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Polycystic ovary syndrome in obstructive sleep apnea-hypopnea syndrome: an updated meta-analysis

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Background: Obstructive sleep apnea-hypopnea syndrome (OSAHS) is correlated with metabolic deterioration in patients experiencing polycystic ovary syndrome (PCOS). Women diagnosed with PCOS exhibit a heightened prevalence of OSAHS. This meta-analysis aims to assess the morbidity of OSAHS in women affected by PCOS and to examine the differences in metabolism-related indicators between OSAHS-positive and OSAHS-negative in women with PCOS.

Methods: A comprehensive literature analysis of OSAHS morbidity in women with PCOS was conducted, utilizing databases such as CNKI, EMBASE, PubMed, Web of Science, and Wanfang. A comparison was carried out between patients with OSAHS-positive and those with OSAHS-negative in terms of their clinical characteristics and metabolic differences. The search language included English and Chinese. The acquired data were analyzed by employing RevMan 5.2 and Stata 11.0. Continuous variables with the same units were combined and analyzed through weighted mean differences (WMDs) as effect sizes, while continuous variables with different units were combined and analyzed through standardized mean differences (SMDs) as effect sizes. A conjoint analysis was performed on the basis of I^2 value, using either a fixed effect model ($I^2 \leq 50\%$) or a random effect model ($I^2 > 50\%$).

Results: A total of 21 articles met the inclusion criteria for this study. The findings indicated that 20.8% of women with PCOS were found to have comorbid OSAHS. The subjects were categorized into various subgroups for meta-analysis on the basis of race, age, disease severity, body mass index (BMI), and diagnostic criteria of PCOS. The results revealed high morbidity of OSAHS in all subgroups. In addition, most metabolic indicators and parameters of metabolic syndrome were notably worse in women suffering from both PCOS and OSAHS in comparison to their counterparts solely diagnosed with PCOS.

Conclusion: The current literature indicates higher morbidity of OSAHS among women with PCOS, linking OSAHS with worse metabolic status and obesity in this population. Consequently, clinicians are advised to prioritize the detection and management of OSAHS in women with PCOS.

Systematic Review Registration: <https://www.crd.york.ac.uk/PROSPERO/#myprospero> PROSPERO, identifier (CRD42024528264).

KEYWORDS

PCOS, OSAHS, prevalence, metabolism, meta-analysis

1 Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine disorder in women of childbearing age, impacting approximately one out of every ten women (1). It is a metabolic syndrome, presenting with clinical manifestations such as ovulatory dysfunction, hyperandrogenism, and polycystic ovaries (2). Although the exact cause of Polycystic Ovary Syndrome (PCOS) remains unclear, it is likely multifactorial. Insulin resistance (IR) and hyperandrogenism are the two main hormonal disturbances in PCOS. Obesity, genetics, lifestyle, and environmental factors also contribute to the multifactorial etiology of PCOS (3–7). Women with PCOS may experience numerous reproductive, metabolic, psychological, and anthropometric complications (8–10). The most common characteristic of PCOS is ovarian dysfunction caused by hyperandrogenism, leading to chronic oligo-ovulation/anovulation and menstrual irregularities (11–13). Infertility in women with PCOS is the most common cause of anovulatory infertility, but not all women with PCOS are infertile. There are, however, some risks associated with pregnancy and foetal complications regardless of the mode of conception for those who become pregnant (14, 15). Furthermore, affected women are more likely to experience moderate to severe depression and anxiety symptoms compared to healthy women (16). PCOS has metabolic effects, including insulin resistance (IR), dyslipidemia, and abnormal glucose metabolism (17). Additionally, women with PCOS show a tendency toward excessive weight gain, which exacerbates these symptoms (18). Accompanied by increased cardiovascular risk factors such as chronic inflammation, oxidative stress, and impaired fibrinolysis, there is evidence suggesting a higher prevalence of cardiovascular disease in PCOS patients (19).

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common medical condition that affects not only women with PCOS and obesity but also non-PCOS women. (20, 21). The clinical presentation of OSAHS in women differs from that in men and may vary with age and physiological status (such as menopause and pregnancy) (22). Overall, compared to men, women seem to have more symptoms of OSAHS, with lower Apnea-Hypopnea Index scores. Furthermore, they appear to have longer periods of partial

upper airway obstruction, and may more frequently report insomnia as a symptom of OSAHS (23). It is marked by recurrent episodes of decreased oxygen saturation, sleep fragmentation, and upper airway occlusion, followed by aberrant secretion of gonadotropin-releasing hormone, increased sympathetic activity, insulin resistance (IR), and oxidative stress (OS) (24). These hormonal imbalances and metabolic irregularities are also commonly observed in PCOS and are believed to contribute to its etiology. Thus some researchers argue that OSAHS may exacerbate the severity of PCOS in affected women (25).

Numerous studies have investigated the association between PCOS and OSAHS. However, the available evidence presents some contradictions. A meta-analysis conducted by Kahal et al. (26) demonstrated no considerable difference in total testosterone (TT) and free testosterone (FT) levels between women diagnosed with both PCOS and OSAHS in comparison to those with PCOS alone. Nevertheless, Fogel et al. (27) reported that TT and FT were positively correlated with the apnea-hypopnea index (AHI). In addition, certain studies have indicated a heightened prevalence of OSAHS among women with PCOS (11, 27). This is further supported by the *Endocrine Society Clinical Practice Guideline* (28), which in its analysis of the evidence states that “the rate of OSAHS in women with PCOS equals or exceeds that in men.” Nevertheless, there is a wide range of reported rates of OSAHS in women diagnosed with PCOS, ranging from 0% to 70% (12, 29), potentially influenced by the sample size of the study.

Therefore, this study summarizes the existing published literature related to PCOS and OSAHS and conducts a comprehensive analysis of the morbidity of OSAHS in women affected by PCOS. Moreover, a systematic review and meta-analysis are performed to explore the correlation between OSAHS and metabolic irregularities in women affected by PCOS. Furthermore, apart from weight loss, women with both PCOS and obesity have limited options for safe and effective treatment. Research has demonstrated that continuous positive airway pressure (CPAP) can ameliorate IR, mitigate OS and inflammatory status, and enhance the quality of life in patients diagnosed with OSAHS. Thus, investigating the effect of OSAHS on women suffering from PCOS may contribute to the development of new therapeutic strategies for this population.

2 Methods

The systematic evaluation methodology used in this study has been registered prospectively at PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/#myprosperto>, ID: CRD42024528264). The findings of this study are reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Inclusion and exclusion criteria

This systematic review and meta-analysis will include cross-sectional, cohort, case-control studies and randomized control trials. These studies were designed to detect whether women with PCOS had OSAHS. The included studies utilized polysomnography (PSG) or class III devices for diagnosing OSAHS. Subjects met the diagnostic criteria for OSAHS based on PSG or class III devices (adults: AHI \geq 5/h; children: AHI \geq 1/h) (30).

The study encompassed women with PCOS, irrespective of age (adolescents-postmenarcheal and adults-postmenopausal and premenopausal), race, or PCOS diagnostic criteria. Polycystic ovary syndrome was diagnosed according to the revised 2003 Rotterdam criteria (31). Several studies reported that the diagnosis of polycystic ovary syndrome broadly followed the consensus criteria from the National Institutes of Health of anovulation and hyperandrogenaemia (32).

The exclusion criteria encompassed conditions with a similar phenotype to PCOS, such as androgen-secreting tumors, Cushing syndrome, prolactinoma, congenital adrenal hyperplasia, and thyroid diseases. Abstracts, letters to the editor, reference papers (most conference papers only have abstracts instead of complete data), animal experiments, and case studies were also excluded from this study.

2.2 Main results

Morbidity of OSAHS in women with PCOS.

2.3 Secondary results

Morbidity of OSAHS in women with PCOS in comparison to women without PCOS.

Differences between women diagnosed with both PCOS and OSAHS and women with PCOS alone regarding blood lipid, blood pressure (BP), body mass index (BMI), blood glucose, hemoglobin (HGB), hypertrichosis, waistline, insulin (INS), IR, low-density lipoprotein (LDL), waist-to-hip ratio (WHR), two-hour oral glucose tolerance test (2-h OGTT), TT, FT, sex hormone-binding globulin (SHBG), etc.

2.4 Search methodology

Searches were conducted across CNKI, EMBASE, PubMed, Web of Science, and Wanfang databases for non-English and English articles. The keywords and subject terms used were “polycystic ovary syndrome” or “ovary polycystic disease” or “PCOS” or “stein leventhal” or “hyperandrogenic anovulation” and “Obstructive Sleep Apnea-Hypopnea Syndrome” or “Obstructive Sleep Apnea” or “Obstructive Sleep Apnea Syndrome” or “OSA” or “OSAHS” or “OSAS”. The retrieval spanned from the inception of the databases up to March 1, 2024. In addition to the computerized search, a manual search was conducted on all retrieved articles. Articles with potential relevance were assessed according to pre-specified inclusion and exclusion criteria.

2.5 Literature selection

Two authors (He J and Ruan X) independently screened the title and abstract of each article. All articles with potential relevance were thoroughly reviewed. Any differences between the two authors were resolved through consensus and, if necessary, discussed with a third author (Li J).

2.6 Data extraction and management

Data extraction was independently conducted by two authors (He J and Ruan X). In the case of multiple publications, the primary study or paper was included, with **Supplementary Information** extracted from secondary papers where necessary. As needed, the authors of the papers were contacted to address data queries and resolve disputes regarding the data. In case of duplicate publications, the original authors were contacted to clarify the main publication. If no response was received, the study with the highest number of participants was selected. Details that were extracted from each study included participant characteristics, study design, and morbidity data.

2.7 Assessing risk of bias

Quality assessment was carried out independently by two reviewers (He J and Ruan X) and any differences were resolved through negotiation and discussion with the third reviewer (Li J). The non-randomized Study Bias Risk Assessment Tool (RoBANS) (33) was used to assess the risk of bias in each included study, assessing the following areas of bias risk: selection bias (sample population), selection bias (confounding variables), performance bias (exposure measures), performance bias (analytical methods to control for bias), and other biases. Each area is classified as high risk; low risk; or not clear.

2.8 Statistical analyses

We pooled prevalence estimates using the DerSimonian-Laird random-effects model (34). We assessed inter-study differences in prevalence estimates using Higgins I^2 statistics, with values more than 50% being considered moderately heterogeneous according to recommendations (35, 36). We performed a series of meta-regressions and subgroup analyses to explore the effect of covariates on prevalence estimates. The following factors were considered: race, age, BMI (obese and non-obese), and PCOS definition. For continuous variables, fixed-effect model analyses combined statistically homogeneous findings. Otherwise, we used random-effects meta-analysis. The (weighted) mean difference and SD were calculated to describe the continuous outcomes that were measured on the same scale. The SMD and SD were used to describe continuous outcomes that were not measured on the same scale. Inter-study heterogeneity was assessed using Higgins's I^2 statistic, with values more than 50% indicating moderate heterogeneity. All analyses were performed in Stata version 11 for Windows (Stata Corp, College Station, Texas).

3 Results

3.1 Search results and study attributes

A total of 1241 relevant studies were retrieved from the database. Removing duplicate studies by reading abstracts and titles; 612 articles were eliminated, leaving 38. We downloaded the 36 articles and read through them, excluding 14 papers based on inclusion and exclusion criteria. The articles were excluded for the following reasons: two were animal experiments, four were reviews, three were letters to the editor, and five lacked relevant data. We identified 21 studies (11, 12, 26, 27, 29, 37–57) involving OSAHS incidence in PCOS patients, as shown in Table 1. There are 9 literature (11, 37, 39, 41, 43, 50, 53, 56, 57) comparing the clinical characteristics of PCOS patients with OSAHS positive and OSAHS negative (Table 1). The flow chart of systematic reviews and meta-analyses for the selection and screening of articles is shown in Figure 1. The basic information of the studies is summarized in Table 1.

3.2 Risk of bias for inclusion of studies

Supplementary Figure 1 lists the risk assessment of bias for each study. 9 studies had high selection bias due to inadequate selection of subjects, 2 studies had low risk, and the remaining 13 studies were unclear. Selection bias due to inadequate identification and consideration of confounding variables was high in most studies (14 of 24), low in only 1 study, and unclear in the remaining 9 studies. Performance bias due to inadequate exposure measurements was low in 19 studies, high in 4 studies, and unclear in the remaining 1 study. Most studies (10 of the 24 studies) had low detection bias due

to inadequate blindness in outcome assessment, and only 3 studies had high detection bias. Loss of follow-up bias due to mishandling of incomplete outcome data was low across all 24 studies. Most studies (18 out of 24) had low reporting bias due to selective reporting.

3.3 Prevalence of OSAHS in women diagnosed with PCOS

Figure 2 presents the prevalence of OSAHS in women affected by PCOS. The morbidity of OSAHS in all studies was about 20.8% [95% confidence interval (CI): 14.7 – 27.6%]. The I^2 value of 98% indicated statistically significant heterogeneity among the studies. Supplementary Figure 1 displays the contour-enhanced funnel plot for the publication bias test. Evidence of publication bias was found in the meta-analysis, and the funnel plot showed asymmetry. This was confirmed through a formal test using Egger's regression test ($P=0.013$) (Supplementary Figure 2). Sensitivity analysis revealed that the exclusion of any individual study from the analysis did not undermine the overall findings of the combined analysis.

3.4 Subgroup analysis

Evidence suggests that factors, such as disease severity, BMI, race, age, and diagnostic criteria, influence the morbidity of OSAHS. In a subgroup analysis based on disease severity, it was observed that women with PCOS exhibited an increased proportion of moderate OSAHS than those with mild OSAHS (38.8% vs. 29.9%). Due to the limited number of studies examining severe cases of OSAHS, it was not possible to assess the morbidity of severe OSAHS. Analysis based on BMI revealed that women diagnosed with both PCOS and obesity exhibited an elevated morbidity of OSAHS than women with PCOS but without obesity (27.5% vs. 15.8%). A subgroup analysis based on age revealed that adult women with PCOS had greater morbidity of OSAHS than adolescent women with PCOS (21.5% vs. 17.4%). Following that, a subgroup analysis based on race depicted that Caucasian woman affected by PCOS had greater morbidity of OSAHS than Asian women with PCOS (27.2% vs. 9.6%). Additionally, it was observed that studies using the Rotterdam criteria (25.4%) and studies not specifying how PCOS was diagnosed (5.6%) tended to exhibit lower morbidity of OSAHS compared to studies employing the NIH PCOS definition (31.9%) (Table 2).

3.5 Meta-regression analysis

Table 3 displays the factors identified through meta-regression analysis that are correlated with morbidity estimates. We expected to identify sources of heterogeneity through meta-regression analysis, but none of the factors studied were found to be substantially correlated with the morbidity estimates in meta-regression analyses.

TABLE 1 Characteristics of included studies.

Author	Year	Country	Study design	N		Ethnicity	Age (year)	BMI (kg/m ²)	PCOS	OSAHS	Outcomes
				Case	Control						
Fogel RB	2001	USA	CSS	18	18	Caucasian	31.1 ± 5.5	36.9 ± 5.5	NIH	PSG	①②④⑬
Vgontzas AN	2001	USA	CSS	53	452	Caucasian	30.4 ± 6.6	38.7 ± 8.0	NIH	PSG	①②⑪⑮⑯
Gopal M	2002	USA	CSS	23	NR	Caucasian	NR	42.5 ± 8.5	NR	PSG	①②
Tasali E	2008	USA	CSS	52	21	Caucasian	29.7 ± 5.1	39.2 ± 7.2	NIH	PSG	①②⑧⑪⑫⑬⑭⑮⑯
Yang HP	2009	China	CSS	18	10	Asian	29.1 ± 6.1	21.7 ± 2.4	Rotterdam	PSG	①②③④⑥⑦⑧⑨⑪⑫⑬⑭⑮
de Sousa G	2012	Germany	CSS	35	19	Caucasian	15.3 ± 1.2	32.9 ± 6.4	NIH	PSG	①②③⑧⑨⑪⑫⑬⑭⑮
Nandalike K	2012	USA	CSS	28	56	Mixed	16.8 ± 1.9	44.8 ± 8.8	Rotterdam	PSG	①②③⑥⑨⑩⑪⑫⑬⑭⑮⑯
Mokhlesi B	2013	USA	CSS	44	34	Caucasian	27 ± 5	35.1 ± 11.4	NIH	PSG	①②③④⑧⑪⑫⑬⑭⑮
Chatterjee B	2014	India	CSS	50	NR	Caucasian	NR	28 ± 3.0	Rotterdam	PSG	①②③⑥⑦⑧⑩⑪⑫⑬⑭⑮⑯⑰⑱
Sirmans SM	2014	USA	CSS	1689	5067	Mixed	25.24	>30	NR	NR	①
Tock L	2014	Brazil	CSS	38	NR	Caucasian	28.3 ± 6.8	32.9 ± 7.7	Rotterdam	PSG	①②③④⑧⑨⑩⑪⑫⑬⑭⑮⑯⑰⑱
Lin TY	2017	China	CSS	4595	4595	Asian	28.0 ± 6.79	NR	NR	NR	①
Kumarendra B	2019	UK	CS	76978	143077	Caucasian	30.2 ± 7.4	28.6 ± 7.6	NR	NR	①②
Torres-Zegarra C	2021	USA	CS	92	NR	Mixed	15.4 ± 2.3	35.5 ± 6.6	NR	NR	①②⑨⑬⑮⑱
Zhou X	2021	USA	CSS	200	NR	Mixed	28.0 ± 6.2	30.9 ± 9.0	Rotterdam	BQ	①②③⑥⑨⑩⑪⑫⑬⑭⑮⑯⑰⑱
Underland LJ (obesity)	2022	USA	CSS	21	8	Caucasian	16.38 ± 2.4	38.4 ± 2.5	NR	PSG	①②③⑧⑩⑫⑬⑭⑮⑯⑰⑱
Underland LJ (non-obesity)	2022	USA	CSS	10	8	Caucasian	17.50 ± 1.8	23.0 ± 1.8	NR	PSG	①②③⑧⑩⑫⑬⑭⑮⑯⑰⑱
Yang R (Mild)	2022	China	CSS	328	NR	Asian	29.2 ± 3.9	28.4 ± 3.7	Rotterdam	PSG	①②⑥⑫⑬⑭⑮⑯⑰⑱
Yang R (Moderate)	2022	China	CSS	328	NR	Asian	30.0 ± 4.0	31.7 ± 4.9	Rotterdam	PSG	①②⑥⑫⑬⑭⑮⑯⑰⑱
Yang R (Severe)	2022	China	CSS	328	NR	Asian	33.5 ± 3.6	32.1 ± 3.3	Rotterdam	PSG	①②⑥⑫⑬⑭⑮⑯⑰⑱
Ibrahim S	2023	USA	CSS	48	NR	Caucasian	NR	NR	NR	BQ	①②⑥
Zhang Q	2024	China	CS	156	NR	Asian	30.1 ± 3.5	23.9 ± 3.6	Rotterdam	PSG	①②⑨⑪
Christ JP	2024	USA	CSS	309	NR	Caucasian	18-44	38 ± 9.1	Rotterdam	BQ	①②③⑧⑨⑩⑪⑫⑬⑭⑮⑯⑰⑱

CSS, cross-sectional study; CS, cohort study; NR, Not reported; BQ, Berlin Questionnaire; PSG, Polysomnography; NIH, National Institutes of Health; BMI, body mass index. ①: Prevalence; ② BMI; ③: Waist circumference; ④: Waist-hip-ratio (WHR); ⑤: BMI Z-score; ⑥: Blood pressure; ⑦: Modified Ferriman-Gallwey score for Hirsutism; ⑧: Sex hormone binding globulin (SHBG); ⑨: Total Testosterone; ⑩: Free Testosterone; ⑪: Fasting plasma glucose; ⑫: 2-hour plasma glucose on OGTT; ⑬: Hemoglobin A1c; ⑭: Insulin resistance (HOMA-IR); ⑮: Fasting Insulin; ⑯: Total cholesterol; ⑰: Low density lipoprotein(LDL); ⑱: Triglycerides; ⑲: High density lipoprotein(HDL); PCOS, polycystic ovary syndrome; OSAHS, obstructive sleep apnea-hypopnea syndrome.

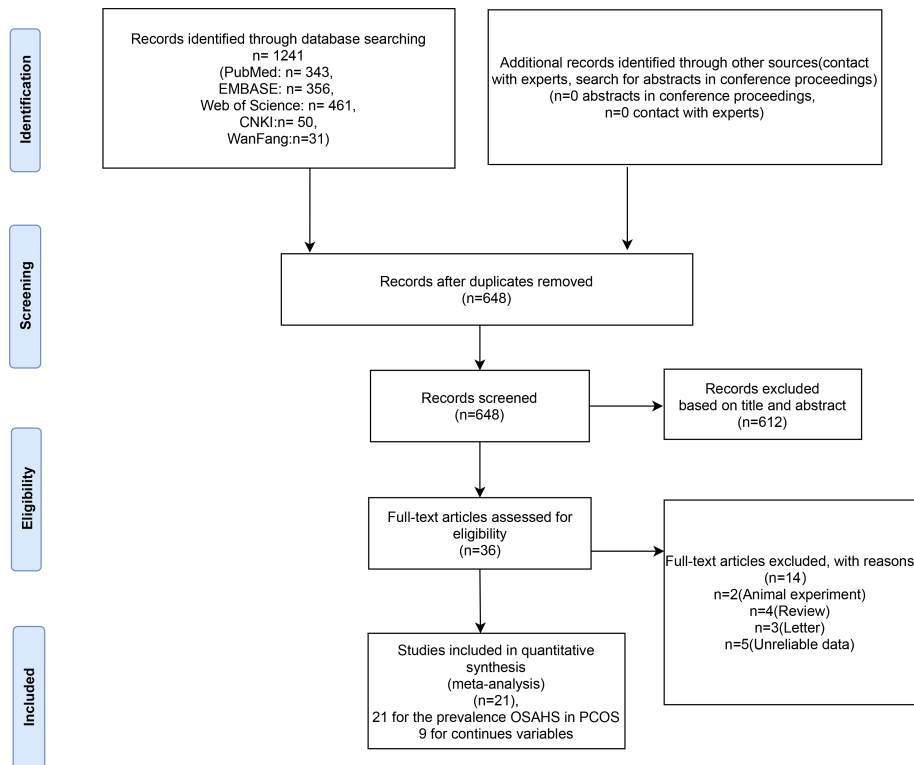


FIGURE 1
Flow chart of inclusion criteria in the study.

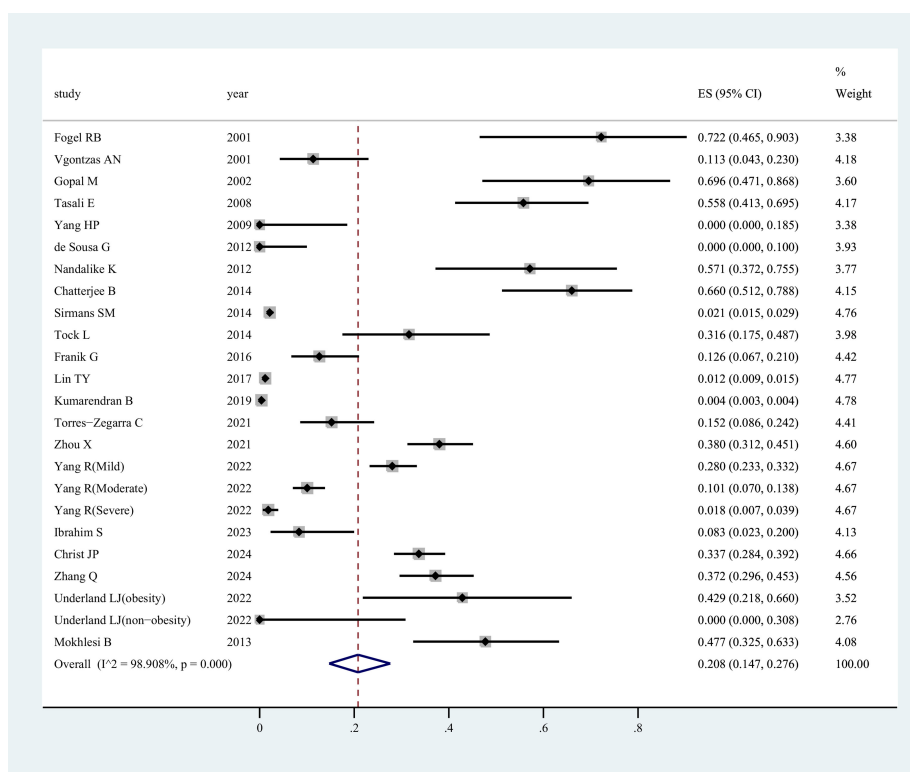


FIGURE 2
Prevalence of OSAHS in patients with PCOS as determined by the random effects model.

TABLE 2 Subgroup analyses of obstructive sleep apnea in different conditions.

Subgroup Analysis of Obstructive Sleep Apnea(n)	ES (95% CI)	P Value	I ² (%)	P _h
Overall (24)	0.208 (0.147,0.276)	<0.001	98.91%	<0.001
Severity				
Mild (2)	0.299 (0.251,0.348)	<0.001	0	0
Moderate (5)	0.388 (0.175,0.625)	<0.001	96.02%	<0.001
Severe (1)	NA	NA	NA	NA
Not mentioned (16)	0.157 (0.101,0.222)	<0.001	98.75%	<0.001
BMI				
BMI<30 (6)	0.158 (0.001,0.457)	<0.001	99.28%	<0.001
BMI>30 (15)	0.275 (0.156,0.411)	<0.001	97.94%	<0.001
Not mentioned (3)	0.060 (0.000,0.186)	<0.001	0	<0.001
Age				
Adult (19)	0.215 (0.149,0.289)	<0.001	99.08%	<0.001
Adolescent (5)	0.174 (0.014,0.430)	<0.001	91.68%	<0.001
Race				
Caucasian (14)	0.272 (0.101,0.485)	<0.001	98.75%	<0.001
Asian (6)	0.096 (0.012,0.239)	<0.001	98.88%	<0.001
Mixed (4)	0.237 (0.027,0.557)	<0.001	98.81%	<0.001
Diagnostic Criteria				
NIH (5)	0.319 (0.073,0.633)	<0.001	94.97%	<0.001
Rotterdam (11)	0.254 (0.142,0.384)	<0.001	97.04%	<0.001
Not mentioned (8)	0.056 (0.028,0.091)	<0.001	97.22%	<0.001

ES, effect size; NA, not applicable; NIH, National Institutes of Health; P_h, P heterogeneity.

3.6 OSAHS in PCOS vs. OSAHS in non-PCOS

Among women in the general population, the prevalence of OSAHS ranges from 6% to 19% (58). In the current research, 12 studies compared the morbidity of OSAHS in women with PCOS and matched controls, with the majority indicating a heightened prevalence of OSAHS among women with PCOS (Figure 3A). Women affected by PCOS were 2.86 times more likely to have

TABLE 3 Factors associated with OSAHS prevalence estimates identified by meta-regression analysis.

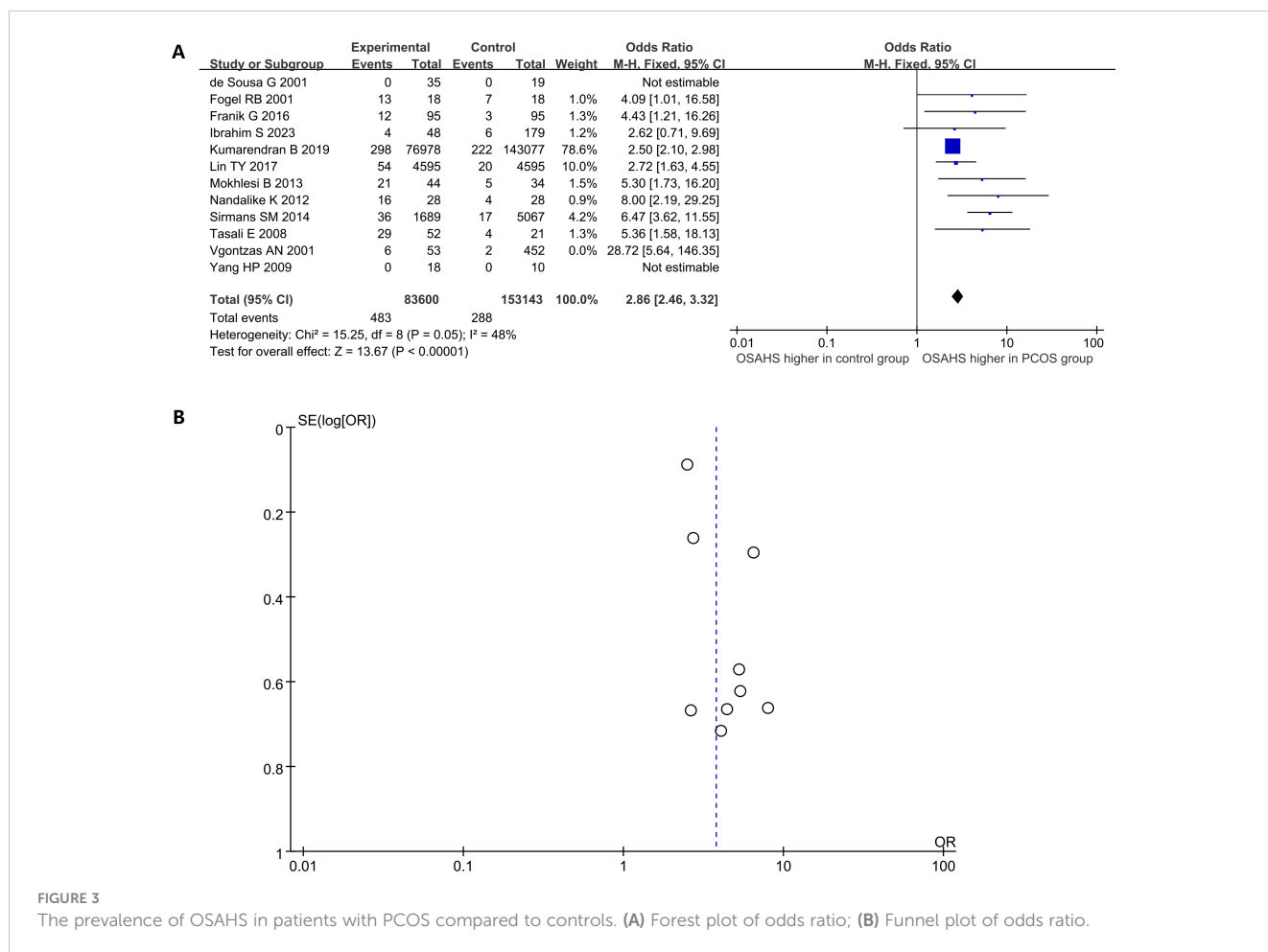
Factor	OR (95% CI)	p-value	Explained variation (%)
Age: adult (vs. adolescent)	0.51 (0.22 to 1.78)	0.259	11.3
BMI			8.4
< 30	1 (reference)		
> 30	0.75 (0.38 to 4.23)	0.702	
Not reported	1.02 (0.25 to 7.58)	0.852	
Ethnicity			4.2
Caucasian	1 (reference)		
Asian	0.82 (0.13 to 5.17)	0.817	
Mixed	1.15 (0.16 to 4.58)	0.724	
Diagnostic criteria			0.0
NIH definition	1 (reference)		
Rotterdam criteria	0.75 (0.16to 4.56)	0.806	
Not reported	1.12 (0.20 to 5.41)	0.859	
Severity			0.0
Mild	1 (reference)		0.0
Moderate	0.92 (0.13 to 2.27)	0.324	
Severe	1.04 (0.15 to 3.88)	0.439	
Not reported	0.82 (0.21 to 5.27)	0.628	

OSAHS than controls (OR: 2.86; 95% CI: 2.46 – 3.32; 12 studies). Additionally, evidence of publication bias was found, as the funnel plot displayed asymmetry, indicating the potential existence of publication bias (Figure 3B). Sensitivity analysis indicated a significant reduction in heterogeneity by 15% upon excluding the study of Vgontzas AN (11), prompting its exclusion from the analysis.

3.7 Impact of OSAHS on clinical outcomes in women with PCOS

3.7.1 Body measurement

Women diagnosed with both PCOS and OSAHS have a significantly higher BMI [mean difference (MD): 7.10kg/m²; 95% CI: 5.07 – 9.14; I² = 92%; 10 studies] (Figure 4A). Similarly, waistline (MD: 15.74cm; 95% CI: 7.73 – 23.74; I² = 79%; 3 studies) (Figure 4B) and WHR (MD: 0.10; 95% CI: 0.08 – 0.12;



I² = 0%; 2 studies) were significantly elevated (Figure 4C). A study (39) reported that there was no considerable difference in BMI-Z scores between girls with and without OSAHS in a subgroup of adolescent girls with PCOS and obesity (Figure 4D).

3.7.2 Blood pressure

Six studies depicted the impact of OSAHS on BP in women with PCOS. A meta-analysis revealed that mean systolic pressure was substantially higher in women with both PCOS and OSAHS in comparison to the women with PCOS alone, with a difference of 8.85 mmHg (95% CI: 5.16 – 12.53; I² = 62%; 6 studies) (Supplementary Figure 3A). Similarly, diastolic pressure was significantly higher in women diagnosed with both PCOS and OSAHS in comparison to the women with PCOS but without OSAHS (MD: 4.45 mmHg; 95% CI: 2.81 – 6.08; I² = 17%; 6 studies) (Supplementary Figure 3B).

3.8 Impact of OSAHS on hormonal/metabolic parameters in women affected by PCOS

3.8.1 Hypertrichosis

One study (41) included in the analysis utilized the Ferriman-Gallwey (FG) Score as an indicator of hypertrichosis (Supplementary

Figure 4A). The findings showed that this score was greater in women with both PCOS and OSAHS in comparison to the women affected by PCOS alone (MD: 1.82; 95% CI: 0.30 – 3.34).

3.8.2 Sex hormone-binding globulin

Three studies included in the analysis reported SHBG levels. Women with both PCOS and OSAHS had lower SHBG levels than patients without OSAHS (MD: -22.8 nmol/L; 95% CI: -39.53 – -6.07, I² = 91%) (Supplementary Figure 4B).

3.8.3 Impact of OSAHS on testosterone in women affected by PCOS

Women with both PCOS and OSAHS had higher testosterone: total testosterone (SMD: 0.02; 95% CI: -0.28 – 0.31; I² = 81%; 10 studies) (Figure 5A); free testosterone (SMD: 0.35; 95% CI: 0.09 – 0.61; I² = 52%; 7 studies) (Figure 5B).

3.8.4 Glucose metabolism and IR

Women diagnosed with both PCOS and OSAHS exhibited elevated levels of blood glucose. Fasting plasma glucose (FPG) (MD: 0.46 mmol/L; 95% CI: 0.23 – 0.69; I² = 57%; 8 studies) (Figure 6A). 2-h OGTT (MD: 1.04 mmol/L; 95% CI: 0.72 – 1.36; I² = 9%; 6 studies) (Figure 6B).

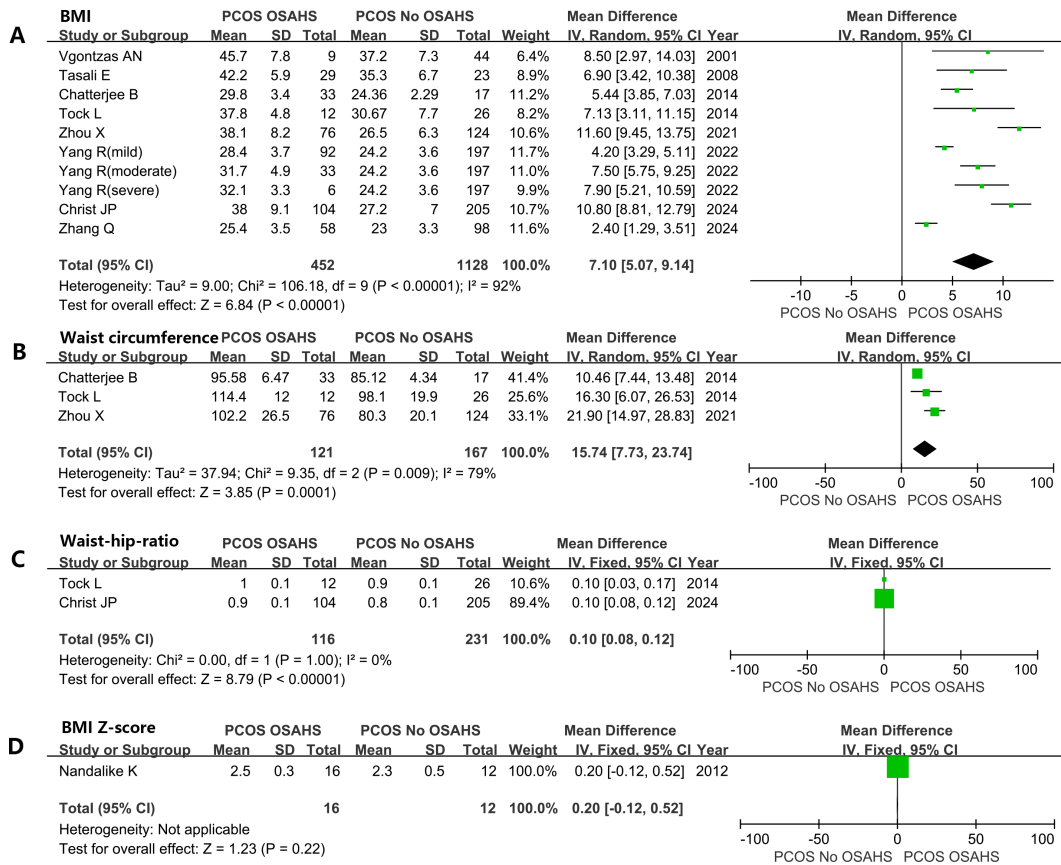


FIGURE 4 Effect of OSAHS on anthropometric measures in patients with PCOS. (A) BMI, (B) waist circumference, (C) Waist-hip-ratio, (D) BMI Z-score.

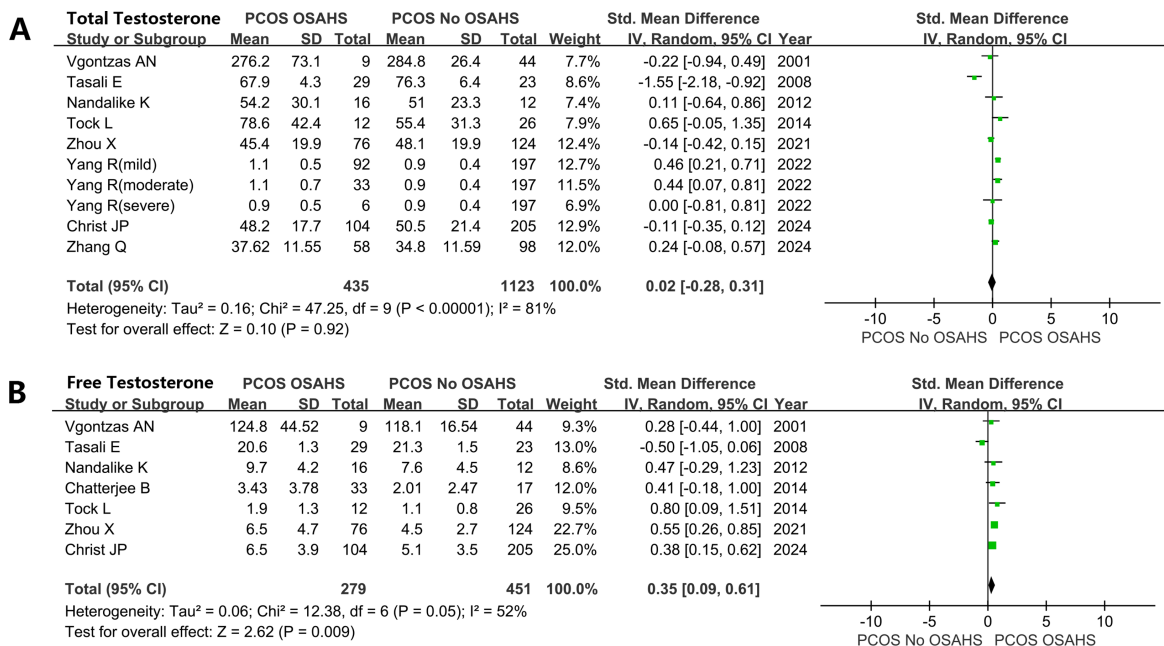


FIGURE 5 Effect of OSAHS on testosterone in patients with PCOS. (A) total testosterone, (B) free testosterone.

glycosylated hemoglobin (MD: 0.22%; 95% CI: 0.06 – 0.38; $I^2 = 64\%$; 5 studies) (Figure 6C). Homeostatic model assessment for insulin resistance (HOMA-IR) (MD: 2.54; 95% CI: 1.85 – 3.23; $I^2 = 0\%$; 6 studies) (Figure 6D). Fasting serum INS (FINS) (MD: 10.30 μ U/mL; 95% CI: 6.13 – 14.47; $I^2 = 67\%$; 6 studies) (Figure 6E).

0.52; $I^2 = 0\%$; 8 studies) (Figure 7C). In contrast, plasma high-density lipoprotein (HDL) levels were lower in women diagnosed with both PCOS and OSAHS in comparison to the women affected by PCOS only (MD: -0.24 mmol/L; 95% CI: -0.27 – -0.20, $I^2 = 7\%$; 8 studies) (Figure 7D).

3.8.5 Blood lipid

Women with PCOS, OSAHS, and obesity hypoventilation syndrome (OHS) exhibit notably elevated levels of plasma cholesterol. Total cholesterol (TC) (MD: 0.44mmol/L; 95% CI: -0.08 – 0.96; $I^2 = 71\%$; 3 studies) (Figure 7A). low-density lipoprotein (MD: 0.30mmol/L; 95% CI: 0.20 – 0.40; $I^2 = 24\%$; 6 studies) (Figure 7B). Triglyceride (MD: 0.43mmol/L; 95% CI: 0.33 –

4 Discussion

Our analysis of the available data suggested a high morbidity of OSAHS in women with PCOS. The included population was mostly Caucasians, encompassing women diagnosed with both PCOS and obesity and exhibited a significant level of selection bias. Therefore,

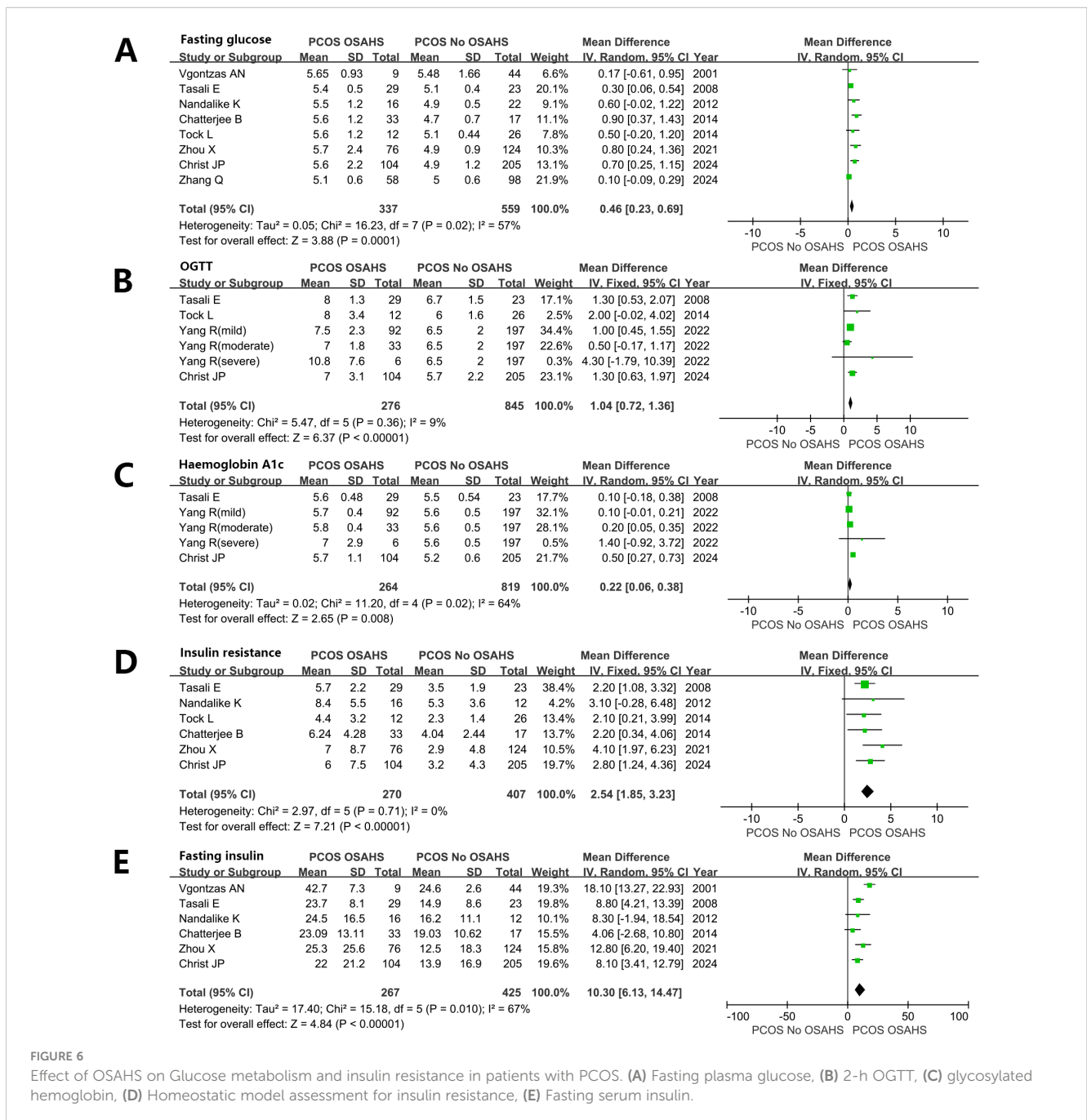


FIGURE 6

Effect of OSAHS on Glucose metabolism and insulin resistance in patients with PCOS. (A) Fasting plasma glucose, (B) 2-h OGTT, (C) glycosylated hemoglobin, (D) Homeostatic model assessment for insulin resistance, (E) Fasting serum insulin.

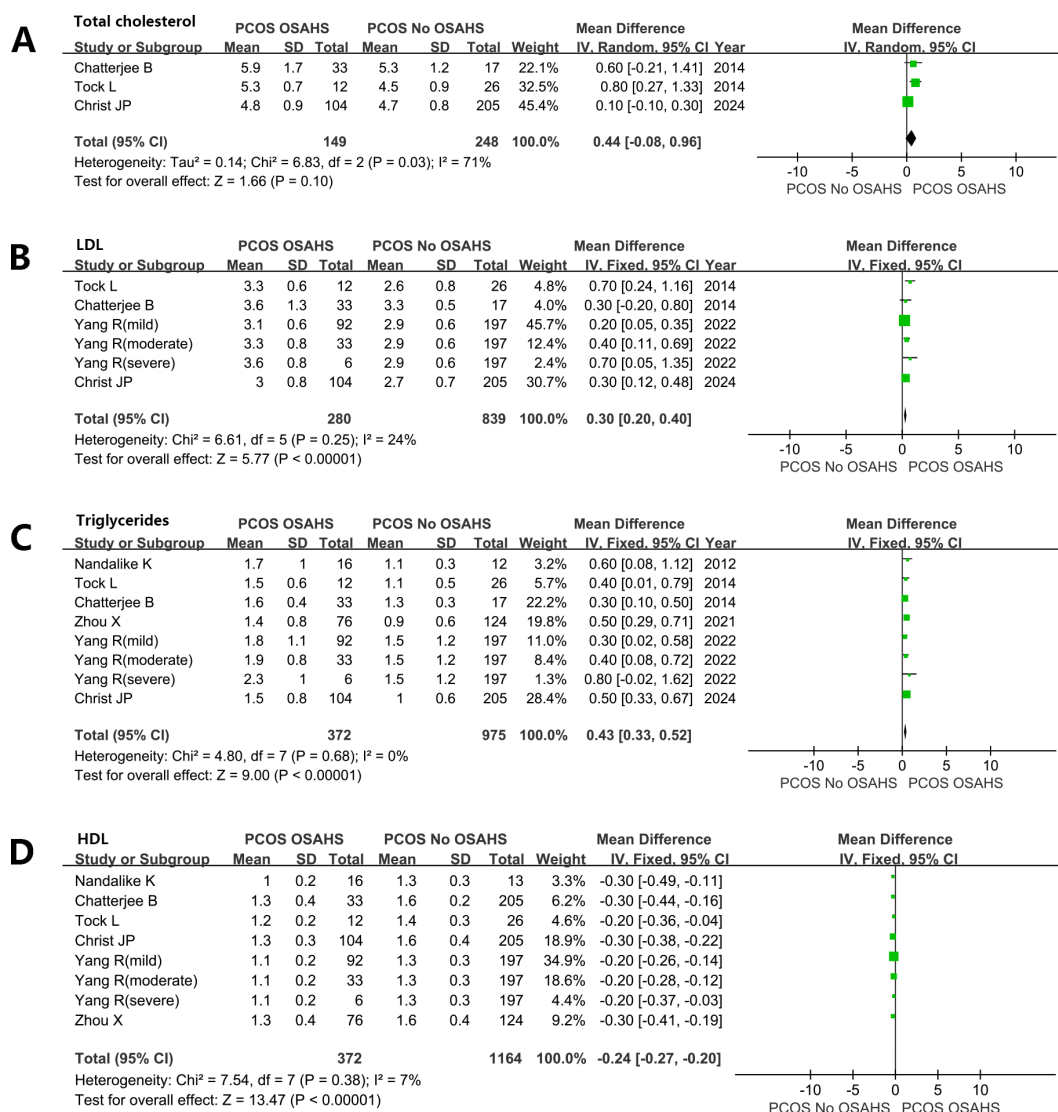


FIGURE 7 Effect of OSAHS on blood lipid in patients with PCOS. (A) Total cholesterol, (B) low-density lipoprotein, (C) Triglyceride, (D) high-density lipoprotein.

drawing definitive conclusions about the actual morbidity of OSAHS in women with PCOS is challenging due to the limitations of the available data. The meta-analysis showed that the prevalence of OSAHS is higher in adult patients with PCOS compared to adolescent patients with PCOS, and obese patients were more likely to have OSAHS. Patients with PCOS combined with OSAHS were more prone to metabolic and androgen level disorders.

According to the current meta-analysis, nearly 21% of women with PCOS suffer from OSAHS. In a meta-analysis conducted by Kahal et al. (59), the morbidity of OSAHS in women with PCOS was as high as 35% (95% CI: 22.0% – 48.9%). The reported high morbidity of OSAHS can be explained by differences in study methodology and diverse PCOS diagnostic criteria. In the study conducted by Kahal et al. (59), the included studies encompassed conference abstracts, and the predominant diagnostic criteria utilized for PCOS were the Rotterdam criteria. Moreover, when comparing the morbidity of OSAHS in PCOS and non-PCOS

groups, the meta-analysis included an article by Vgontzas (11), which yielded an odds ratio (OR) of 28.72. This particular research introduced substantial heterogeneity, a factor that significantly reduced after the exclusion of this study, as shown in Figure 3. The morbidity of OSAHS in PCOS derived from this study is similar to the findings of a meta-analysis by Helvacı (22%) (60). Johnson et al. (61) employed the androgen excess mouse model of PCOS for ovarian circadian assessment and revealed that an impaired circadian clock could hamper the regulation of peripheral steroid metabolism in PCOS. Altered expression of ovarian core clock genes (Clock, Bmal1 and Per2) was found in dehydroepiandrosterone-treated PCOS mice. The intermittent hypoxia and sleep fragmentation caused by OSAHS can lead to delayed circadian rhythms and insufficient sleep. This might be the mechanism by which OSAHS affects PCOS.

Among women in the general population, the prevalence of OSAHS ranges from 6% to 19% (58). The present study proposes

that women affected by PCOS are 3 times more likely to develop OSAHS than women without PCOS. However, these studies did not adequately account for important confounding factors known to influence the risk of OSAHS, encompassing age, abdominal obesity, and race. In addition, women diagnosed with PCOS were recruited from specialized clinics, whereas controls were drawn from the general population. Consequently, it remains unclear whether women with PCOS in the community face a greater risk of OSAHS than age- and obesity-matched controls. Therefore, favorable large-scale observational studies in the general population are required for it.

The findings of this study revealed a higher prevalence of OSAHS among adult women with PCOS than in adolescents. Moreover, OSAHS was more prevalent in women affected by both PCOS and obesity than in women with PCOS alone. These trends align with the increased risk of OSAHS associated with age and obesity observed in the general population (62, 63). Thus, PCOS is likely to precede the onset of OSAHS, especially in preadolescent girls in whom PCOS is a common feature (64, 65). However, in some women, OSAHS may also precede the onset of PCOS. For example, in research by Nandalike et al. (39), it was demonstrated that one-third of adolescent girls with PCOS had a history of tonsillectomy. Notably, tonsillitis and/or enlarged tonsils were identified as the primary causes of OSAHS in children (66, 67).

The limited available data propose that women with PCOS develop moderate OSAHS at a higher rate than those who develop mild OSAHS. This finding is drawn from seven studies encompassing a total of 620 participants exhibiting such characteristics. However, the sample size was insufficient to draw definite conclusions.

Obesity stands as a well-recognized risk factor associated with the onset and progression of OSAHS. Increased obesity is linked to an elevated risk of developing OSAHS (68). Thus, according to this analysis, women with both PCOS and OSAHS had higher BMI and waistline than women without OSAHS, which also suggests that women with PCOS combined with OSAHS tend to have abdominal obesity. This excessive obesity could potentially elevate the risk of type 2 diabetes and CVDs among these women. However, the precise contribution of excessive obesity or OSAHS to this increased risk has yet to be thoroughly examined. Obesity can contribute to OSAHS by causing increased parapharyngeal fat deposition, which leads to the narrowing of the upper airway. Additionally, the fat deposition in the abdomen and around the ribcage decreases thoracic compliance and reduces functional residual capacity. These factors, along with changes in neural compensatory mechanisms and the respiratory control system, further exacerbate the condition (69). Additionally, studies have demonstrated that obesity and PCOS have an inverse relationship; obesity increases PCOS prevalence while PCOS leads to weight gain and obesity (70). Obesity, PCOS and OSAHS might have a complex and controversial relationship with each other.

In addition, our meta-analysis revealed that women diagnosed with both PCOS and OSAHS exhibited higher levels of BP, resulting in higher blood lipids for atherosclerosis, compared to women without OSAHS. Although this indicates a potentially heightened

risk of CVDs among women with both PCOS and OSAHS than women with PCOS alone, it is challenging to exclude the influence of obesity in this correlation based on available studies. However, in the general population, OSAHS is also correlated with heightened risks of CVDs, hypertension, and mortality (71–73). Endothelial dysfunction, increased IR, intermittent hypoxia, inflammation, sympathetic overactivity, and OS are all factors that could contribute to the emergence of cardiometabolic comorbidities in patients with OSAHS. Patel et al. (74) reported that high risk for OSAHS was an independent predictor for postoperative atrial fibrillation in patients undergoing coronary artery bypass surgery. Some researchers suggested that genetically predicted OSAHS is a potential causal risk factor for heart failure based on a large-scale population of Mendelian randomization study (75). Notably, Tasali et al. (76) treated women affected by both PCOS and OSAHS with CPAP for 8 consecutive weeks. Following this treatment, reductions were observed in diastolic pressure and morning and evening levels of norepinephrine in these patients. OSAHS may represent a significant variable risk factor in the management of women with PCOS because PCOS is correlated with an elevated risk of CVDs (77). Gao et al. (78) found that PCOS could affect cardiovascular health in women, and promote myocardial macrophage accumulation and post-myocardial infarction cardiac remodeling because of augmented splenic myelopoiesis. OSAHS and PCOS also share common pathophysiological mechanisms leading to atherosclerosis. Considering that the coexistence of OSAHS and PCOS is an independent and cumulative risk factor for cardiovascular mortality, more so than the two diseases separately, clinicians and healthcare professionals should be aware of and screen for OSAHS in patients with PCOS.

Although excess androgen is an attribute of PCOS, its involvement in the pathogenesis of OSAHS in women affected by PCOS remains controversial. Some studies have failed to establish a significant correlation between androgen levels and the severity of OSAHS (37, 79). In this study, nine studies were collectively analyzed, revealing that the levels of FT in the PCOS + OSAHS group did not exhibit substantial differences from those of the PCOS group. However, it was observed that the FT levels in the PCOS + OSAHS group were higher than those of the PCOS group. As per the free hormone hypothesis, only FT is available to interact with the androgen receptor, establishing it as the primary indicator of testosterone bioactivity (80). Furthermore, a study showed that OSAHS severity in PCOS was significantly and positively correlated with FT, even after adjusting for obesity factors (43). The modified FG Score is commonly used to assess and quantify hair growth in nine androgen-dependent regions of the body, encompassing the arms, chest, chin, lower abdomen, lower back, upper abdomen, upper back, thighs, and upper lip (81). The present study demonstrated higher FG scores in women with both PCOS and OSAHS along with lower SHBG levels in these patients. Based on the available data, a hypothesis was drawn that hyperandrogenism in women with PCOS may influence the risk of developing OSAHS. The involvement of Androgen in the pathogenesis of OSAHS is believed to occur through the mechanism of excessive androgen levels, which may be driven by increasing pharyngeal soft tissue

deposition, thereby affecting respiration and increasing the risk of OSAHS. Moreover, excessive androgen is associated with impaired sensitivity and responsiveness of ventilatory chemoreceptors, potentially contributing to the higher morbidity of OSAHS in men compared to women (82, 83).

The meta-analysis suggested that IR was stronger in women with both PCOS and OSAHS than in women suffering from PCOS alone. The substantial variations in BMI observed between these two groups in the incorporated studies pose challenges in excluding obesity as a confounding factor in this correlation, even with statistical adjustments made for BMI in some of these studies (37). However, research conducted on the general population has also indicated a correlation between OSAHS and IR (84). This correlation between OSAHS and IR in women diagnosed with PCOS was further confirmed by an interventional study encompassing 19 women affected by PCOS, OSAHS, and obesity. They underwent an 8-week long CPAP treatment, resulting in a notable improvement in INS sensitivity (76). However, the reported results of these studies are based on small-sample self-controlled pre- and post-control experiments. Additionally, the risk of developing type 2 diabetes is reported to be five times higher in women with PCOS than in healthy women (85). OSAHS is additionally recognized as an independent risk factor for developing type 2 diabetes in a general population study (86). Therefore, further investigation is warranted to determine whether the primary cause of the elevated risk of type 2 diabetes development is PCOS or OSAHS. We can only hypothesize that IR is more pronounced in women affected by PCOS in the presence of significant OSAHS. However, this hypothesis needs well-conducted large cohort and interventional studies to evaluate the morbidity of type 2 diabetes and the effect of CPAP treatment on INS sensitivity and glucose metabolism in women affected by both PCOS and OSAHS.

There is a lack of studies investigating the effect of OSAHS on fertility outcomes in women diagnosed with PCOS. Since PCOS is the leading cause of anovulatory infertility (87) and OSAHS is very prevalent in women affected by both PCOS and obesity, it becomes crucial to detect whether OSAHS exerts an influence on fertility in women diagnosed with PCOS. Furthermore, there is also a lack of research examining the impact of OSAHS on mental health, depression, or anxiety in women affected by PCOS. Since both OSAHS and PCOS are independently correlated with impaired quality of life and low mood, OSAHS may exert an influence on the mental health of women with PCOS. Therefore, targeted research specifically in this domain is warranted.

Another crucial aspect of research that lacks data is race and its effect on the interaction of PCOS and OSAHS. The present study highlights a significant contrast in the morbidity of OSAHS between Asian and Caucasian individuals with PCOS, which is related to racial differences in craniofacial anatomy, fat distribution, and low arousal thresholds (88, 89). It is important to note that various facets of the clinical and metabolic profile of PCOS, such as IR, hypertrichosis, obesity, risk of type 2 diabetes, risk of CVDs, and potential response to fertility treatments, are affected by race (90,

91). Therefore, subsequent studies should analyze the metabolic and clinical characteristics of women patients from different racial backgrounds. This approach can identify high-risk populations and those particularly vulnerable to the effects of PCOS combined with OSAHS, potentially enhancing the effectiveness of interventions targeting OSAHS treatment.

CPAP is regarded as an efficient treatment for patients diagnosed with OSAHS. Observational studies have shown that patients who adhere to treatment (utilizing CPAP for >4 hours/night) experience improvements in nocturnal apnea and daytime somnolence, alongside improvements in IR, OS, and sympathetic overactivity (92, 93). Given that these mechanisms could potentially contribute to the etiology of PCOS, CPAP therapy might offer clinical benefits for women with both PCOS and OSAHS.

Notably, this study still has some limitations. Firstly, the systematic evaluation analyzed the association between OSAHS and metabolic profiles of women affected by PCOS, yet some of the included literature was at high risk of selection bias. Secondly, important confounding factors were not considered, which may lead to publication bias. Thirdly, most of the study populations were Caucasians and featured relatively small sample sizes. Thus, conclusive interpretations regarding the independent effects of OSAHS on metabolic outcomes in women affected by PCOS are difficult to make. In determining the impact of OSAHS on hyperandrogenism in women diagnosed with PCOS, the SMD analysis was applied due to the varying measures and units reported across studies. Since most studies did not report specific AHI values, it is not possible to interpret the impact of different severities of OSAHS on women with PCOS.

5 Conclusion

In conclusion, this meta-analysis suggests that adult women diagnosed with PCOS have a greater likelihood of suffering from OSAHS. The available results suggest that abdominal obesity, hyperandrogenism, and IR may be associated with the development of OSAHS in women affected by PCOS.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

Author contributions

JH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. XR: Conceptualization, Data curation, Formal analysis,

Funding acquisition, Methodology, Writing – original draft. JL: Conceptualization, Methodology, Software, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1418933/full#supplementary-material>

SUPPLEMENTARY FIGURE 1
Risk of bias of included studies.

SUPPLEMENTARY FIGURE 2
Funnel plot for prevalence of OSAHS in patients with PCOS.

SUPPLEMENTARY FIGURE 3
Effect of OSAHS on blood pressure in patients with PCOS. (A) systolic blood pressure, (B) diastolic blood pressure.

SUPPLEMENTARY FIGURE 4
Effect of OSAHS on Ferriman-Gallwey (FG) Score and Sex hormone-binding globulin (SHBG) in patients with PCOS. (A) FG, (B) SHBG.

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