



## REVIEW

# Is obstructive sleep apnea associated with erythrocytosis? A systematic review and meta-analysis

Min-Seok Rha MD, PhD<sup>1</sup> | Yeonsu Jeong MD<sup>1</sup> | Jungghi Kim MD<sup>1</sup> |  
Chang-Hoon Kim MD, PhD<sup>1,2,3,4</sup>  | Joo-Heon Yoon MD, PhD<sup>1,2,3,5</sup> |  
Hyung-Ju Cho MD, PhD<sup>1,2,3</sup> 

<sup>1</sup>Department of Otorhinolaryngology, Yonsei University College of Medicine, Seoul, Republic of Korea

<sup>2</sup>The Airway Mucus Institute, Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea

<sup>3</sup>The Korea Mouse Phenotyping Center, Yonsei University College of Medicine, Seoul, Republic of Korea

<sup>4</sup>Taste Research Center, Yonsei University College of Medicine, Seoul, Republic of Korea

<sup>5</sup>Global Research Laboratory for Allergic Airway Diseases, Yonsei University College of Medicine, Seoul, Republic of Korea

## Correspondence

Hyung-Ju Cho, Department of Otorhinolaryngology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea.  
Email: hyungjucho@yuhs.ac

## Funding information

National Research Foundation of Korea, Grant/Award Numbers: 2021R111A1A01047571, NRF-2021R1A2C2010811; Yonsei University College of Medicine, Grant/Award Number: 6-2021-0005

## Abstract

**Objective:** The aim of this systematic review and meta-analysis was to investigate the association between obstructive sleep apnea (OSA) and erythrocytosis.

**Methods:** The PubMed, Web of Science, and Cochrane Library databases were searched for articles examining hematocrit values in patients with OSA and control individuals published till September 1, 2021. The pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated, and subgroup analyses were performed.

**Results:** Eleven eligible studies with a total of 4608 patients with OSA were included in this meta-analysis. Pooled outcomes revealed that hematocrit values were significantly higher in patients with OSA than in controls (SMD, 0.19; 95% CI, 0.08–0.29;  $p < .01$ ). When studies were stratified by disease severity, the significant differences in hematocrit values between patients and controls were only observed in the severe OSA group (SMD, 0.34; 95% CI, 0.08–0.59;  $p < .01$ ), but not in the mild and moderate OSA groups. In subgroup analyses according to sex and publication year, significant differences in hematocrit values between patients and controls remained stable in studies with only female patients (SMD, 0.25; 95% CI, 0.12–0.38;  $p < .01$ ) and in studies published after 2012 (SMD, 0.17; 95% CI, 0.06–0.28,  $p < .01$ ).

**Conclusion:** Our meta-analysis revealed that the hematocrit value was significantly increased in patients with OSA, particularly in severe patients, compared with that in controls. However, the elevation was modest, and the hematocrit value is expected to be within the normal range in patients with OSA. These data suggest that OSA leads to slight increases in hematocrit but does not cause clinically significant erythrocytosis.

## KEYWORDS

erythrocytosis, hematocrit, obstructive sleep apnea, polycythemia, sleep apnea

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC on behalf of The Triological Society.

## 1 | INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, causing intermittent hypoxia.<sup>1</sup> The prevalence of OSA in the general population is reported to be 3%–9%,<sup>2</sup> and OSA is a serious health problem associated with various types of morbidities and mortalities, such as cardiovascular and cerebrovascular diseases.<sup>1,3–6</sup> Intermittent hypoxia during OSA is largely responsible for oxidative stress, which in turn promotes sympathetic activation and inflammation,<sup>1,7–9</sup> leading to endothelial dysfunction, hypertension, and atherosclerosis.<sup>10,11</sup> However, the exact hematological consequences of OSA and the underlying pathophysiological mechanisms are not fully understood.

Erythrocytosis is characterized by an increase in red cell mass and is classified as primary if there is a defect in the erythroid compartment of the bone marrow or secondary when it occurs due to other erythropoiesis-stimulating factors.<sup>12,13</sup> Absolute erythrocytosis is defined as a red cell mass > 125% of that predicted according to sex and body mass.<sup>12</sup> Generally, erythrocytosis is suspected when the hematocrit is > 0.52 in men or > 0.48 in women.<sup>12,14</sup> Chronic hypoxemia caused by a variety of conditions, including cyanotic heart disease, chronic lung disease, and smoking, is a well-described etiology for secondary erythrocytosis.<sup>13,14</sup> Hypoxemia is a potent stimulus for the release of erythropoietin (EPO), resulting in increased red blood cell production in the bone marrow.<sup>15</sup>

In the work-up for the diagnosis of secondary erythrocytosis, previous guidelines recommend an evaluation for OSA.<sup>12,14</sup> However, the association between OSA and clinically significant erythrocytosis has not been fully established. Although several studies have investigated the relationship between OSA and secondary erythrocytosis, the results are inconsistent and controversial. Some studies found a significantly increased hematocrit value in patients with OSA compared to that in the control group,<sup>16–21</sup> whereas others did not.<sup>22,23</sup> This discrepancy may be due to several factors, such as the statistical power of the study and differences in the composition of the study populations. In the present study, we aimed to investigate whether patients with OSA are associated with clinically significant erythrocytosis. Therefore, we conducted a systematic review and meta-analysis to examine the difference in hematocrit values between patients with OSA and individuals without OSA.

## 2 | MATERIALS AND METHODS

### 2.1 | Search strategy

This study was reported following guidelines of the preferred reporting items for systematic reviews and meta-analyses guidelines.<sup>24</sup> A systematic search for studies published up to September 1, 2021 was conducted in the PubMed, Web of science, and Cochrane library databases using the following MeSH terms and keywords: “sleep apnea syndromes”[MeSH], “obstructive sleep apnea”, “obstructive sleep apnoea”, “sleep apnea”, “sleep apnoea”,

“erythrocytosis”, “hematocrit”, “polycythemia”, and “polycythaemia.” The full search strategy is presented in Table S1.

### 2.2 | Eligibility criteria, study selection, and quality assessment

The population, intervention, comparator, outcome, and study design (PICOS) approaches were utilized to define study eligibility. (1) P: adult patients with OSA (determined by sleep study); (2) I: assessment of hematocrit; (3) C: control individuals without OSA; (4) O: the hematocrit value; and (5) S: randomized controlled trials or observational studies including cross-sectional studies, cohort studies, case-control studies, or case series. In addition, articles were eligible if they were written in English and full-text publications.

Abstracts of retrieved studies were screened independently by two investigators to examine the relevance of the studies. If relevant, two authors independently reviewed the full articles. The references of the retrieved articles were searched to identify additional studies. Any disagreement between the reviewers was resolved by a third investigator.

The quality of each study was assessed using the modified Newcastle-Ottawa scale (NOS),<sup>25</sup> with a maximum of seven points for observational studies based on the following components: patient selection, comparability, and outcome. Two researchers independently evaluated the quality of each study. Disagreements between the researchers were resolved through consensus. Studies with five or more stars were considered high-quality studies.

### 2.3 | Data extraction

The following information was extracted from the included studies: authors, publication year, study design, geographic location of studies, number of study subjects, age, sex composition of the cohort, mean body mass index (BMI), OSA severity, and hematocrit value. OSA severity was determined by the apnea hypopnea index (AHI) or respiratory disturbance index (RDI): mild [ $5 \leq \text{AHI (RDI)} < 15$ ], moderate [ $15 \leq \text{AHI (RDI)} < 30$ ], and severe [ $30 \leq \text{AHI (RDI)}$ ].

### 2.4 | Statistical analysis

A meta-analysis of the included studies was performed using R 4.1.1 version statistical software (R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>). The difference in hematocrit values between patients with OSA and controls was assessed using the standardized mean difference (SMD). For interpreting the effect size calculated by SMD, we used the benchmark values suggested by Cohen (0.2, small effect; 0.5, medium effect; 0.8, large effect).<sup>26</sup> Significance was set at  $p < .05$ . Heterogeneity between the included studies was calculated using the  $I^2$  test:  $I^2 > 50\%$  indicated significant heterogeneity across studies.<sup>27</sup> In these cases, a random-effects model was used to generate pooled outcomes. In contrast,

studies that did not present a significant value of heterogeneity ( $I^2 < 50$ ) were analyzed using the fixed-effects model. Subgroup analysis was performed to evaluate the impact of disease severity, sex, and publication year of the studies on the outcomes. In addition, we conducted a meta-regression analysis to identify possible sources of heterogeneity. Funnel plots and Egger's test were used to detect publication bias.<sup>28</sup> Sensitivity analyses were performed to estimate the influence of each study on the overall results.<sup>29</sup>

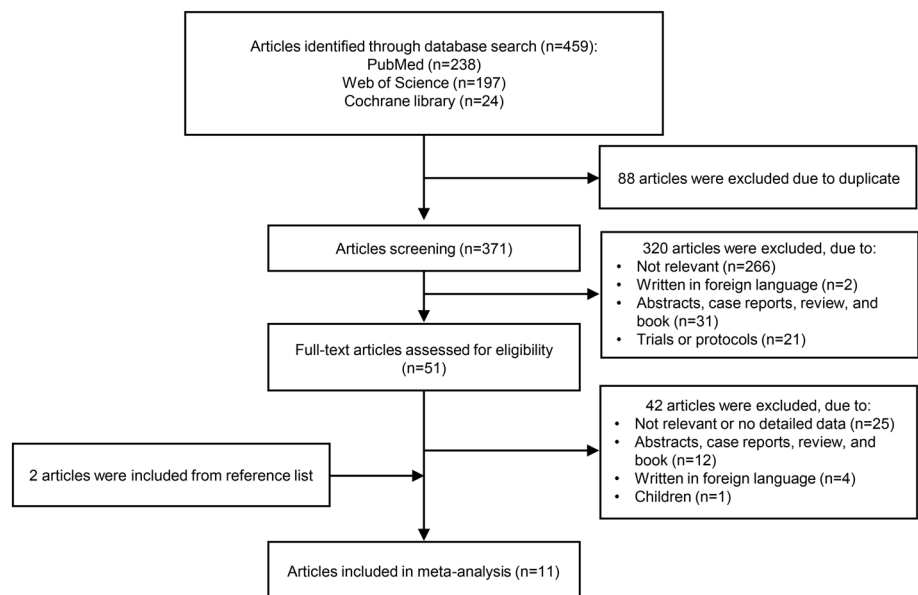
### 3 | RESULTS

#### 3.1 | Literature search and study characteristics

The database search retrieved a total of 459 articles, of which 88 articles were excluded due to duplication. After title and abstract

screening, we excluded 320 articles and assessed the full texts of 51 articles. In addition, two articles from the reference lists of retrieved articles were assessed. Finally, 11 articles<sup>16-23,30-32</sup> with a total of 4608 patients with OSA and 1484 individuals without OSA were included in the meta-analysis. A flowchart of the study selection process is shown in Figure 1.

The publication year of the included studies ranged from 1994 to 2021. All included studies were hospital-based cross-sectional studies. Among the 11 studies, six,<sup>17,18,21,22,31,32</sup> one,<sup>16</sup> and two<sup>19,20</sup> studies divided patients with OSA into subgroups according to disease severity, sex, and both severity and sex, respectively. The characteristics of the included studies and patient data from the included studies are presented in Tables 1 and 2, respectively. Table 3 presents the quality assessment of the included studies. The NOS scores of all the included studies were 6, indicating that all studies were high-quality.



**FIGURE 1** Flow chart of study search and selection

**TABLE 1** Summary of included studies

Study	Year	Country	Study design	OSA assessment	Inclusion criteria
Hoffstein et al.	1994	Canada	Cross-sectional	PSG	10 < AHI
Choi et al.	2006	USA	Cross-sectional	PSG	5 ≤ RDI
Dikmenoglu et al.	2006	Turkey	Cross-sectional	PSG	30 < AHI
Sinnaph et al.	2015	France	Cross-sectional	PSG and type 3 sleep study	5 ≤ AHI
Nguyen et al.	2017	USA	Cross-sectional	PSG or type 3 sleep study	5 ≤ AHI
Fan et al.	2018	China	Cross-sectional	PSG	5 ≤ AHI
Li et al. (1)	2019	China	Cross-sectional	PSG	5 ≤ AHI
Xie et al.	2020	China	Cross-sectional	PSG	5 ≤ AHI
Li et al. (2)	2020	China	Cross-sectional	PSG	5 ≤ AHI
Waltz et al.	2021	Canada	Cross-sectional	Type 3 sleep study	15 ≤ ODI & SaO <sub>2</sub> < 90% (≥12% of total time)
Cummins et al.	2021	Canada & Malaysia	Cross-sectional	PSG or type 3 sleep study	5 ≤ AHI

Abbreviations: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polysomnography; RDI, respiratory disturbance index.

TABLE 2 Characteristics of patients

Study	OSA severity	OSA					Control				
		n	Age	Sex (M/F)	BMI (mean)	Hct (%)	n	Age	Sex (M/F)	BMI (mean)	Hct (%)
Hoffstein (male) <sup>a</sup>	28 ≤ AHI ≤ 129	113	n/a	113/0	n/a	44.0 ± 5.0	118	n/a	118/0	n/a	44.0 ± 5.0
Hoffstein (female) <sup>a</sup>	14 ≤ AHI ≤ 120	43	n/a	0/43	n/a	40.0 ± 3.0	46	n/a	0/46	n/a	40.0 ± 3.0
Choi (mild-moderate) <sup>b</sup>	Mild-moderate	91	44.1 ± 8.9	62/29	28.50	41.2 ± 4.0	61	37.6 ± 8.4	29/32	24.9	39.8 ± 4.0
Choi (severe) <sup>b</sup>	Severe	111	47.3 ± 9.3	98/13	32.0	43.5 ± 3.6	61	37.6 ± 8.4	29/32	24.9	39.8 ± 4.0
Dikmenoglu	Severe	11	50.2 ± 7.7	8/3	31.1	40.6 ± 4.0	11	46.3 ± 8.1	8/3	26.5	42.1 ± 3.0
Sinnaph (mild) <sup>b</sup>	Mild	25	n/a	n/a	29.1	41.3 ± 4.5	50	n/a	n/a	27.64	41.4 ± 4.6
Sinnaph (moderate) <sup>b</sup>	Moderate	11	n/a	n/a	29.9	41.3 ± 4.1	50	n/a	n/a	27.64	41.4 ± 4.6
Sinnaph (severe) <sup>b</sup>	Severe	11	n/a	n/a	34.4	43.6 ± 4.1	50	n/a	n/a	27.64	41.4 ± 4.6
Nguyen (mild) <sup>b</sup>	Mild	467	58.2 ± 13.1	417/50	31.8	42.7 ± 4.2	364	50.8 ± 15.1	309/55	29.6	42.7 ± 3.9
Nguyen (moderate) <sup>b</sup>	Moderate	355	60.4 ± 11.5	342/13	32.9	42.8 ± 4.0	364	50.8 ± 15.1	309/55	29.6	42.7 ± 3.9
Nguyen (severe) <sup>b</sup>	Severe	418	60.5 ± 11.4	408/10	35.7	42.2 ± 4.5	364	50.8 ± 15.1	309/55	29.6	42.7 ± 3.9
Fan (mild) <sup>b</sup>	Mild	185	44.9 ± 11.1	185/0	25.4	43.9 ± 3.1	135	46.3 ± 12.0	135/0	24.0	42.9 ± 3.2
Fan (moderate) <sup>b</sup>	Moderate	171	46.0 ± 11.2	171/0	26.7	43.9 ± 2.9	135	46.3 ± 12.0	135/0	24.0	42.9 ± 3.2
Fan (severe) <sup>b</sup>	Severe	596	43.5 ± 10.9	596/0	29.1	45.7 ± 3.3	135	46.3 ± 12.0	135/0	24.0	42.9 ± 3.2
Li (1) (male, mild-moderate) <sup>a,b</sup>	Mild-moderate	110	29.9 ± 7.6	110/0	32.9	43.8 ± 2.7	53	28.7 ± 7.6	53/0	33.4	43.7 ± 3.1
Li (1) (male, severe) <sup>a,b</sup>	Severe	220	34.6 ± 6.1	220/0	31.6	44.9 ± 3.3	53	28.7 ± 7.6	53/0	33.4	43.7 ± 3.1
Li (1) (female, mild-moderate) <sup>a,b</sup>	Mild-moderate	88	27.5 ± 5.9	0/88	33.2	39.4 ± 2.7	102	25.9 ± 5.3	0/102	31.8	39.1 ± 2.6
Li (1) (female, severe) <sup>a,b</sup>	Severe	32	31.2 ± 7.0	0/32	35.9	40.0 ± 4.3	102	25.9 ± 5.3	0/102	31.8	39.1 ± 2.6
Xie (mild-moderate) <sup>b</sup>	Mild-moderate	48	48.2 ± 14.0	35/13	26.0	42.0 ± 5.0	34	34.7 ± 0.14.0	18/16	23.8	43.0 ± 5.0
Xie (severe) <sup>b</sup>	Severe	59	48.2 ± 11.7	52/7	29.3	45.0 ± 4.0	34	34.7 ± 0.14.0	18/16	23.8	43.0 ± 5.0
Li (2) (male, mild) <sup>a,b</sup>	Mild	97	43.4 ± 12.0	97/0	24.9	47.0 ± 3.0	85	40.2 ± 0.13.9	85/0	22.8	47.0 ± 3.0
Li (2) (male, moderate) <sup>a,b</sup>	Moderate	84	47.4 ± 11.8	84/0	25.1	46.0 ± 4.0	85	40.2 ± 0.13.9	85/0	22.8	47.0 ± 3.0
Li (2) (male, severe) <sup>a,b</sup>	Severe	341	46.3 ± 10.8	341/0	27.6	47.0 ± 4.0	85	40.2 ± 0.13.9	85/0	22.8	47.0 ± 3.0
Li (2) (female, mild) <sup>a,b</sup>	Mild	76	48.9 ± 13.0	0/76	23.4	41.0 ± 3.0	168	40.4 ± 0.11.9	168/0	22.3	40.0 ± 3.0
Li (2) (female, moderate) <sup>a,b</sup>	Moderate	54	51.9 ± 11.2	0/54	25.9	41.0 ± 3.0	168	40.4 ± 0.11.9	168/0	22.3	40.0 ± 3.0
Li (2) (female, severe) <sup>a,b</sup>	Severe	71	55.6 ± 12.3	0/71	27.2	42.0 ± 4.0	168	40.4 ± 0.11.9	168/0	22.3	40.0 ± 3.0
Waltz	All	23	47.7 ± 0.9.8	21/2	31.8	48.0 ± 3.3	13	51.5 ± 0.9.8	10/3	28.0	46.9 ± 3.5
Cummins (mild) <sup>b</sup>	Mild	294	63.2 ± 10.5	130/164	31.0	39.7 ± 5.0	244	60.2 ± 11.2	102/142	30.2	39.6 ± 5.0
Cummins (moderate) <sup>b</sup>	Moderate	223	62.5 ± 10.2	124/99	31.9	40.5 ± 5.0	244	60.2 ± 11.2	102/142	30.2	39.6 ± 5.0
Cummins (severe) <sup>b</sup>	Severe	180	64.8 ± 10.4	119/61	32.7	40.7 ± 5.0	244	60.2 ± 11.2	102/142	30.2	39.6 ± 5.0

Note: Data are presented as mean ± SD.

Abbreviations: Hct, hematocrit; n/a, not available; OSA, obstructive sleep apnea.

<sup>a</sup>These articles divided patients into subgroups according to sex: male and female.

<sup>b</sup>These articles divided patients into two (mild-moderate [5 ≤ AHI (RDI) < 30] and severe [30 ≤ AHI (RDI)]) or three (mild [5 ≤ AHI < 15], moderate [15 ≤ AHI < 30], and severe [30 ≤ AHI]) subgroups according to disease severity.

### 3.2 | Association between OSA and elevation of hematocrit

We examined whether patients with OSA had higher hematocrit values than control individuals. Because there was significant heterogeneity across the included studies ( $I^2 = 78\%$ ), the random-effects model was used. We found a significant difference in the hematocrit value between patients with OSA and controls (SMD, 0.19; 95% CI, 0.08–0.29;  $p < .01$ ; Figure 2).

### 3.3 | Publication bias

Visual inspection of the funnel plots suggested the existence of asymmetry (Figure S1). However, Egger's regression test did not show evidence of publication bias in the analysis of hematocrit values ( $t = 0.92$ ,  $p = .36$ ).

### 3.4 | Sensitivity analysis

The stability of the results of the hematocrit value was evaluated through a sensitivity analysis. The corresponding pooled SMD (range, 0.153–0.202) was not substantially altered when single studies were sequentially removed, suggesting that the results of the meta-analysis were stable (Figure S2).

### 3.5 | Subgroup analysis

Subgroup analysis was performed according to disease severity, sex, and publication year. Only studies for which detailed information on each parameter was available were included in the subgroup analyses. When studies were stratified according to disease severity ("mild", "moderate", and "severe"), the hematocrit value of patients with "mild"

and "moderate" OSA did not significantly differ from that of controls ( $p = .06$  and  $p = .19$ , respectively; Figure 3A,B). In contrast, a significant difference in hematocrit values was found between patients with "severe" OSA and controls (SMD, 0.34; 95% CI, 0.08–0.59;  $p < .01$ ; Figure 3C). In the subgroup analysis according to sex, the difference in hematocrit values between patients and control individuals was not significant in studies including only men ( $p = .12$ ; Figure 4A), whereas it was significant in studies including only women (SMD, 0.25; 95% CI, 0.12–0.38;  $p < .01$ ; Figure 4B). As the American Academy of Sleep Medicine (AASM) criteria for scoring hypopnea was substantially revised in 2012,<sup>33</sup> we divided the studies into two subgroups based on publication year: "pre-2012" and "post-2012." A significant difference in the hematocrit value between patients and controls was observed in the post-2012 group (SMD, 0.17; 95% CI, 0.06–0.28,  $p < .01$ ), but not in the pre-2012 group ( $p = .28$ ) (Figure S3A,B).

### 3.6 | Meta-regression analysis

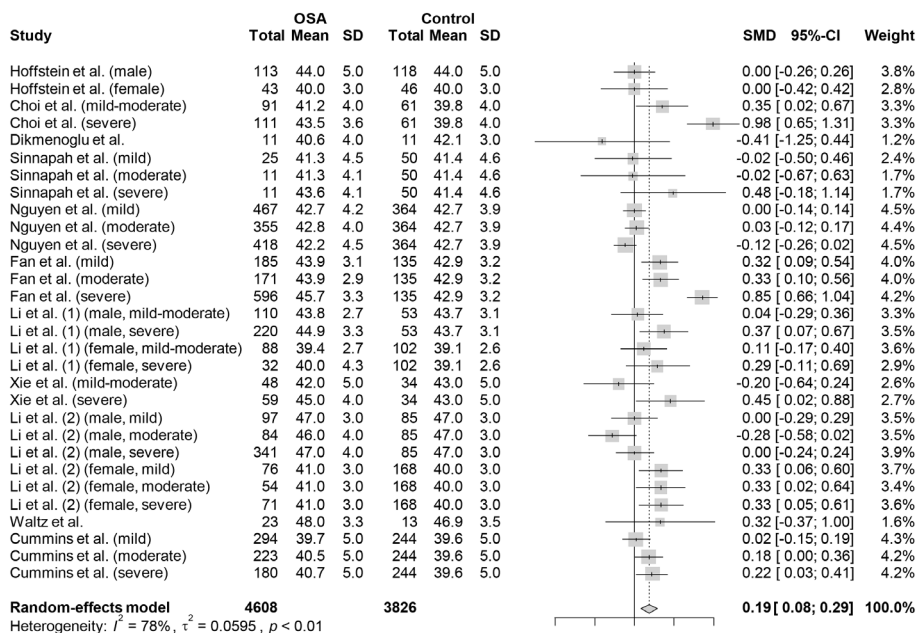
We conducted a meta-regression analysis to assess the effects of confounding factors on differences in hematocrit values between patients with OSA and controls. The outcome variable was the SMD, and the covariates included differences in the mean values of age (years), BMI, and the proportion of male patients (%) between patients with OSA and controls. We found that differences in mean age ( $p = .77$ ), mean BMI ( $p = .09$ ), and the proportion of male patients (%) ( $p = .10$ ) showed no significant effect (Figure S4).

## 4 | DISCUSSION

OSA is traditionally considered to be one of the causes of secondary erythrocytosis. However, evidence showing an association between OSA and secondary erythrocytosis is largely anecdotal. In addition,

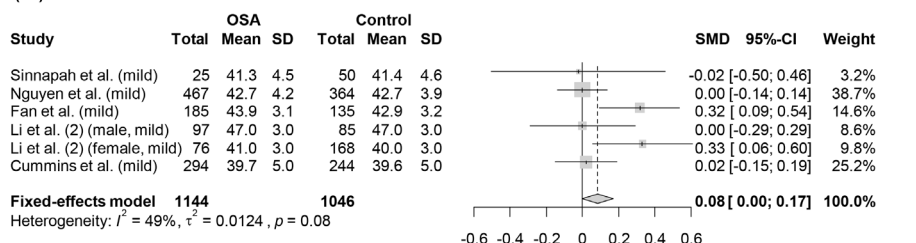
**TABLE 3** Quality assessment of included studies

Study	Selection			Comparability	Outcome		Total score
	Representativeness	Selection of the nonexposed cohort	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis (maximum ★★)	Assessment of outcome	Adequacy of follow-up	
Hoffstein et al.	★	★	★	★	★	★	6
Choi et al.	★	★	★	★	★	★	6
Dikmenoglu et al.	★	★	★	★	★	★	6
Sinnapah et al.	★	★	★	★	★	★	6
Nguyen et al.	★	★	★	★	★	★	6
Fan et al.	★	★	★	★	★	★	6
Li et al. (1)	★	★	★	★	★	★	6
Xie et al.	★	★	★	★	★	★	6
Li et al. (2)	★	★	★	★	★	★	6
Waltz et al.	★	★	★	★	★	★	6
Cummins et al.	★	★	★	★	★	★	6

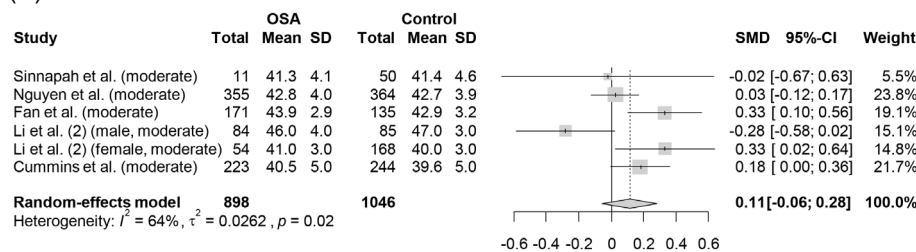


**FIGURE 2** Comparison of hematocrit values between patients with OSA and controls. Forest plots comparing hematocrit values between patients with OSA and controls. Results are expressed as the SMD with 95% CI. The calculation is based on a random-effects model. CI, confidence interval; OSA, obstructive sleep apnea; SMD, standardized mean difference

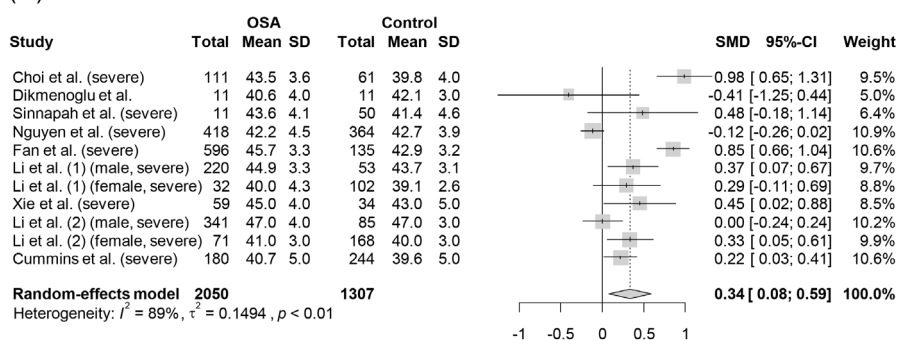
(A) Mild



(B) Moderate



(C) Severe



**FIGURE 3** Subgroup analysis of hematocrit values based on disease severity of OSA. The studies were divided into three subgroups according to disease severity: (A) mild ( $5 \leq \text{AHI} < 15$ ), (B) moderate ( $15 \leq \text{AHI} < 30$ ), and (C) severe ( $30 \geq \text{AHI}$ ). Forest plots comparing hematocrit values between patients with OSA and controls. The results are expressed as SMD and 95% CI. AHI, apnea hypopnea index; CI, confidence interval; OSA, obstructive sleep apnea; SMD, standardized mean difference

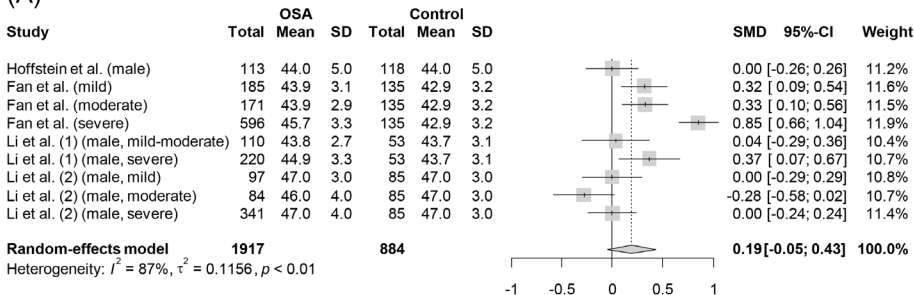
whether erythrocyte values are elevated in patients with OSA is controversial. In the present study, we comprehensively analyzed the results of 11 studies through a meta-analysis and found that

hematocrit values were significantly higher in patients with OSA than in controls. Although we found significant increases in hematocrit, the value in patients with OSA was estimated to remain within the normal

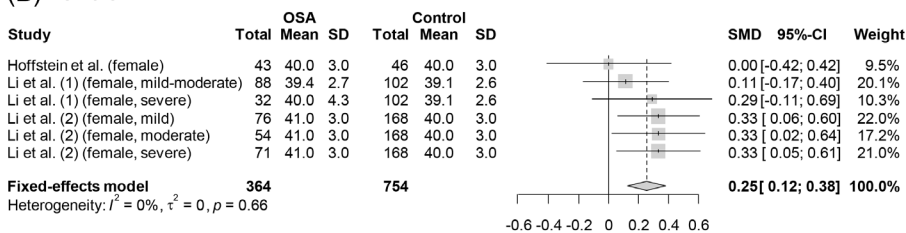


**FIGURE 4** Subgroup analysis of the hematocrit value according to participants' sex. The studies were divided into two subgroups according to the sex of participants: (A) male and (B) female. Forest plots comparing hematocrit values between patients with OSA and controls. The results are expressed as SMD and 95% CI. CI, confidence interval; OSA, obstructive sleep apnea; SMD, standardized mean difference

## (A) Male



## (B) Female



range. These results suggest that OSA may lead to minor increases in hematocrit, but rarely causes clinically significant erythrocytosis.

Mechanisms underlying the elevation of hematocrit in patients with OSA may involve increased erythropoiesis driven by intermittent hypoxia. It has been shown that exposure to hypoxia stabilizes hypoxia-inducible factors, resulting in gene transcription and production of EPO, a glycoprotein that stimulates red blood cell production.<sup>15,34</sup> This hypothesis is supported by a recent study showing that intermittent hypoxia can upregulate serum EPO values in healthy individuals.<sup>35</sup> Similarly, a meta-analysis of nine studies showed that EPO values in patients with sleep apnea were significantly higher than those in the control group.<sup>36</sup> Another possible mechanism explaining the elevation of erythrocyte measures in patients with OSA is a reduction in plasma volume resulting from fluid shift from the intravascular to the extravascular bed.<sup>37</sup> This fluid shift may be caused by increased atrial natriuretic peptide release, which is reduced after treatment with continuous positive airway pressure.<sup>38,39</sup>

In the subgroup analysis according to disease severity, we found that compared with controls, a significant difference in hematocrit value was observed only in patients with severe OSA, but not in patients with mild or moderate OSA. Although the SMD between severe patients and controls was 0.34, which would be considered a small effect size,<sup>26</sup> these findings indicate that the elevation of erythrocyte measures is more exaggerated in patients with severe disease. As the severity of OSA is determined by the frequency of apnea/hypopnea, more frequent hypoxia in patients with severe OSA induces significant EPO production, which subsequently stimulates erythropoiesis. Indeed, a previous study reported that 8-cycle intermittent hypoxia, but not 5-cycle intermittent hypoxia, increased serum EPO levels in healthy individuals, suggesting that a sufficient frequency of intermittent hypoxia is needed to induce erythropoiesis.<sup>35</sup>

An increase in hematocrit is associated with cardiovascular mortality and morbidity.<sup>40</sup> A previous study reported significant

correlations between erythrocyte measures and markers associated with cardiovascular risk, such as BMI and blood pressure, in patients with OSA.<sup>20</sup> In addition, it has been shown that mice with excessive EPO-induced erythrocytosis showed elevated endothelin-1,<sup>41</sup> a potent vasoconstrictor that is increased upon chronic intermittent hypoxia.<sup>42</sup> Given that endothelin-1 promotes elevation of blood pressure through vasoconstriction, it seems plausible that erythrocytosis is associated with adverse cardiovascular events. Further studies would be required to assess the potential contribution of increased erythrocyte measures to the development of cardiovascular diseases in patients with OSA, particularly in patients with severe OSA.

Since OSA is more prevalent in men,<sup>1</sup> the participants in most previous studies were predominantly men. However, considering that men and women have different normal ranges of hematocrit values, the sex composition of study cohorts may be a confounding factor for the analysis of the association between erythrocyte measures and OSA. Furthermore, it has been suggested that the relationship between erythrocyte measures and cardiovascular disease risk differs by sex.<sup>43</sup> Intriguingly, we found significantly elevated hematocrit values compared to controls in women, but not in men, suggesting a sex-specific association between OSA and hematocrit elevation. Therefore, it would be of interest to investigate whether response to intermittent hypoxia is different in men and women. In addition, as the definition and scoring rule for hypopnea by AASM was remarkably changed in 2012,<sup>33</sup> we separately analyzed the pre-2012 and post-2012 groups. The significant elevation of hematocrit values in patients with OSA remained stable in the subgroup analysis of the post-2012 group, indicating that the results were preserved when the current scoring rule was applied.

This study had several limitations. First, there might be a selection bias because all the studies included in this meta-analysis were hospital-based studies. Population-based studies may provide more accurate information on the general population. Second, we excluded articles in languages other than English, which may have biased the

results. Third, co-morbidities such as hypertension and smoking history of patients with OSA were unknown, which may be uncontrollable confounding factors in our analysis. However, the strength of this meta-analysis is that it included the largest number of studies to investigate the association between OSA and hematocrit.

## 5 | CONCLUSION

In summary, the current meta-analysis showed that patients with OSA, particularly severe patients, had significantly higher hematocrit values than controls. However, the elevation of hematocrit was modest and the value was estimated to be within the normal range. These data suggest that OSA is associated with a slight increase in hematocrit but does not cause clinically significant erythrocytosis. Therefore, evaluation of OSA may not be mandatory for the diagnostic work-up of secondary erythrocytosis without cardiovascular diseases.

## ACKNOWLEDGMENTS

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2021R1A2C2010811), the “Team Science Award” of Yonsei University College of Medicine (6-2021-0005), and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2021R11A1A01047571).

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ORCID

Chang-Hoon Kim  <https://orcid.org/0000-0003-1238-6396>

Hyung-Ju Cho  <https://orcid.org/0000-0002-2851-3225>

## REFERENCES

- Levy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1:15015.
- Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165:1217-1239.
- McNicholas WT, Bonsignore MR. Management committee of ECAB. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J*. 2007;29(1):156-178.
- Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342(19):1378-1384.
- Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA*. 2003;290(14):1906-1914.
- Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing. *J Am Coll Cardiol*. 2008;52(8):686-717.
- Lavie L. Obstructive sleep apnoea syndrome: an oxidative stress disorder. *Sleep Med Rev*. 2003;7(1):35-51.
- Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. *Eur Respir J*. 2009;33(6):1467-1484.
- Rha MS, Kim CH, Yoon JH, Cho HJ. Association between the neutrophil-to-lymphocyte ratio and obstructive sleep apnea: a meta-analysis. *Sci Rep*. 2020;10(1):10862.
- Lavie L. Oxidative stress inflammation and endothelial dysfunction in obstructive sleep apnea. *Front Biosci (Elite Ed)*. 2012;4:1391-1403.
- Levy P, Pepin JL, Arnaud C, Baguet JP, Dematteis M, Mach F. Obstructive sleep apnea and atherosclerosis. *Prog Cardiovasc Dis*. 2009;51(5):400-410.
- Keohane C, McMullin MF, Harrison C. The diagnosis and management of erythrocytosis. *BMJ*. 2013;347:f6667.
- McMullin MF. The classification and diagnosis of erythrocytosis. *Int J Lab Hematol*. 2008;30(6):447-459.
- McMullin MF, Bareford D, Campbell P, et al. Guidelines for the diagnosis, investigation and management of polycythaemia/ erythrocytosis. *Br J Haematol*. 2005;130(2):174-195.
- Jelkmann W. Erythropoietin: structure, control of production, and function. *Physiol Rev*. 1992;72(2):449-489.
- Hoffstein V, Herridge M, Mateika S, Redline S, Strohl KP. Hematocrit levels in sleep apnea. *Chest*. 1994;106(3):787-791.
- Choi JB, Loreda JS, Norman D, et al. Does obstructive sleep apnea increase hematocrit? *Sleep Breath*. 2006;10(3):155-160.
- Fan Z, Lu X, Long H, Li T, Zhang Y. The association of hemocyte profile and obstructive sleep apnea. *J Clin Lab Anal*. 2019;33(2):e22680.
- Li N, Li HP, Wang P, Yan YR, Li SQ, Li QY. Nocturnal mean oxygen saturation is associated with secondary polycythemia in young adults with obstructive sleep apnea, especially in men. *Nat Sci Sleep*. 2019;11:377-386.
- Li T, Covassin N, Tan L, et al. Sex-specific associations between erythrocyte measures and obstructive sleep apnea. *J Clin Sleep Med*. 2020;16(7):1063-1072.
- Cummins E, Waseem R, Piyasena D, et al. Can the complete blood count be used as a reliable screening tool for obstructive sleep apnea? *Sleep Breath*. 2021. doi:10.1007/s11325-021-02383-3
- Nguyen CD, Holty JC. Does untreated obstructive sleep apnea cause secondary erythrocytosis? *Respir Med*. 2017;130:27-34.
- Waltz X, Beaudin AE, Belaidi E, et al. Impact of obstructive sleep apnea and intermittent hypoxia on blood rheology: a translational study. *Eur Respir J*. 2021;58(4):2100352.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605.
- Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol*. 2013;4:863.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
- Lubin JH, Boice JD Jr. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. *J Natl Cancer Inst*. 1997;89(1):49-57.
- Dikmenoglu N, Ciftci B, Ileri E et al. Erythrocyte deformability, plasma viscosity and oxidative status in patients with severe obstructive sleep apnea syndrome. *Sleep Med* 2006; 7(3):255–261.
- Sinnaph S, Cadelis G, Waltz X, Lamarre Y, Connes P. Overweight explains the increased red blood cell aggregation in patients with obstructive sleep apnea. *Clin Hemorheol Microcirc*. 2015;59(1):17-26.
- Xie JY, Liu WX, Ji L, et al. Relationship between inflammatory factors and arrhythmia and heart rate variability in OSAS patients. *Eur Rev Med Pharmacol Sci*. 2020;24(4):2037-2053.



33. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. *J Clin Sleep Med*. 2012;8(5):597-619.
34. Song J, Sundar K, Gangaraju R, Prchal JT. Regulation of erythropoiesis after normoxic return from chronic sustained and intermittent hypoxia. *J Appl Physiol (1985)*. 2017;123(6):1671-1675.
35. Wojan F, Stray-Gundersen S, Nagel MJ, Lalande S. Short exposure to intermittent hypoxia increases erythropoietin levels in healthy individuals. *J Appl Physiol (1985)*. 2021;130(6):1955-1960.
36. Zhang XB, Zeng YM, Zeng HQ, Zhang HP, Wang HL. Erythropoietin levels in patients with sleep apnea: a meta-analysis. *Eur Arch Otorhinolaryngol*. 2017;274(6):2505-2512.
37. Eisensehr I, Noachtar S. Haematological aspects of obstructive sleep apnoea. *Sleep Med Rev*. 2001;5(3):207-221.
38. Krieger J, Laks L, Wilcox I, et al. Atrial natriuretic peptide release during sleep in patients with obstructive sleep apnoea before and during treatment with nasal continuous positive airway pressure. *Clin Sci (Lond)*. 1989;77(4):407-411.
39. Krieger J, Follenius M, Sforza E, Brandenberger G, Peter JD. Effects of treatment with nasal continuous positive airway pressure on atrial natriuretic peptide and arginine vasopressin release during sleep in patients with obstructive sleep apnoea. *Clin Sci (Lond)*. 1991;80(5):443-449.
40. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease--the Framingham study: a 34-year follow-up. *Am Heart J*. 1994;127(3):674-682.
41. Quaschnig T, Ruschitzka F, Stallmach T, et al. Erythropoietin-induced excessive erythrocytosis activates the tissue endothelin system in mice. *FASEB J*. 2003;17(2):259-261.
42. Cho HJ, Heo W, Han JW, et al. Chronological change of right ventricle by chronic intermittent hypoxia in mice. *Sleep*. 2017;40(8):zsx103, doi:10.1093/sleep/zsx103.
43. Brown DW, Giles WH, Croft JB. Hematocrit and the risk of coronary heart disease mortality. *Am Heart J*. 2001;142(4):657-663.

#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Rha M-S, Jeong Y, Kim J, Kim C-H, Yoon J-H, Cho H-J. Is obstructive sleep apnea associated with erythrocytosis? A systematic review and meta-analysis. *Laryngoscope Investigative Otolaryngology*. 2022;7(2):627-635. doi:10.1002/lio2.751