Impact of Gender on Symptoms and Comorbidities in Obstructive Sleep Apnea

Ozge Can Bostan[1,3], Beyza Akcan[2], Cihan Durmus Saydam[2], Muhammet Tekin[2], Omur Dasci[2], Baran Balcan[3]

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[1]Department of Allergy and Immunology, Hacettepe University School of Medicine, Ankara, Turkey
[2]Department of Sleep Clinic, Marmara University School of Medicine, Istanbul, Turkey
[3]Department of Pulmonary Medicine, Marmara University School of Medicine, Istanbul, Turkey

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Correspondence to: Baran Balcan
E-mail: drbaranbalcan@gmail.com

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is more common in men than in women. In this study, we aimed to address the impact of gender on symptoms and comorbidities in patients with OSA.

Materials and Methods: This cross-sectional study was conducted among 1,317 consecutive patients, who were admitted to the Sleep Apnea Clinic of the Marmara University Hospital between November 2015 and October 2018, and who completed questionnaires and a sleep study with cardiorespiratory polygraphy. OSA was defined as Apnea Hypopnea Index (AHI) ≥15/hour.

Results: In all, 1,042 patients (334 women) fulfilled the inclusion criteria. OSA was observed in 589 patients (56.5%). Women were older than men (50.2±12.5 versus 45.6±15.1 years) and had lower AHI (22.1±20.1 versus 26.8±21.9 events/h). In the OSA group, women were older (53.7±11.5 versus 47.8±12.8 years) and more obese (BMI 34.6 versus 31.8 kg/m^2). Symptoms were categorized as frequent/very frequent, and women with OSA complained more about daytime fatigue (74.6% versus 63.7%), nocturia (69.7% versus 51.8%), headache in the morning (50.0% versus 28.4%), depressive mood (49.0% versus 19.5%), and restless legs symptoms (43.1% versus 17.2%), than did men (all p values <0.05). Comorbidities were observed more in women than in men (lung disease [25.4% versus 13.7%], hypertension [29.6% versus 15.0%], diabetes [20.3% versus 11.3%], and hypothyroidism [14.0 % versus 4.1%]). In regression analysis, age (OR 1.03, p<0.001), BMI (OR 1.13, p<0.001), and male sex (OR 2.08, p<0.001) were significantly predictive for OSA while history of tonsillectomy was protective (OR 0.48, p=0.033).

Conclusion: Fatigue, nocturia, headache, depressive mood, restless leg, and comorbidities were observed more in women. OSA-related symptoms develop late and/or the referral of women for diagnostic evaluation of OSA is delayed. Symptoms and comorbidities in women should be evaluated more attentively for earlier referral and diagnosis of OSA.

Keywords: Obstructive sleep apnea, gender difference, symptoms, comorbidities

Introduction

Obstructive sleep apnea (OSA) is characterized by frequent collapse of the upper airway during sleep, resulting in repetitive desaturations in arterial oxygen and arousal from sleep, as well as daytime symptoms, such as headache in the morning, fatigue, disturbed quality of life, depressive mood, and excessive daytime sleepiness (EDS) [1]. Estimated prevalence of OSA is approximately 22% in men and 17% in women [2]. Witnessed apnea, EDS, and snoring are the cardinal symptoms of OSA; however, symptoms related to OSA may show differences according to gender [3]. For females who do not present with the cardinal symptoms of OSA, depressive mood, fatigue, morning headache, and restless leg syndrome may be the symptoms of OSA [4]. Diagnosis of sleep disordered breathing (SBD) in women is usually delayed or missed due to different presentation of the symptoms, rather than classic exhibition, and women tend to underreport their symptoms [5]. In the previous literature, it was reported that moderate-to-severe OSA was undiagnosed in more than 90 % of women, and it was also suggested that mortality among undiagnosed women was significantly higher compared with diagnosed OSA patients [6]. Prevalence of OSA is higher in males when compared with females due to an increase in upper airway resistance and collapsibility; moreover, women's hormones have a protective function in premenopausal period [7, 8]. Women with OSA

have higher levels of body mass index (BMI), and they are older compared with men with OSA. In addition, co-morbid conditions such as hypertension, diabetes mellitus, and thyroid disease are observed more in women [9, 10]. In this study, our aim was to evaluate the symptoms and comorbidities in men and women and to identify the important sex-related differences in symptoms, thereby aiding physicians to diagnose OSA and refer patients to sleep clinics.

Materials and Methods

Participants

This cross-sectional study was conducted among 1,315 consecutive patients, who were admitted to the Sleep Apnea Outpatient Clinic of the Department of Pulmonary Medicine, Marmara University Hospital between November 2015 and October 2018, and who had complete questionnaires and a sleep study with cardiorespiratory polygraphy. Data of the participants were collected retrospectively, and ethical approval was taken from Marmara University ethical committee (approval number: 09.2017.650).

Cardiorespiratory polygraphy

Sleep studies were performed with portable cardiorespiratory polygraphy (CRPG) (NOX T3, Nox Medical Inc., Reykjavik, Iceland) device. Nasal cannula or pressure transducer system was used for detection of nasal pressure, thoracic and abdominal plethysmography belts were used to detect thoraco-abdominal movement and body position, and heart rate as well as oxyhemoglobin saturation (SpO_2) were measured by a finger pulse oximeter. Snoring was recorded using a microphone in built in the CRPG device. Estimated sleep time was calculated via self-report by the participants and the pattern of the sleep recordings. Participants whose estimated sleep time was less than four hours were excluded from the protocol. Apnea was defined as a complete (≥90%) cessation of airflow, and hypopnea was defined as a reduction in nasal pressure amplitude of ≥30% and/or thoraco-abdominal movement ≥30% for ≥10 seconds if there was a significant oxyhemoglobin desaturation (decrease by at least 3% from the immediate preceding baseline value) according to the latest recommendations of the American Academy of Sleep Medicine [1]. Moderate-to-severe OSA was defined as an apnea-hypopnea index (AHI) ≥15 events/h of the total estimated sleep time. In order to avoid misdiagnosis, mild OSA participants were not included in the analysis. Healthy participants with AHI <5 might be classified as mild OSA when sleep study is done with a polygraphy because real sleep time cannot be calculated with polygraphy, and estimated sleep time usually exceeds total sleep time.

Main Points

- This is a single center study that evaluates cardiorespiratory findings of more than 1000 patients.
- We evaluated the impact of gender on symptoms of obstructive sleep apnea, co-morbid diseases, and associates of moderate-to-severe obstructive sleep apnea was evaluated.
- This study suggest that Symptoms and comorbidities in women should be evaluated more attentively for earlier referral and adequate diagnosis and treatment of OSA.

Epworth sleepiness scale

Epworth sleepiness scale (ESS) questionnaire was used to evaluate daytime sleepiness of the participants [11, 12]. The ESS consists of eight questions for assessing the chance of dozing off under eight situations in the past month. Each item is scored from 0 to 3 (0, would never doze; 1, slight chance of dozing; 2, moderate change of dozing; 3, high chance of dozing). The ESS score ranges from 0 to 24. Excessive daytime sleepiness (EDS) was defined as the ESS score of at least 11 [13].

Comorbidities and symptoms

Baseline anthropometrics, smoking habits, medical histories, and co-morbid conditions such as hypertension, cardiac disease, and diabetes mellitus were recorded, and symptoms of the participants were obtained from a questionnaire, which was filled when the patients first presented to the outpatient clinic. Symptoms of OSA were classified as never, rarely, sometimes, frequent, and very frequent; symptoms were accepted as positive when reported as frequent and very frequent.

Statistical Analysis

Data were demonstrated as mean ± standard deviation or standard error of mean for continuous variables, and categorical variables were represented as numbers and percent-

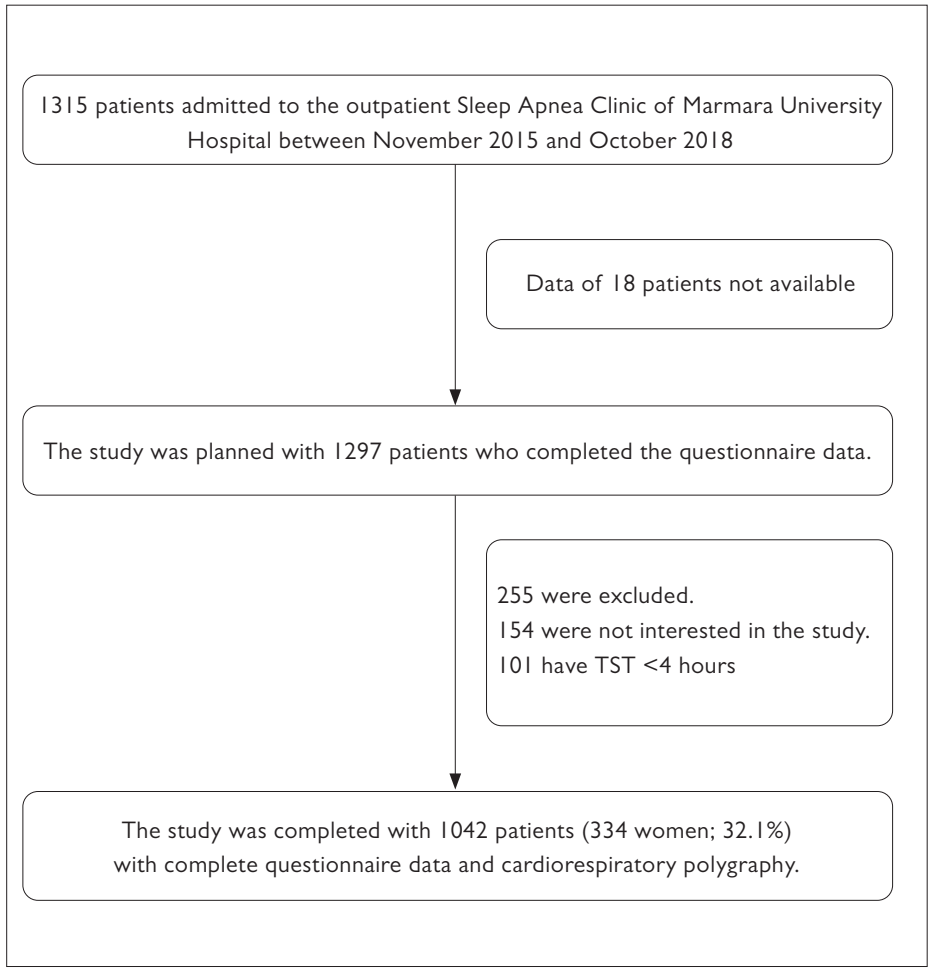

Figure 1. Flow chart of the participants evaluated in the protocol

Table 1. Baseline clinical characteristics of the study population (n=1042)

	Female	Male	p value
Age, years	50.2±12.5	45.6±15.1	<0.001
Married, %	46.4	50.3	0.243
BMI, kg/m^2	32.6 ± 7.8	30.4 ± 5.7	<0.001
Obesity, %	64.4	48.3	<0.001
Smoker, %	31.4	46.0	<0.001
Alcohol consumption	5.7	12.9	<0.001
AHI, events/h	22.1±20.1	26.8±21.9	0.001
ODI, events/h	20.7±18.7	24.9±21.5	0.003
OSA, %	84.9	89.8	0.025
Moderate-to-severe OSA, %	53.1	61.8	0.009
Supine position, %	39.9	40.9	0.730
Supine AHI, events/h	33.2	42.3	0.004
Time below 90 %, %	12.8	14.2	0.579
ESS	9.1±5.9	9.3±5.7	0.603
Sleepy (ESS ≥ 11), %	40.8	39.3	0.715
Comorbidities			
Tonsillectomy, %	6.0	4.7	0.363
Nasal operation, %	9.0	13.3	0.046
UPPP, %	1.5	2.1	0.631
Pulmonary disease, %	25.4	13.7	<0.001
Hypertension, %	29.6	15.0	<0.001
Cardiac disease, %	13.5	9.0	0.029
Diabetes mellitus, %	17.1	8.8	<0.001
Stroke, %	2.1	0.7	0.063
Hypothyroidism, %	15.6	4.0	<0.001
Symptoms			
Snoring, %	83.9	85.2	0.635
Witnessed apnea, %	51.6	55.7	0.311
Nocturnal sweating, %	46.9	49.7	0.490
Nocturia, %	61.7	47.9	0.001
Headache, %	45.0	28.3	<0.001
RLS, %	40.7	18.1	<0.001
Sleepy, %	65.2	59.0	0.178
Fatique, %	74.6	63.7	0.004
Depressive mood, %	49.3	21.9	<0.001

Definition of abbreviations: AHI, apnea-hypopnea index; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; PCI, percutaneous coronary angiography; UPPP, Uvulopalatopharyngoplasty

ages. An independent sampled t-test was used for differences in means between groups, and the chi-squared test (or when appropriate, Fisher's exact test) was used to compare categorical variables. A logistic regression analysis was applied for the associates of OSA. Variables that were significant in univariable regression were analyzed in the multivariable model and odds ratios (ORs) with 95% confidence intervals (CI) were reported. All statistical tests were two-sided, and p <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences, version 22.0 for Windows® system (IBM Corp.; Armonk, NY, USA)

Results

As illustrated in Figure 1, a total of 1,315 participants were screened in the main study. Eighteen of them who did not fill the questionnaires completely (ESS and sleep symptoms) were not included in the main protocol. In addition, 154 patients who did not want to perform CRPG and 101 whose total sleep time was less than 4 hours/night were excluded from the study. The protocol was completed with 1,042 (334 female, 32.1%) patients. OSA was observed in 589 (56.5%) patients. As shown in Table 1, women were older (50.2±12.5 years versus 45.6±15.1, p <0.001) and had higher levels of BMI (32.6±7.8 versus 30.4±5.7, p <0.001). On the other hand, men had higher levels of AHI (26.8±21.9 versus 22.1±20.1, 0.001), and the proportion of patients with OSA was higher among males (89.8% versus 84.9%, p=0.025). Furthermore, moderate-to-severe OSA was observed more in males (61.8% versus 53.1%, p=0.009).

As shown in Table 2, we evaluated the same parameters in OSA patients. In this group, women were older (53.7±11.5 versus 47.8±12.8 years; p <0.001) and more obese (BMI 34.6 versus 31.8 kg/m^2; p <0.001). When the symptoms were categorized based on their frequency, women with OSA had more nocturia (69.7% versus 51.8%, p=0.001), morning headache (50.0% versus 28.4%, p<0.001), restless leg syndrome (43.1% versus 17.2%, p<0.001), and depressive mood (49.0% versus 19.5%, p<0.001). Cardinal symptoms of OSA, such as loud snoring and witnessed apneas were observed more in males, and it was not statistically significant. Pulmonary disease (21.5% versus 14.9%, p=0.050), hypertension (35.5% versus 18.0%, p<0.001), diabetes mellitus (20.3% versus 11.3%, p=0.004), and hypothyroidism (14.0% versus 4.1%, p<0.001) were the co-morbid diseases observed in OSA patients.

As shown in Table 3, variables that were significant in univariate regression analysis were analyzed in the multivariate model. Two different models were done in multivariate analysis; in model 1 adjustment was done with co-morbid conditions, and in model 2 adjustment was done with symptoms. In the multivariate model, when adjusted for co-morbid diseases, age (OR 1.03; p<0.001), BMI (OR 1.14; p<0.001), male gender (OR 2.23; p<0.001), and tonsillectomy (OR 0.41; p=0.009) remained significant, and when adjusted for symptoms age (OR 1.04; p<0.001), BMI (OR 1.12; p<0.001), male gender (OR

Table 2. Clinical characteristics of Obstructive sleep apnea patients (n=589)

	Female	Male	p value
Age, years	53.7±11.5	47.8±12.8	<0.001
Elderly	17.2	8.6	0.003
Married, %	42.4	50.4	0.080
BMI, kg/m^2	34.6±6.1	31.8±5.5	<0.001
Obesity, %	78.9	59.9	<0.001
Smoker, %	25.6	47.0	<0.001
Alcohol consumption	2.3	13.2	<0.001
AHI, events/h	35.1±19.7	38.4±20.3	0.067
ODI, events/h	33.1±18.1	35.4±20.9	0.180
Time below 90 %, %*	27.1	23.2	0.191
ESS	9.9±6.2	9.8±5.8	0.785
Sleepy (ESS ≥ 11), %	43.8	43.6	0.974
Comorbidities			
Tonsillectomy, %	4.1	4.1	0.997
Nasal operation, %	7.6	12.5	0.084
UPPP, %	2.3	1.7	0.598
Pulmonary disease, %	21.5	14.9	0.050
Hypertension, %	35.5	18.0	<0.001
Cardiac disease, %	15.1	12.0	0.304
Diabetes mellitus, %	20.3	11.3	0.004
Stroke, %	0.6	1.0	0.649
Hypothyroidism, %	14.0	4.1	<0.001
Symptoms			
Snoring, %	90.8	91.7	0.791
Witnessed apnea, %	62.4	61.4	0.858
Nocturnal sweating, %	518	53.6	0.748
Nocturia, %	69.7	51.8	0.001
Morning headache, %	50.0	28.4	<0.001
RLS, %	43.1	17.2	<0.001
Sleepy, %	66.1	61.6	0.419
Fatique, %	72.9	65.3	0.156
Depressive mood, %	49.0	19.5	<0.001

2.35; p<0.001), and loud snoring (OR 2.66; p<0.001) were still significant.

In Table 4, associates of OSA for both females and males are summarized. For females in model 1, age (OR 1.04; p=0.003) and BMI (OR 1.09; p<0.001) were significant and in model 2, age (OR 1.05; p<0.001) and BMI (OR 1.09; p=0.001), as well as witnessed apneas (OR 2.20; p=0.013) were significant. For males in model 1, age (OR 1.03; p=0.001), BMI (OR 1.53; p=<0.001), and cardiac disease (OR 2.03, p=0.043), and in model 2, age (OR 1.04; p<0.001) and BMI (OR 1.17; p<0.001) as well as snoring (OR 3.01; p<0.001) remained significant.

Discussion

In this cross-sectional study, we observed that women with moderate-to-severe OSA were older, more obese, had more co-morbid diseases than men with OSA. When considering cardinal symptoms of OSA (loud snoring, witnessed apnea, and excessive daytime sleepiness [EDS]), there was no significant difference among the men and women; however, more unusual symptoms of OSA, such as morning headache, fatigue, and depressive mood were observed more in women.

Among the patients referred to our clinic, we observed OSA more in men, and average AHI levels were higher in men. We also observed that the proportion of moderate-to-severe OSA among the participants was observed more in men when compared with women. Previous studies have reported that the prevalence of OSA has been known to be more in men when compared with women, and the severity of OSA was worse in men [14]. These findings could be attributed to the fact that milder events are observed in women with sleep apnea when compared with men with sleep apnea. The difference in the architecture of the upper airway anatomy between the sexes (women having a shorter and thus less collapsible pharynx) [15] may contribute to the lack of cardinal symptoms of OSA in women, thus delaying the diagnosis of OSA in women. Undiagnosed OSA in women due to lack of cardinal symptoms may be another reason for the low prevalence of OSA in women [16].

When the symptoms were evaluated in participants with moderate-to-severe OSA, cardinal symptoms, such as loud snoring, EDS, and witnessed apnea had shown no significant difference between sexes; however, most of the studies reported that cardinal symptoms were the indicators of OSA, particularly in men [3, 17]. Morning headache, nocturia, and depressive mood were observed significantly more in women with moderate-to-severe OSA in this study. These underestimated and unusual symptoms might be the only sign of OSA, especially in women [18].

The average age and BMI were higher among women in moderate-to-severe OSA participants. It is known that increased age and BMI are the risk factors for OSA [19, 20]. Women had less incidences of OSA before menopause when compared with men; however, after menopause there was no difference in the prevalence of OSA between genders [20]; therefore, incidence of OSA increases with advanced age in women [16].

In this study, as expected, advanced age and increased BMI were reported to be predictors of moderate-to-severe OSA. Previously, significant association between OSA and age as well as BMI were reported, and it was also described that

Table 3. Associates of obstructive sleep apnea (AHI ≥ 15 events/h) in the whole study population (n=1042)

	OR	95% CI	p value
Univariate			
Age	1.04	1.02 – 1.05	<0.001
Age ≥ 65 years	2.50	1.48 – 4.25	0.001
Male gender	1.42	1.09 – 1.87	0.010
BMI	1.14	1.10 – 1.17	<0.001
Obesity	3.27	2.51 – 4.26	<0.001
ODI	1.50	1.41 – 1.59	<0.001
ESS	1.04	1.01 – 1.07	0.004
Sleepiness (ESS≥11)	1.43	1.06 – 1.94	0.020
Marital status	0.79	0.61 – 1.02	0.069
Smoking status	0.85	0.66 – 1.09	0.194
Tonsillectomy	1.79	1.03 – 3.13	0.040
Nasal operation	0.74	0.51 – 1.08	0.115
UPPP	0.85	0.35 – 2.07	0.716
Allergy	0.69	0.50 – 0.95	0.022
Pulmonary disease	0.81	0.58 – 1.12	0.198
Hypertension	1.48	1.07 – 2.04	0.017
Cardiac disease	1.75	1.13 – 2.70	0.012
Diabetes mellitus	1.68	1.11 – 2.54	0.014
Stroke	0.49	0.16 – 1.56	0.230
Hypothyroidism	0.71	0.45 – 1.13	0.145
Snoring	3.25	2.09 – 5.06	<0.001
Witnessed apnea	1.95	1.43 – 2.65	<0.001
Nocturnal sweating	1.47	1.09 – 1.99	0.012
Nocturia	1.48	1.09 – 1.99	0.011
Headache	1.06	0.77 – 1.46	0.726
Restless leg syndrome	0.92	0.66 – 1.30	0.924
Sleepy	1.14	0.84 – 1.56	0.392
Fatigue	1.04	0.75 – 1.43	0.832
Depressive mood	0.760	0.55 – 1.06	0.103
Multivariate			
Model 1*			
Age	1.03	1.02 – 1.04	<0.001
BMI	1.14	1.10 – 1.17	<0.001
Male gender	2.08	1.51 – 2.87	<0.001
Tonsillectomy	0.48	0.25 – 0.95	0.033
Model 2**			
Age	1.05	1.03 – 1.06	<0.001
BMI	1.13	1.08 – 1.17	<0.001
Male gender	2.08	1.35 – 3.20	<0.001
Snoring	2.87	1.69 – 4.87	<0.001
Depressive mood	0.61	0.40 – 0.93	0.023

Definition of abbreviations: AHI, apnea-hypopnea index; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; PCI, percutaneous coronary angiography; UPPP, Uvulopalatopharyngoplasty
*adjusted for co-morbid diseases (history of tonsillectomy, hypertension, diabetes mellitus, nasal operation, allergy, stroke, hypothyroidism, pulmonary and cardiac disease)
**adjusted for symptoms (sleepiness, snoring, witnessed apnea, nocturnal sweating, depressive mood and nocturia)

the prevalence of OSA was higher in men, and the male gender was found to be a risk factor for OSA [21, 22]. Besides these known associates, we found an inverse relationship between OSA and history of tonsillectomy. Previously, Kang et al. reported tonsillectomy as an effective management option for OSA in children; however, they also reported that residual OSA is frequently observed after tonsillectomy [23]. In management of OSA in children, tonsillectomy is an effective method, and the history of tonsillectomy in childhood can also be protective against occurrence of OSA in advanced age.

The most important limitation of this study was the diagnostic method of OSA as diagnosis was based on cardiorespiratory sleep studies. Therefore, the total sleep time and sleep stages could not be recorded exactly. However, the cut-off value for AHI (15/h) chosen for OSA diagnosis was previously shown to be reliable for the polygraph system [24] used in the current protocol.

In this sleep clinic cohort, there was no gender difference regarding the cardinal symptoms, such as loud snoring, witnessed apnea, and daytime sleepiness while women presented with fatigue, nocturia, headache, depressive mood, and restless legs symptoms more frequently. In addition, comorbidities were more prevalent in women. Our findings hypothesize that OSA-related symptoms develop late and/or the referral of women for diagnostic evaluation of OSA is delayed. Symptoms and comorbidities in women should be evaluated more attentively for earlier referral and adequate diagnosis and treatment of OSA.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Marmara University (approval number: 09.2017.650).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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Table 4. Associates of obstructive sleep apnea (AHI ≥ 15 events/h) in females and males

	OR	95% CI	p value
Females			
Model 1*			
Age	1.04	1.01 – 1.07	0.003
BMI	1.09	1.04 – 1.15	<0.001
ESS	1.03	0.99 – 1.08	0.174
Smoking history	0.83	0.47 – 1.47	0.527
Hypertension	1.12	0.58 – 2.12	0.739
Model 2**			
Age	1.05	1.02 – 1.08	<0.001
BMI	1.09	1.03 – 1.14	0.001
Snoring	2.16	0.85 – 5.50	0.107
Witnessed apnea	2.20	1.18 – 4.11	0.013
Nocturia	1.18	0.62 – 2.26	0.616
Males			
Model 1			
Age	1.03	1.01 – 1.04	0.001
BMI	1.53	1.11 – 1.20	<0.001
Hypertension	0.81	0.48 – 1.36	0.417
Diabetes mellitus	1.28	0.64 – 2.58	0.485
Cardiac disease	2.03	1.02 – 4.03	0.043
Model 2			
Age	1.04	1.02 – 1.06	<0.001
BMI	1.17	1.10 – 1.23	<0.001
Sleepy (ESS≥11)	1.15	0.73 – 1.80	0.543
Snoring	3.01	1.64 – 5.53	<0.001
Witnessed apnea	1.54	0.99 – 2.37	0.054
Nocturnal sweating	1.36	0.88 – 2.12	0.161

Definition of abbreviations: AHI, apnea-hypopnea index; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; PCI, percutaneous coronary angiography; UPPP, Uvulopalatopharyngoplasty
*adjusted for age, BMI, ESS, smoking history and hypertension
**adjusted for age, BMI, snoring, witnessed apnea, and nocturia
†adjusted for age, BMI, hypertension, diabetes mellitus, and cardiac disease
††adjusted for age, BMI, sleepy, snoring, witnessed apnea

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