

# Continuous positive airway pressure can improve depression in patients with obstructive sleep apnoea syndrome: a meta-analysis based on randomized controlled trials

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## Abstract

**Objective:** Substantial research indicates a clear relationship between obstructive sleep apnoea syndrome (OSAS) and depression. The study aim was to quantitatively evaluate whether continuous positive airway pressure (CPAP) therapy improves mood symptoms in OSAS patients.

**Methods:** PubMed and Embase databases were systematically searched up to 2017 for publications on the impact of CPAP on mood symptoms in OSAS patients.

**Results:** For the final analysis, nine randomized controlled trials comprising 1,052 patients were selected. The pooled standard mean difference (SMD) of the effect of CPAP on depression was 0.31 (95% confidence interval 0.18, 0.43). A subgroup analysis showed that when CPAP use was greater than 4 hours per night, it tended to be effective in improving patients' mood symptoms (SMD = 0.38; confidence interval 0.23, 0.54). Analysis of publication bias using Egger's test found no evidence of publication bias.

**Conclusion:** CPAP treatment can improve depression in OSAS patients.

## Keywords

Continuous positive airway pressure, obstructive sleep apnoea syndrome, depression, randomised controlled trial, meta-analysis, China, systematic review

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## Introduction

The breathing disorder<sup>1,2</sup> obstructive sleep apnoea (OSA) is usually caused by airway occlusion during sleep secondary to pharyngeal collapse and is characterized by repetitive breathing interruptions when sleeping.<sup>3,4</sup> The main clinical features of OSA mostly appear as respiratory problems when sleeping, sleepiness and impaired cognitive performance in the day and dysphoric mood. OSA was first described accurately in 1976.<sup>5</sup> An estimated 14% to 55% of adults have OSA depending on age, group and sex; OSA is more common in men than in women.<sup>6</sup> OSA has a high prevalence and its effects are becoming more serious because of an increase in the average population body weight.<sup>7</sup> People with OSA usually experience poor quality of life and poor health owing to sleepiness during the day and poor sleep quality at night.<sup>8</sup> Studies have revealed that OSA is associated with serious long-term diseases such as hypertension, cardiovascular disease, stroke, diabetes, neurocognitive deficits and depression.<sup>9-13</sup> Although patients with OSA show a higher rate of depression than patients without OSA, this does not indicate a cause-and-effect relationship. The mechanism is complicated and remains largely unclear. Interestingly, Phillips et al. reported no difference in the prevalence of depression between patients with mild OSA and those without OSA in a longitudinal study.<sup>14</sup> Pillar and Lavie also found no relationship between OSA and depression in a study with a large sample of male patients.<sup>15</sup>

There are many treatment options for OSA, from surgical interventions to non-invasive methods.<sup>16</sup> Non-invasive conservative treatment includes weight control, lifestyle change, drug control, oral appliances and continuous positive airway pressure (CPAP). However, some patients cannot tolerate CPAP and may experience nasal airway problems, mouth leakage and discomfort wearing masks<sup>17,18</sup> CPAP is still the gold standard

treatment for OSA.<sup>19</sup> However, alternative treatments can be useful. Oral appliances such as mandibular advancement devices, the most commonly used OSA device, can treat occlusion of the upper airway with minimal invasion.<sup>20-23</sup>

Research indicates that CPAP is effective in reducing the severity of OSA.<sup>24-26</sup> CPAP treatment can help to relieve sleep apnoea symptoms and improve daytime functioning in mild and severe OSA patients. Many studies show that CPAP treatment can also relieve OSA patients' mood symptoms,<sup>27-29</sup> but researchers disagree on whether CPAP can improve depression and quality of life. Borak et al.<sup>30</sup> reported that CPAP treatment significantly improved cognitive function in the early stages, but did not improve emotional status in patients with severe OSA. These conflicting findings may be because of differences across study populations in apnoea severity, sample size, study design, treatment device and inconsistent compliance with CPAP.<sup>31-33</sup> Povitz et al. concluded that CPAP may be useful in treating depressive symptoms in patients with OSA and depression,<sup>34</sup> whereas Gupta et al. reported that positive airway pressure (PAP) was no more effective at reducing depression than sham PAP.<sup>35</sup> Given the lack of clear conclusions regarding the effectiveness of CPAP, the objective of this systematic review and meta-analysis was to explore whether CPAP therapy improves depression in patients with OSA in comparison to placebo.

## Materials and methods

### *Inclusion criteria and outcomes*

All parallel group randomized controlled trials (RCTs) investigating CPAP interventions for OSA were reviewed. Sample patients were adults  $\geq 18$  years old with both OSA and depressive symptoms. Trials were included if they reported a diagnosis of sleep

apnoea based on sleep studies that produced a respiratory disturbance index (RDI), apnoea hypopnea index (AHI) or oxygen desaturation index >5 events/hour. Trials were excluded if they used only questionnaires to diagnose OSA. A depression diagnosis at baseline was not necessary, but included trials had to contain measures of depressive symptoms using questionnaires such as the Hospital Anxiety and Depression Scale depression subscale (HADSd), the Beck Depression Inventory (BDI), the Profile of Mood States depression subscale (POMSd) and the Health Survey Short Form-36 (SF-36) (i.e. the SF-36 mental component score (SF-36 MCS) and the SF-36 mental health subscale (SF-36 MH)). Studies investigating schizophrenia, comorbid bipolar disorder or other psychiatric diagnoses were excluded. For trials that compared three treatments (placebo, CPAP and mandibular advancement devices), only the comparison of CPAP and control results were examined for this meta-analysis.

The primary outcome was change in depression scores between the treatment and control groups during the whole trial. As different depression measurement scales were used, the directions of the change scores were reversed as necessary to obtain a consistent direction of effect across trials. Subgroup analysis was carried out to study factors leading to heterogeneity in the effectiveness of CPAP. Potential influencing factors such as region, evaluation tools, length of follow-up and CPAP adherence time were also assessed.

### *Literature search*

PubMed and Embase databases were searched for publications up to December 2017. RCTs that examined the effect of CPAP treatment on mood symptoms in OSA patients were reviewed. The search included the following terms: 'CPAP',

'BiPAP' (i.e. bilevel PAP), 'Psych', 'Depress', 'Random', 'exp sleep disordered breathing', 'exp positive end expiratory pressure', 'Sleep Apnea', 'Positive-pressure respiration', 'Positive-pressure respiration', 'exp Oxygen', 'exp Randomized Controlled Trial', and 'exp randomization'. Both relevant articles and abstracts were reviewed, and the computer search was supplemented with manual searches of reference lists for additional trials. The searches were limited to articles on randomized clinical trials and those published in English.

### *Study selection and data extraction*

Two independent reviewers (XY, JY) assessed the studies by screening titles and abstracts to evaluate eligibility. A consensus vote was taken when there were disagreements. For the included studies, two investigators (XY, JY) independently extracted and compiled data in Microsoft Excel 2010 for over 2 weeks. The following information was extracted using a predesigned form: study characteristics (study design, methodology and publication details), samples (size, sex and age), intervention strategies, the type of depression evaluation scale, scores before and after treatment, and study duration.

### *Quality assessment*

The developed star system of the Newcastle–Ottawa Scale,<sup>36</sup> which ranges from 0 to 9 stars, was used to assess the quality of each case control study. Included studies were evaluated according to three categories: selections (4 stars), comparability of study groups (2 stars) and assessment of the outcome of interest (3 stars). The total score indicates the quality; 0 to 5 stars represents low quality and 6 to 9 stars high quality.

### *Statistical analysis*

The primary outcome measure was change in depression scores between the treatment

and control groups during the whole trial process. For categorical outcomes, the combined statistics used were odds ratio (OR) and 95% confidence interval (CI). For numerical outcomes, the combined statistics used were mean difference (MD) or standardized mean difference (SMD) and 95% CI. The  $I^2$  and Q tests were used to evaluate the heterogeneity of the included publications. When  $P < 0.05$ , the heterogeneity was considered statistically significant and the effects were combined using a random effects model; otherwise, a fixed effects model was used. If between-study heterogeneity was identified, subgroup analysis or meta-regression was used to determine the source of heterogeneity. Egger's test was used to identify publication bias;  $P < 0.1$  was considered to indicate publication bias. Sensitivity analysis was used to exclude high-risk studies to examine the impact of methodological quality on the results. All statistical analyses were carried out using STATA 12.0 statistical software (StataCorp LP., College Station, TX, USA).

This study was conducted under the PRISMA guidelines for reporting systematic reviews and meta-analyses.

## Results

### *Study selection and characteristics of included studies*

The flow of the trial selection process is shown in Figure 1. A total of 323 studies were identified from searched databases and 9 trials were finally included. The 1,052 OSA patients were divided into a CPAP treatment group ( $n = 529$ ) and a control group ( $n = 523$ ). The characteristics of the nine trials are shown in Table 1.<sup>37-45</sup> Three trials were conducted in the United States or Canada, and six were conducted in Europe. The nine studies were all parallel design RCTs. The sample size difference between the studies was 34 to 391. Several

depression evaluation scales were used in these studies, including the SF-36 MH, POMSd, BDI, SF-36 MCS and HADSd.

### *Primary analysis*

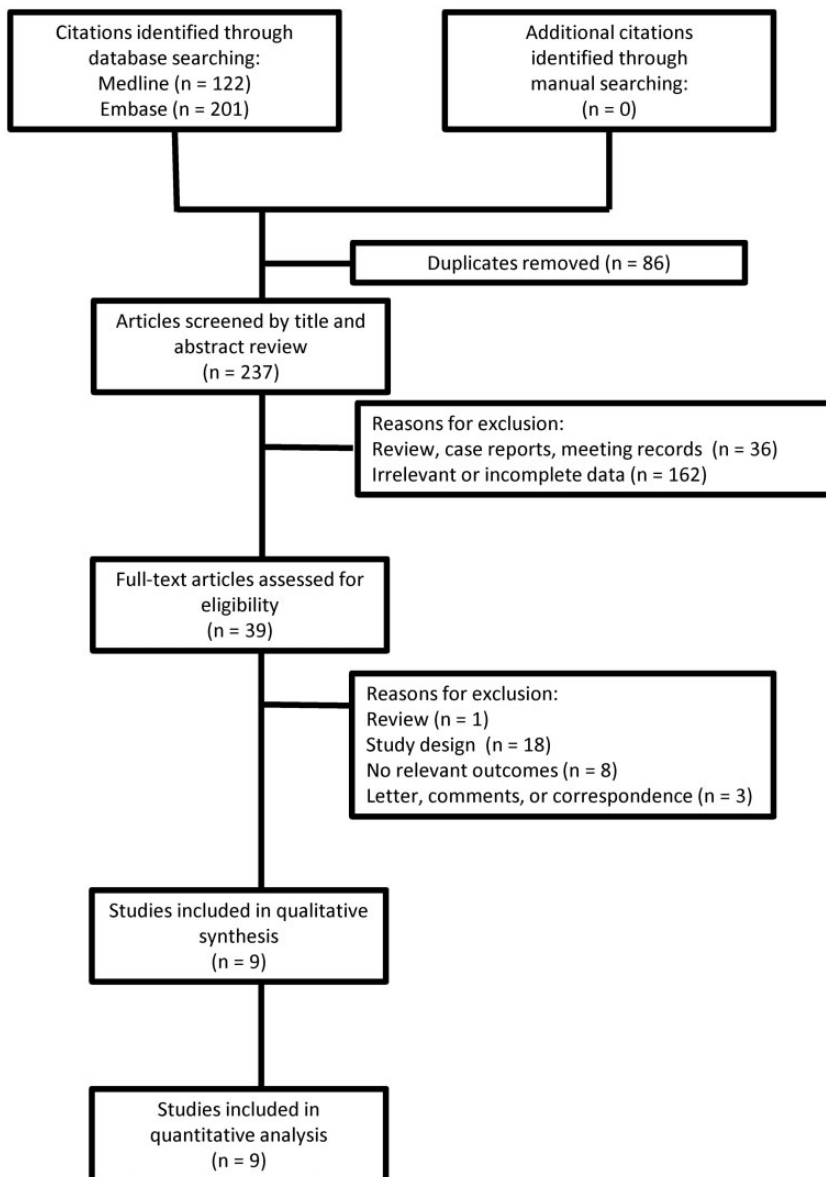
Nine RCTs comprising 1,052 patients were selected for final analysis. First, a heterogeneity test was performed on these nine original studies. The results showed that  $I^2 = 21.3\%$ , and indicated that the inter-study heterogeneity was not statistically significant. Consequently, the fixed effects model was used for meta-merging. The combined effect value was  $SMD = 0.31$  (CI: 0.18, 0.43),  $P < 0.01$ . Compared with the control group, the depression score of the CPAP group was  $SMD = 0.31$ , which was statistically significant (Figure 2).

### *Subgroup analysis*

Subgroup analysis was performed to explore factors that may have caused the heterogeneity in the effectiveness of CPAP. Potential influencing factors such as region, evaluation tools, length of follow-up and CPAP adherence time were assessed.

We performed a meta-analysis on the six studies conducted in Europe. The results showed that  $SMD = 0.34$  (CI: 0.21, 0.47),  $P < 0.01$ , which was statistically significant. The results of a meta-analysis on the other three studies conducted in the United States or Canada were  $SMD = 0.10$  (CI: -0.24, 0.44), which was not statistically significant. Statistical analysis of the combination of the above two meta-analyses revealed no significant difference (Figure 3a).

Three studies used the POMSd evaluation tool. The results of the meta-analysis of these studies were  $SMD = 0.21$  (CI: -0.13, 0.54). The results of the meta-analysis of the three studies that used the SF-36 MH were  $SMD = 0.42$  (CI: 0.17, 0.68),  $P < 0.01$ . The statistical analysis of



**Figure 1.** Flow diagram showing inclusion and exclusion of studies.

the combination of the above two meta-analyses revealed no significant difference. The number of studies using other evaluation tools, such as the BDI and SF-36 MCS, was too small to perform meta-analysis (Figure 3b).

The length of follow-up of these studies was divided into <4 weeks, 4 to 8 weeks, and >8 weeks. The length of one study was 4 to 8 weeks, and the length of two other studies was >8 weeks. The number of studies was too small to perform a

Table 1. Characteristics of included studies.

Study	Location	Design	Sample (intervention/ control)	MD-CPAP	MD-Control	Age	Sex (male/female)	Evaluation tool
Craig et al. (2005)	Europe	RCT-Parallel	195/196	3.80 ± 10.10	1.90 ± 11.20	57.8	305/86	SF-36 MCS
Haensel et al. (2007)	Europe	RCT-Parallel	25/25	-1.80 ± 2.10	-0.80 ± 2.00	48.6	40/10	POMSd
Jenkinson et al. (1999)	Europe	RCT-Parallel	52/49	12.30 ± 15.20	7.10 ± 18.10	49	101/0	SF-36 MH
Lee et al. (2012)	America	RCT-Parallel	26/30	0.20 ± 9.40	0.90 ± 7.20	48.3	37/19	POMSd
Montserrat et al. (2001)	Europe	RCT-Parallel	23/22	3.10 ± 4.60	2.90 ± 3.60	54.2	41/4	SF-36 MH
Ryan et al. (2011)	Canada	RCT-Parallel	22/22	-2.70 ± 6.70	-1.40 ± 7.10	61.8	38/10	BDI
Siccoli et al. (2008)	Europe	RCT-Parallel	51/51	21.40 ± 37.60	-0.10 ± 20.30	48.4	102/0	SF-36 MH
Yu et al. (1999)	America	RCT-Parallel	20/14	-6.10 ± 13.10	-6.10 ± 9.90	48.2	26/8	POMSd
Martínez-García et al. (2015)	Europe	RCT-Parallel	115/109	-1.30 ± 4.50	0.90 ± 4.10	75.5 ± 3.9	154/71	HADSd

MD: mean difference; RCT: randomized controlled trial; CPAP: continuous positive airway pressure; SF-36: Health Survey Short Form-36; POMSd: Profile of Mood States depression subscale; HADSd: Hospital Anxiety and Depression Scale depression subscale; BDI: Beck Depression Inventory.

meta-analysis. Six studies had a follow-up of <4 weeks; the results of a meta-analysis of these studies were SMD = 0.36 (CI: 0.16, 0.56),  $P < 0.01$ , which was statistically significant (Figure 3c).

The average CPAP adherence time for the nine studies was divided into  $\leq 4$  hours/night and  $> 4$  hours/night. One study had an average adherence time of  $\leq 4$  hours/night, and could not be included in the meta-analysis. The average adherence time for the other eight studies was  $> 4$  hours/night, and the results of a meta-analysis on these studies were SMD = 0.38 (CI: 0.23, 0.54),  $P < 0.01$ , which was statistically significant (Figure 3d).

### Methodological quality evaluation

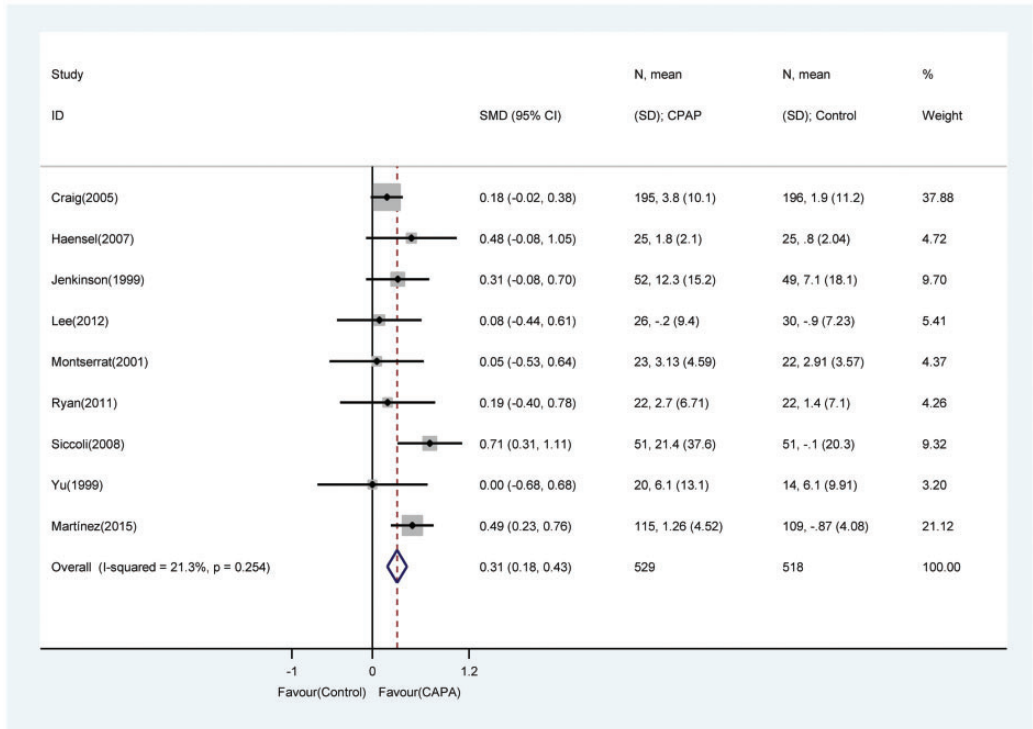
The methodological quality of the included studies was evaluated using the Cochrane RCT Evaluation Scale.<sup>46</sup> As shown in Table 2, 55.6% of the studies showed a low risk of selection bias (distribution concealment), implementation bias, measurement bias, follow-up bias and reporting bias, and 11.1% of the studies showed a low risk of selection bias (random sequence generation). There was insufficient reporting of other biases (Table 2).

### Sensitivity analysis

The sensitivity analysis examined the results of combining the effect values of the remaining studies after excluding each study. As shown in Figure 4, after excluding Craig (2005), Siccoli (2008) and Martínez-García et al. (2015), the effect values were greatly changed, indicating that these three studies had a substantial impact on the results.

### Publication bias

To test the publication bias of the nine studies, we performed Egger's test. As shown in Figure 5, the results were not



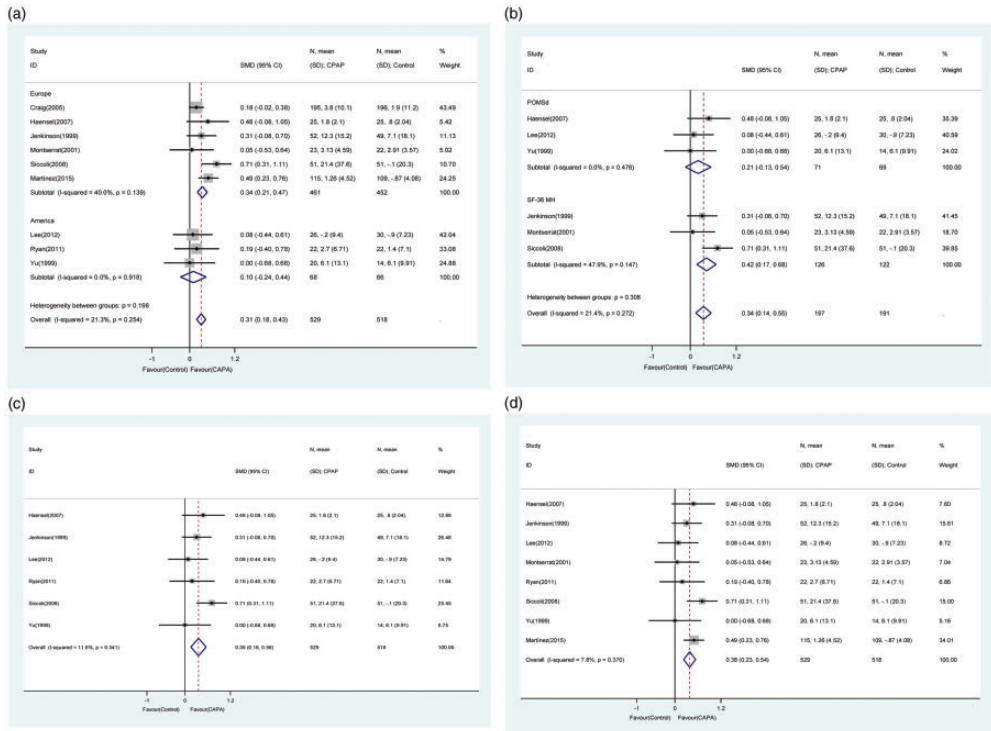
**Figure 2.** Meta-analysis of nine randomized controlled trials of CPAP for patients with OSA. CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea; SMD: standard mean difference; CI: confidence interval.

significant, suggesting that there was no publication bias.

### Discussion

The breathing disorder OSA is very common among middle-aged and elderly people but is usually ignored. OSA is closely associated with a variety of medical comorbidities such as obesity, hypertension, type 2 diabetes and depression.<sup>47</sup> PAP can be categorized as CPAP, BiPAP or autotitrating PAP according to the delivery mode. It is a standard treatment for patients with moderate (RDI >15/hour and >30/hour) to severe (RDI >30/hour) OSA.<sup>4,48</sup> The psychological symptoms of patients suffering from OSA were not recognized until the 1970s,<sup>49</sup> and the number of OSA patients presenting

with depressive symptoms increased substantially in the early 2000s.<sup>50</sup> The specific mechanism that links OSA and psychiatric conditions remains unclear despite extensive research. Currently, biological metabolic dysregulation and neurological dysregulation, presenting as psychiatric disorders, sleep fragmentation, cardiovascular and metabolic disease,<sup>50–52</sup> are thought to contribute to psychiatric conditions in patients with OSA. Depression symptoms may be improved by CPAP therapy owing to improvements in sleep and energy, which increases OSA patients' quality of life. However, it is still unclear whether depression symptoms directly respond to CPAP treatment. Accumulating evidence indicates that the AHI is insufficient for diagnosis and treatment of individuals with OSA. It is



**Figure 3.** Subgroup analysis of region (a), evaluation tool (b), length of follow-up (c) and CPAP adherence time (d). CPAP: continuous positive airway pressure.

**Table 2.** Methodological quality evaluation results.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Implementation bias	Measurement bias	Follow-up bias	Report bias	Other bias
Craig et al. (2005)	High risk	High risk	Low risk	Low risk	High risk	Low risk	Unclear
Haensel et al. (2007)	Unclear	Low risk	High risk	Low risk	Low risk	High risk	Unclear
Jenkinson et al. (1999)	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Unclear
Lee et al. (2012)	High risk	Low risk	High risk	High risk	Unclear	Low risk	Unclear
Montserrat et al. (2001)	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Ryan et al. (2011)	High risk	Low risk	High risk	Low risk	Low risk	High risk	Unclear
Siccoli et al. (2008)	Unclear	High risk	Low risk	High risk	Low risk	Low risk	Unclear
Yu et al. (1999)	Unclear	High risk	High risk	High risk	Unclear	High risk	Unclear
Martinez-Garcia et al. (2015)	Unclear	High risk	Low risk	Low risk	High risk	Low risk	Unclear

necessary to classify the disorder into more homogeneous categories; these have been termed ‘phenotypes’ and are based on clinical, pathophysiologic, molecular and cellular

characteristics. An AHI-centred approach, without stratification by other syndrome characteristics, likely hinders understanding of the genetic and biological underpinnings



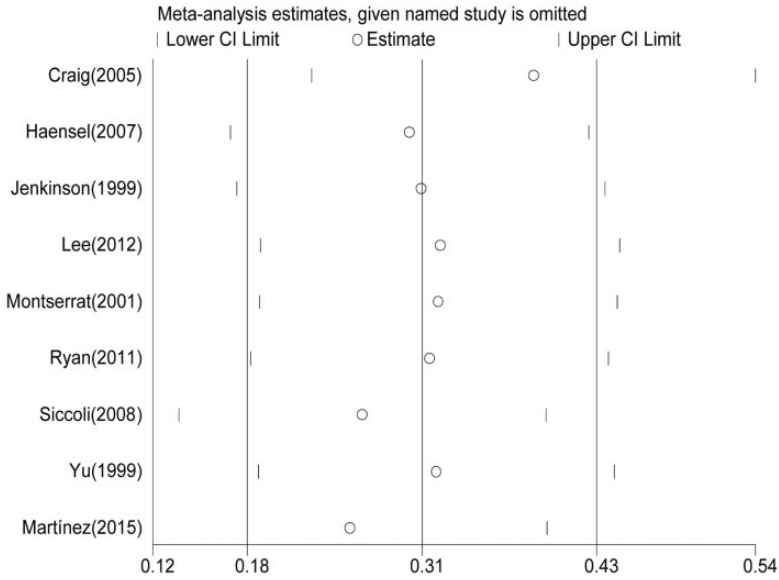


Figure 4. Sensitivity analysis of nine randomized controlled trials. CI: confidence interval.

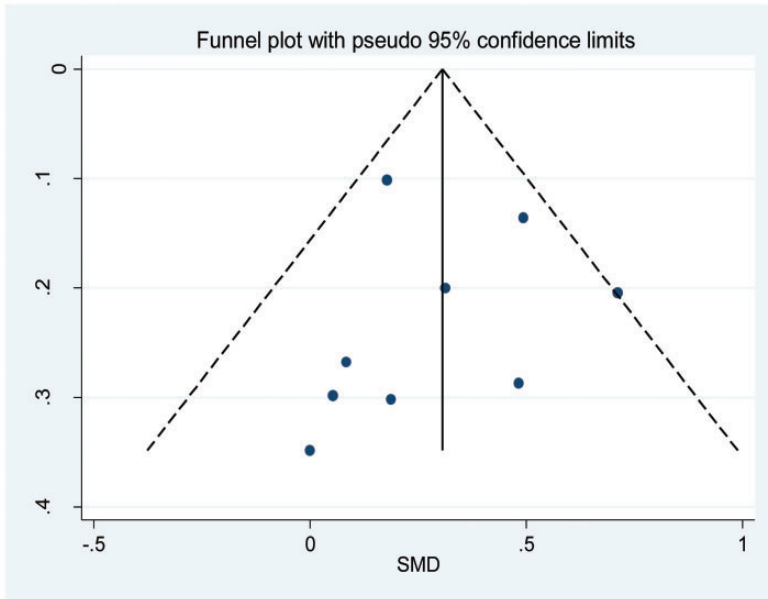


Figure 5. Funnel plot for publication bias analysis. SMD: standard mean difference.

of the disorder and the effects of CPAP.<sup>53</sup> Some researchers have found that CPAP therapy improves mood symptoms,<sup>54</sup> but converse findings have also been reported.

These conflicting results may stem from different OSA phenotypes.

This meta-analysis quantitatively explored the effect of CPAP therapy on depression in

OSA patients. Compared with the control group, the CPAP group showed a significant improvement in psychological symptoms. The subgroup analyses also produced important findings. CPAP treatment of >4 hours/night tended to be more effective in relieving depression. The sensitivity analysis indicated that these findings were robust. No significant publication bias was observed between different studies. A similar study conducted by Povitz et al. showed inconclusive findings for the effect of CPAP on depression in OSA patients.<sup>34</sup> Both significant heterogeneity between trials and study design were important modifiers of the treatment effect. The greatest effect of CPAP on depression symptoms occurred in patients with a higher burden of depression at baseline.<sup>34</sup> Interestingly, another previous study showed that PAP has clinical effects on depressive symptoms in OSA patients, but the effect was not superior to dental applications or sham PAP.<sup>35</sup>

This study has its strengths. First, the data have important clinical significance, and indicate that CPAP treatment significantly improves depression in patients with OSA. Second, this is the first meta-analysis to include all relevant RCTs on the subject carried out in the past decades and published as full-length articles.

Several limitations of the present study must also be acknowledged. First, although an exhaustive literature search was performed, only nine relevant RCTs with 1,052 patients were identified, which may be insufficient to draw firm conclusions. Additional multiple, large-scale studies are needed to further examine the effect of CPAP on depression. The accuracy of results may have been affected by the absence of individual participant data. Third, psychiatric counselling or psychotropic medications for patients were not available in the early part of the research period examined. Fourth, most studies did not examine in detail potential influencing

factors for mood status, including medication and food. Fifth, only trials reported in English were examined, which may have led to publication bias. Sixth, different evaluation tools were used in different studies. Seventh, we did not run the meta-analysis for patient sex and age, which are critical factors in the association between OSA and depression. Eighth, we did not include somnolence scores, which can be evaluated by the Epworth Sleepiness Scale.

Overall, the present findings indicate that effective CPAP >4 hours/night can significantly improve psychological symptoms in patients with OSA.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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