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SCIENTIFIC INVESTIGATIONS

Sex-specific associations between erythrocyte measures and obstructive sleep apnea

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Study Objectives: Hypoxemic effects of obstructive sleep apnea (OSA) have been implicated in changes in erythropoiesis and hence erythrocyte measures. Sex differences are evident in both OSA and erythropoiesis. Whether sex modulates the relationship between severity of OSA and erythrocyte measures has not previously been studied.

Methods: We examined a sample of 976 patients (38% women) who underwent overnight polysomnography and measurement of red blood cell count, hemoglobin, and hematocrit. Patients were divided into primary snoring and mild, moderate, and severe OSA groups, separately by sex.

Results: In multiple regression models, we found significant interactions between sex and oxygen desaturation index and apnea-hypopnea index on erythrocyte measures. Higher oxygen desaturation index and higher apnea-hypopnea index were independently associated with higher red blood cell count, hemoglobin, and hematocrit in women but not in men. Further ordinal logistic regression analysis showed a significant association between oxygen desaturation index (odds ratio, 2.33; 95% confidence interval, 1.17–4.66) and apnea-hypopnea index (odds ratio, 2.44; 95% confidence interval, 1.23–4.84) and red blood cell count in women only. Correlation analysis also showed that erythrocyte measures and markers of cardiometabolic risk were more closely correlated in women than in men.

Conclusions: This study provides novel data suggesting a significant association between erythrocyte measures and OSA severity in women but not in men. Similarly, the relationship between hematologic metrics and cardiometabolic risk markers was more pronounced in women than in men. Our findings suggest a sex-specific impact of OSA on erythrocyte measures and on their relationship with indexes of cardiometabolic risk.

Keywords: cardiometabolic risk factors, erythrocyte measures, hematocrit, obstructive sleep apnea, sex differences

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) and erythrocyte measures are both linked to cardiometabolic diseases. Sex differences are evident in both OSA and erythropoiesis. However, little is known regarding the relationship between sex, OSA severity, erythrocyte measures, and cardiometabolic risk markers.

Study Impact: This study revealed significant interactions between sex and metrics of OSA severity on erythrocyte parameters, suggesting that OSA is associated with hematologic measures in women but not in men. Closer associations between erythrocyte measures and cardiometabolic risk markers were found in women than in men.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent sleep disorder characterized by upper airway obstruction and recurrent intermittent hypoxemia during sleep.[1] Repetitive intermittent hypoxemia may induce cardiometabolic dysfunction, favoring obesity, hypertension, and increased risk of adverse cardiovascular events and sudden death.[2] Hypoxemia is a potent stimulus for production and release of erythropoietin resulting in increased red blood cell production in bone marrow and in circulating erythrocyte measures (red blood cell count, hemoglobin, hematocrit).[3] A well-described determinant of increased erythrocyte parameters is chronic hypoxemia, which may be caused by environmental conditions, such as hypobaric hypoxia, and by medical disorders such as chronic obstructive pulmonary disease. Elevated erythrocyte measures have been linked to poor cardiovascular health in both cross-sectional and longitudinal studies. Increased levels of red blood cells, hemoglobin, and hematocrit have been found to predict concurrent and future metabolic syndrome.[4,5] Associations between erythrocyte measures and heightened risk of coronary heart disease have been also reported.[6,7]

Intermittent hypoxemia may also stimulate erythropoiesis. As outlined in the guidelines for evaluation and management of polycythemia, OSA is considered as a differential diagnosis of secondary polycythemia.[8,9] Indeed, there is evidence that OSA

may induce increases in erythropoietin.[10] However, the evidence that OSA can cause clinically significant polycythemia is largely anecdotal or based on case reports.[11] To date, only a few studies have examined the association between OSA and erythrocyte measures.[12–16] Choi et al[13] found that patients with severe OSA had higher hematocrit and hemoglobin than patients without OSA and patients with mild-to-moderate OSA, but red blood cell count was not reported. Conversely, other studies did not find any associations between OSA severity and hematocrit or hemoglobin level,[12,14,15] although 1 study found significant differences in red blood cell count among different OSA severity groups.[14] Collectively, these studies concluded that OSA does not cause clinically significant polycythemia, thus challenging current recommendations.

Sex differences have been reported with regard to both erythrocyte measures and OSA. Women are known to have lower levels of hemoglobin in venous blood than men,[17] and sex-specific associations between erythrocyte measures and cardiovascular disease have been documented.[18] A longitudinal analysis of the Second National Health and Nutrition Examination Survey showed that women in the upper tertile of hematocrit levels were more likely to die from coronary heart disease than those in the lowest tertile, whereas no association was found in men.[18] Sex differences are also evident in OSA. The prevalence of sleep apnea is higher in young and middle-aged men than in their female counterparts,[19] but the morbidity gap narrows among older adults, as the likelihood of OSA in women increases markedly after menopause.[20,21] Importantly, the relationship between OSA and cardiovascular disease appears to be modified by sex, although evidence in this matter remains controversial. For instance, numerous studies found male patients with OSA to be more likely to have cardiovascular disease than female counterparts.[22,23] Roca et al[24] found that OSA was independently associated with incident heart failure or death only in women.

Little is known regarding the relationship between sex, OSA severity, and erythrocyte measures. In a study of 624 patients with a mean apnea-hypopnea index (AHI) of 18 events/h, Hoffstein et al[12] found no significant differences in hemoglobin concentration or hematocrit between the lowest (0–4 events/h) and the highest quartile of AHI (28–129 events/h) in either male or female patients. It should be pointed out that, despite the large sample size, half of the patients included in this study did not have OSA, and hypoxemia during the night was, on average, only mild. In another retrospective study of patients with OSA, significant differences in red blood cell count were found among women with OSA but not among men.[14] Importantly, this study did not take into account potential confounders such as age and body mass index (BMI). Thus, it remains unclear whether there is any relation between OSA severity and elevated erythrocyte measures and whether and how it is influenced by sex.

Additionally, although OSA and increased erythrocyte measures are both associated with unfavorable cardiometabolic risk profiles, the relation between erythrocyte measures and cardiometabolic markers in patients with OSA are not well understood. Given the established sex differences in OSA and in erythrocyte measures, we sought to examine whether the association between OSA severity and erythrocyte measures are modulated by sex, using a large sample of male and female patients with OSA. We further assessed the relationship between hematologic measures and cardiometabolic risk indices separately in both sexes.

METHODS

Study design and setting

This was a cross-sectional, retrospective study carried out in the Sleep Medicine Center, West China Hospital, Sichuan University, China. The study protocol was approved by the University's Institutional Review Board, and informed consent was obtained from each participant when undergoing polysomnography (PSG).

Participants

All participants were Chinese adults (>18 years old) with suspected OSA. Based on self-reported medical history, we excluded patients with severe heart disease, liver disease, kidney disease, severe anemia, chronic obstructive pulmonary disease, and use of medications affecting erythropoiesis, such as polyferose complex.

Overnight PSG

All participants underwent overnight PSG between June 2014 and November 2017. Recording techniques and estimation of sleep parameters followed the American Academy of Sleep Medicine standards.[25] Sleep data were collected and scored via the Alice 5 Diagnostic Sleep System (Philips Respironics, Bend, OR). Measures included electroencephalography (F4–M1, C4–M1, O2–M1, F3–M2, C3–M2, O1–M2), bilateral electrooculography, electrocardiography, electromyography (submental and anterior tibialis), nasal and oral thermal airflow, nasal pressure, thoracoabdominal movements, and peripheral arterial oxygen saturation. Sleep was scored by a senior technician who was blind to any diagnosis. An oxygen desaturation event was defined as at least 3% reduction in oxygen saturation. Oxygen desaturation index (ODI) was computed as the sum of oxygen desaturation events divided by total sleep time. An apnea was defined as more than 90% reduction in airflow for at least 10 seconds and hypopnea as 30% or more reduction of nasal pressure for at least 10 seconds associated with at least 3% reduction in oxygen saturation or arousal. AHI was computed as the sum of apneic and hypopneic events divided by total sleep time. OSA was defined as AHI $\geq$ 5 events/h, whereas snorers with AHI < 5 events/h were included in the primary snoring group. Sleep apnea severity was graded by using AHI as mild (5–14.9 events/h), moderate (15–29.9 events/h), or severe (≥30 events/h). Arousal index was computed as the total number of arousals divided by total sleep time.

Clinical and blood measurements

All participants completed a comprehensive questionnaire assessing history of sleep complaints, general health, and medication use. Menopause status was ascertained based on the characteristics of menses or time since amenorrhea.[26] Postmenopause was defined as 12 or more months of amenorrhea

occurring naturally or because of surgical interventions such as bilateral oophorectomy.

Body weight was measured to the nearest 0.1 kg by using a scale, with participants in light clothing without shoes. Height was measured to the nearest 0.5 cm by using a stadiometer, with the participant barefoot. BMI was calculated as kilograms divided by meters squared. Neck circumference was measured at the upper margin of the thyroid cartilage. Waist circumference was measured at the navel level and hip circumference at the level of maximum extension of the hip. All circumference measurements were taken at the end of expiration to the nearest 0.1 cm by using a tape.

Supine blood pressure (BP) was measured by a pneumoelectric microprocessor–controlled instrument (DS-1902, Nissei, Gunma, Japan) in the evening, before beginning the PSG, and in the morning at the end of the sleep study, with the patient recumbent. The accuracy of the instrument is ±3 mm Hg, with internal calibration conducted before each measurement; calibration against mercury sphygmomanometer was conducted at least annually. Evening and morning BP values were averaged for analysis. Hypertension was defined as (1) systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg, (2) taking antihypertensive medication, or (3) diagnosis of hypertension by a physician.

Venous blood samples were drawn in the morning after overnight PSG recording. Hematocrit level, hemoglobin value, and red blood cell counts were measured using an automated hematology analyzer (SYSMEXXE-5000, Sysmex, Kobe, Japan). Polycythemia was defined as hemoglobin greater than 185 g/L or hematocrit greater than 0.52 in men or greater than 165 g/L and 0.48 in women, respectively.[8]

Statistical analysis

Data are presented as mean and standard deviation for continuous variables and count and percentage for categorical variables. Comparisons across different OSA severity groups were performed separately by sex using one-way analysis of variance and Mann-Whitney *U* tests for normally and nonnormally distributed data, respectively, and a χ^2 test for categorical variables.

Crude and adjusted linear regression models with entering method were applied to calculate the coefficient and 95% confidence interval (CI) for the relationship between OSA and erythrocyte measures. Estimates were calculated for every 5-unit increment in ODI and AHI. Model 1 included age and BMI as covariates, whereas model 2 further adjusted for neck circumference, waist-to-hip ratio, smoking, alcohol use, and hypertension (plus menopausal status for women). Two-way interaction terms (sex × AHI or sex × ODI) were added to multivariable linear regression models to test the moderating effect of sex on the association between AHI or ODI and erythrocyte parameters.

We further computed tertiles of red blood cell, hemoglobin, and hematocrit values in men and women separately. Ordinal logistic regression analysis was used to assess independent associations between tertiles of erythrocyte measures and OSA severity, defined by AHI and ODI, in female and male participants. Adjusted odds ratios were estimated by correcting for the covariates mentioned in model 1 and model 2. Correlation analysis was used to explore the association between erythrocyte and cardiometabolic measures. Moreover, to account for sex differences in age, BMI and AHI and their possible effects on outcomes of interest, we conducted a secondary comparison analysis on a subset of male and female participants matched for such variables. Analysis of covariance was also used to examine dose-response associations between OSA severity and erythrocyte measures in matched male and female participants after controlling for potential confounders.

RESULTS

A total of 976 patients were included in our study, of whom 607 were men and 369 were women. **Table S1** in the supplemental material presents demographic and clinical characteristics of female and male participants. As shown in the table, women were older, had lower BMI, and were less likely to smoke, drink alcohol, and have hypertension and OSA compared with men. Characteristics of women and men with primary snoring and different levels of OSA severity are described in **Table 1** and **Table 2**. Patients with severe OSA were older, with higher BMI, and greater prevalence of hypertension, irrespective of sex. Women with higher AHI were also more likely to be postmenopause. Non–rapid eye movement sleep stage 3, non–rapid eye movement stage 2, and mean oxygen saturation decreased, whereas non–rapid eye movement sleep stage 1, AHI, and ODI increased both in women and men with increasing OSA severity. Regarding hematologic measures, mean red blood cell, hemoglobin, and hematocrit levels were in clinically accepted normal ranges both in men and women. Among all patients, 42 (4.3%) met the diagnosis of polycythemia, and 37 of them were diagnosed with severe OSA (mean AHI = 66.5 events/h). Women with severe OSA had progressively higher levels of red blood cell count and hematocrit than those with milder disease. Conversely, men with moderate OSA had lower erythrocyte parameters than those with primary snoring and severe OSA.

Scatter plots illustrate the association between AHI or ODI and red blood cell, hemoglobin, and hematocrit in men and women (**Figure 1** and **Figure S1**). Multiple linear regression models with interaction terms (sex × AHI) showed significant sex by AHI interactions on all hematologic measures (**Figure 2**). Similar sex interactions were found using ODI as a predictor (**Figure S2**). Results of the linear regression models on the association between AHI or ODI and erythrocyte measures in men and in women are presented in **Table 3**. In univariate models, higher AHI was significantly associated with higher red blood cell count, hemoglobin, and hematocrit in both sexes. In women, the associations between AHI and red blood cell count and hematocrit withstood after adjustment for age and BMI (model 1), whereas the relation with hemoglobin was marginally nonsignificant ($P = .07$). After further controlling for neck circumference, waist-to-hip ratio, smoking, alcohol use, and hypertension (plus menopausal status for women; model 2), AHI remained significantly associated with higher red blood cell count and hematocrit in female patients. Adjusted models showed no associations between AHI and hematologic parameters in men. For ODI, greater ODI was significantly associated with

Table 1—Demographic, clinical, sleep, and erythrocyte characteristics of primary snoring and OSA women.

	Primary snoring (n = 168)	OSA			*P*
		Mild OSA (n = 76)	Moderate OSA (n = 54)	Severe OSA (n = 71)	
Age (yr)	40.44 ± 11.91	48.86 ± 12.98	51.93 ± 11.17	55.62 ± 12.30	<.001
BMI (kg/m^2)	22.31 ± 3.58	23.42 ± 3.85	25.85 ± 3.45	27.23 ± 4.55	<.001
Neck circumference (cm)	33.28 ± 3.65	33.48 ± 2.79	34.32 ± 2.80	35.64 ± 3.56	<.001
Waist circumference (cm)	79.39 ± 9.57	82.92 ± 10.09	89.90 ± 10.09	95.46 ± 13.32	<.001
Hip circumference (cm)	93.58 ± 6.64	95.19 ± 7.19	99.44 ± 6.11	102.15 ± 9.22	<.001
Waist-to-hip ratio	0.85 ± 0.07	0.87 ± 0.07	0.89 ± 0.10	0.94 ± 0.07	.001
Postmenopause, n (%)	36(21.43)	31(40.79)	35(64.81)	51(71.83)	<.001
Smoking, n (%)	7(4.17)	7(9.21)	2(3.70)	4(5.63)	.06
Alcohol use, n (%)	13(7.74)	4(5.26)	4(7.41)	5(7.04)	.09
Hypertension, n (%)	33(19.64)	33(43.42)	21(38.89)	52(73.24)	<.001
Diabetes, n (%)	4(2.38)	3(3.95)	3(5.56)	8(11.27)	.01
Polycythemia, n (%)	1(0.60)	1(0.60)	0(0)	4(5.63)	.03
SBP, mm Hg	117.13 ± 15.86	123.70 ± 18.25	126.78 ± 14.53	136.36 ± 18.26	<.001
DBP, mm Hg	73.63 ± 10.34	76.89 ± 11.65	78.37 ± 10.31	82.17 ± 10.04	<.001
ESS	5.97 ± 5.94	7.47 ± 6.20	5.42 ± 4.96	8.71 ± 6.47	.003
TST (min)	410.66 ± 86.07	406.37 ± 79.15	406.80 ± 99.34	412.12 ± 100.96	.97
N1 (%)	18.08 ± 10.37	20.37 ± 8.79	22.10 ± 12.40	41.85 ± 20.72	<.001
N2 (%)	54.85 ± 11.97	54.93 ± 10.21	52.71 ± 12.58	38.44 ± 17.96	<.001
N3 (%)	9.42 ± 7.88	7.85 ± 6.96	7.43 ± 7.97	4.69 ± 6.77	<.001
R (%)	17.66 ± 6.23	16.85 ± 6.24	17.77 ± 6.63	15.01 ± 5.68	.02
AHI (events/h)	1.67 ± 1.42	9.20 ± 2.82	21.97 ± 4.49	62.95 ± 21.96	<.001
ODI (events/h)	1.56 ± 1.60	8.01 ± 3.91	20.55 ± 6.71	60.77 ± 23.93	<.001
Mean SaO_2 (%)	96.43 ± 1.12	95.58 ± 1.34	94.63 ± 2.38	92.01 ± 4.88	<.001
Nadir SaO_2 (%)	90.68 ± 3.53	85.03 ± 9.69	77.70 ± 15.42	67.51 ± 19.93	<.001
Arousal index (events/h)	12.03 ± 7.46	14.35 ± 9.49	15.60 ± 10.39	31.69 ± 18.76	<.001
RBC (10^{12}/L)	4.44 ± 0.37	4.47 ± 0.38	4.55 ± 0.39	4.68 ± 0.49	<.001
Hb (g/L)	132.64 ± 11.48	133.25 ± 10.79	134.35 ± 11.65	136.55 ± 13.22	.12
Hct (L/L)	0.40 ± 0.03	0.41 ± 0.03	0.41 ± 0.03	0.42 ± 0.04	.03

Categorical variables are presented as number and percentages, and continuous variables are presented as mean ± SD. AHI = apnea hypopnea index, BMI = body mass index, DBP = diastolic blood pressure, ESS = Epworth Sleepiness Scale, Hb = hemoglobin, Hct = hematocrit, N1–3 = non–rapid eye movement sleep 1–3, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, R = rapid eye movement sleep, RBC = red blood cell, SaO_2 = oxygen saturation, SBP = systolic blood pressure, TST = total sleep time.

higher red blood cell count, hemoglobin, and hematocrit in women both in crude models and in fully adjusted models. Conversely, the associations between ODI and hematologic parameters in men evident in univariate models did not retain significant in multivariable adjusted analysis.

When we further examined the association between OSA severity and hematologic parameters categorized as tertiles, we found that women with AHI ≥ 30 events/h had 2.44 times higher odds for higher red blood cell count compared with those with primary snoring in the fully adjusted model (odds ratio, 2.44; 95% CI: 1.23–4.84; **Table 4**). Similarly, the odds for higher red blood cell count were 2.33 times greater in women with ODI ≥ 30 events/h compared with those with ODI < 5 events/h in the fully adjusted model (odds ratio, 2.33; 95% CI: 1.17–4.66; **Table 4**). **Table 5** shows the results of the correlation analysis between erythrocyte measures and cardiometabolic risk markers in all participants and separately in men and women. In the entire sample, erythrocyte measures were positively associated with BMI, waist and hip circumference, waist-to-hip ratio, BP, and comorbid hypertension. When examined separately in female and male participants, such associations were more consistently observed in women than in men, and correlation coefficients were overall higher in the former group.

In secondary analysis restricted to men and women matched for age, BMI, and AHI (n = 53 in each group), comparisons between sexes showed that only female patients with higher AHI had higher red blood cell count, hemoglobin, and hematocrit than those with lower AHI (**Table S2**). Further insight into the observed dose-response associations between OSA severity and erythrocyte measures in matched female and male

Table 2—Demographic, clinical, sleep, and erythrocyte characteristics of primary snoring and OSA men.

	Primary snoring (n = 85)	OSA			*P*
		Mild OSA (n = 97)	Moderate OSA (n = 84)	Severe OSA (n = 341)	
Age (yr)	40.23 ± 13.86	43.37 ± 11.96	47.37 ± 11.75	46.26 ± 10.84	<.001
BMI (kg/m^2)	22.83 ± 2.82	24.92 ± 2.87	25.09 ± 3.05	27.57 ± 3.47	<.001
Neck circumference (cm)	37.04 ± 3.27	38.30 ± 2.94	38.00 ± 3.42	40.28 ± 3.21	<.001
Waist circumference (cm)	84.91 ± 7.71	90.35 ± 8.98	90.41 ± 8.06	97.21 ± 9.98	<.001
Hip circumference (cm)	95.20 ± 6.26	99.39 ± 6.47	98.62 ± 6.81	102.98 ± 7.52	<.001
Waist-to-hip ratio	0.90 ± 0.07	0.91 ± 0.06	0.92 ± 0.05	0.94 ± 0.06	.001
Smoking, n (%)	35(41.18)	45(46.39)	39(46.43)	162(47.51)	.74
Alcohol drinking, n (%)	31(36.47)	42(43.30)	35(41.67)	166(48.68)	.17
Hypertension, n (%)	25(29.41)	26(26.80)	38(45.23)	229(67.16)	<.001
Diabetes, n (%)	1(1.18)	4(4.12)	7(8.05)	25(7.33)	.11
Polycythemia, n (%)	4(4.71)	3(3.09)	2(2.38)	27(7.92)	.12
SBP, mm Hg	121.94 ± 12.24	122.22 ± 12.29	128.01 ± 13.74	130.64 ± 13.54	<.001
DBP, mm Hg	78.52 ± 8.60	78.16 ± 8.35	83.51 ± 9.42	86.41 ± 10.27	<.001
ESS	6.24 ± 5.64	7.37 ± 5.40	7.92 ± 5.66	10.05 ± 6.15	<.001
TST (min)	411.53 ± 85.86	443.74 ± 71.51	419.37 ± 74.72	445.33 ± 71.78	<.001
N1 (%)	22.94 ± 11.31	22.65 ± 11.05	29.70 ± 13.62	47.32 ± 19.81	<.001
N2 (%)	50.36 ± 12.41	52.68 ± 11.39	48.35 ± 11.63	34.65 ± 17.04	<.001
N3 (%)	8.18 ± 8.12	6.21 ± 5.91	5.01 ± 4.74	2.98 ± 4.73	<.001
R (%)	18.52 ± 6.08	18.45 ± 5.90	16.93 ± 6.02	15.05 ± 5.73	<.001
AHI (events/h)	2.12 ± 1.36	9.38 ± 2.98	21.65 ± 3.99	62.73 ± 19.33	<.001
ODI (events/h)	2.20 ± 2.32	8.60 ± 8.71	18.41 ± 7.42	60.81 ± 22.03	<.001
Mean SaO_2 (%)	95.80 ± 1.20	95.49 ± 1.16	94.90 ± 1.29	90.93 ± 4.67	<.001
Nadir SaO_2 (%)	86.77 ± 10.38	84.54 ± 7.65	80.73 ± 8.03	61.38 ± 17.98	<.001
Arousal index (events/h)	17.35 ± 10.12	19.60 ± 11.69	23.49 ± 12.20	41.61 ± 21.70	<.001
RBC (10^{12}/L)	5.28 ± 0.20	5.19 ± 0.49	5.08 ± 0.49	5.27 ± 0.51	.01
Hb (g/L)	157.57 ± 12.15	155.99 ± 11.76	153.31 ± 14.77	157.99 ± 13.11	.02
Hct (L/L)	0.47 ± 0.03	0.47 ± 0.03	0.46 ± 0.04	0.47 ± 0.04	.007

Categorical variables are presented as number and percentages, and continuous variables are presented as mean ± SD. AHI = apnea-hypopnea index, BMI = body mass index, DBP = diastolic blood pressure, ESS = Epworth Sleepiness Scale, Hb = hemoglobin, Hct = hematocrit, N1–3 = non–rapid eye movement sleep 1–3, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, R = rapid eye movement sleep, RBC = red blood cell, SaO_2 = oxygen saturation, SBP = systolic blood pressure, TST = total sleep time.

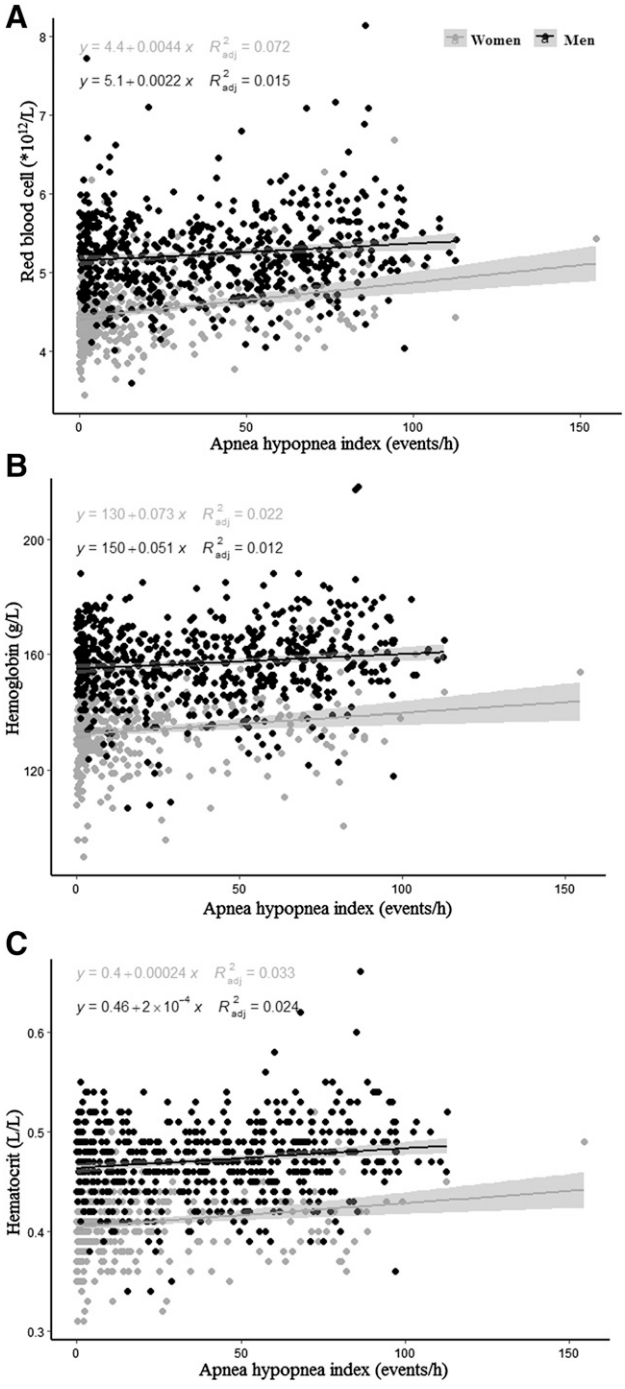
patients are provided in **Figure S3**. After multivariable adjustment, greater OSA severity remained significantly associated with increased red blood cell count and hematocrit only in women (*P* for trend < .05), consistent with the analysis on the entire sample. Last, the pattern of correlations between hematologic measures and cardiometabolic indices in the matched subgroup resembled again that seen in the entire sample, with stronger correlations between measures seen in women (**Table S3**).

DISCUSSION

In this cross-sectional study, we observed significant interactions between sex and metrics of OSA severity on erythrocyte measures. We showed, for the first time, that greater AHI and ODI were independently associated with higher erythrocyte parameters in women but not in men. Importantly, erythrocyte measures and cardiometabolic risk markers were more closely correlated in women with OSA than in men with OSA.

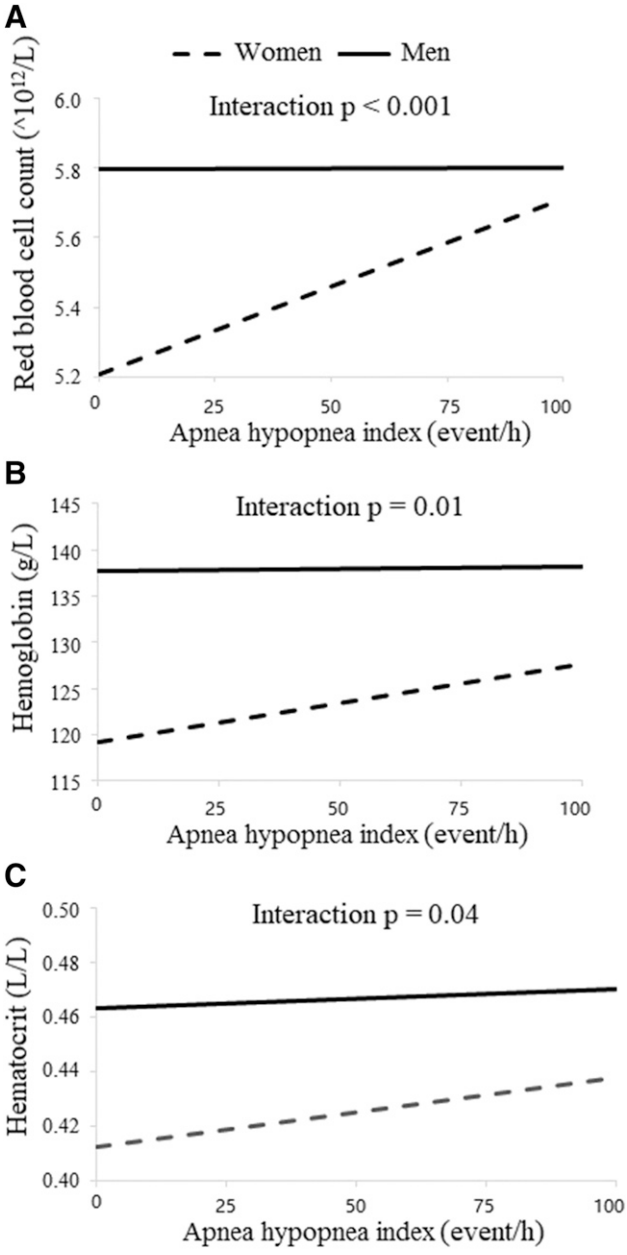
The implications of OSA on erythropoiesis have not been fully established, as only a few large studies have investigated erythrocyte measures in relation to OSA, yielding conflicting results. In our sample of 976 patients, we found significant associations between AHI or ODI and erythrocyte parameters after multivariable adjustment. This is consistent with the findings reported by Choi et al[13] in a sample of 263 patients (72% male). On the other hand, others did not find any associations between OSA severity and hemoglobin or hematocrit.[12,14,15] It is conceivable that such a discrepancy can be partly attributed to the effects of sex differences, although this hypothesis has

Figure 1—Scatter plots of apnea-hypopnea index vs red blood cell, hemoglobin, and hematocrit.



Gray area indicates the associated 95% confidence interval.

Figure 2—Effects of sex and apnea-hypopnea index.



Interaction effect of sex and apnea-hypopnea index on red blood cell **(A)**, hemoglobin **(B)**, and hematocrit **(C)** after adjustment for age, body mass index, neck circumference, waist-to-hip ratio, smoking, alcohol use, and hypertension.

not been systematically investigated in prior studies. Hoffstein et al[12] did not report sex differences when comparing erythrocyte measures across different groups of OSA severity. Another study found higher red blood cell count in women with more severe OSA than in those with mild OSA but no differences in men.[14] However, this study did not control for potential confounders. In our study, we observed that erythrocyte measures increased with OSA severity (defined by AHI and ODI) in women, whereas no clear pattern was discernible in men. When we further examined the association between OSA severity and hematologic parameters categorized as tertiles, the odds ratios (95% CI) for higher red blood cell count were 2.44 (1.23, 4.84) with AHI ≥ 30 events/h and 2.33 (1.17, 4.66) with ODI ≥ 30 events/h compared with those with primary snoring in women after adjusting for multiple covariates, but no associations was evident in men. Unlike most previous studies that assessed predominantly male samples (with men comprising up to 92% of the study population),[15] our study has

Table 3—Relationship between AHI and ODI and red blood cell count, hemoglobin, and hematocrit in female and male participants.

	Crude Model		Model 1		Model 2	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
AHI						
Red blood cell						
Women	0.02 (0.01, 0.03)	<.001	0.02 (0.01, 0.03)	<.001	0.02 (0.01, 0.03)	<.001
Men	0.01 (0.004, 0.02)	.001	0.003 (−0.004, 0.01)	.44	−0.001 (−0.009, 0.008)	.89
Hemoglobin						
Women	0.37 (0.13, 0.60)	.003	0.25 (−0.03, 0.52)	.07	0.23 (−0.04, 0.51)	.10
Men	0.26 (0.08, 0.43)	.004	0.08 (−0.11, 0.27)	.43	0.06 (−0.15, 0.27)	.55
Hematocrit						
Women	0.001 (0.001, 0.002)	<.001	0.001 (0.0002, 0.002)	.02	0.001 (0.0001, 0.002)	.03
Men	0.001 (0.0005, 0.001)	<.001	0.0004 (−0.0002, 0.001)	.19	0.0004 (−0.0002, 0.001)	.21
ODI						
Red blood cell						
Women	0.02 (0.02, 0.03)	<.001	0.02 (0.01, 0.03)	<.001	0.02 (0.01, 0.03)	<.001
Men	0.01 (0.006, 0.02)	<.001	0.004 (−0.003, 0.01)	.24	0.001 (−0.007, 0.009)	.74
Hemoglobin						
Women	0.42 (0.18, 0.66)	.001	0.32 (0.04, 0.60)	.03	0.31 (0.02, 0.59)	.03
Men	0.26 (0.10, 0.43)	.002	0.07 (−0.12, 0.26)	.49	0.06 (−0.15, 0.26)	.59
Hematocrit						
Women	0.001 (0.001, 0.002)	<.001	0.001 (0.0003, 0.002)	.007	0.001 (0.0002, 0.002)	.01
Men	0.001 (0.0005, 0.001)	<.001	0.0003 (−0.0002, 0.001)	.22	0.0004 (−0.0002, 0.001)	.21

Model 1: adjusted for age and body mass index. Model 2: adjusted for variables included in model 1 and for neck circumference, waist-to-hip ratio, smoking, alcohol use and hypertension (plus menopausal status in women). Estimates are calculated for every 5-unit increase in apnea-hypopnea index (AHI) and oxygen desaturation index (ODI). CI = confidence interval.

the important strength of including a substantial proportion of female patients with OSA, thus providing us with sufficient power to investigate sex effects that previously may have evaded detection.

The mechanisms involved in the sex-specific relationship between OSA and erythrocyte measures are unclear. In line with the literature,[27] women with more severe OSA were more likely to be older and to be postmenopause, and these factors could reasonably be implicated in our findings. Consistent with sex differences in the epidemiologic characteristics of OSA,[28,29] our female patients with OSA were also on average older than their male counterparts, and this age gap broadened with increasing sleep disorder severity. Age is a well-recognized determinant of erythropoiesis. In men, the mean levels of erythrocyte parameters tend to drop after 40 years old, whereas the opposite occurs in women.[30] These age-related variations are presumably caused by the decrease of androgen that stimulates erythropoiesis in men, whereas postmenopausal status ceases menstrual blood loss in women. Furthermore, menopause is linked to numerous physiologic modifications in hormones, insulin sensitivity, body fat distribution, and inflammation.[31,32] Women experience markedly increased insulin resistance during menopause, largely because of the substantial metabolic consequences of hormonal changes.[33] Previous studies found that insulin resistance is associated with erythropoiesis, as insulin and insulin growth factors I and II have been showed to promote erythropoiesis in both in vitro and in vivo studies.[34,35] Notably, insulin resistance is common in patients with OSA.[36] Another potential mechanism that may affect erythropoiesis is inflammation.[37] In healthy individuals, peripheral inflammation markers such as C-reactive protein are higher in women compared with men.[38] Moreover, both menopause and OSA are associated with heightened inflammation.[39,40] Thus, age and menopause may conceivably contribute to these sex-specific associations between erythrocyte measures and OSA. However, it should be noted that our results from regression models with multivariable adjustment and from a secondary comparison on a subset of age-, BMI-, and AHI-matched female and male patients strongly suggest an independent, sex-specific effect of OSA on erythrocyte measures.

Although we showed significant increases in erythrocyte measures in women, the average values remain within normal ranges. Among all patients, only 42 (4.3%, including 36 men and 6 women) met the diagnosis of polycythemia. Notwithstanding this, even within the normal spectrum, elevated hematologic measures may exert detrimental effects on health.[41] In our study, we observed significant associations between erythrocyte measures and cardiometabolic risk markers, such as BMI and blood pressure, in patients with OSA. In the general population, elevated erythrocyte measures have been

Table 4—Ordinal logistic regression analysis for the association between AHI levels and ODI levels and tertiles of red blood cell count, hemoglobin, and hematocrit in female and male participants.

	Predictors	Women			Men		
		n	Model 1	Model 2	n	Model 1	Model 2
AHI							
Red blood cell	Primary snoring	168	Reference	Reference	85	Reference	Reference
	15 > AHI ≥ 5	76	1.31 (0.78, 2.22)	1.25 (0.70, 2.23)	97	0.71 (0.40, 1.25)	0.66 (0.36, 1.22)
	30 > AHI ≥ 15	54	1.72 (0.91, 3.22)	1.53 (0.78, 3.00)	84	0.57 (0.31, 1.04)	0.48 (0.26, 0.92)
	AHI ≥ 30	71	2.54 (1.36, 4.74)	2.44 (1.23, 4.84)	341	0.95 (0.56, 1.60)	0.76 (0.44, 1.33)
Hemoglobin	Primary snoring	168	Reference	Reference	85	Reference	Reference
	15 > AHI ≥ 5	76	0.89 (0.53, 1.51)	0.83 (0.47, 1.47)	97	0.76 (0.43, 1.35)	0.63 (0.35, 1.16)
	30 > AHI ≥ 15	54	1.20 (0.64, 2.25)	1.17 (0.60, 2.28)	84	0.88 (0.49, 1.60)	0.87 (0.46, 1.64)
	AHI ≥ 30	71	1.32 (0.71, 2.45)	1.38 (0.70, 2.72)	341	0.95 (0.57, 1.60)	0.85 (0.49, 1.48)
Hematocrit	Primary snoring	168	Reference	Reference	85	Reference	Reference
	15 > AHI ≥ 5	76	1.22 (0.72, 2.06)	1.20 (0.67, 2.13)	97	0.71 (0.40, 1.24)	0.61 (0.34, 1.10)
	30 > AHI ≥ 15	54	1.41 (0.74, 2.65)	1.31 (0.67, 2.58)	84	0.78 (0.43, 1.62)	0.74 (0.40, 1.39)
	AHI ≥ 30	71	1.53 (0.82, 2.87)	1.51 (0.76, 3.00)	341	1.01 (0.61, 1.69)	0.90 (0.52, 1.56)
ODI							
Red blood cell	ODI < 5	177	Reference	Reference	112	Reference	Reference
	15 > ODI ≥ 5	74	1.75 (0.99, 3.07)	1.52 (0.82, 2.79)	96	0.80 (0.47, 1.37)	0.67 (0.38, 1.17)
	30 > ODI ≥ 15	48	2.03(1.05, 3.93)	2.03 (1.00, 4.13)	72	0.68 (0.37, 1.23)	0.56 (0.30, 1.05)
	ODI ≥ 30	70	2.61(1.37, 4.97)	2.33 (1.17, 4.66)	327	1.22 (0.75, 1.97)	0.96 (0.58, 1.60)
Hemoglobin	ODI < 5	177	Reference	Reference	112	Reference	Reference
	15 > ODI ≥ 5	74	1.46 (0.84, 2.55)	1.31 (0.72, 2.39)	96	0.96 (0.57, 1.63)	0.90 (0.52, 1.58)
	30 > ODI ≥ 15	48	1.34 (0.70, 2.58)	1.37 (0.68, 2.76)	72	1.05 (0.58, 1.89)	1.06 (0.57, 1.97)
	ODI ≥ 30	70	1.58 (0.84, 2.98)	1.56 (0.79, 3.09)	327	1.21 (0.75, 1.95)	1.13 (0.68, 1.87)
Hematocrit	ODI < 5	177	Reference	Reference	112	Reference	Reference
	15 > ODI ≥ 5	74	1.58 (0.90, 2.77)	1.24 (0.68, 2.28)	96	0.78 (0.46, 1.31)	0.69 (0.40, 1.20)
	30 > ODI ≥ 15	48	1.46 (0.75, 2.83)	1.45 (0.71, 2.97)	72	0.71 (0.40, 1.27)	0.67 (0.37, 1.24)
	ODI ≥ 30	70	1.65 (0.87, 3.13)	1.39 (0.70, 2.79)	327	1.15 (0.72, 1.85)	1.04 (0.63, 1.71)

Values are odds ratio (95% confidence intervals). Red blood cell, hemoglobin, and hematocrit were categorized in tertiles in men (red blood cell: <5.02, 5.02–5.39, >5.39 × 10^{12}/L; hemoglobin: <153, 153.00–162.54, >162.54 g/L; hematocrit: <0.46, 0.46–0.49, >0.49L/L) and in women (red blood cell: <4.32, 4.32–4.63, >4.63 × 10^{12}/L; hemoglobin: <130, 130–138, >138 g/L; hematocrit: <0.40, 0.40–0.42, >0.42 L/L). Model 1: adjusted for age and body mass index. Model 2: adjusted for variables included in model 1 and for neck circumference, waist-to-hip ratio, smoking, alcohol use, and hypertension (plus menopausal status in women). AHI = apnea-hypopnea index (events/h), ODI = oxygen desaturation index (events/h).

associated with prevalent and incident metabolic syndrome.[4,5] In patients with OSA, significant relations between hematocrit and BMI and BP have also been reported,[13] consistent with our results. However, it is noteworthy that when we examined female and male patients with OSA separately, the correlation coefficients between erythrocyte measures and cardiometabolic risk markers were overall higher in women with OSA than in men with OSA. Notably, it has been reported that women but not men with higher hematocrit were more likely to have fatal coronary events than those with lower hematocrit.[18] This suggests that, although women overall have lower levels of red blood cells, hemoglobin, and hematocrit than men, the increase of erythrocyte measures is associated with greater cardiometabolic risk in women.

There are several limitations to be taken into account when interpreting our findings. First, unmeasured confounders and selection bias could influence the association between OSA and erythrocyte measures in this clinical sample. Second, because of the cross-sectional study design, we cannot draw causal inferences regarding the relationships among OSA, erythrocyte measures, and cardiometabolic risk markers. Longitudinal studies are needed to assess whether OSA predicts future elevation in hematologic measures and whether such increments mediate the onset of adverse events in a sex-dependent manner. With regard to treatment, few studies (predominantly on male participants) found significant decreased hematocrit levels after short-term (1 night) or long-term (6 months) continuous positive airway pressure therapy,[42–44] possibly as a result of ameliorated hypoxia and inflammation and fluid redistribution.[45] Further investigations are warranted to determine whether OSA therapy can contribute to lower other erythrocyte measures and whether the anticipated positive effects are

Table 5—Correlation coefficients between red blood cell count, hemoglobin, hematocrit, and cardiometabolic markers in all participants and separately by sex.

	Red blood cell count			Hemoglobin			Hematocrit		
	Total	Women	Men	Total	Women	Men	Total	Women	Men
BMI	0.323[b]	0.234[a]	0.221[b]	0.314[b]	0.200[b]	0.204[b]	0.329[b]	0.202[a]	0.242[b]
Waist circumference	0.357[b]	0.237[b]	0.177[b]	0.356[b]	0.215[b]	0.148[b]	0.374[b]	0.223[b]	0.193[b]
Hip circumference	0.307[b]	0.237[b]	0.184[b]	0.297[b]	0.257[b]	0.132[b]	0.321[b]	0.269[b]	0.183[b]
Waist-to-hip ratio	0.260[b]	0.139[b]	0.051	0.280[b]	0.122[b]	0.06	0.287[b]	0.122[a]	0.083
Hypertension	0.153[b]	0.154[b]	0.058	0.105[b]	0.075	−0.012	0.113[b]	0.099	−0.044
SBP	0.154[b]	0.188[b]	0.044	0.113[b]	0.144[b]	−0.036	0.123[b]	0.163[b]	−0.019
DBP	0.340[b]	0.260[b]	0.183[b]	0.327[b]	0.168[b]	0.181[b]	0.327[b]	0.171[b]	0.174[b]

[a]$P < .05$; [b]$P < .01$. BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure.

magnified in women. Third, the exclusion of patients with severe diseases that may affect erythropoiesis, such as chronic obstructive pulmonary disease, was solely based on patient-reported medical history.

CONCLUSIONS

In conclusion, our study provides novel evidence of sex-dependent associations between OSA severity and elevated erythrocyte measures, showing that such relationships are evident in women with OSA but not in men. Importantly, erythrocyte measures are more closely related to cardiometabolic risk markers in women than in men, suggesting that the impact of OSA on erythropoiesis and cardiometabolic disease may be potentiated in women.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
BP, blood pressure
CI, confidence interval
OSA, obstructive sleep apnea
PSG, polysomnography

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