMI only becomes an insignificant predictor in multivariate analysis in females when NC is included as a variable.

Table 4 Adjusted odds ratios of having moderate to severe OSA for each variable included in the multivariate model without and with Bonferroni correction analyzed separately for all subjects, males, and females

Variable	aOR (95% CI)	*p* value	Bonferroni corrected aOR (95% CI)	*p* value
Total[a]				
BMI ≥ 38 kg/m^2	2.91 (1.85–4.58)	< 0.001	2.92 (1.86–4.60)	< 0.001
NC ≥ 17 in.	2.85 (1.77–4.59)	< 0.001	2.76 (1.72–4.44)	< 0.001
Age ≥ 49 years	2.18 (1.45–3.30)	< 0.001	2.13 (1.41–3.21)	< 0.001
Male sex	1.95 (1.22–3.14)	0.006	1.88 (1.17–3.01)	0.006
Awaken gasping	1.62 (1.06–2.49)	0.027	N/A	
Witnessed apneas	1.28 (0.84–1.96)	0.252	1.55 (1.05–2.29)	0.028
Males				
BMI ≥ 38 kg/m^2	5.80 (2.58–13.03)	< 0.001	5.80 (2.58–13.03)	< 0.001
NC ≥ 17 in.	2.52 (1.40–4.55)	0.002	2.52 (1.40–4.55)	0.002
ESS ≥ 3	2.22 (1.17–4.23)	0.015	2.22 (1.17–4.23)	0.015
Females				
Age ≥ 50 years	4.19 (2.21–7.94)	< 0.001	3.52 (1.92–6.43)	< 0.001
NC ≥ 14.5 in.	3.13 (1.46–6.70)	0.003	3.19 (1.51–6.72)	0.002
Morning headaches	2.00 (1.03–3.85)	0.039	N/A	
Witnessed apneas	1.51 (0.81–2.82)	0.217	N/A	
BMI ≥ 35 kg/m^2	1.41 (0.71–2.82)	0.330	1.50 (0.76–2.94)	0.242
Awaken gasping	1.11 (0.58–2.11)	0.749	N/A	

aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; NC, neck circumference; ESS, Epworth sleepiness scale. [a] Age was included as a continuous variable in the multivariate analysis model with resulting β coefficient − 0.010 ± 0.010 ($p = 0.322$). The area under the curve for each of the receive operator characteristic curves generated by the models were 0.738, 0.755, and 0.745 for all subjects, males, and females, respectively without Bonferroni correction and 0.728, 0.755, and 0.706 with correction

Table 5 shows predictive parameters at various cutoff points using models containing only significant predictors determined from the univariate or multivariate analysis. For all subjects, at a cutoff of 2 points (subjects that have at least 2 of the 5 variables), there is good sensitivity (82.0%) and negative predictive value (NPV, 82.1%), but relatively poor specificity (43.8%) and positive predictive value (PPV, 43.7%), and only 57.1% of subjects are accurately classified. Better PPV, accuracy, and OR is achieved at higher cutoffs, but at the cost of substantially lower sensitivity. Using a 3-variable model for both males and females, sensitivity of nearly 80% is achieved at cutoffs of 1 point and 2 points, respectively, with specificities, PPVs, NPVs, accuracies, and ORs similar to or better than the 5-variable model used for all subjects.

Discussion

We identified notable differences between males and females in which factors are most predictive of moderate to severe OSA. As has been established [14, 15, 17–19, 22], male sex was a predictor of moderate to severe OSA when all subjects included in analysis were evaluated. When males and females were evaluated separately, only 3 factors were shown to be significant predictors of moderate to severe OSA in each sex. For males this included BMI ≥ 38 kg/m^2, NC ≥ 17 in., and ESS ≥ 13. For females this included age ≥ 50 years, NC ≥ 14.5 in., and report of morning headaches. Following Bonferroni correction, only two variable remained significant: BMI and NC for males, and age and NC for females. Thus, physical attributes were ultimately the strongest predictors in both males and females, while symptoms were largely not strong predictors. A similar conclusion was reached in a study evaluating OSA predictors in a patient population presenting for bariatric surgery [18]. Notably absent from the list of predictive variables for females is excessive sleepiness, which currently stands as a requirement for selecting patients at high risk for moderate to severe OSA in the AASM guidelines [8].

Although older age has generally been shown to correlate with a higher AHI [22], age was not predictive of moderate to severe OSA in males. There is evidence that age correlates with OSA severity only in non-obese males [22], so this finding could be explained by a referral bias in that there would be a tendency to refer overweight males for a sleep study, evidenced by the high average BMI of males in our study (33.4 kg/m^2). In the obese male patient population, age therefore does not seem to be a significant predictor of moderate to severe OSA. In contrast to males, age was the most predictive variable in females. This is most likely due to the appearance of menopause in this age group, which is associated with worsening severity of OSA [23].

As noted, symptoms were largely not strong predictors of moderate to severe OSA in this subject population. In females, there was a clear trend in univariate analysis of multiple OSA symptoms (loud snoring, witnessed apneas, awaken gasping, and morning headaches) being predictive, though only morning headaches was shown to be a significant independent predictor. In males, none of these symptoms was predictive, though pathologic sleepiness measured as a high ESS ≥ 13 was a significant independent predictor. This was discordant with reported symptoms of sleepiness, including daytime sleepiness, intentional naps, and MVA or near MVA due to

Table 5 Predictive parameters of models using significant predictors of moderate to severe OSA from multivariate analysis for all subjects, males, and females at various cutoff points

Points[a]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	OR (95% CI)
Total						
≥ 1	97.9	9.0	36.3	88.9	39.8	4.57 (1.59–13.12)
≥ 2	84.7	43.5	44.3	84.2	57.8	4.25 (2.72–6.66)
≥ 3	55.0	78.7	57.8	76.7	70.5	4.51 (3.07–6.61)
≥ 4	21.7	96.6	77.4	69.9	70.6	7.94 (4.06–15.54)
5	2.6	99.7	83.3	65.9	66.1	9.65 (1.12–83.18)
Males						
≥ 1	82.3	52.4	57.8	78.9	65.6	5.13 (2.86–9.20)
≥ 2	46.9	88.1	75.7	67.7	69.9	6.55 (3.50–12.25)
3	12.4	97.2	77.8	58.4	59.8	4.91 (1.57–15.38)
Females						
≥ 1	98.7	5.2	27.1	91.7	29.8	4.08 (0.52–32.18)
≥ 2	88.2	43.2	35.6	91.1	55.0	5.66 (2.68–11.94)
3	35.5	90.1	56.3	79.7	75.8	5.04 (2.63–9.66)

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; CI, confidence interval. [a] Points represent the number of variables subjects possess from models using only the significant ($p < 0.05$) predictors for all subjects (5 variables), males (3 variables), and females (3 variables) shown in Table 4 left column (without Bonferroni correction)

sleepiness, none of which was a significant predictor in males. This may be a reflection of the fairly high reliability of ESS as a tool to measure sleepiness [24].

In contrast, ESS was not predictive in females. In fact, there was a trend towards an inverse correlation of ESS with AHI in females. Similarly, a report of daytime sleepiness in females suggested a lower likelihood of moderate to severe OSA with an unadjusted OR of 0.75, though this was not significant. Interestingly, the unadjusted OR for daytime sleepiness in females with any degree of OSA (AHI ≥5) was significant at 0.47 (0.28–0.77, $p = 0.005$). Thus, while pathologic sleepiness determined by a high ESS is predictive of moderate to severe OSA in males, the report of sleepiness in females made the diagnosis of OSA less likely.

There was not a substantial difference in the percentage of females who reported daytime sleepiness compared to males in our subject population (65.4% vs 58.2%, respectively; $p = 0.085$), nor in mean ESS score (10.0 ± 5.3 vs 9.9 ± 4.8, respectively; $p = 0.910$), suggesting that females are more likely to have a cause of daytime sleepiness other than OSA. Supporting this hypothesis, depression was more prevalent in females than males (41.2% vs 23.4%, respectively; $p < 0.001$), as was chronic pain (32.5% vs 17.2%, respectively; $p < 0.001$).

The fact that loud snoring or hypertension did not significantly predict moderate to severe OSA for males or females contrasts with prior studies that have demonstrated one or both of these variables are predictive of AHI ≥ 15/h [13, 14, 17–19]. This may be due to differences in patient populations and referral bias in our study with 79.1% of subjects reporting loud snoring. As loud snoring is frequently noted by bed partners, our data might underestimate the true presence of loud snoring by not assessing the presence of a bed partner. It is also unknown if males or females in our sample are more likely sleep alone and are thus less likely to report snoring. However, the data collected represent what was knowable to the clinician about the presence of snoring at the time the decision to order an HSAT or PSG would have been made.

It should be noted that in our subject population, both loud snoring and hypertension were predictive of AHI ≥ 5/h with unadjusted ORs of 1.65 (1.08–2.51, $p = 0.03$) and 1.56 (1.10–2.23, $p = 0.02$), respectively (multivariate analysis was not performed for AHI ≥ 5/h). This means that loud snoring and hypertension are not useful in distinguishing mild from moderate to severe OSA for the purpose of making a clinical decision regarding the use of HSAT.

One limitation of this study is that the subjects included in analysis were already suspected of having a sleep disorder such as OSA, creating referral bias and limiting the ability to generalize the results to the population as a whole. The results and conclusions are therefore best applied to those patients presenting with sleep complaints, especially if sleep apnea is suspected, such as when the decision to obtain a PSG versus an HSAT is made. Also, while the purpose of the study was to evaluate which patients have a high likelihood of moderate to severe OSA and therefore would be amenable to undergo HSAT, we excluded subjects who underwent HSAT from analysis. The primary reason is that in-lab polysomnogram is considered the gold standard for OSA diagnosis, yielding the most accurate assessment of AHI compared to HSAT [8]. Another limitation is the use of two different definitions for hypopnea, which reduces the homogeneity of the study population. However, this mimics many practice settings and thus provides a "real world" analysis. It is unlikely that scoring all studies using the same hypopnea criteria would have a significant impact on the findings.

In conclusion, the identification of sex-specific predictors of moderate to severe OSA in this study should modify OSA risk assessment when considering which patients to refer for HSAT, as this is recommended only for patients with a higher likelihood of moderate to severe OSA. For males, BMI ≥ 38 kg/m^2, NC ≥ 17 in., and ESS ≥ 13, and for females age ≥ 50 years, NC ≥ 14.5 in., and report of morning headaches, were the only significant independent predictors of moderate to severe OSA in patients referred for polysomnography at a tertiary sleep center.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent This study was approved by the Duke University Health System Institutional Review Board. For retrospective chart reviews, formal consent is not required.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical publication statement We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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