Title: The association between Obstructive Sleep Apnoea and metabolic abnormalities in women with Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis.

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Short title: OSA and PCOS relationship

Abstract

Study Objectives

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

Methods

Electronic databases (Medline, Embase, Cinahl, PsycInfo, Scopus, Web of Science, Opengrey, 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, as well as worse lipids' profile and impaired glucose regulation compared to 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 (USA); 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.

Key words: Polycystic ovary syndrome; PCOS; Obstructive Sleep Apnoea; OSA; Hyperandrogenism; Obesity; Insulin Resistance.

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 apnoea (OSA) are more obese and have a worse metabolic profile compared to 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.

1. Introduction

Obstructive sleep apnoea (OSA) is a common medical condition that is highly prevalent in women with polycystic ovary syndrome (PCOS) and obesity [1]. OSA is characterised 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 are also commonly seen in PCOS and are 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 quality of life in patients with OSA [2]; hence examining the impact of OSA in women with PCOS might allow identifying new treatment strategies.

2. Objectives

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

3. 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].

3.1 Selection criteria

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

3.2 Study outcomes

Differences between women with PCOS and OSA compared to 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, T2DM and CVD prevalence.

3.3 Search strategy

The initial search for relevant articles was conducted on the 11th of April 2016 and was updated on the 7th of February 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 Appendix 1 in the online data supplement.

3.4 Selection of studies

The screening of the titles and abstracts was conducted independently by two authors (HK and IK) 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 (OU), if necessary.

3.6 Data extraction and management

Data from included studies were extracted by two authors (HK and IK) 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 (OU), if necessary.

3.7 Risk of bias

The risk of bias of included studies was assessed by two authors (HK and IK) independently and any disagreements were resolved by consensus and discussion with a third author (OU), 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 Nonrandomised Studies (RoBANS) [16] to appraise the risk of bias for each included study. Each domain was classified as high risk; low risk; or unclear.

3.8 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/L; 2-hour plasma glucose 7.8–11 mmol/L after a standard oral glucose tolerance test (OGTT); or haemoglobin A1C (HbA1C) 42–47 mmol/mol); T2DM [fasting plasma glucose ≥7.0 mmol/L; 2-hour plasma glucose ≥11.1 mmol/L after a standard OGTT; or HbA1C ≥48 mmol/mol] [17,18]; period regularity (number of periods per year); blood pressure (mmHg); 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 recognised criteria). For biochemical and hormonal measurements SI units were used and conversion to SI units was performed, if needed. Data are 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/).

3.9 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).

4. Results

4.1 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 summarised in **Table 1** and **Table S1**, in the online data supplement, respectively. Of the six included studies: (i) 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); (ii) 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 USA. All studies used polysomnography to diagnose OSA. One study, Nandalike et al. 2012 [21], was a retrospective chart review study.

4.2 Risk of bias of included studies

The risk of bias assessment for each study is summarised 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.

4.3 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 sub group of adolescent girls with PCOS and obesity, there was no significant difference in BMI-Z scores between girls with OSA compared to 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 mmHg in women with PCOS and OSA compared to 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 mmHg 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. While 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 to 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.

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

Sex Hormone binding globulin (SHBG)

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 to 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 to women with PCOS without OSA (**Table 2**).

Glucose metabolism and insulin resistance measures

Women with PCOS and OSA had significantly higher: (i) fasting plasma glucose levels (MD: 0.45 mmol/L, 95% CI: 0.21-0.69; I^2 = 17%; five studies; 221 participants); (ii) 2-hour plasma glucose on OGTT (MD: 1.39 mmol/L, 95% CI: 0.67-2.11; I^2 = 0%; two studies; 90 participants); (iii) HOMA-IR (MD: 2.23, 95% CI: 1.41-3.06; I^2 = 0%; four studies; 168 participants); and (iv) 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 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: (i) total cholesterol (MD: 0.74 mmol/L, 95% CI: 0.30-1.18; I^2 = 0%; two studies; 88 participants); (ii) LDL cholesterol (MD: 0.52 mmol/L, 95% CI: 0.18-0.86; I^2 = 25%; two studies; 88 participants); and (iii) triglycerides (MD: 0.35 mmol/L, 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 to those without OSA (MD: -0.26 mmol/L, 95% CI: -0.36- -0.16, I^2 = 0%; three studies; 116 participants) (**Figure 7**). None 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 to women with PCOS without OSA (rate difference = 37.2%, 95% CI: 19.3-55.1; I^2 = 0%; two studies; 78 participants) (**Figure 8**).

4.5 Effect of OSA in women with PCOS on psychological outcomes

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

5. 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 generalised obesity and exhibit a more severe metabolic profile compared to women with PCOS without OSA. However, the relationship between OSA and the clinical features of PCOS (such as hirsutism, and menstrual irregularities) as well as CVD, QoL and fertility outcomes remains 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 to 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 to women without PCOS [21,24,25]; but differences in studies populations (e.g. obesity, ethnicity) or methods of participants' recruitment (e.g. community, specialised 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 to those without OSA. There was a trend for women with PCOS and OSA to have lower SHBG compared to 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 to 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 to 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 to 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 [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 to 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 to those without OSA. While this suggests that women with PCOS and OSA represent a group of patients at higher CVD risk compared to 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 been also associated with increased risk of 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 mmHg) 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, oligomenorrhoea, and possibly response to fertility treatment, are also influenced by ethnicity [43,44]. Subsequently, research focused on the prevalence and impact of OSA in 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 hours/night) not only notice improvement in night-time apnoeas 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 favourable impact on the clinical manifestations of the syndrome including hypertension, increased risk of T2DM and CVD, poor psychological health, and subfertility.

6. 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 USA); 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 have affected our results as the AHI cut-

373 off to diagnose OSA is different in children than in adults; all the studies included have used
374 polysomnography to diagnose OSA; and all have used the NIH or the Rotterdam criteria to diagnose
375 PCOS (**Table 1**).

376

377 **7. Study strengths**

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

383

384 **8. Conclusions**

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

391

392 **9. Abbreviations list**

393 - AASM American Academy of Sleep Medicine

394 - AA African American

395 - AHI Apnoea/hypopnoea index

396 - AI Apnoea index

397 - BMI Body mass index

398 - C. abstract Conference abstract

399 - CIs Confidence intervals

400 - CPAP Continuous positive airway pressure

401 - CS Cross-sectional study

402 - CVD Cardiovascular disease

403 - GnRH Gonadotropin releasing hormone

404 - h Hour

- HbA1C Haemoglobin A1C
- HOMA-IR Homeostatic model assessment of insulin resistance
- IR Insulin resistance
- J. Article Journal article
- MD Mean difference
- N Sample size
- NIH National Institutes of Health
- NR Not reported
- NS Not significant
- OGTT Oral glucose tolerance test
- OSA Obstructive sleep apnoea
- PCOS Polycystic ovary syndrome
- PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analyses
- PSG Polysomnography
- QoL Quality of life
- RDI Respiratory distress index
- SD Standard deviation
- SEM Standard error of the mean
- SHBG Sex hormone binding globulin
- T2DM Type 2 diabetes mellitus
- WHR Waist-to-hip ratio
- Yr Years

10. Authors' contribution

HK, IK, OAU, AM, PDHW, AAT, HSR contributed to study design. AB, and SJ designed search strategies and performed literature search. HK and IK selected studies, extracted data and assessed risk of bias. OAU performed data analyses. HK, IK, OAU, AM, AAT, and HSR contributed to data interpretation. HK wrote first draft of report. All authors critically reviewed the paper and approved the final version of the manuscript. AAT and HSR are joint senior authors; contributed equally to the manuscript.

11. Disclosure statement

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Figure 1. PRISMA flow diagram.

Figure 2. Risk of bias of included studies.

Figure 3. Effect of obstructive sleep apnoea (OSA) on anthropometric measures in women with polycystic ovary syndrome (PCOS) [body mass index (BMI in kg/m^2) for adult women with PCOS; BMI Z-score for the sub group of adolescent girls with obesity and PCOS; waist circumference; waist-to-hip ratio (WHR); women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

Figure 4. Effect of obstructive sleep apnoea (OSA) on systolic and diastolic blood pressure in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

Figure 5. Effect of obstructive sleep apnoea (OSA) on hirsutism (based on the modified Ferriman-Gallwey score) and sex hormone binding globulin in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

Figure 6. Effect of obstructive sleep apnoea (OSA) on measures of glucose metabolism and insulin resistance in women with polycystic ovary syndrome (PCOS) [fasting plasma glucose; 2-hour 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)].

Figure 7. Effect of obstructive sleep apnoea (OSA) on blood lipids in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

Figure 8. Effect of obstructive sleep apnoea (OSA) on the incidence of metabolic syndrome in women with polycystic ovary syndrome (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 Programme, Adult Treatment Panel (NCEP ACT III) criteria [47].

Table 1. Characteristics of included studies *[ordered alphabetically based on the first author's surname]*.

Study	Country	Study design	Publication type	Population	N	Ethnicity	Age	BMI	PCOS diagnosis	OSA diagnosis		Age (per group)			AHI (per group)		
							(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, Apnoea hypopnoea index; AI, apnoea index; BMI, body mass 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; OSA, obstructive sleep apnoea; PCOS, polycystic ovary syndrome; 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/pre-menopausal.

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

Study	**Number of Participants**	**Total Testosterone**			**Free Testosterone**		
	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/L	284.8 ±26.4 nmol/L	NS	124.8 ±44.52 nmol/L	118.1 ±16.54 nmol/L	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

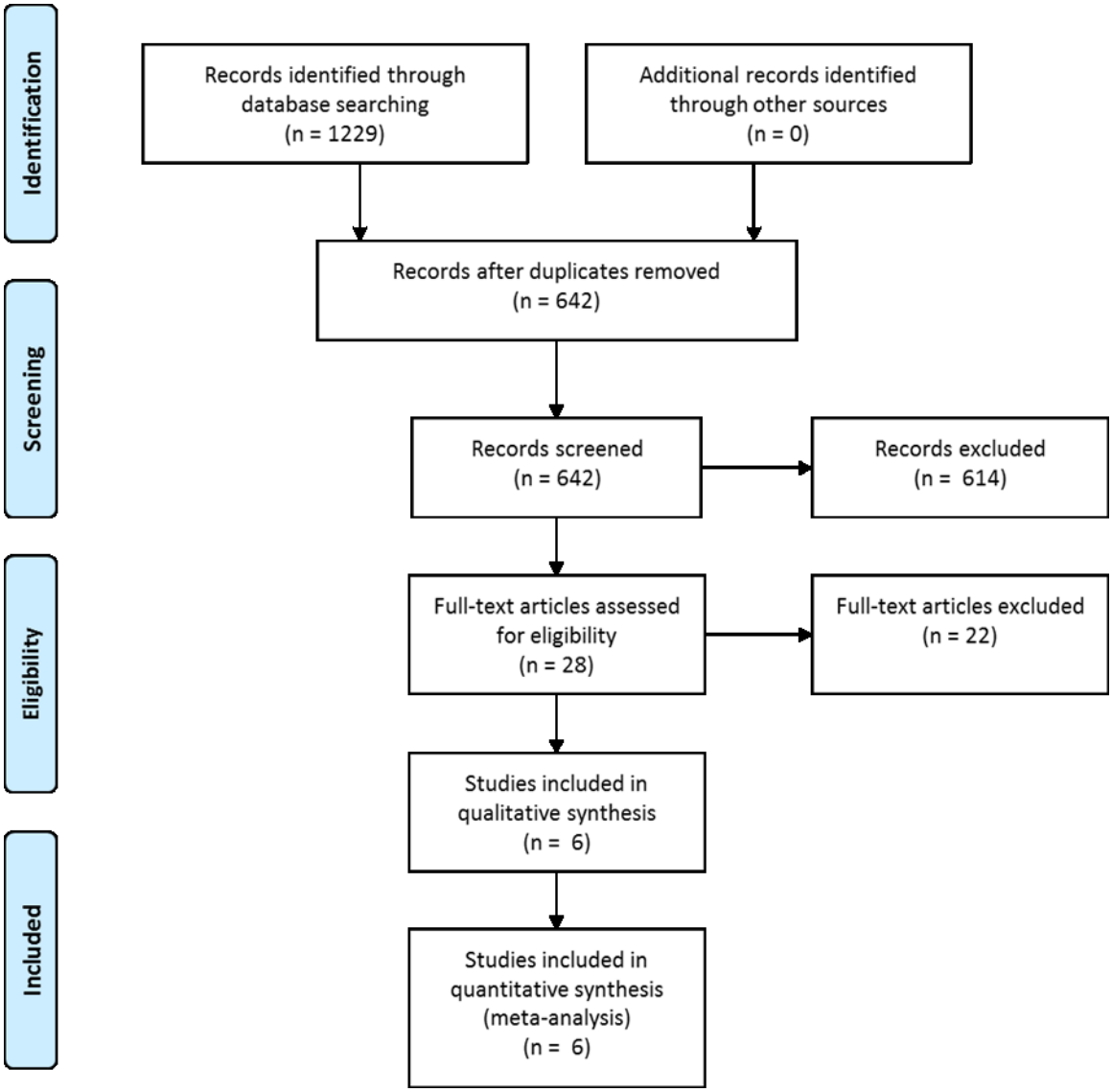
Data presented as mean ±standard deviation. NA, not available; NS, not significant.

13. Supplementary data

This paper includes an online supplement:

Table S1. Characteristics of excluded studies.

Appendix 1. Search strategy.


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1229)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 642)
Records screened (n = 642)
Records excluded (n = 614)
Full-text articles assessed for eligibility (n = 28)
Full-text articles excluded (n = 22)
Studies included in qualitative synthesis (n = 6)
Studies included in quantitative synthesis (meta-analysis) (n = 6)

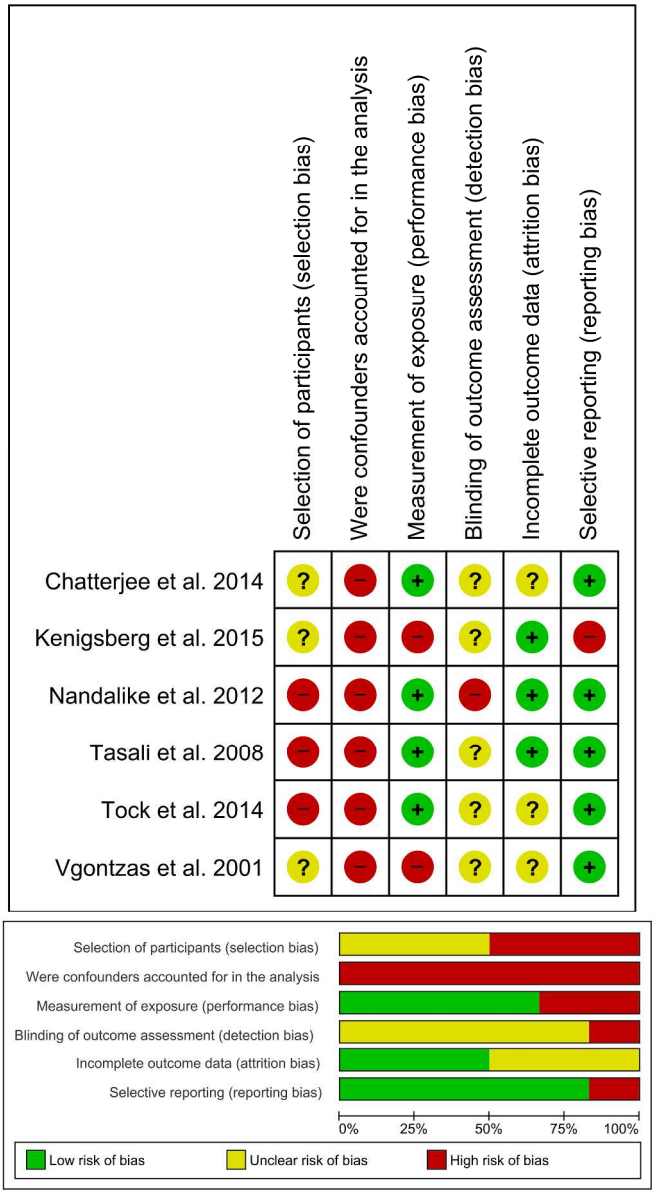


Figure 2. Risk of bias of included studies.

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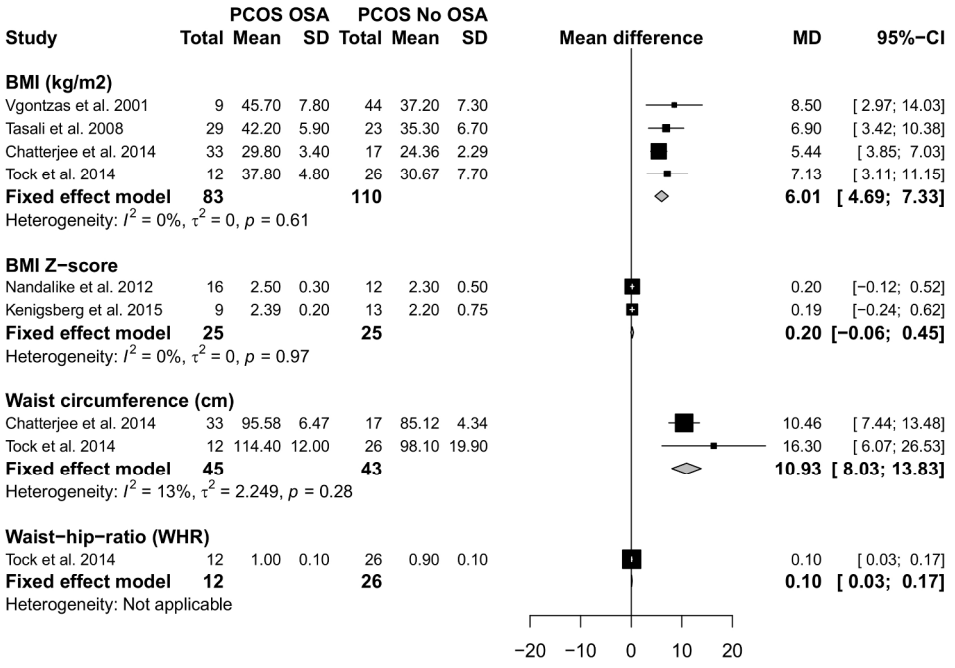

Figure 3. Effect of obstructive sleep apnoea (OSA) on anthropometric measures in women with polycystic ovary syndrome (PCOS) [body mass index (BMI in kg/m2) for adult women with PCOS; BMI Z-score for the sub group of adolescent girls with obesity and PCOS; waist circumference; waist-to-hip ratio (WHR); women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

223x156mm (300 x 300 DPI)

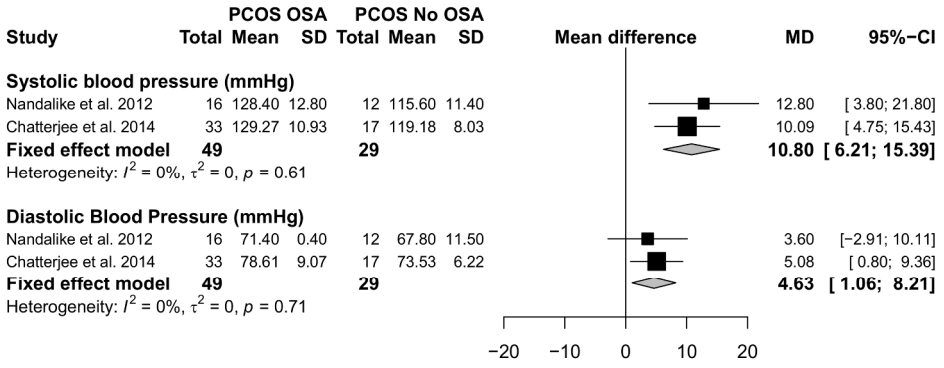

Figure 4. Effect of obstructive sleep apnoea (OSA) on systolic and diastolic blood pressure in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

226x95mm (300 x 300 DPI)

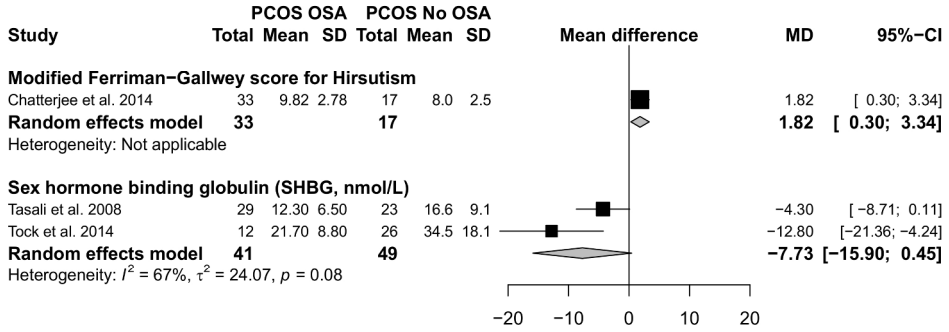

Figure 5. Effect of obstructive sleep apnoea (OSA) on hirsutism (based on the modified Ferriman-Gallwey score) and sex hormone binding globulin in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

232x91mm (300 x 300 DPI)

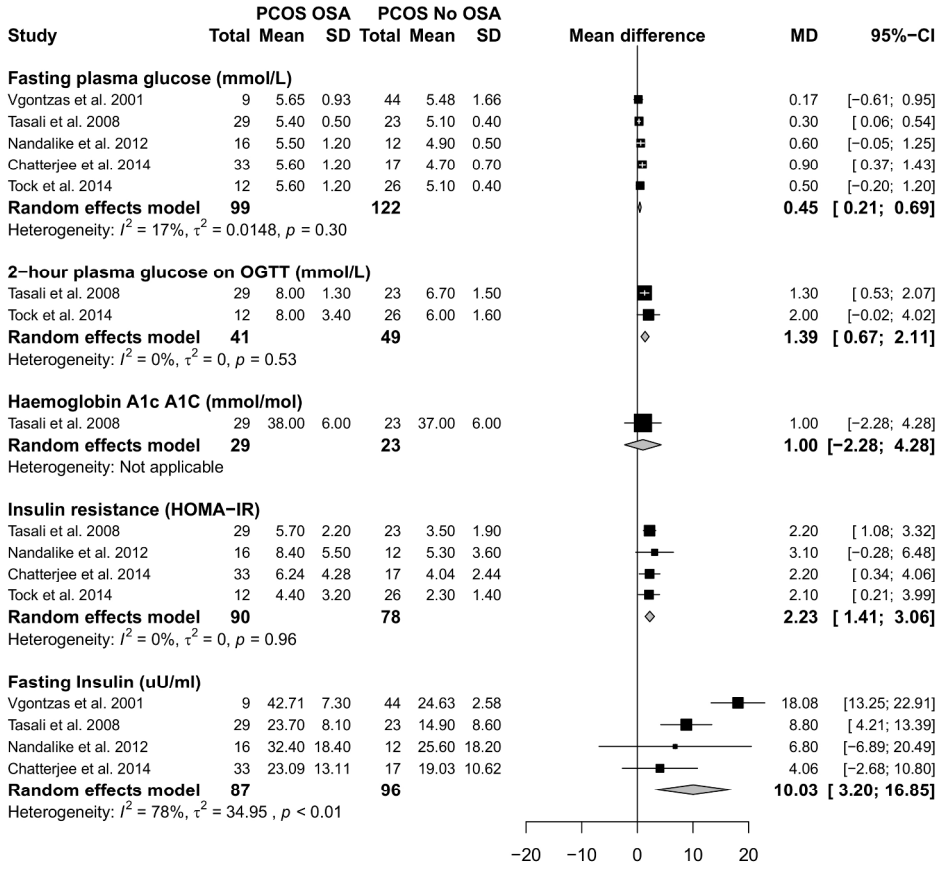

Figure 6. Effect of obstructive sleep apnoea (OSA) on measures of glucose metabolism and insulin resistance in women with polycystic ovary syndrome (PCOS) [fasting plasma glucose; 2-hour plasma glucose after a standard oral glucose tolerance test (OGTT); haemoglobin A1C (HbA1C); homeostasis model for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

235x219mm (300 x 300 DPI)

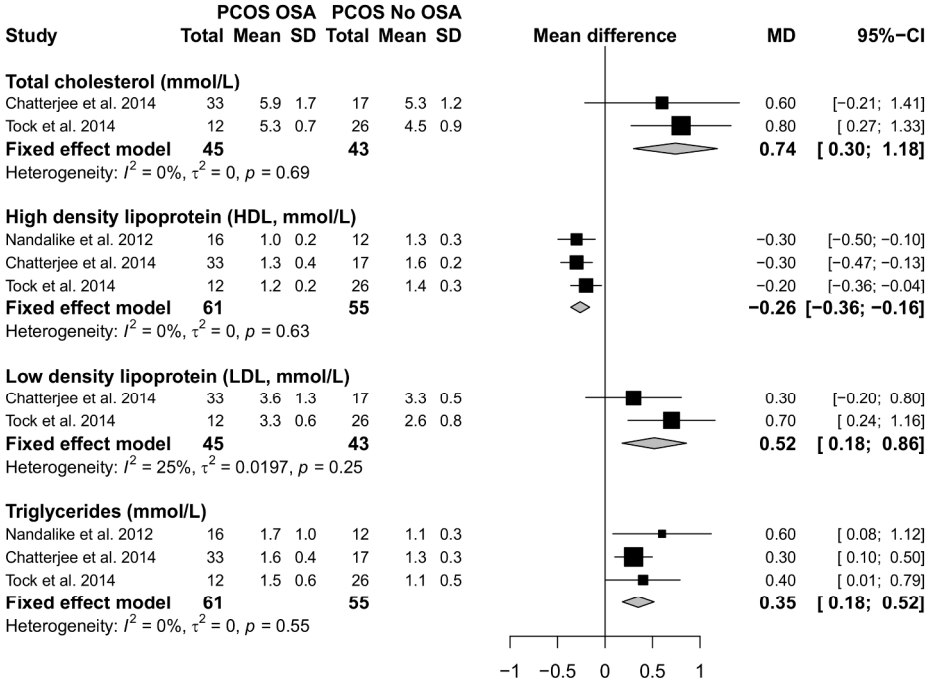

Figure 7. Effect of obstructive sleep apnoea (OSA) on blood lipids in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)].

223x158mm (300 x 300 DPI)

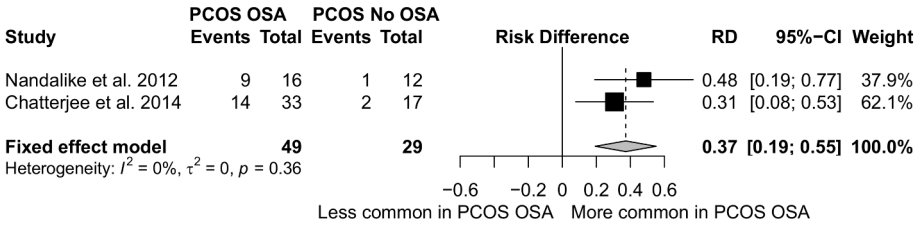

Figure 8. Effect of obstructive sleep apnoea (OSA) on the incidence of metabolic syndrome in women with polycystic ovary syndrome (PCOS) [women with PCOS and OSA (PCOS OSA); women with PCOS without OSA (PCOS No OSA)]. The study by Nandalike et al. included adolescent girls with PCOS and the diagnosis of the metabolic syndrome was based on the Weiss criteria (ref 65). The study by Chatterjee et al. included adult women with PCOS and the metabolic syndrome was diagnosed based on the National Cholesterol Education Programme, Adult Treatment Panel (NCEP ACT III) criteria (ref 66).

229x66mm (300 x 300 DPI)

Online data supplement

Table S1. Characteristics of excluded studies *[ordered by year of publication]*.

Study	Reason for exclusion
Fogel et al. 2001 [1]	No comparisons were made between women with polycystic ovary syndrome (PCOS) and obstructive sleep apnoea (OSA) and those with PCOS without OSA.
Gopal et al. 2002 [2]	No comparisons were made between women with PCOS and OSA and those with PCOS without OSA
Tasali et al. 2006 [3]	No information on how many women had OSA
Vgontzas et al. 2006 [4]	Only participants without OSA were included
Yang et al. 2009 [5]	None of the study participants had OSA
De Sousa et al. 2010 [6]	None of the study participants had OSA - Duplicate publication to De Sousa 2012 [7].
De Sousa et al. 2010a [8]	None of the study participants had OSA - Duplicate publication to De Sousa 2012 [7].
Yang et al. 2010 [9]	Duplicate publication to Yang 2009 [5]
De Sousa et al. 2011 [10]	None of the study participants had OSA - Duplicate publication to De Sousa 2012 [7].
De Sousa et al. 2011a [11]	None of the study participants had OSA - Duplicate publication to De Sousa 2012 [7].
Nandalike et al. 2011 [12]	No sleep studies performed for OSA diagnosis
Tasali et al. 2011 [13]	Only women with OSA were included
De Sousa et al. 2012 [7]	None of the study participants had OSA
De Sousa et al. 2012a [14]	None of the study participants had OSA - Duplicate publication to De Sousa 2012 [7].
Mokhlesi et al. 2012 [15]	No sleep studies performed for OSA diagnosis
AbdelWahab et al. 2013 [16]	No comparisons were made between women with PCOS and OSA and those with PCOS without OSA.
Gateva et al. 2013 [17]	Only two patients had OSA. No data comparing women with PCOS and OSA to women with PCOS without OSA
Morselli et al. 2013 [18]	No comparisons were made between women with PCOS and OSA and those with PCOS without OSA
Temple et al. 2013 [19]	No comparisons were made between women with PCOS and OSA and those with PCOS without OSA
Temple et al. 2013a [20]	No comparisons were made between women with PCOS and OSA and those with PCOS without OSA
Zea-Hernandez et al. 2014 [21]	No comparisons were made between women with PCOS and OSA and those with PCOS without OSA
Suri et al. 2016 [22]	Duplicate publication to Chatterjee 2014 [23]

References:

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2. Gopal M, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. Sleep Med. 2002; 3 (5): 401-404.
3. Tasali E, Van Cauter E, Ehrmann DA. Relationships between sleep disordered breathing and glucose metabolism in polycystic ovary syndrome. J Clin Endocrinol Metab. 2006; 91 (1): 36-42.
4. Vgontzas AN, Trakada G, Bixler EO, et al. Plasma interleukin 6 levels are elevated in polycystic ovary syndrome independently of obesity or sleep apnea. Metabolism. 2006; 55 (8): 1076-1082.
5. Yang HP, Kang JH, Su HY, Tzeng CR, Liu WM, Huang SY. Apnea-hypopnea index in nonobese women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2009; 105 (3): 226-229.
6. de Sousa G, Schluter B, Buschatz D, et al. A comparison of polysomnographic variables between obese adolescents with polycystic ovarian syndrome and healthy, normal-weight and obese adolescents. Sleep Breath. 2010; 14 (1): 33-38.
7. de Sousa G, Schluter B, Buschatz D, et al. The impact of insulin resistance and hyperandrogenemia on polysomnographic variables in obese adolescents with polycystic ovarian syndrome. Sleep Breath. 2012; 16 (1): 169-175.
8. de Sousa G, Schlüter B, Menke T, Trowitzsch E, Andler W, Reinehr T. A Comparison of Polysomnographic Variables between Adolescents with Polycystic Ovarian Syndrome and Healthy Controls. Int J Clinical Medicine. 2010; 1: 48-53.
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11. de Sousa G, Schluter B, Menke T, Trowitzsch E, Andler W, Reinehr T. A comparison of polysomnographic variables between adolescents with polycystic ovarian syndrome with and without the metabolic syndrome. Metab Syndr Relat Disord. 2011; 9 (3): 191-196.
12. Nandalike K, Strauss T, Agarwal C, et al. Screening for sleep-disordered breathing and excessive daytime sleepiness in adolescent girls with polycystic ovarian syndrome. J Pediatr. 2011; 159 (4): 591-596.
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15. Mokhlesi B, Scoccia B, Mazzone T, Sam S. Risk of obstructive sleep apnea in obese and nonobese women with polycystic ovary syndrome and healthy reproductively normal women. Fertil Steril. 2012; 97 (3): 786-791.

16. AbdelWahab NH, Mahmoud MI, Abdelnaby MA, Morsi TS, Abdelfatah MF. Sleep related breathing disorders in Egyptian females with polycystic ovary syndrome. American Thoracic Society International Conference, ATS; 2013; Philadelphia.
17. Gateva A, Kamenov Z, Mondeshki T, Bilyukov R, Georgiev O. Obstructive sleep apnea in Bulgarian patients with polycystic ovarian syndrome. 15th European Congress of Endocrinology; 2013; Copenhagen, Denmark.
18. Morselli LL, Temple KA, Mokhlesi B, et al. Effects of polycystic ovary syndrome (PCOS) on REM and non-REM sleep in African-American (AA) women. 95th Annual Meeting and Expo of the Endocrine Society, ENDO; 2013; San Francisco, CA United States.
19. Temple KA, Leproult R, Whitmore H, Mokhlesi B, Van Cauter E, Ehrmann DA. Adiponectin levels in obese women with and without PCOS: Impact of obstructive sleep apnea. 95th Annual Meeting and Expo of the Endocrine Society, ENDO; 2013; San Francisco, CA United States.
20. Temple KA, Tasali E, Mokhlesi B, et al. Abnormal glucose tolerance in women with polycystic ovary syndrome (PCOS): Role of sex steroids and obstructive sleep apnea. 73rd Scientific Sessions of the American Diabetes Association; 2013; Chicago, IL United States.
21. Zea-Hernandez J, Sin S, Graw-Panzer K, Arens R. Sleep disordered breathing in adolescent girls with polycystic ovary syndrome. . American Thoracic Society International Conference, ATS. ; 2014.
22. Suri J, Suri JC, Chatterjee B, Mittal P, Adhikari T. Obesity may be the common pathway for sleep-disordered breathing in women with polycystic ovary syndrome. Sleep Med. 2016; 24: 32-39.
23. Chatterjee B, Suri J, Suri JC, Mittal P, Adhikari T. Impact of sleep-disordered breathing on metabolic dysfunctions in patients with polycystic ovary syndrome. Sleep Med. 2014; 15 (12): 1547-1553.

Appendix 1. Search strategy

The initial search was performed on 11th of April 2016 and a second search was performed on 7th of February 2017. In addition to the electronic databases below we manually searched the references of all relevant papers and review articles.

- **Medline (Ebsco)**

#	Query	Limiters/Expanders
S1	MH "Polycystic Ovary Syndrome"	Search modes - Boolean/Phrase
S2	(polycystic N3 ovar*) or PCOS or "stein leventhal" or (sclerocystic N3 ovar*) or "hyperandrogenic anovulation"	Search modes - Boolean/Phrase
S3	(MH "Sleep Apnea Syndromes+")	Search modes - Boolean/Phrase
S4	(sleep* N3 (apnea* or apnoea* or respirat* or breath*)) or OSA or SHS or OSAHS or SAHS or hypopnea* or hypopnoea*	Search modes - Boolean/Phrase
S5	(S1 OR S2) AND (S3 OR S4)	Search modes - Boolean/Phrase

- **Embase (Ovid)**

#	Search Terms
1	exp ovary polycystic disease
2	((polycystic adj3 ovar*) or PCOS or "stein leventhal" or (sclerocystic adj3 ovar*) or "hyperandrogenic anovulation").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3	exp sleep disordered breathing
4	((sleep* adj3 (apnea* or apnoea* or respirat* or breath*)) or OSA or SHS or OSAHS or SAHS or hypopnea* or hypopnoea*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5	1 or 2
6	3 or 4
7	5 and 6

- **CINAHL (Ebsco)**

#	Search Terms	Search Options
S1	(MH "Polycystic Ovary Syndrome")	Search modes - Boolean/Phrase
S2	(polycystic N3 ovar*) or PCOS or "stein leventhal" or (sclerocystic N3 ovar*) or "hyperandrogenic anovulation"	Search modes - Boolean/Phrase
S3	(MH "Sleep Apnea Syndromes+")	Search modes - Boolean/Phrase
S4	(sleep* N3 (apnea* or apnoea* or respirat* or breath*)) or OSA or SHS or OSAHS or SAHS or hypopnea* or hypopnoea*	Search modes - Boolean/Phrase
S5	S1 OR S2	Search modes - Boolean/Phrase
S6	S3 OR S4	Search modes - Boolean/Phrase
S7	S5 AND S6	Search modes - Boolean/Phrase

- **Opengrey (http://www.opengrey.eu/)**

((polycystic NEAR/3 ovar*) OR PCOS OR "stein leventhal" OR (sclerocystic NEAR/3 ovar*) OR "hyperandrogenic anovulation") AND ((sleep NEAR/3 (apnea* or apnoea* or respirat* or breath*)) OR OSA OR SHS OR OSAHS OR SAHS OR hypopnea* or hypopnoea*).

- **Web of Science**

#	Search Term
#1	**TOPIC:** ("polycystic ovary syndrome" or "ovary polycystic disease*" or pcos or "stein leventhal" or "hyperandrogenic anovulation") *OR* **TOPIC:** (polycystic near/3 ovar*) *OR* **TOPIC:** (sclerocystic near/3 ovar*) *DocType=All document types; Language=All languages;*
#2	**TOPIC:** ("sleep apnea syndrome" or "sleep disordered breathing") *OR* **TOPIC:** (sleep near/3 (apnea or apnoea or respirat* or breath*)) *OR* **TOPIC:** (osa or shs or osahs or sahs or hypopnea* or hypopnoea*) *DocType=All document types; Language=All languages;*
#3	#2 AND #1 *DocType=All document types; Language=All languages;*

- **Scopus**

(TITLE-ABS-KEY (sclerocystic W/3 ovar*) OR TITLE-ABS-KEY (polycystic W/3 ovar*) OR TITLE-ABS-KEY ("polycystic ovary syndrome" OR "ovary polycystic disease*" OR pcos OR "stein leventhal" OR "hyperandrogenic anovulation")) AND ((TITLE-ABS-KEY ("sleep apnea syndrome" OR "sleep disordered breathing") OR TITLE-ABS-KEY (sleep W/3 (apnea OR apnoea OR respirat* OR breath*)) OR TITLE-ABS-KEY (osa OR shs OR osahs OR sahs OR hypopnea* OR hypopnoea*)))

- **PsycInfo (ProQuest)**

(SU.EXACT.EXPLODE("Sleep Apnea") OR ((sleep* N/3 (apnea* or apnoea* or respirat* or breath*)) or OSA or SHS or OSAHS or SAHS or hypopnea* or hypopnoea*)) AND ((polycystic N/3 ovar*) or PCOS or "stein leventhal" or (sclerocystic N/3 ovar*) or "hyperandrogenic anovulation").

- **Endocrine abstracts (**http://www.endocrine-abstracts.org/**)**

Search terms	Advanced search options
Polycystic ovaries and sleep apnea	Boolean Search for grammatical variations Similarity to search phrase: Generous differences

- **American Endocrine Society meeting abstracts (**http://press.endocrine.org/series/endo-meetings**)**

Search terms: Polycystic ovary and sleep apnea
Search filters: Meeting Abstracts.

- **American Thoracic Society meeting abstracts (**http://www.atsjournals.org/search/advanced**)**

Search Terms: PCOS or polycystic.

- **Sleep (the joint meeting of the American Academy of Sleep Medicine and the Sleep Research Society) (**http://www.sleepmeeting.org/abstract-supplements**)**

Search terms: PCOS or polycystic.