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Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: a cross-sectional population-based study

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Abstract

Objective: The current study aimed to investigate stages of reproductive aging as an associated factor for obstructive sleep apnea syndrome (OSAS) among women in a representative sample of Sao Paulo, Brazil.

Methods: Four hundred seven women underwent clinical evaluation, polysomnography, and biochemical analysis. Stages of reproductive aging were defined as premenopause, early postmenopause, and late postmenopause.

Results: OSAS was more frequent in the postmenopausal groups, with 68.4% of women affected by severe OSAS belonging to the late postmenopause group. After adjustment for potential confounding factors, associated factors for OSAS, regardless of its severity, were waist circumference, modified Mallampati score IV, and both postmenopause stages. For moderate to severe OSAS and severe OSAS, we found waist circumference and both postmenopause stages to be the main factors. We carried out a receiver operating characteristic curve analysis, which demonstrated that the cutoff value for waist circumference was 87.5 cm, with a maximum of 75.7% accuracy for the classification of women as OSAS or non-OSAS.

Conclusions: OSAS is prevalent in postmenopausal women, especially in late postmenopause. This study highlights the association between waist circumference, early postmenopause and late postmenopause, and severity of OSAS. Our findings suggest that postmenopause stages may potentially exacerbate the presence of sleep disturbance and that reducing waist circumference may be an important strategy for managing OSAS in women.

Key Words: Obstructive sleep apnea syndrome – Menopause – Waist circumference – Postmenopause.

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder characterized by repetitive, partial, or complete collapse of the upper airway. During sleep, OSAS promotes a change in an individual's ventilatory pattern, leading to intermittent hypoxia and hypercapnia, and sleep fragmentation. As a consequence, OSAS is associated with several adverse health outcomes such as excessive daytime sleepiness[1] and metabolic impairment (cognitive, immune, and cardiovascular impairment, and diabetes),[2-4] leading to increased morbidity and mortality.[5]

Estimates for the worldwide prevalence of OSAS range between 2% and 32.8%.[6-8] Although OSAS has been thought of as a disease that mainly affects men, a recent study observed that OSAS affects 26.1% of women in the general population.[8] OSAS is considered a public health problem worldwide, with some factors, including age, sex, obesity, craniofacial abnormalities, menopause, and others,[8,9] increasing an individual's vulnerability to the condition. The incidence, diagnosis, and clinical manifestation of the disease can be different in women compared with men.[10,11] Women have less severe obstructive sleep apnea (OSA) and present more nonspecific symptoms, which may lead to underrecognition of OSAS by clinicians.[11] Furthermore, women with OSAS were two to three times less likely than men to report the classic symptoms of the disease, such as snoring, gasping, snorting, and apnea, even after adjusting for OSA severity, and tend to have more coexisting problems and a higher level of

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healthcare utilization than men.[11,12] For women in particular, the clinical condition of sleep apnea increases the risk for stroke[13] and may lead to development of insulin resistance.[14] Moreover, women diagnosed with OSAS have a body mass index (BMI) that is higher than average.[15,16] The highest increase in the incidence of OSA in women occurs in the transition from the fourth decade (18.5%) to the fifth decade (43.9%) of life.[8] Despite the high incidence of sleep disorders in women,[17] approximately 90% of individuals with OSAS are undiagnosed,[18] suggesting an important need to better elucidate its associated factors to identify the magnitude of the problem and its health impact.

Thus, the aims of our study were to investigate the association between OSAS and stages of reproductive aging and to identify possible associated factors for OSAS in a representative population sample of women from Sao Paulo (Brazil).

METHODS

Volunteers were randomly selected to represent the population of Sao Paulo according to sex, age (20-80 y), and socioeconomic status. The method used to recruit volunteers to this cross-sectional study was similar to the conceptual framework used for the North American National Health Surveys.[19]

In the first stage, to ensure the representativeness of different levels of wealth, we proportionally selected 96 districts (from 1,500 districts [into which the city was divided for census purposes]) from the four homogenous socioeconomic macroregions of Sao Paulo. Slums and shantytowns were excluded because of high criminal activity. Households were selected if they were permanently occupied private homes; thus, clinics, schools, and other commercial and noncommercial establishments were excluded. In the second stage, selection of a given household was performed by randomly picking the first home and subsequently skipping a specified number (calculated by dividing the total number of homes by a fixed number) to select 11 households in each sector. Each apartment in a building was considered a home, and counting was carried out from the upper floor to the lower floor. Finally, in the third stage of sampling, all eligible residents of each chosen home were ranged from the youngest to the oldest; the participant was selected by means of 96 preestablished random tables, which designated the rank number to be chosen for each of the 11 households, from the 96 selected districts.

Pregnant and lactating women, people with physical or mental impairments preventing self-care, individuals younger than 20 years or older than 80 years, and people who work every night were not included in the selection from the household. Substitutes were chosen from the next home following the same random selection criteria described previously. In addition, individuals were not included in the following instances: three unsuccessful attempts to contact the target individual, total refusal to participate, obstruction by a family member, or inability to participate for a specified reason.[20] These individuals were replaced using the same method described previously.

Participants

An initial sample size of 1,056 participants of both sexes was defined to obtain a representative sample of Sao Paulo City, using a three-stage cluster sampling technique, in a large epidemiologic sleep study called EPISONO.[20] A total of 1,101 volunteers were selected to participate in the study and answered questionnaires at home during visits. Of these, 59 refused to undergo a complete full-night polysomnography (PSG), leading to a final sample size of 1,042 (refusal rate, 5.4%). Of these, 574 were women and were included in the current study. Thus, the entire female population of the representative sample of Sao Paulo (EPISONO) was considered for this study. At the time of selection, all volunteers read and signed an informed consent form, which authorized us to collect and use data for future research studies. For volunteers who had agreed to visit the Sleep Institute, a driver picked them up on the scheduled visit date at a place of their choice about 2 hours before their usual bedtime. A generated weight variable was applied to match the sample by sex, age, and socioeconomic status, with demographic projections for city inhabitants in 2007. These projections were derived from the 2000 city census. The study was approved by the Ethics Committee for Research at the Universidade Federal de Sao Paulo (CEP 0593/06) and registered with ClinicalTrials.gov (NCT00596713).

Clinical assessment

Female volunteers were categorized into premenopause (PRM), early postmenopause (EPM), or late postmenopause (LPM). For gynecological status, study participants were grouped into the following menopause status: PRM, perimenopause, and postmenopause. This classification was based on their responses to the gynecological questionnaire and on hormone measurements evaluated on the morning after PSG. The gynecological questionnaire included questions about menstrual cycles, premenstrual complaints, use of hormonal contraceptives, dysmenorrhea, menopause, hot flushes, and hormone therapy. PRM status was defined as ongoing menstrual cycle. This group was classified as follows: follicular phase, women in the first 12 days of their menstrual cycle; periovulatory, women near the 14th day of the menstrual cycle with a luteinizing hormone (LH) concentration of approximately 50 mIU/mL; luteal phase, women in the second half of the menstrual cycle; anovulatory, women experiencing amenorrhea with follicle-stimulating hormone (FSH) and LH concentrations lower than 30 mIU/mL and taking hormonal contraceptives. Perimenopausal women referred to those who had irregular menstrual cycles within the past year and FSH and LH concentrations no higher than 30 mIU/mL.[21] The postmenopausal group was defined by amenorrhea for more than 1 year or FSH and LH concentrations higher than 30 mIU/mL. This group was divided into EPM (in menopause for up to 5 y) and LPM (in menopause for >5 y), in accordance with the Stages of Reproductive Aging Workshop staging system.[22] The exclusion criteria for this study were as follows: participants with missing values (n = 103), undetermined

stage (n = 22), undergoing hormone therapy (n = 19), perimenopause (n = 15), taking isoflavone compounds (n = 6), and pregnancy (n = 2).

Pregnant women were excluded from the study because sleep disorders may be caused by the physiological and clinical changes in pregnancy.[23] Postmenopausal women taking alternative therapy (hormonal or other) to improve quality of sleep or for other reasons were excluded from the study. Previous studies indicated that women undergoing these therapies had subjective and objective improvements in sleep quality.[24] Women in perimenopause were excluded from the study because this group has transitional characteristics of PRM to postmenopause.[25,26]

Anthropometric measurements and questionnaires

Craniofacial factors, as assessed by modified Mallampati score, are involved in the pathophysiology of OSAS because of their relationship with internal upper airway size. The modified Mallampati score considers tongue size in the oral cavity and the degree of difficulty of visualization of the pharynx. In sleep medicine, the score is used to identify individuals who have a higher risk for OSAS.[27] Mallampati score is classified as follows: class I, soft palate, fauces, pillars, and uvula are visible; class II, soft palate, fauces, and uvula are visible; class III, soft palate and base of uvula are visible; class IV, soft palate is not visible at all.[28]

General physical measurements and modified Mallampati score were taken by trained personnel immediately before participants were prepared for PSG hookup, following recommended procedures and using precise instruments. Other measurements were taken by trained technicians and included systolic blood pressure (SBP; mm Hg), diastolic blood pressure (DBP; mm Hg), body weight (kg), height (meters), BMI (weight/height^2), waist circumference (cm), and neck circumference (cm). Volunteers were also asked about their use of hormonal contraceptives, history of diabetes, and occurrence of stroke and myocardial infarction.

Ethnicity and social class

Individuals self-reported their ethnic origin according to the following classifications used by the Brazilian Institute of Geography and Statistics: white, Afro-Brazilian, mixed race (mulatto), Asian, native (indigenous), and unknown/other. Social class was defined as high (annual household income ≥US$15,961), middle (annual household income between US$4,561 and US$15,960), or low (annual household income ≤US$4,560), according to the Brazilian Economic Classification Criteria (www.abep.org.br).

Polysomnography

Full-night PSG was performed, using a digital system (EMBLA S7000; Embla Systems Inc, Broomfield, CO), at the sleep laboratory during the participant's habitual sleep time, which had previously been established with the participant.[8] The following physiological variables were monitored simultaneously: electroencephalogram; electro-oculogram; electrocardiogram; airflow; surface electromyogram (submental, temporal, masseter, and tibialis anterior muscles); respiratory effort of the thorax and abdomen (using inductance plethysmography); snoring and body position; saturation of peripheral oxygen (SpO_2); and pulse rate.

OSAS was diagnosed according to the criteria of the *International Classification of Sleep Disorders*.[29] OSAS classification was defined according to the apnea-hypopnea index (AHI).[30] The diagnosis of OSAS did not differ between men and women. Participants were diagnosed with OSAS if they presented an AHI of 5 or higher and at least one of the following complaints: loud snoring, daytime sleepiness, fatigue, or breathing interruptions during sleep. Participants with an AHI of 15 or higher were diagnosed with OSAS, regardless of whether they had any additional complaints. Participants were distributed into four groups based on OSAS severity: control group (<5 events/h), mild OSAS (5-14, events/h), moderate OSAS (15-30 events/h), and severe OSAS (>30 events/h). Four trained technicians visually scored all of the PSG data according to standardized criteria for investigating sleep.[31] Hypopnea was defined using the alternative rule.[32] For PSG, random rescoring of 4% of all recordings showed a mean (SEM) agreement rate of 93.3% (5.1%) with a mean (SEM) κ of 0.91 (0.03), which guarantees the scoring reliability of PSG.

Sample collection and biochemical analysis

Biochemical variables were assessed as possible confounding factors for OSAS. On the morning after PSG, venous blood was collected from the participant's forearm after overnight fasting. Blood analysis included the following: cortisol, progesterone, LH, FSH, 17β-estradiol, total testosterone, triglycerides, homocysteine, tumor necrosis factor-α (TNF-α), uric acid, total cholesterol, and fractions (ADVIA 1650 chemistry system; Siemens Healthcare Diagnostics Inc). Within-assay sensitivity and between-assay sensitivity of all biochemical parameters have been previously described in detail.[20]

Statistical analysis

Data that did not meet the assumptions of normality and homogeneity were *z*-score-transformed for suitable parametric evaluation. Statistical analysis of the sample was carried out using General Linear Model through one-way analysis of variance followed by Bonferroni's post hoc test, when necessary. χ^2 test was performed to determine the association between categorical variables and the presence of OSAS. To evaluate the relationship between AHI and OSAS-related factors, we performed Pearson's correlation test with the following factors: TNF-α, low-density lipoprotein (LDL), total cholesterol, homocysteine, triglycerides, uric acid, neck circumference, SBP, waist circumference, basal SpO_2, high-density lipoprotein (HDL), and total testosterone. For determination of the possible associated factors for OSAS levels in women, continuous variables with a significant correlation coefficient higher than 0.20 obtained by Pearson's correlation test with AHI were included in a binary logistic regression using the backward Wald method. HDL and total testosterone levels were not added in regression analysis. Furthermore, all categorical variables considered to be potentially related to OSAS were

considered in logistic regression analysis. The continuous variables chosen for logistic regression included SBP, uric acid, baseline SpO_2, neck circumference, and waist circumference. The categorical variables chosen for logistic regression included age (≤43 or ≥44 y), BMI (<26.9 or ≥26.9 kg/m^2), use of hormonal contraceptives, modified Mallampati score, stage of reproductive aging, history of diabetes, and previous myocardial infarction and stroke.

Three logistic regression models were also performed to identify factors associated with OSAS in three statistical models. The first logistic model identified the main associated factors for OSAS in women, regardless of its severity (presence or absence). The second logistic model was performed to evaluate associated factors for moderate to severe OSAS in women. The third logistic model aimed at analyzing possible predictor factors for severe OSAS in women.

Receiver operating characteristic (ROC) curve was used to determine the optimal cutoff point for waist circumference as classifier of women with or without OSAS. The ROC curve is a plot of the sensitivity of a test versus its false-positive rate for all possible cutoff points. In medicine, the ROC curve is used to evaluate the potential biomarker by cutoff value in a clinical test. The parameter used to identify the best cutoff point was based on a judgment of accuracy provided by the measure. The *y* axis represents "sensitivity," and the *x* axis represents "1 − specificity" when specificity is reported as a value from 0 to 1.0. Accuracy, sensibility, specificity, positive predictive value, and negative predictive value were determined similarly to Krag et al.[33] Significance level was set to $P < 0.05$. Data are presented as mean (SEM) or as frequency (percentage). All analyses were performed using SPSS version 20 (SPSS Inc, Chicago, IL).

RESULTS

From a total of 574 women included in the study, our final sample consisted of 407 women after exclusion. Figure 1 shows a flow diagram for study identification, selection, and exclusion. The PRM group was composed of women in the following categories: 109, follicular phase; 57, luteal phase; 73, taking hormonal contraceptives; 14, periovulatory; 15, anovulatory (totaling 268 women). Postmenopausal women were grouped into EPM (43) and LPM (96). Descriptive parameters in Table 1 show that stage of reproductive aging affects the following parameters: age ($F_{2,404} = 454.27$, $P < 0.001$), BMI ($F_{2,404} = 17.50$, $P < 0.001$), progesterone level ($F_{2,404} = 14.71$, $P < 0.001$), estradiol level ($F_{2,404} = 52.36$, $P < 0.001$), LH level ($F_{2,404} = 131.40$, $P < 0.001$), FSH level ($F_{2,404} = 426.89$, $P < 0.001$), AHI ($F_{2,404} = 58.84$, $P < 0.001$), basal SpO_2 ($F_{2,404} = 113.37$, $P < 0.001$), mean SpO_2 ($F_{2,404} = 120.60$, $P < 0.001$), and minimal SpO_2 ($F_{2,404} = 111.29$, $P < 0.001$). Post hoc test revealed that the EPM and LPM groups were older and had higher BMI than the PRM group ($P < 0.001$). Progesterone and estradiol levels at baseline, mean SpO_2, and minimal SpO_2 were lower in the EPM and LPM groups compared with the PRM group ($P < 0.001$). LH, FSH, and AHI were statistically higher in the postmenopausal groups than in the PRM group ($P < 0.001$). Age and LH levels for the LPM group were significantly higher than those for the EPM group ($P < 0.001$).

Table 1 also shows that the occurrence of previous myocardial infarction was higher in the EPM group compared with the other groups ($\chi^2 = 9.80$, $df = 2$, $P < 0.01$). Frequency of previous stroke ($\chi^2 = 8.46$, $df = 2$, $P < 0.05$), modified Mallampati score IV ($\chi^2 = 12.40$, $df = 6$, $P < 0.05$), and history of diabetes ($\chi^2 = 14.13$, $df = 2$, $P < 0.01$) were higher in the

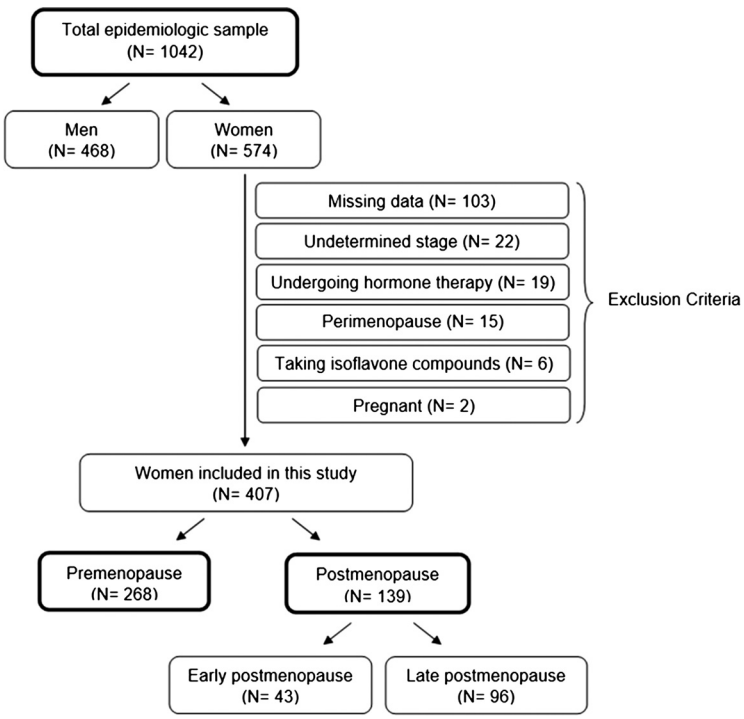

FIG. 1. Flow chart of criteria for selecting study participants.

TABLE 1. *Demographic parameters for the epidemiologic sample, by stage of reproductive aging*

		Postmenopause		
	Premenopause (n = 268)	Early postmenopause (n = 43)	Late postmenopause (n = 96)	*P*
Age, mean (SEM), y	34.8 (0.5)	52.6 (0.9)[a]	62.8 (0.8)[a,b]	<0.001
Body mass index, mean (SEM), kg/m^2	25.8 (0.3)	29.5 (0.8)[a]	28.92 (0.6)[a]	<0.001
Progesterone, mean (SEM), ng/mL	3.8 (0.4)	1.3 (0.6)[a]	0.4 (0.2)[a]	<0.001
Estradiol, mean (SEM), pg/mL	95.5 (5.4)	21.4 (3.5)[a]	16.6 (1.2)[a]	<0.001
Luteinizing hormone, mean (SEM), mIU/mL	9.0 (0.8)	40.4 (3.4)[a]	30.6 (1.4)[a,b]	<0.001
Follicle-stimulating hormone, mean (SEM), mIU/mL	6.0 (0.5)	59.2 (4.6)[a]	56.2 (2.5)[a]	<0.001
Apnea-hypopnea index, mean (SEM)	2.04 (0.3)	10.8 (2.1)[a]	14.3 (1.7)[a]	<0.001
Basal SpO_2, mean (SEM)	96.9 (0.1)	95.8 (0.3)[a]	94.7 (0.2)[a]	<0.001
Mean SpO_2, mean (SEM)	96.3 (0.1)	93.9 (0.3)[a]	93.7 (0.2)[a]	<0.001
Minimal SpO_2, mean (SEM)	91.5 (0.2)	84.9 (0.9)[a]	84.2 (0.6)[a]	<0.001
Diagnosed obstructive sleep apnea syndrome, %	9.3	48.8[c]	52.1[c]	<0.001
Use of hormonal contraceptives, %	26.9	0.0	0.0	<0.001
History of diabetes, %	1.5	9.3	9.4[d]	<0.01
Previous myocardial infarction, %	0	4.7[d]	2.1	<0.01
Previous stroke, %	0.4	4.7	4.2[e]	<0.05
Modified Mallampati score, %				
Class I	12.0	1.7	2.2	
Class II	16.2	1.5	4.4	<0.05
Class III	21.4	3.4	7.6	
Class IV	16.2	3.9	9.3[e]	
Ethnicity, %				
White	38.1	5.9	13.5	
Afro-Brazilian	9.6	2.0	2.7	NS
Mulatto	6.9	1.2	2.7	
Native	2.9	0.5	1.7	
Asian	2.5	0.2	1.0	
Other/unknown	5.9	0.7	2.0	
Social class, %				
High income	31.9	5.9	10.6	
Middle income	27.0	3.4	10.3	NS
Low income	6.9	1.2	2.7	

SpO_2, saturation of peripheral oxygen; NS, nonsignificant.
[a]$P < 0.001$ compared with the premenopause group.
[b]$P < 0.001$ compared with the early postmenopause group.
[c]Frequency higher than expected ($P < 0.001$).
[d]Frequency higher than expected ($P < 0.01$).
[e]Frequency higher than expected ($P < 0.05$).

LPM group compared with the other groups. Use of hormonal contraceptives was more frequent in the PRM group (χ^2 = 67.96, *df* = 2, $P < 0.001$). No association between ethnic group ($\chi^2 = 2.80$, *df* = 10, $P > 0.05$) and social class ($\chi^2 = 1.77$, *df* = 4, $P > 0.05$) was found for stages of reproductive aging.

Figure 2 shows the sample distribution of OSAS severity in each group. χ^2 analysis showed an association between OSAS and EPM and LPM (χ^2 = 103.8, *df* = 6, $P < 0.001$) and a higher frequency of women without OSAS in the PRM group. The group of women with moderate OSAS had greater

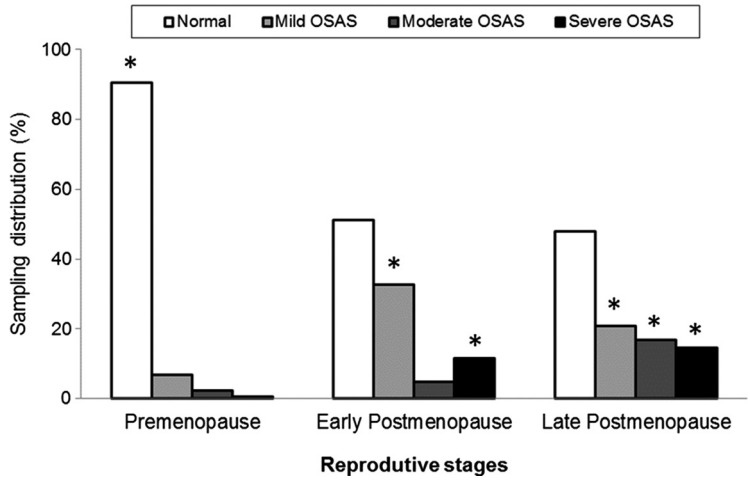

FIG. 2. Frequency of normal breathing (n = 311), mild obstructive sleep apnea syndrome (OSAS; n = 53), moderate OSAS (n = 24), and severe OSAS (n = 19), by stage of reproductive aging: premenopause, early postmenopause, and late postmenopause. *Frequency higher than expected ($P < 0.05$).

TABLE 2. *Descriptive parameters for variables associated with obstructive sleep apnea, by stage of reproductive aging*

		Postmenopause		
	Premenopause	Early postmenopause	Late postmenopause	*P*
Homocysteine, μmol/L	8.3 (0.2)	9.6 (0.4)[a]	10.6 (0.3)[b]	<0.001
Uric acid, mg/dL	4.2 (0.1)	4.5 (0.2)	4.9 (0.1)[a]	<0.05
Neck circumference, cm	33.3 (0.2)	34.7 (0.4)[a]	34.6 (0.3)[b]	<0.001
Waist circumference, cm	79.2 (0.7)	90.1 (1.8)[b]	88.6 (1.2)[b]	<0.001
Systolic blood pressure, mm Hg	117.6 (1.2)	132.7 (3.1)[b]	142.1 (2.1)[b,c]	<0.001
Diastolic blood pressure, mm Hg	76.8 (0.7)	82.4 (1.7)[a]	84.3 (1.1)[b]	<0.001
Tumor necrosis factor-α, pg/mL	8.8 (0.4)	10.3 (0.9)	10.6 (0.6)[a]	<0.05
Triglycerides, mg/dL	100.4 (3.4)	131.1 (8.6)[a]	127.7 (5.8)[b]	<0.001
Total cholesterol, mg/dL	181.0 (2.2)	213.5 (5.5)[b]	206.8 (3.7)[b]	<0.001
Low-density lipoprotein, mg/dL	103.7 (1.8)	129.0 (4.5)[b]	122.7 (3.0)[b]	<0.001
High-density lipoprotein, mg/dL	57.2 (0.8)	58.2 (2.0)	58.7 (1.4)	NS
Total testosterone, ng/dL	47.6 (1.6)	38.9 (4.0)	44.7 (2.7)	NS

Data are presented as mean (SEM).
NS, nonsignificant.
[a] $P < 0.05$ compared with the premenopause group.
[b] $P < 0.001$ compared with the premenopause group.
[c] $P < 0.05$ compared with the early postmenopause group.

frequency in the LPM group (66.7%). Frequency of women with severe OSAS was higher in the EPM (26.3%) and LPM (68.4%) groups compared with the PRM group (5.3%).

In addition, Table 2 shows that stage of reproductive aging affects the following parameters: homocysteine ($F_{2,404}$ = 33.38, $P < 0.001$), uric acid ($F_{2,404}$ = 17.25, $P < 0.001$), neck circumference ($F_{2,404}$ = 12.07, $P < 0.001$), waist circumference ($F_{2,404}$ = 32.54, $P < 0.001$), SBP ($F_{2,404}$ = 55.05, $P < 0.001$), DBP ($F_{2,404}$ = 18.68, $P < 0.001$), TNF-α ($F_{2,404}$ = 3.60, $P < 0.001$), triglycerides ($F_{2,404}$ = 11.67, $P < 0.001$), total cholesterol ($F_{2,404}$ = 28.32, $P < 0.001$), and LDL fraction ($F_{2,404}$ = 23.63, $P < 0.001$). No differences in HDL and total testosterone levels were observed. Post hoc analysis revealed increases in homocysteine, neck circumference, waist circumference, SBP, DBP, triglycerides, total cholesterol, and LDL in both EPM and LPM groups compared with the PRM group ($P < 0.001$). Uric acid and TNF-α levels were significantly higher only in the LPM group compared with the PRM group ($P < 0.05$). SBP was also higher in LPM compared with EPM ($P < 0.05$).

All potentially confounding variables were correlated with AHI through Pearson's correlation test and are shown in Table 3. Variables that fulfilled the selection criteria for logistic model analysis were as follows: uric acid, neck circumference, SBP, waist circumference, and baseline SpO_2. Moreover, Figure 3A depicts AHI adjusted for all confounders at each stage of reproductive aging. Analysis of covariance showed a significant effect of postmenopausal groups ($F_{2,386}$ = 4.05, $P < 0.05$) on AHI, as increase in AHI was observed in the LPM group compared with the PRM group independent of confounders. As a consequence of AHI, mean SpO_2 (Fig. 3B; $F_{2,388}$ = 3.37, $P < 0.05$) and minimal SpO_2 (Fig. 3C; $F_{2,388}$ = 11.87, $P < 0.001$) were also affected by stages of reproductive aging. Lower levels of mean SpO_2 and minimal SpO_2 were observed in LPM compared with PRM. Minimal SpO_2 was lower in the EPM group compared with the PRM group.

Table 4 depicts three logistic models identifying associated factors for OSAS. Factors for mild to moderate to severe OSAS indicate the corresponding adjusted odds ratio (AOR) for each independent associated factor (−2LL = 317.83; Cox-Snell R^2 = 0.27; Nagelkerke R^2 = 0.40). The significant factors were waist circumference, modified Mallampati score IV, EPM, and LPM. A 1-cm increase in waist circumference represented a 6% increase in the risk for developing OSAS. Participants with modified Mallampati score IV showed a 2.91-fold increase in the relative risk for developing OSAS. Diagnosis in the EPM and LPM groups represented a 5.92- and 7.53-fold increase, respectively, in the relative risk for developing OSAS.

Associated factors for moderate to severe OSAS describe the AOR for each independent predictor (−2LL = 210.15; Cox-Snell R^2 = 0.15; Nagelkerke R^2 = 0.30). Analysis indicated that the significant factors were waist circumference and stage of reproductive aging. Results showed that a 1-cm increase in waist circumference increased the likelihood of developing moderate to severe OSAS by 5%. Women in the EPM and LPM groups showed a 4.68- and 11.66-fold increase, respectively, in the relative risk for developing OSAS.

In the last logistic analysis, factors for severe OSAS show AOR only for each independent predictor (−2LL = 133.33;

TABLE 3. *Correlations between apnea-hypopnea index and risk factors for obstructive sleep apnea in women*

Parameters	*r*	*P*
Tumor necrosis factor-α	0.14	<0.01
Low-density lipoprotein	0.14	<0.01
Total cholesterol	0.16	<0.001
Homocysteine	0.17	<0.001
Triglycerides	0.18	<0.001
Uric acid	0.23	<0.001
Neck circumference	0.26	<0.001
Systolic blood pressure	0.34	<0.001
Waist circumference	0.38	<0.001
Basal SpO_2	−0.39	<0.001
High-density lipoprotein	−0.20	NS
Total testosterone	0.003	NS

SpO_2, saturation of peripheral oxygen; NS, nonsignificant.

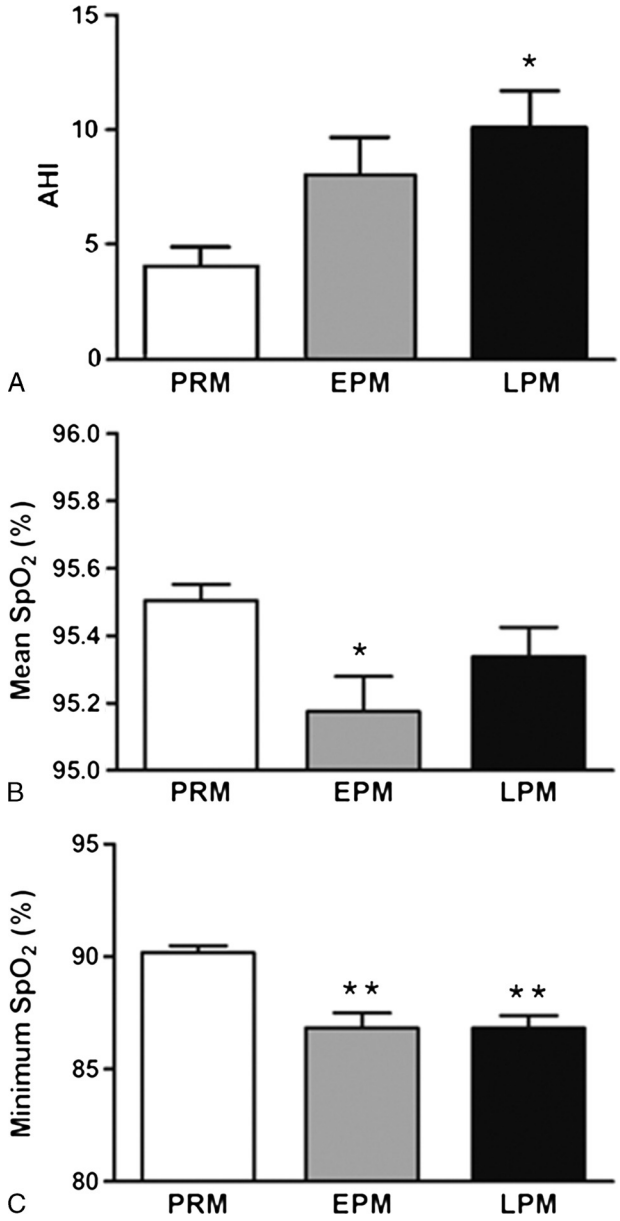

FIG. 3. Adjusted apnea-hypopnea index (AHI) (**A**), mean saturation of peripheral oxygen (SpO_2) (**B**), and minimal SpO_2 (**C**) levels, by stage of reproductive aging: premenopause (PRM), early postmenopause (EPM), and late postmenopause (LPM). Data are presented as mean (SEM) and adjusted for confounders such as age, body mass index, systolic blood pressure, neck circumference, waist circumference, basal SpO_2, total cholesterol and low-density lipoprotein fraction, triglycerides, uric acid, homocysteine, tumor necrosis factor-α, history of diabetes, modified Mallampati score, use of hormonal contraceptives, stroke, and myocardial infarction. $^{*}P < 0.05$ compared with the PRM group. $^{**}P < 0.001$ compared with the PRM group.

Cox-Snell $R^2 = 0.09$; Nagelkerke $R^2 = 0.30$). Analysis revealed that, in EPM and LPM, waist circumference was also the independent factor associated with severe OSAS in women. A 1-cm increase in waist circumference represented a 5% increase in the risk for developing OSAS. Diagnosis in the EPM and LPM groups represented a 21.85- and 27.94-fold increase, respectively, in the relative risk for developing OSAS.

The ROC curve demonstrated that the cutoff value for waist circumference was 87.5 cm, with a maximum of 75.7% accuracy for classification of women as having or not having OSAS (Fig. 4). Results indicated that waist circumference had a large mean (SEM) area under the curve—0.784 (0.025); asymptotic significance was less than 0.001 (95% CI, 0.74-0.83). The cutoff value for waist circumference resulted in 63.5% sensitivity, 79.4% specificity, 48.8% positive predictive value, and 87.6% negative predictive value. The measure afforded identification of 247 individuals in the non-OSAS group and 61 women in the OSAS group. Results also indicated the presence of 35 false-negative cases and 64 false-positive cases.

DISCUSSION

Findings in a representative sample of Sao Paulo City revealed that postmenopausal women are more likely to present OSAS than those in PRM. Physiological hormonal changes mediated by menopause can influence respiratory parameters during sleep and are associated with OSAS and its degree of severity in women. About 68.4% of individuals affected by severe OSAS were in the LPM group. Based on Stages of Reproductive Aging Workshop criteria, previous findings had shown that women in LPM had higher AHI and respiratory disturbance index during sleep compared with women at the peak of PRM.[22,34] The association between OSAS and postmenopause stages found in the current study may also be related to obesity (measured by waist circumference) and aging (by postmenopause stage). A high modified Mallampati score indicates a reduction in the size of the upper airway, triggering obstruction during sleep, which can also be influenced by obesity[35] and restriction of skeletal measurements, including a smaller maxilla, a retropositioned mandible, and a shorter anterior cranial base.[36]

Owing to the increase in OSAS diagnosis in postmenopause stages, an increase in AHI was also followed by lower levels of SpO_2 during both wakefulness and sleep. Clinical studies indicate that estradiol therapy, alone or in combination with progesterone, can contribute significantly to the reduction of AHI.[37] Although induction of hormonal suppression in young women was not associated with sleep fragmentation or sleep-disordered breathing,[38] hormonal changes found in the menopausal period may be related to increased susceptibility to sleep apnea, with age and weight acting synergistically in the development of OSAS.[39] The pathophysiology of OSAS is complex and multifactorial, including factors such as anatomy, age, sex, and hormonal changes. Hormonal fluctuations characteristic of the female sex affect sleep patterns.[21] Progesterone increases the ventilatory drive and action of the dilator muscles of the upper airway, thereby acting as a protective factor in premenopausal women.[40,41] Postmenopausal women have increased incidence of OSAS, but it has been observed that hormone therapy (estrogen and progesterone) can act as a protective factor against OSAS and thus decrease the prevalence of the sleep disorder. Because the objective of this study was to determine the prevalence of OSAS

TABLE 4. *Binary logistic regression models for calculation of AOR for OSAS*

	COR	95% CI for COR	*P*	AOR	95% CI for AOR	*P*
Risk factors for mild to moderate to severe OSAS (model 1)						
Constant	–	–	–	<0.001	–	<0.001
Mallampati class I		Reference group			Reference group	
Mallampati class II	1.15	0.42-3.16	0.781	1.15	0.36-3.61	0.815
Mallampati class III	2.99	1.25-7.17	0.014	2.48	0.92-6.72	0.073
Mallampati class IV	4.63	1.94-11.03	0.001	2.91	1.09-7.81	0.033
Waist circumference	1.08	1.06-1.11	<0.001	1.06	1.04-1.09	<0.001
Premenopause		Reference group			Reference group	
Early postmenopause	9.28	4.49-19.18	<0.001	5.92	2.70-12.97	<0.001
Late postmenopause	10.57	5.95-18.76	<0.001	7.53	4.08-13.92	<0.001
Risk factors for moderate to severe OSAS (model 2)						
Constant	–	–	–	0.001	–	<0.001
Waist circumference	1.06	1.04-1.09	<0.001	1.05	1.02-1.08	0.001
Premenopause		Reference group			Reference group	
Early postmenopause	7.25	2.40-21.87	<0.001	4.68	1.49-16.65	0.008
Late postmenopause	16.14	6.78-38.44	<0.001	11.66	4.80-28.33	<0.001
Risk factors for severe OSAS (model 3)						
Constant	–	–	–	<0.001	–	<0.001
Waist circumference	1.07	1.04-1.11	<0.001	1.05	1.01-1.09	0.008
Premenopause		Reference group			Reference group	
Early postmenopause	35.13	4.00-308.85	0.001	21.85	2.42-197.39	0.006
Late postmenopause	41.82	5.39-324.46	<0.001	27.94	3.53-220.93	0.002

AOR, adjusted odds ratio; OSAS, obstructive sleep apnea syndrome; COR, crude odds ratio.

and its associated factors in women at different stages of reproductive aging (PRM, EPM, and LPM), women who received hormone therapy were excluded to avoid this confounding effect.

AHI is considered as a potential marker of health in postmenopausal women[42] because mean and minimal oxygen saturation levels are among the major negative consequences of OSAS on the body.[43] The mean value for minimal SpO_2 in postmenopausal women was around 85%. However, physicians consider hypoxemia to be harmful to the body when saturation levels are lower than 90%.[44] Intermittent hypoxia provokes a cascade of events harmful to the body, with impairment of vascular function[45,46] and organs that demand a great quantity of oxygen, such as the central nervous system.[47] The main hypothesis is that this is caused by the formation of free radicals or reactive oxygen species caused by intermittent hypoxia.[48] Neuronal degeneration related to hypoxia can promote activation of microglia.[49] Decreased availability of nitric oxide attenuates nitric oxide-dependent vasodilatation and can lead to endothelial dysfunction, inflammation, and atherosclerosis.[50,51]

Previous studies indicated that individuals affected by cardiovascular disorders, such as myocardial infarction or stroke, have more associated sleep disturbances.[52] In the present study, the percentage of women previously affected by these disorders was elevated in the postmenopausal groups. The modified Mallampati score is a parameter directly correlated with AHI.[53,54] Even though Hukins[55] considered the modified Mallampati classification as an inefficient measure of clinical assessment, our data showed that modified Mallampati score was an associated factor for OSAS. Moreover, a higher modified Mallampati score was a predictor of mild to moderate to severe OSAS.

The homocysteine and uric acid levels found in our sample corroborated the findings of other studies—a gradual increase with aging,[56] along with increases in waist circumference and neck circumference.[57] BMI, neck circumference, waist-to-hip ratio, and prevalence of OSA are frequently higher in postmenopausal women than in premenopausal women. Postmenopause stages potentially modulate the development of OSA in women.[58] Furthermore, cardiovascular (SBP and DBP), lipid (triglycerides, total cholesterol, and LDL fraction), and inflammatory (TNF-α) assessments were significantly affected in the postmenopausal groups compared with the PRM group, corroborating previous studies of factors usually associated with aging and OSA.[59-61]

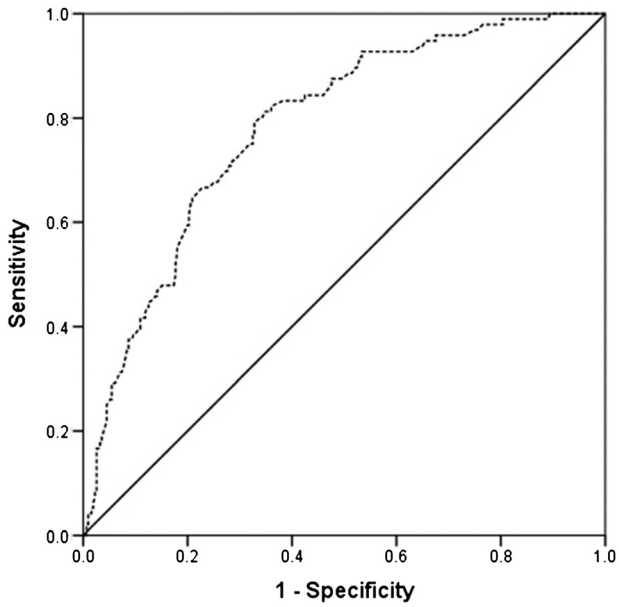

FIG. 4. Receiver operating characteristic curve analysis of waist circumference as classifier for obstructive sleep apnea syndrome diagnosis. The *y* axis represents true-positive rates (sensitivity), whereas the *x* axis represents false-positive rates (100 − specificity).

The identification of factors associated with the development of OSAS in each logistic regression model evaluated the impact of anthropometric and hormonal factors. Previous studies showed menopause to be a risk factor for sleep-disordered breathing.[6,58] However, development of OSAS is also related to other factors such as obesity and metabolic syndrome and is not exclusively linked to hormonal changes.

The low odds ratio for waist circumference in the models is attributable to its great variability as a numeric variable compared with categorical variables such as modified Mallampati score and both postmenopause stages. Thus, in this case, interpretation should be relative because a one-point increase on the scale (1 cm in waist circumference) represents a certain percentage of increased risk. In this sense, categorical variables have few subcategories, leading to higher odds ratio. Moreover, waist circumference affected the risk for mild, moderate, and severe OSAS models similarly; although the odds ratio for waist circumference was small, this risk may increase accordingly with great changes in waist circumference.

Results of ROC curve analysis demonstrated that 87.5 cm is the critical measure for OSAS. It allowed a diagnosis of OSAS in 75.7% of the sample. Few studies have used the optimal cutoff value for OSAS diagnosis using the ROC curve. In spite of this, our cutoff point for waist circumference is corroborated by other studies that identified 88 cm as the cutoff value.[62,63] Anthropometric parameters, such as neck circumference and waist circumference, are associated with severity of OSAS.[64,65] Moreover, abdominal obesity is considered an independent risk factor for predicting sleep duration and sleep disorders.[66,67] Based on waist circumference, the specificity provided by the ROC curve was greater than 85% and therefore has a great value as a screening method for women without accurately diagnosed OSAS.

Some limitations of the study need to be considered. There was a loss of 18.4% of individuals in our sample owing to missing values. Because this is a cross-sectional study, cause-consequence analysis cannot be made. Future studies should investigate the use of hormone therapy in EPM to clarify the relationship between menopause and breathing disorders and the possibility of treatment with continuous positive airway pressure. Despite these limitations, this study reveals the association between obesity and menopause status in women diagnosed with OSAS.

CONCLUSIONS

The current study of women from Sao Paulo City identifies a higher frequency of OSAS in postmenopause stages. Diagnosis of severe OSAS is highest in LPM. Moreover, modified Mallampati score IV, waist circumference, and postmenopause stages are considered factors independently associated with OSAS, regardless of its severity. These factors are associated with increased AHI, suggesting that hormonal and physical factors may contribute to worsening of sleep health in women.

Thus, we can conclude that postmenopause stages may potentially exacerbate the presence of sleep disturbances. Reduction of waist circumference would be one important strategy for managing OSAS in women. In this sense, regular physical activity, healthy diet, sleep hygiene, and stress management are beneficial for women's health and may assist in the reduction of waist circumference. Adopting these measures may, to some extent, help avoid the development of OSAS and promote better quality of life.

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