SLEEPJ, 2018, 1–12

doi: 10.1093/sleep/zsy085
Advance Access publication Date: AADay AAMonth AAYear
Original Article

ORIGINAL ARTICLE

The association between obstructive sleep apnea and metabolic abnormalities in women with polycystic ovary syndrome: a systematic review and meta-analysis

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Abstract

Study Objectives: In this systematic review and meta-analysis, we aimed to examine the relationship between obstructive sleep apnea (OSA) and metabolic abnormalities in women with polycystic ovary syndrome (PCOS).

Methods: Electronic databases (Medline, Embase, Cinahl, PsycInfo, Scopus, Web of Science, Opengrey, and CENTRAL), conference abstracts, and reference lists of relevant articles were searched. No restriction was applied for language or publication status.

Results: Six studies involving 252 participants were included. Women with PCOS and OSA had significantly higher body mass index (mean difference [MD]: 6.01 kg/m^2, 95% confidence intervals [CI]: 4.69–7.33), waist circumference (MD: 10.93 cm, 95% CI: 8.03–13.83), insulin resistance, systolic and diastolic blood pressure, and worse lipids' profile and impaired glucose regulation compared with women with PCOS without OSA. Most studies did not adjust for weight in their between-groups analysis. Total and free testosterone levels were not significantly different between the two groups. The majority of studies were found to be at high risk of selection bias, did not account for important confounders, were conducted in one country (United States), and used different methodologies to assess testosterone levels (preventing a meta-analysis for this specific outcome).

Conclusions: OSA is associated with obesity and worse metabolic profiles in women with PCOS. However, whether the effects of OSA are independent of obesity remain unclear. As OSA is a treatable condition, research focused on the independent effects of OSA on key clinical outcomes in women with PCOS, including fertility, psychological health, type 2 diabetes, and cardiovascular risk, is lacking and needed.

PROSPERO registration number: CRD42016048587.

Statement of Significance

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is associated with significant comorbidities. Our systematic review and meta-analysis showed that women with PCOS and obstructive sleep apnea (OSA) are more obese and have a worse metabolic profile compared with women with PCOS without OSA. However, whether the effects of OSA are independent of obesity remain unclear. In particular, the independent effects of OSA on important clinical outcomes in women with PCOS, including fertility, type 2 diabetes, psychological health, quality of life, and cardiovascular disease, are yet to be investigated. Future studies need to assess the impact of OSA, and its treatment, on important clinical outcomes in women with PCOS.

Key words: polycystic ovary syndrome; obstructive sleep apnea; hyperandrogenism; obesity; insulin resistance

Submitted: 30 November, 2017; **Revised:** 28 January, 2018

Introduction

Obstructive sleep apnea (OSA) is a common medical condition that is highly prevalent in women with polycystic ovary syndrome (PCOS) and obesity [1]. OSA is characterized by recurrent episodes of upper airway closure, drop in oxygen levels, and sleep fragmentation, with subsequent increase in sympathetic activity, insulin resistance, oxidative stress, and abnormal gonadotropin releasing hormone (GnRH) secretion [2]. The same spectrum of hormonal and metabolic abnormalities is also commonly seen in PCOS and is thought to play a role in its aetiology [1]. This led some investigators to suggest that OSA may lead to a more severe form of PCOS in affected women [3].

PCOS is the most prevalent endocrine disorder in women of reproductive age [4, 5] and is associated with significant comorbidities, including subfertility [6], impaired quality of life (QoL) [7–9], and increased risk of type 2 diabetes [10] and cardiovascular disease (CVD) [11]. Hence, in this study, we aimed to conduct a systematic review and meta-analysis examining the relationship between OSA and metabolic abnormalities in women with PCOS. Moreover, apart from weight loss, there are limited safe and effective treatment options available for women with PCOS and obesity [12]. Continuous positive airway pressure (CPAP) has been shown to improve insulin resistance, reduce oxidative stress and inflammation, and improve QoL in patients with OSA [2]; hence, examining the impact of OSA on women with PCOS might allow identifying new treatment strategies.

Objectives

To examine the effect of OSA on clinical, metabolic, and psychological health in women with PCOS.

Methods

Our systematic review protocol was prospectively registered with PROSPERO: CRD42016048587 (http://www.crd.york.ac.uk/PROSPERO/), and herein, we report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [13, 14].

Selection criteria

We included any human study, observational or interventional, that included two groups of women with PCOS based on the presence or absence of OSA (namely, a PCOS group with OSA and a PCOS group without OSA) and reported any clinical, metabolic, or psychological outcomes or measures in these women.

Only studies that used cardiorespiratory monitoring devices (polysomnography or Level III devices) for the diagnosis of OSA were included, regardless of the cut-offs used to diagnose OSA. Level III devices are acceptable methods to diagnose OSA as detailed in the latest American Academy of Sleep Medicine (AASM) guidelines [15]. Level III devices were defined, as per AASM guidelines, as portable machines that could be used at home and record two respiratory variables (e.g. effort to breathe and airflow), oxygen saturation, and a cardiac variable (e.g. heart rate or electrocardiogram) [15].

Both studies published in peer-reviewed journals and conference abstracts were included.

Studies in both adolescent (postmenarchal) girls and adult (premenopausal and postmenopausal) women with PCOS were included (no age limit). Articles that examined women with PCOS were included, regardless of the diagnostic criteria used for PCOS diagnosis. Women with PCOS from any ethnicity were included.

Study outcomes

Differences between women with PCOS and OSA compared with women with PCOS without OSA in weight, body mass index (BMI), waist circumference, waist-to-hip-ratio (WHR), IR, impaired glucose regulation, free testosterone, total testosterone, sex hormone–binding globulin (SHBG), lipids profile, blood pressure, hirsutism, QoL, psychological health, menstrual period regularity, previous diagnosis of subfertility, type 2 diabetes mellitus (T2DM), and CVD prevalence.

Search strategy

The initial search for relevant articles was conducted on April 11, 2016 and was updated on February 7, 2017. The search was not restricted by language or publication status. We searched the following electronic databases: Medline (Ebsco), Embase (Ovid), Cinahl (Ebsco), PsycInfo (ProQuest), Scopus, Web of Science, Opengrey, and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we also searched major respiratory and endocrinology conferences for relevant abstracts. We also manually searched the references of relevant papers and review articles. The detailed search strategy for each database is provided in Supplementary Appendix 1.

Selection of studies

The screening of the titles and abstracts was conducted independently by two authors (H.K. and I.K.) and we discarded studies that were not relevant and did not meet the systematic review selection criteria. Full text articles of all potentially relevant articles were reviewed. Any disagreements between the two authors were resolved by consensus and discussion with a third author (O.U.), if necessary.

Data extraction and management

Data from included studies were extracted by two authors (H.K. and I.K.) independently. Where studies had multiple publications, the main study report was used as the reference and additional details supplied from secondary papers. Review authors corresponded with study investigators in order to resolve any data queries, as required. For each study that met the selection criteria, details were extracted on study design, study population characteristics, and prevalence estimates. Any disagreements were resolved by consensus and discussion with a third author (O.U.), if necessary.

Risk of bias

The risk of bias of included studies was assessed by two authors (H.K. and I.K.) independently and any disagreements were

resolved by consensus and discussion with a third author (O.U.), if necessary. The following domains of risk of bias were assessed "selection bias (sample population), selection bias (confounding variables), performance bias (measurement of exposure), performance bias (analytical methods to control for bias) and other bias," using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) [16] to appraise the risk of bias for each included study. Each domain was classified as high risk, low risk, or unclear.

Unit of analysis

The following definitions were used: fertility (fecundity [number of children], needing assisted fertility, infertility [failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse], and number of miscarriages); IR (homeostasis model for insulin resistance [HOMA-IR]); impaired glucose regulation (IGT: fasting plasma glucose 6.1–6.9 mmol/liter, 2 hr plasma glucose 7.8–11 mmol/liter after a standard oral glucose tolerance test [OGTT], or haemoglobin A1C [HbA1C] 42–47 mmol/mol); T2DM (fasting plasma glucose ≥7.0 mmol/liter, 2 hr plasma glucose ≥11.1 mmol/liter after a standard OGTT, or HbA1C ≥48 mmol/mol) [17, 18]; period regularity (number of periods per year); blood pressure (mm Hg); hirsutism (modified Ferriman–Gallwey score); weight (kg); BMI (kg/m^2); waist circumference (cm); QoL (using any validated QoL questionnaire); depression (either using questionnaires or clinical, for example taking medications for depression); anxiety (using questionnaires); and metabolic syndrome (using any internationally recognized criteria). For biochemical and hormonal measurements, SI units were used and conversion to SI units was performed, if needed. Data are

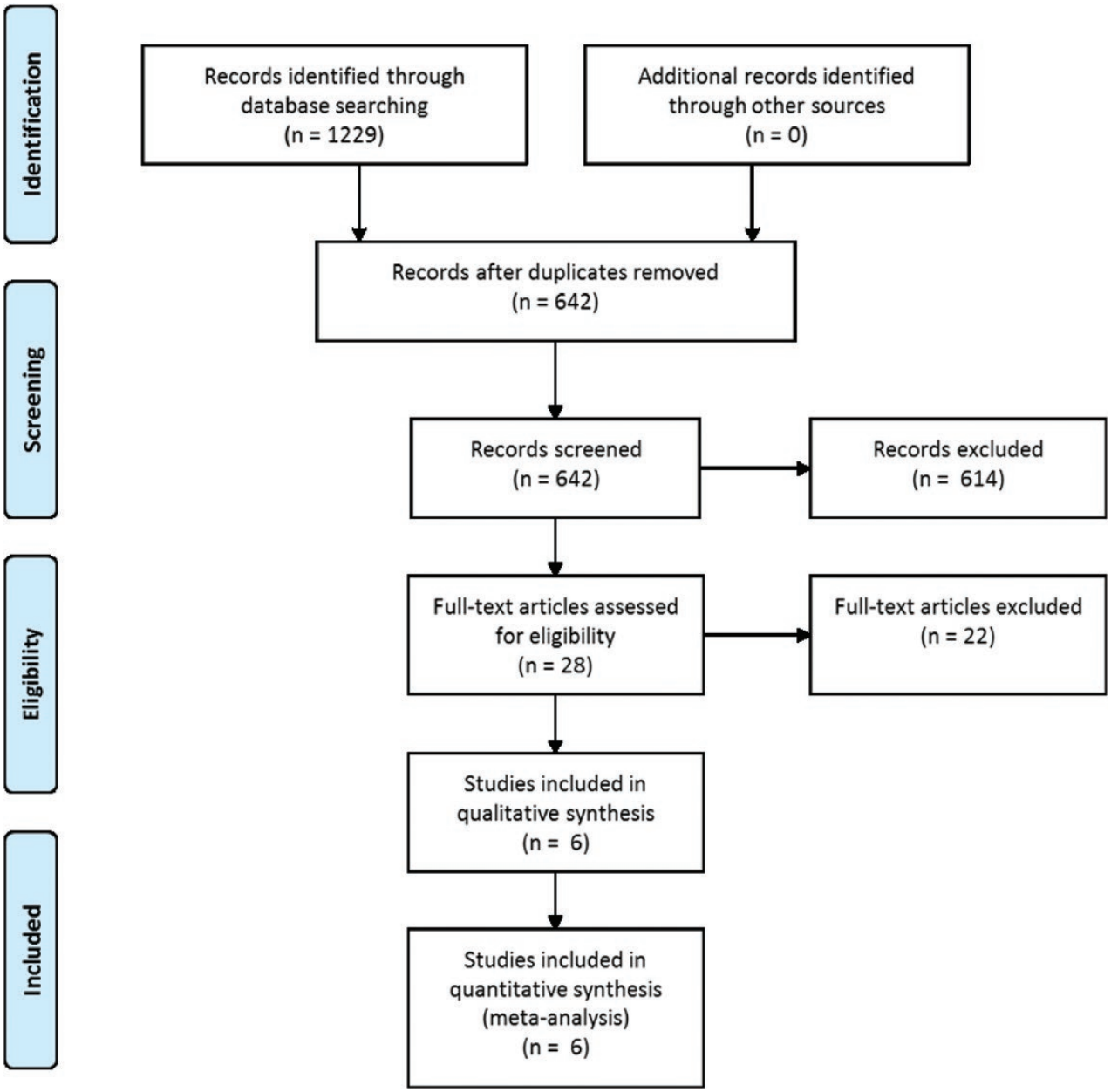

Figure 1. PRISMA flow diagram.

presented as mean ± standard deviation (SD) and conversion from 95% confidence intervals (CI) and standard error of the mean (SEM) values to SD was performed, if needed, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org/).

Data synthesis

The results of the studies which were found to be statistically homogeneous were pooled using the fixed-effect meta-analysis. Otherwise, we used random-effects meta-analysis. For continuous outcomes that were measured on the same scale, we combined the mean differences to calculate the (weighted) mean difference and SD. Between studies, heterogeneity was assessed using Higgins's I^2 statistics and a value greater than 50% was considered to be indicative of moderate heterogeneity [19, 20]. All analyses were conducted in Stata version 14 for Windows (Stata Corp, College Station, Texas).

Results

Search results and study characteristics

A PRISMA flow diagram of the search results is shown in Figure 1. The main characteristics of the six included and 22 excluded studies are summarized in Table 1 and Supplementary Table S1, respectively. Of the six included studies: (1) four studies included women with obesity; one study included overweight women; and one study did not report the exact BMI values of the participants (although 22 participants were obese and 9 were lean); (2) one study included adolescent girls, three studies included mixed populations (adolescents and adults), and two studies included adult women with PCOS (Table 1). Of note, the majority of the included studies (four out of six) were conducted in one country, namely, in the United States. All studies used polysomnography to diagnose OSA. One study was a retrospective chart review study [21].

Risk of bias of included studies

The risk of bias assessment for each study is summarized in Figure 2. The selection bias due to inadequate selection of participants was high in three studies and unclear in the remaining three. The selection bias caused by inadequate confirmation and consideration of confounding variable(s) was high in all six studies. The performance bias due to inadequate measurement of exposure was low in four studies and high two studies. The detection bias due to inadequate blinding of outcome assessments was high in one study and unclear in the remaining five. The attrition bias due to inadequate handling of incomplete outcome data was low in three studies and unclear in three studies. The reporting bias due to selective reporting was low in five studies and high only in one study.

Table 1. Characteristics of included studies (ordered alphabetically based on the first author's surname)

							Age	BMI	PCOS diagnosis	OSA diagnosis		Age (per group)			AHI (per group)		
Study	Country	Study design	Publication type	Population	N	Ethnicity	(yr)	(Kg/m^2)	Criteria	Method	events/h	PCOS OSA	PCOS no OSA	P-value	PCOS OSA	PCOS no OSA	P-value
Chatterjee et al. 2014 [23]	India	CS	J. Article	Adults	50	South Asian	NR	28 ± 3.0	Rotterdam	PSG	RDI ≥5 + symptoms or RDI >15	NR	NR		NR	NR	
Kenigsberg et al. 2015 [22]	USA	CS	C. Abstract	Mixed (13–21 yr)	31	NR	16.7 ± 2.4	NR	Rotterdam	PSG	AHI>2	NR	NR		NR	NR	
Nandalike et al. 2012 [21]	USA	CS	J. Article	Adolescents	28	17.9% AA, 14.3% Hispanic, 14.3% White, 53.6% Mixed	16.8 ± 1.9	44.8 ± 8.8	Rotterdam*	PSG	AHI > 5 or AI > 1	16.8 ± 2.1	16.6 ± 1.7	0.8	NR	NR	
Tasali et al. 2008 [25]	USA	CS	J. Article	Adults	52	62% AA or Hispanic	29.7 ± 5.1	39.2 ± 7.2	NIH	PSG	AHI > 5	31.6 ± 5.4	27.3 ± 3.4	0.002	19.4 ± 10.8	2.0 ± 1.9	< 0.0001
Tock et al. 2014 [28]	Brazil	CS	J. Article	Mixed (16–45 yr)	38	NR	28.3 ± 6.8	32.9 ± 7.7	Rotterdam	PSG	AHI ≥5	28.3 ± 5	28.4 ± 7.5	0.968	23.7 ± 22.3	1.3 ± 1.5	< 0.001
Vgontzas et al. 2001 [24]	USA	CS	J. Article	Mixed (16–45 yr)	53	NR	30.4 ± 6.6	38.7 ± 8.0	NIH	PSG	AHI ≥ 10 + symptoms	34 ± 8.4	29.6 ± 5.3	NS	NR	NR	

Data presented as mean ± standard deviation.

AA = African–American; AHI = apnea–hypopnea index; AI = apnea index; C = abstract, conference abstract; CS = cross-sectional study; h = hour; J. Article = journal article; N = sample size; NIH = National Institutes of Health; NR = not reported; NS = not significant; PSG = polysomnography; RDI = respiratory distress index; yr = years.

*All participants also fulfilled the NIH criteria for PCOS diagnosis in addition to the 2003 Rotterdam criteria. All the studies were in women of reproductive age/premenopausal.

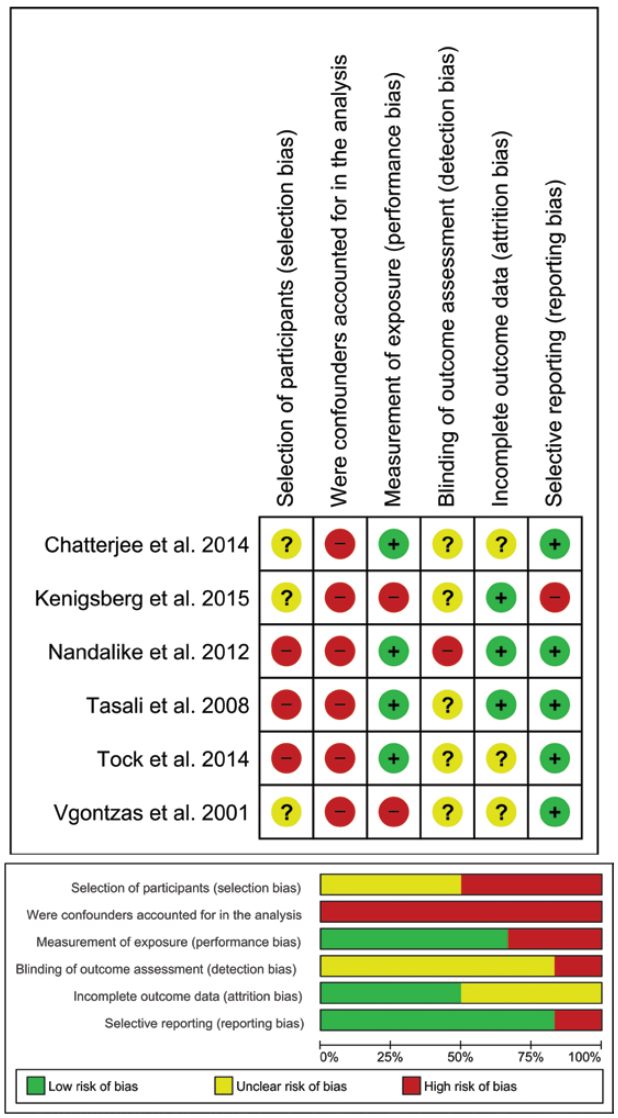

Figure 2. Risk of bias of included studies.

Effect of OSA in women with PCOS on clinical outcomes

Anthropometric measures

Women with PCOS and OSA had significantly higher BMI (mean difference [MD]: 6.01 kg/m^2, 95% CI: 4.69–7.33; I^2 = 0%; four studies; 193 participants), waist circumference (MD: 10.93 cm, 95% CI: 8.03–13.83; I^2 = 13%; two studies; 88 participants), and WHR (MD: 0.10, 95% CI: 0.03–0.17; one study; 38 participants) (Figure 3). In the subgroup of adolescent girls with PCOS and obesity, there was no significant difference in BMI-Z scores between girls with OSA compared with those without OSA, Figure 3. None of the nine lean adolescent girls with PCOS in the study by Kenigsberg et al. had OSA [22].

Blood pressure

Two studies reported the blood pressure effect of OSA in women with PCOS (Figure 4). The pooled association showed that on average the systolic blood pressure was significantly higher by 10.8 mm Hg in women with PCOS and OSA compared with women with PCOS without OSA (95% CI: 6.21–15.39; I^2 = 0%; two studies; 78 participants). Similarly, the diastolic blood pressure was significantly higher by 4.63 mm Hg in women with PCOS and OSA than in women with PCOS without OSA (95% CI: 1.06–8.21; I^2 = 0%; two studies; 78 participants). Neither study adjusted for BMI in their analysis. Although participants in the study by Nandalike et al. [21] had similar age, no age was reported for participants in the study by Chatterjee et al. [23].

Hirsutism and reproductive outcomes

One included study measured the Ferriman–Gallwey score as a marker of hirsutism (Figure 5) and reported that this score was higher in women with PCOS and OSA compared with those without OSA (MD: 1.82, 95% CI: 0.30–3.34; 50 participants), but this difference was not adjusted for BMI which was higher in the PCOS OSA group.

None of the included studies reported outcomes relating to the regularity of menstrual periods or to fertility in women with PCOS and OSA.

Effect of OSA in women with PCOS on hormonal/metabolic outcomes

Sex hormone binding globulin

Two studies reported circulating levels of SHBG. SHBG levels tended to be lower in women with PCOS and OSA than in those without OSA, albeit this trend did not reach statistical significance when these two studies were pooled (MD: –7.73, 95% CI: –15.90–0.45, I^2 = 67%; 90 participants) (Figure 5).

Total and free testosterone plasma levels

Due to the different methods and units used to measure and report testosterone plasma levels, respectively, it was not possible to combine the reported total or free testosterone results between studies. In addition, in certain studies [24, 25], the reported testosterone levels were outside the range expected for women with PCOS. Thus, we adopted a descriptive analysis for this outcome which is presented in Table 2. As such, in each of the four studies that reported total testosterone levels, these were not significantly different between women with PCOS and OSA compared with women with PCOS without OSA. Similarly, free testosterone levels were not significantly different between these two groups in four studies reporting this outcome, whereas one study reported higher free testosterone levels in women with PCOS and OSA compared with women with PCOS without OSA (Table 2).

Glucose metabolism and insulin resistance measures

Women with PCOS and OSA had significantly higher as follows: (1) fasting plasma glucose levels (MD: 0.45 mmol/liter, 95% CI: 0.21–0.69; I^2 = 17%; five studies; 221 participants); (2) 2 hr plasma glucose on OGTT (MD: 1.39 mmol/liter, 95% CI: 0.67–2.11; I^2 = 0%; two studies; 90 participants); (3) HOMA-IR (MD: 2.23, 95% CI: 1.41–3.06; I^2 = 0%; four studies; 168 participants); and (4) fasting plasma insulin levels (MD: 10.03, 95% CI: 3.20–16.85; I^2 = 78%; four studies; 183 participants) (Figure 6). Only two studies [24, 25] adjusted for BMI in their between-group analysis. In the study by Kenigsberg et al. [22], there was no significant difference in insulin resistance, measured using hyperinsulinaemic euglycaemic

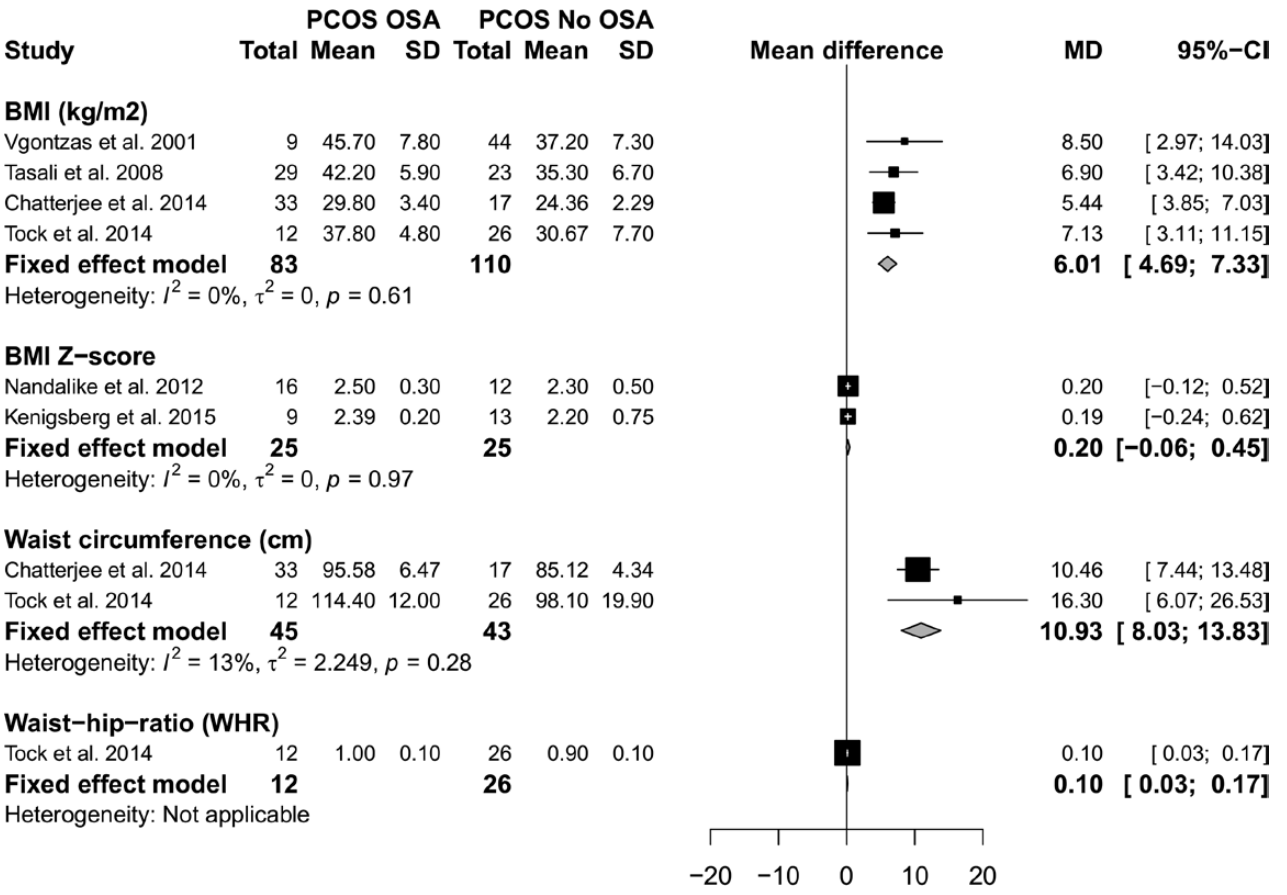

Figure 3. Effect of OSA on anthropometric measures in women with PCOS [BMI in kg/m^2) for adult women with PCOS; BMI Z-score for the subgroup of adolescent girls with obesity and PCOS; waist circumference; WHR; women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

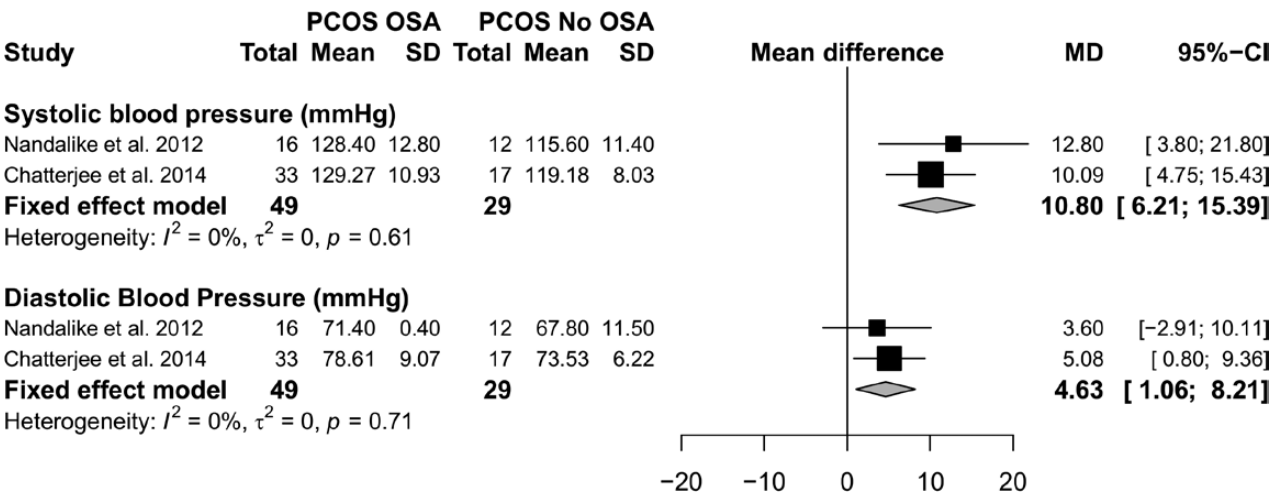

Figure 4. Effect of OSA on systolic and diastolic blood pressure in women with PCOS [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

clamps, in the subgroup analysis between girls with PCOS and obesity with and without OSA.

Blood lipids

Women with PCOS and OSA had significantly higher plasma levels of the following: (1) total cholesterol (MD: 0.74 mmol/liter, 95% CI: 0.30–1.18; I^2 = 0%; two studies; 88 participants); (2) LDL cholesterol (MD: 0.52 mmol/liter, 95% CI: 0.18–0.86; I^2 = 25%; two studies; 88 participants); and (3) triglycerides (MD: 0.35 mmol/liter, 95% CI: 0.18–0.52; I^2 = 0%; three studies; 116 participants). Contrary, HDL cholesterol plasma levels were significantly lower in women with PCOS and OSA compared with those without OSA (MD: –0.26 mmol/liter, 95% CI: –0.36 to –0.16, I^2 = 0%; three studies; 116 participants) (Figure 7). None

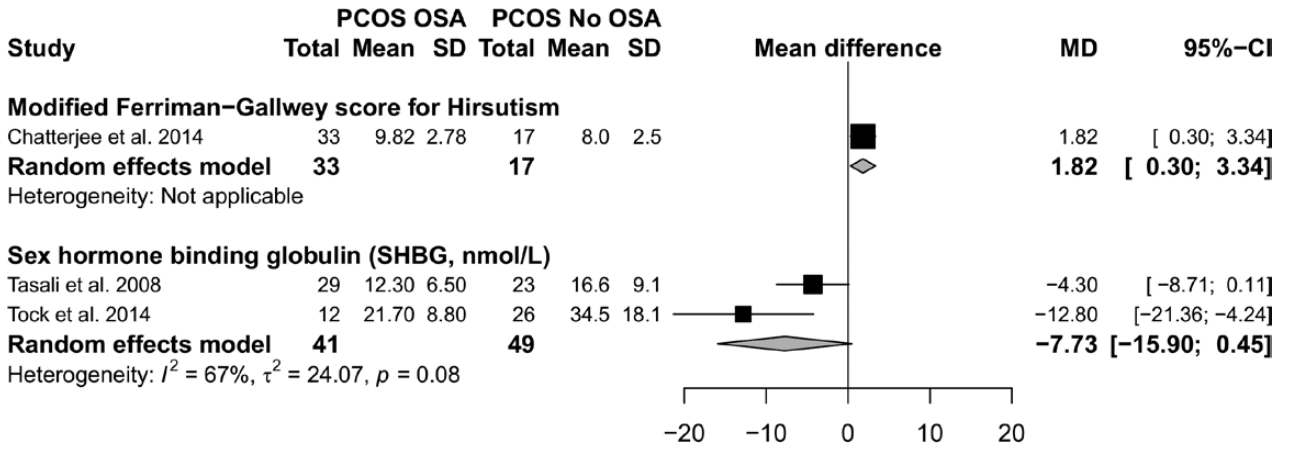

Figure 5. Effect of OSA on hirsutism (based on the modified Ferriman–Gallwey score) and sex hormone binding globulin in women with PCOS [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

of the studies adjusted for BMI in their between-group data analysis.

Metabolic syndrome

Women with PCOS and OSA had a significantly higher metabolic syndrome incidence rate compared with women with PCOS without OSA (rate difference = 37.2%, 95% CI: 19.3–55.1; I^2 = 0%; two studies; 78 participants) (Figure 8).

Effect of OSA in women with PCOS on psychological outcomes

None of the included studies reported on QoL and psychological outcomes.

Discussion

This is the first systematic review and meta-analysis to examine the association of OSA with metabolic abnormalities in women with PCOS. Our data showed that women with PCOS and OSA have more central and generalized obesity and exhibit a more severe metabolic profile compared with women with PCOS without OSA. However, the relationship between OSA and the clinical features of PCOS (such as hirsutism and menstrual irregularities), and CVD, QoL, and fertility outcomes remain unclear.

Obesity is a major risk factor for OSA [26]. Thus, it is not surprising that women with PCOS and OSA were more obese compared with those without OSA in our analysis. This excess adiposity potentially places these women at higher risk of T2DM and CVD, but whether this increased risk is due to excess adiposity or OSA has not been studied yet. It is worth noting that several studies suggested that women with PCOS have a higher prevalence of OSA compared with women without PCOS [21, 24, 25], but differences in studies populations (e.g. obesity and ethnicity) or methods of participants' recruitment (e.g. community and specialized clinics) have generally not been adequately accounted for.

The severity of hirsutism in women with PCOS and OSA was assessed only in one study using the Ferriman–Gallwey score. Although the score was higher when OSA was present, the difference between the two groups was small (MD: 1.82) and, hence, is of doubtful clinical significance. It was also not clear if the assessor was blinded to the OSA status of study participants.

The majority of studies did not show a statistically significant difference in circulating total or free testosterone levels between women with PCOS and OSA compared with those without OSA. There was a trend for women with PCOS and OSA to

Table 2. The relationship between OSA and total and free testosterone plasma levels in women with PCOS [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)]

	Number of participants	Total testosterone			Free testosterone		
Study	PCOS OSA/PCOS no OSA	PCOS OSA	PCOS no OSA	P-value	PCOS OSA	PCOS no OSA	P-value
Vgontzas et al. 2001 [24]	9/44	276.2 ± 73.1 nmol/liter	284.8 ± 26.4 nmol/liter	NS	124.8 ± 44.52 nmol/liter	118.1 ± 16.54 nmol/liter	NS
Tasali et al. 2008 [25]	29/23	67.9 ± 4.3 pg/mL	76.3 ± 6.4 pg/mL	0.19	20.6 ± 7 pg/mL	21.3 ± 7.2 pg/mL	0.32
Nandalike et al. 2012 [21]	16/12	54.2 ± 30.1 ng/dL	51 ± 23.3 ng/dL	0.2	9.7 ± 4.2 pg/mL	7.6 ± 4.5 pg/mL	0.3
Tock et al. 2014 [28]	12/26	78.6 ± 42.4 ng/dL	55.4 ± 31.3 ng/dL	0.066	19 ± 13 pg/mL	11 ± 8 pg/mL	0.014
Chatterjee et al. 2014 [23]	33/17	NA	NA		3.43 ± 3.78 ng/mL	2.01 ± 2.47 ng/mL	0.167

Data presented as mean ± standard deviation.
NA = not available; NS = not significant.

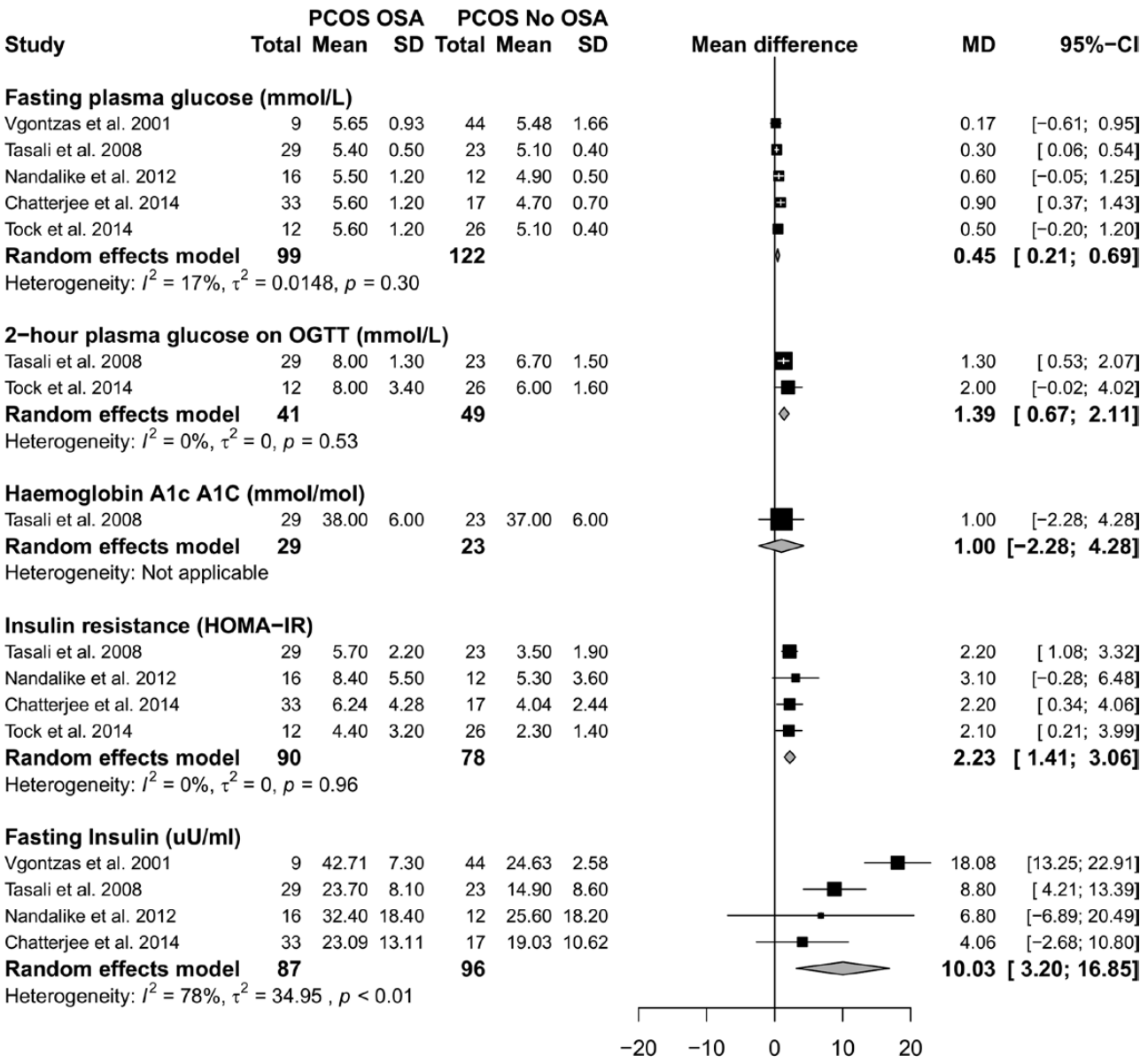

Figure 6. Effect of OSA on measures of glucose metabolism and insulin resistance in women with PCOS [fasting plasma glucose; 2 hr plasma glucose after a standard oral glucose tolerance test (OGTT); haemoglobin A1C (HbA1C); homeostasis model for insulin resistance (HOMA-IR); fasting insulin plasma levels; women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

have lower SHBG compared with women without OSA, but this did not reach statistical significance. Overall, based on the existing studies, our findings suggest that the role of hyperandrogenism in the development of OSA in women with PCOS is probably limited. Of note, this finding challenges previous presumptions that hyperandrogenism is a key factor in the increased risk of OSA in women with PCOS [27, 28]. Hyperandrogenism is thought to be an important factor in the increased prevalence of OSA in men compared with women, through mechanisms including increased upper airway collapsibility and impaired sensitivity and responsiveness of the ventilatory chemoreceptors [29]. However, the level of hyperandrogenism in women with PCOS is much lower compared with that in men which may explain this apparent discrepancy [1].

No study has examined the effects of OSA on fertility outcomes in women with PCOS. As PCOS is the most common cause of ovulatory dysfunction [30], and OSA is highly prevalent in obese women with PCOS [1], it is important to examine whether OSA has an impact on fertility in women with PCOS.

Our meta-analysis showed that women with PCOS and OSA were more insulin resistant compared with women with PCOS without OSA. The large difference in BMI between these two groups (MD: 6.0 kg/m^2) in the included studies makes it difficult to exclude obesity as a confounding factor in this association, despite the statistical adjustment for BMI in some of these studies [25]. However, studies in the general population also suggest an association between OSA and IR [31–33]. This association between OSA and IR in women with PCOS is further supported by an interventional study involving 19 obese women with PCOS and OSA [age (±SEM) 31.2 ± 1.2 years, BMI 46.4 ± 2.4 kg/m^2] who underwent CPAP treatment for 8 weeks that resulted in significant improvement in insulin sensitivity

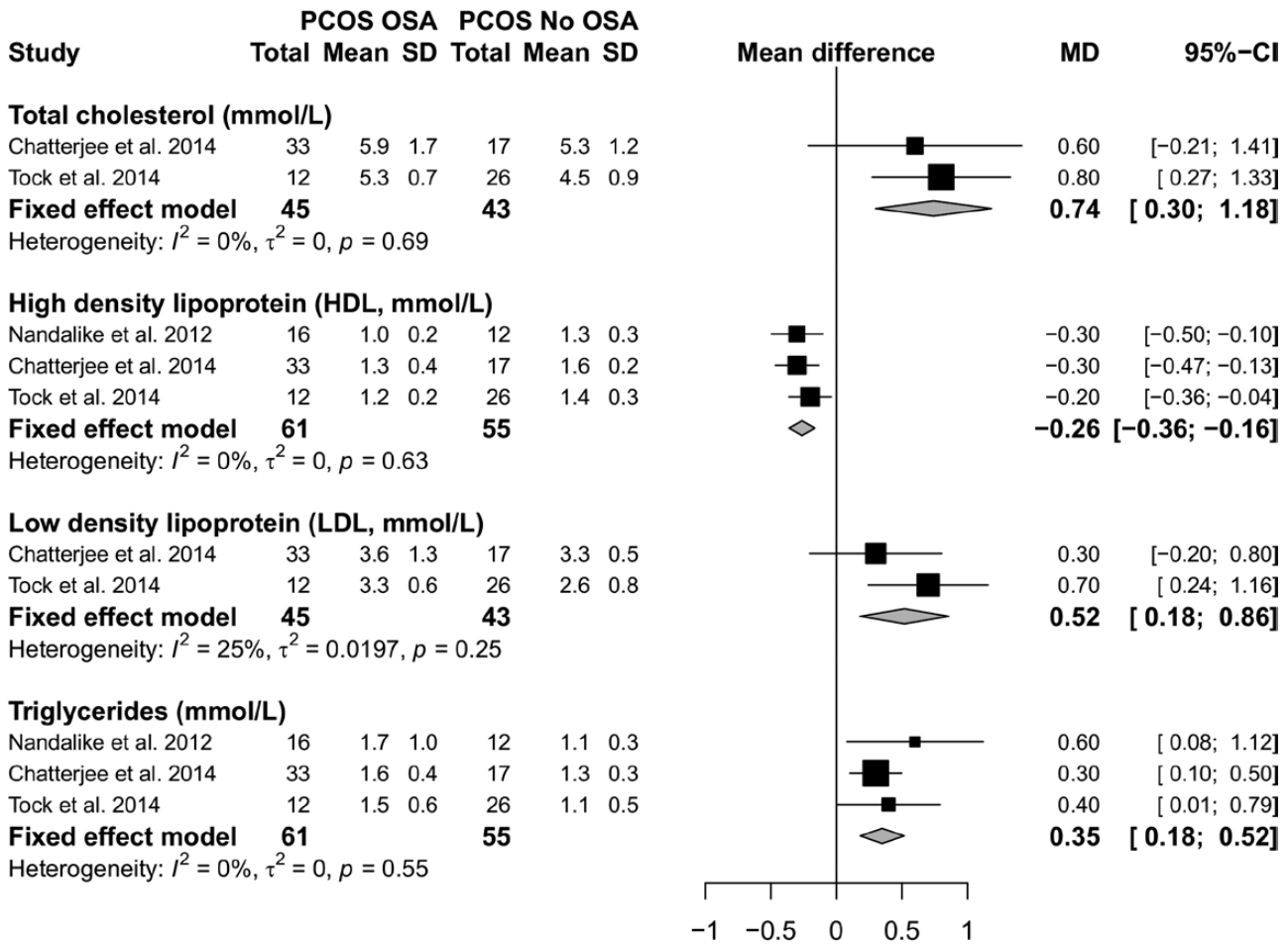

Figure 7. Effect of OSA on blood lipids in women with PCOS [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

[34]. However, the reported results of this study were based on "per protocol" analysis involving a small sample (n = 9) without a control group. Moreover, as women with PCOS have a 4-fold higher risk of T2DM compared with weight-matched controls [10], and OSA is an independent risk factor for the development of T2DM in general population studies [2, 33], it is possible that part of this increased T2DM risk is secondary to undiagnosed OSA which was not accounted for. Well conducted, large, cohort, and interventional studies are needed to assess the incidence of T2DM and the impact of CPAP therapy on insulin sensitivity and glucose metabolism in women with PCOS and OSA.

Our meta-analysis also showed that women with PCOS and OSA had higher blood pressure, more atherogenic plasma lipids profile, and higher incidence rates of the metabolic syndrome compared with those without OSA. Although this suggests that women with PCOS and OSA represent a group of patients at higher CVD risk compared with women with PCOS without OSA, it is difficult to exclude the role of obesity in this association from the conducted studies. However, in the general population, OSA has also been associated with increased risk of

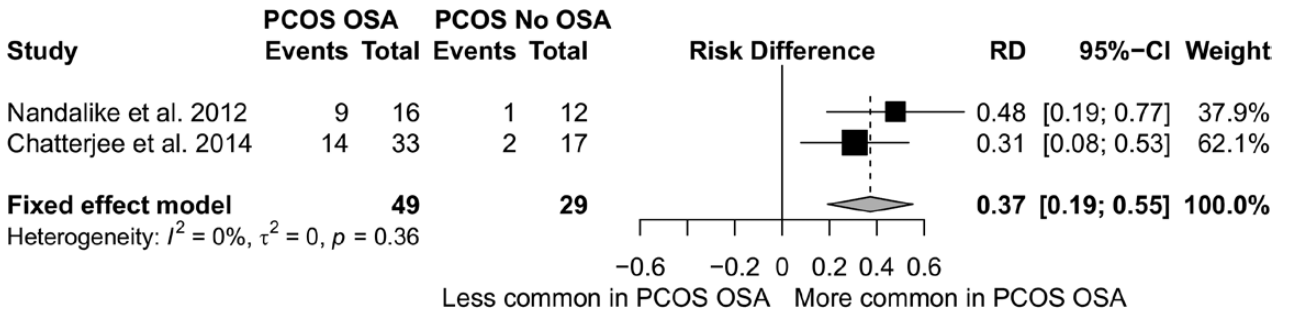

Figure 8. Effect of OSA on the incidence of metabolic syndrome in women with PCOS [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)]. The study by Nandalike et al. included adolescent girls with PCOS and the diagnosis of the metabolic syndrome was based on the Weiss criteria [46]. The study by Chatterjee et al. included adult women with PCOS and the metabolic syndrome was diagnosed based on the National Cholesterol Education Program, Adult Treatment Panel (NCEP ACT III) criteria [47].

hypertension, CVD, and mortality [2, 35]. Intermittent hypoxia, endothelial dysfunction, increased IR, sympathetic overactivity, inflammation, and oxidative stress may play a role in the development of cardiometabolic comorbidities in OSA [36, 37]. Notably, in the aforementioned interventional study by Tasali et al. [34], the 8-week CPAP treatment in women with PCOS and OSA was also associated with a reduction in diastolic blood pressure (by approximately 2.3 mm Hg) and a reduction in day-time and night-time norepinephrine levels. As PCOS is associated with increased CVD risk [11], OSA may represent an important modifiable risk factor in the management of these patients.

No study has examined the effects of OSA on psychological health, anxiety, or depression in women with PCOS. As both OSA [38–40] and PCOS [7–9] are independently associated with low mood and impaired QoL, an effect for OSA on psychological health in women with PCOS is possible. Thus, targeted research is also needed in this area.

Another important area for research where there is a lack of data is ethnicity and its influence on PCOS and OSA interaction. Clinical studies suggest that the prevalence and pathophysiology of OSA are influenced by ethnicity, through mechanisms including body fat distribution, craniofacial anatomy, and low arousal threshold [41, 42]. Of note, multiple aspects of PCOS metabolic and clinical features, including obesity, IR, hirsutism, T2DM risk, CVD risk markers, oligomenorrhea, and possibly response to fertility treatment, are also influenced by ethnicity [43, 44]. Subsequently, research focused on the prevalence and impact of OSA on women with PCOS from different ethnic backgrounds is needed to help identify high risk populations and those who are affected most by the condition and, thus, may potentially benefit more from intervention(s) to treat OSA.

CPAP is an effective treatment for patients with OSA and observational studies suggest that patients who are compliant with treatment (using CPAP > 4 hr/night) not only notice improvement in night-time apneas and daytime sleepiness, but also in IR, oxidative stress and sympathetic overactivity [31, 34, 45]. As these mechanisms may also play a role in the aetiology of PCOS [1], CPAP treatment in women with PCOS and OSA may have a favorable impact on the clinical manifestations of the syndrome, including hypertension, increased risk of T2DM and CVD, poor psychological health, and subfertility.

Study Limitations

Our systematic review has identified a small number of studies that examined the relationship between OSA and metabolic features in women with PCOS, and the majority of them were found to be at high risk of selection bias, did not account for important confounding factors, were conducted in one country (i.e. in the United States), and had relatively small sample sizes. Subsequently, it is difficult to draw firm conclusions on the independent effects of OSA on metabolic outcomes in women with PCOS. Narrative synthesis, rather than meta-analysis, was performed when assessing the effects of OSA on hyperandrogenism in women with PCOS due to the different measurement methods and units reported. It was not possible to account for the severity of OSA as the majority of studies did not report AHI (Table 1); although when AHI was reported, the study population had moderate OSA.

The following deviation from our original protocol should also be noted: for the included studies, we accepted the study authors' own definition of OSA, and PCOS, regardless of the diagnostic criteria used. However, we do not feel that including these studies has affected our results as the AHI cut-off to diagnose OSA is different in children from that in adults; all the studies included have used polysomnography to diagnose OSA, and all have used the NIH or the Rotterdam criteria to diagnose PCOS (Table 1).

Study Strengths

This is the first systematic review to examine the effects of OSA in women with PCOS. We have followed internationally recognized recommendations in conducting and reporting this systematic review and meta-analysis. Our literature search was broad, in terms of the number of different sources/databases searched, and it was not restricted by publication type or year, language, or study design.

Conclusions

OSA is associated with worse clinical and metabolic profiles in women with PCOS, but whether this is independent of obesity remains unclear. The link between OSA and hyperandrogenism in women with PCOS is probably small. Large, well conducted, observational, and interventional studies are needed to examine the independent effect of OSA in women with PCOS. As OSA is highly prevalent and a treatable condition, research focused on OSA and important clinical outcomes in women with PCOS, including fertility, psychological health, CVD, and T2DM risk, is lacking and needed.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Authors' Contribution

H.K., I.K., O.U., A.M., P.W., A.A.T, H.S.R. contributed to the study design. A.B. and S.J. designed search strategies and performed literature search. H.K. and I.K. selected studies, extracted data, and assessed risk of bias. O.U. performed data analyses. H.K., I.K., O.U., A.M., A.A.T., and H.S.R. contributed to data interpretation. H.K. wrote first draft of report. All authors critically reviewed the paper and approved the final version of the manuscript.

Notes

Conflict of interest statement. The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the paper reported. No funding was received for doing this work. Dr. Abd A. Tahrani is a Clinician Scientist supported by the National Institute for Health Research (NIHR). Dr. Olalekan Uthman is supported by the National Institute of Health Research using Official Development Assistance (ODA) funding. NIHR Clinical Lectureship supported Dr. Hassan Kahal. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

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