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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Effects of continuous positive airway pressure therapy on inflammatory markers in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials

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Abstract

Objective In this meta-analysis, we provide the findings of randomized controlled trials on the levels of inflammatory markers in patients with obstructive sleep apnea (OSA) receiving continuous positive airway pressure (CPAP).

Methods Literature published in the PubMed, Web of Science, Embase and Cochrane databases up to May 21, 2024, was comprehensively searched, and inclusion and exclusion criteria were developed. Pooled estimates of CPAP therapy were analyzed via the standardized mean difference (SMD). This meta-analysis follows the PRISMA 2020 guidelines and is registered with PROSPERO (ID CRD42024548588).

Results A total of 15 studies were included, each reporting data on one or more inflammatory markers, as follows: 10 studies on C-reactive protein (CRP), 12 studies on interleukin-6 (IL-6), 3 studies on interleukin-8 (IL-8), and 9 studies on tumor necrosis factor-α (TNF-α). The results revealed that the SMDs (95% confidence intervals [CIs]) for CRP, IL-6, IL-8 and TNF-α levels before and after CPAP treatment were 0.88 (95% CI 0.28–1.48), 0.58 (95% CI 0.12–1.05), 0.20 (95% CI 0.39–0.80) and 0.17 (95% CI 0.05–0.29), separately.

Conclusion CPAP therapy used for a certain duration can lower CRP, IL-6 and TNF-α levels in OSA patients, and there are substantial differences observed in the various inflammatory indicators. To confirm the usefulness of these biomarkers in evaluating CPAP therapy for cardiovascular risk reduction among OSA patients, more randomized controlled trials (RCTs) have to be carried out in the future.

Keywords Obstructive sleep apnea · Continuous positive airway pressure · Inflammatory markers · Meta-analysis

Abbreviations

Abbreviation	Nomenclature
AHI	Apnea-hypopnea index
BMI	Body mass index
CI(s)	Confidence interval(s)
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
ESS	Epworth sleepiness scale
IL-6	Interleukin-6
IL-8	Interleukin-8
OSA	Obstructive sleep apnea
RCT(s)	Randomized controlled trial(s)
SD	Standard deviation
SMD(s)	Standardized mean difference(s)
TNF-α	Tumor necrosis factor-α

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Introduction

The common sleep disease known as obstructive sleep apnea (OSA) is marked by recurrent obstruction of the upper airway while you sleep, which leads to fragmented

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sleep, intermitted low oxygen levels, and significant physiological stress [1]. Obstructive sleep apnea impacts millions of individuals globally, and its prevalence is increasing in tandem with the obesity epidemic. This condition is associated with cardiovascular disease [2, 3], metabolic disorders [4], and cognitive disorders [5, 6]. Among the main pathways that connect OSA to these comorbidities is inflammation caused by intermittent hypoxemia and oxidative stress. Research has demonstrated that inflammatory indicators like C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and interleukin-6 (IL-6) are elevated in OSA patients [7]. These biomarkers indicate systemic inflammation, which can cause endothelial dysfunction, atherosclerosis, and insulin resistance.

Continuous positive airway pressure (CPAP) is the usual therapy for OSA [1]. By maintaining an open airway while sleeping, apnea events can be effectively reduced. New evidence also indicates that CPAP treatment may reduce inflammation degrees in individuals with OSA; however, the results are mixed, and many studies have demonstrated that CPAP therapy has no obvious effect on inflammatory factors [8–10]. The reduction of inflammatory cytokine levels by CPAP therapy is still controversial.

Although meta-analyses on this topic are available, they included observational or cohort studies [11], and the levels of evidence in these studies were low. The literature included in meta-analyses of randomized controlled studies is relatively old [12], and many more randomized controlled trials (RCTs) have been published since then. Therefore, this meta-analysis aimed to combine existing evidence from RCTs to evaluate the impact of CPAP treatment on inflammation indicators in individuals with OSA.

Methods

Search strategy

Up to May 21, 2024, we thoroughly searched the PubMed, Web of Science, Embase, and Cochrane databases, restricting our search to humans, adults (those who are 18 years of age or older), and articles in English. The search terms used were as follows: “OSA”, “obstructive sleep apnea”, “OSAHS”, “obstructive sleep apnea hypopnea syndrome”, “CPAP”, “continuous positive airway pressure”, “inflammatory factors”, “CRP”, “C-reactive protein”, “TNF-α”, “IL-6” and “IL-8”. The reference lists of the identified studies were checked for more relevant articles to review.

Inclusion and exclusion criteria

Randomized participants ≥ 18 years old and diagnosed with OSA (defined by an apnea-hypopnea index (AHI) ≥ 5/h) were compared before and after CPAP treatment. The trial must have also measured and reported data on CRP, IL-6, TNF-α, and IL-8 levels. When a specific patient population was covered in multiple publications, we selected the one that included the complete dataset. Parallel and intersecting RCTs published in English were considered eligible. Reviews, reports, observational studies, uncontrolled trials and articles not in English were excluded.

Study selection and data extraction

The eligibility of the studies was evaluated by two authors. From the eligible research, one author extracted necessary information, and another author then separately examined. The data extracted for each study included the first author’s name, year of publication, country, inclusion and exclusion criteria, sample size, sex distribution, mean age, baseline body mass index (BMI), Epworth sleepiness scale (ESS) score, AHI, duration of treatment, and marker test results. If the study provided the median and quartile rather than the mean and standard deviation (SD), the corresponding mean and SD were calculated according to the method of J. Shi et al. [13, 14]. The primary results were the CRP, IL-6, IL-8, and TNF-α levels, and their analyses were included based on data availability.

Two authors used the Review Manager 5.4 software to assess the risk of bias for each study with the Cochrane risk assessment tool (Online Resource: Fig. S1). In the event of a disagreement, a third researcher was consulted to resolve it.

Statistical analysis

The meta-analysis utilized Stata statistical software, version 17.0. Due to the differences in inflammatory indicators measured by various laboratories, standardized mean differences (SMDs) were utilized instead of absolute levels for calculating the pooled estimates. The SMD values were obtained by dividing the average differences in the levels of specific inflammatory indicators in each study by their corresponding standard deviations, where the SDs were measured before and after CPAP treatment. The I^2 index determined heterogeneity. If the value of I^2 was > 50%, the random- effects model was adopted. Otherwise, a fixed-effect model was used [15]. A random-effects model was used for subgroup analysis to assess the effects of a number of relevant variables, including the AHI (≤ 15 events/h versus > 15 events/h), duration of treatment (≤ 3 months versus > 3 months), and BMI (≤ 35 versus > 35). The aim

of this study was to evaluate the effects of CPAP therapy and explore possible sources of heterogeneity. A sensitivity analysis was performed to assess the robustness of data in every study for the combined impact dimension. Funnel plots and Egger linear regression [16] were utilized to test for publication bias. We also used the shear complement method to detect and adjust for funnel plot asymmetries caused by publication bias [17].

Results

Characteristics of the included studies

As shown in Fig. 1, 1909 studies were retrieved, and 1121 studies remained after we excluded duplicate studies; after reading the titles and abstracts, irrelevant studies, non-English-language studies and reviews were further excluded. From the remaining 77 studies, 62 studies were excluded after the full texts were read; of these, the full texts could not be obtained for 7 studies, 12 studies had incomplete data, 9 studies had mismatched outcome indicators, and 34 studies were nonrandomized controlled trials. Finally, 15 RCTs were included [8–10, 18–29], among which 10 reported CRP levels, 12 reported IL-6 levels, 3 reported IL-8 levels,

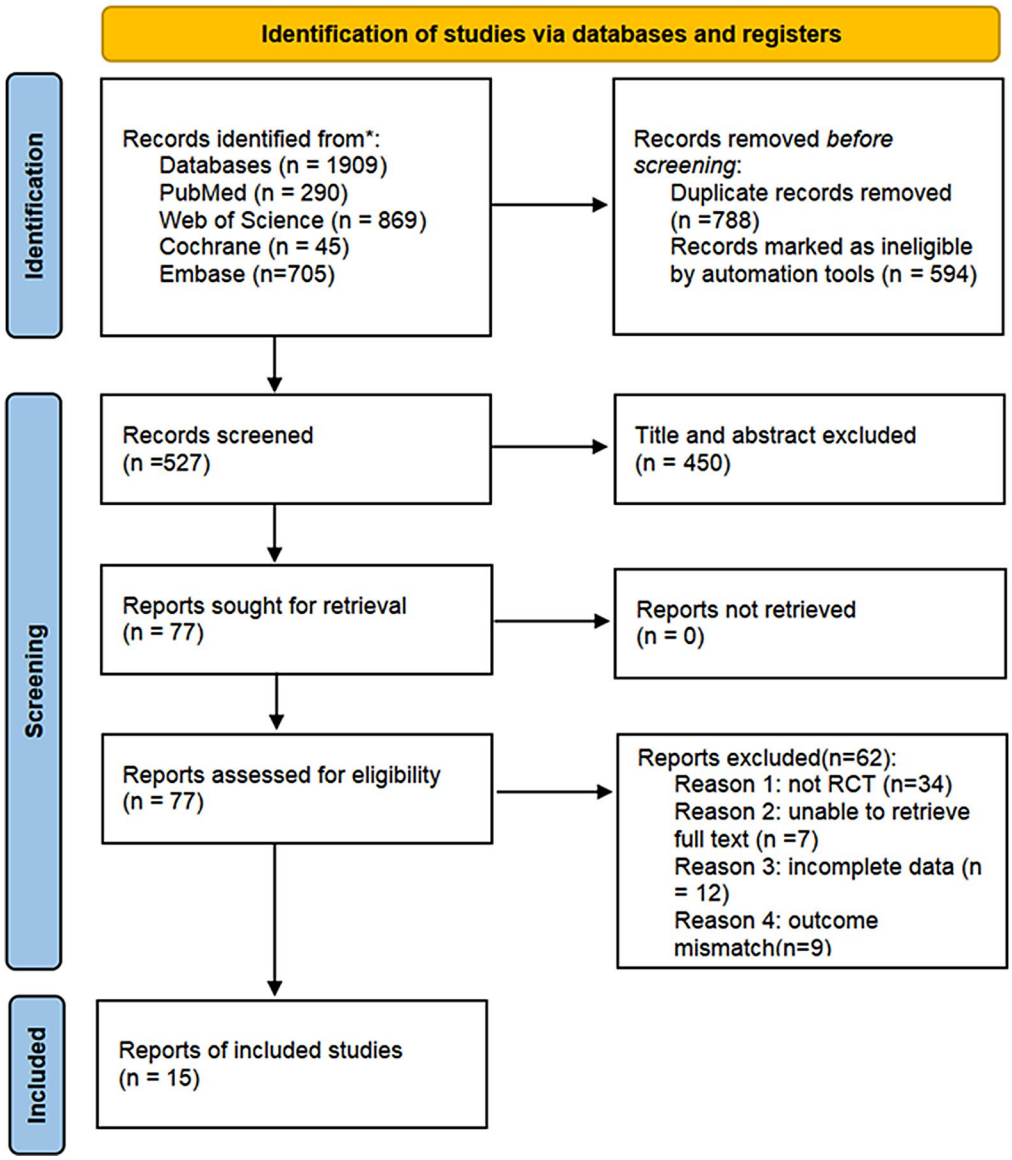

Fig. 1 Flow diagram illustrating the studies included and excluded stud in this meta-analysis

and 9 reported TNF-α levels. The baseline patient characteristics from these studies are summarized in Online Resource: Table S1.

Pooled analysis

Among the 15 studies included, 10 RCTs with 609 participants included CRP analysis. The combined SMD before and after CPAP was 0.88 (95% CI 0.28–1.48; $p=0.004$; Fig. 2). The results revealed high heterogeneity ($I^2=95.5\%$), suggesting that other factors may have influenced the effect of CPAP intervention on the reduction of CRP levels.

Twelve RCTs involving 687 participants included IL-6 analysis. The comprehensive SMD was 0.58 (95% CI 0.12–1.05; $p=0.014$; Fig. 3), with high heterogeneity ($I^2=93.6\%$) of the data.

In 3 studies, IL-8 results were reported for 163 participants, with a combined SMD of 0.20 (95% CI 0.39–0.80; $p=0.502$; Fig. 4), indicating that there was no statistically significant outcome from CPAP treatment, and high heterogeneity ($I^2=82.4\%$) of the data.

Nine RCTs included TNF-α data for 518 participants, showing CPAP therapy led to a decrease in the TNF-α levels, with a SMD of 0.17 (95% CI 0.05–0.29; $p=0.007$; Fig. 5), and no heterogeneity of the data was found ($I^2=0.0\%$).

Subgroup, meta-regression and sensitivity analyses

The effectiveness of CPAP can be affected by many factors. We then assessed the severity of OSA (mild to moderate, AHI ≤ 30 events/h, and severe, AHI > 30 events/h), duration of treatment (< 3 months and ≥ 3 months), age (≤ 55 years and > 55 years) [1, 20, 24], baseline BMI (≤ 35 and > 35) [30, 31], baseline ESS (≤ 10 and > 10), sample size (≤ 50 and > 50) and geographical area (Asia, Europe, and the Americas) groups, as shown in Online Resource: Table S2. The outcome of meta-regression analysis is shown in Online Resource: Table S3.

Subgroup analysis of the CRP levels revealed that the age, baseline BMI, baseline AHI, baseline ESS, and sample size had no significant effects on the results. However, the treatment duration with CPAP of ≥ 3 months was associated with a decrease in CRP levels. Meta-regression and subgroup analyses did not reveal the source of heterogeneity. However, the sensitivity analysis conducted via the Stata statistical software revealed that the study by Wang et al.

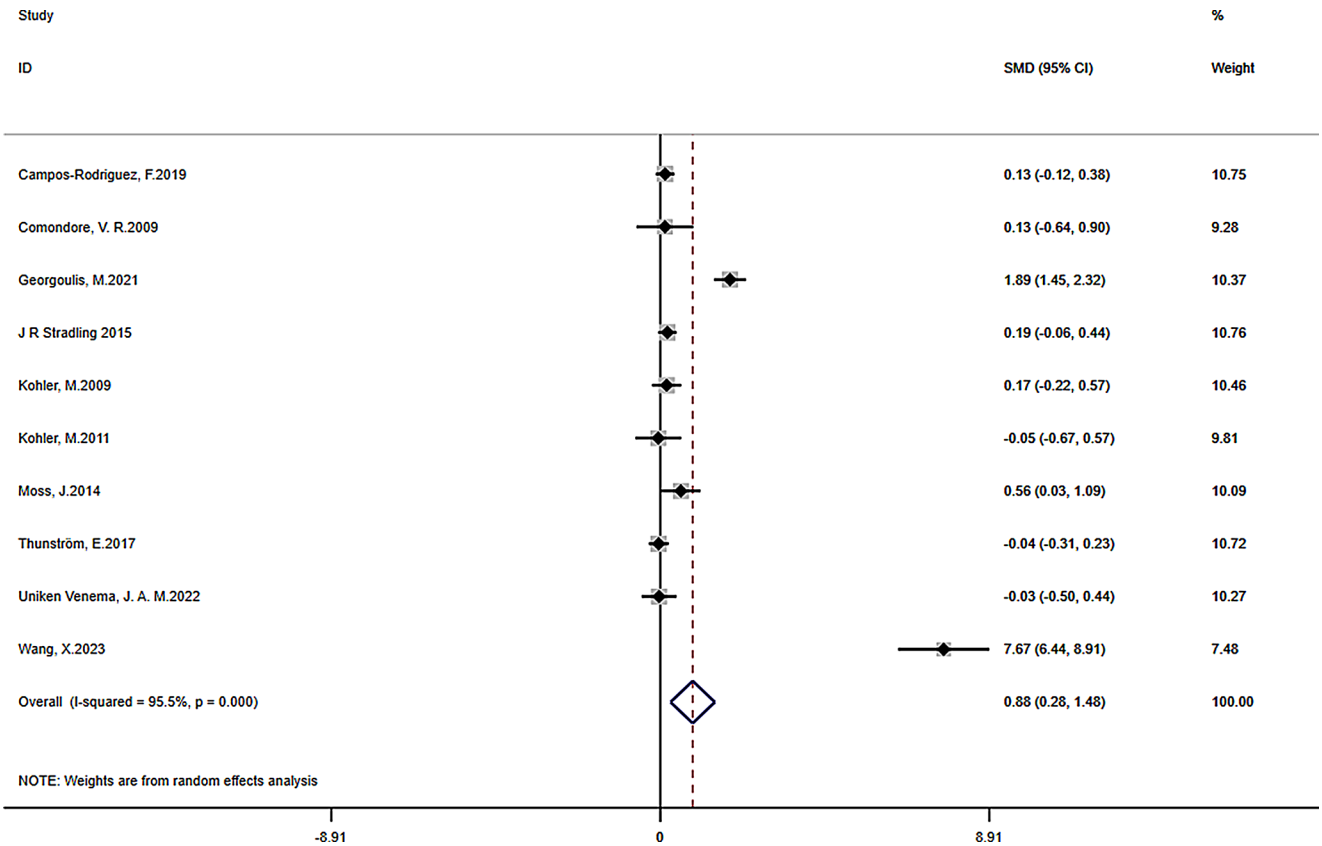

Fig. 2 Comparing C-reactive protein levels in the 10 included studies before and after CPAP therapy. Abbreviations: SMD, standardized mean difference; CI, confidence interval

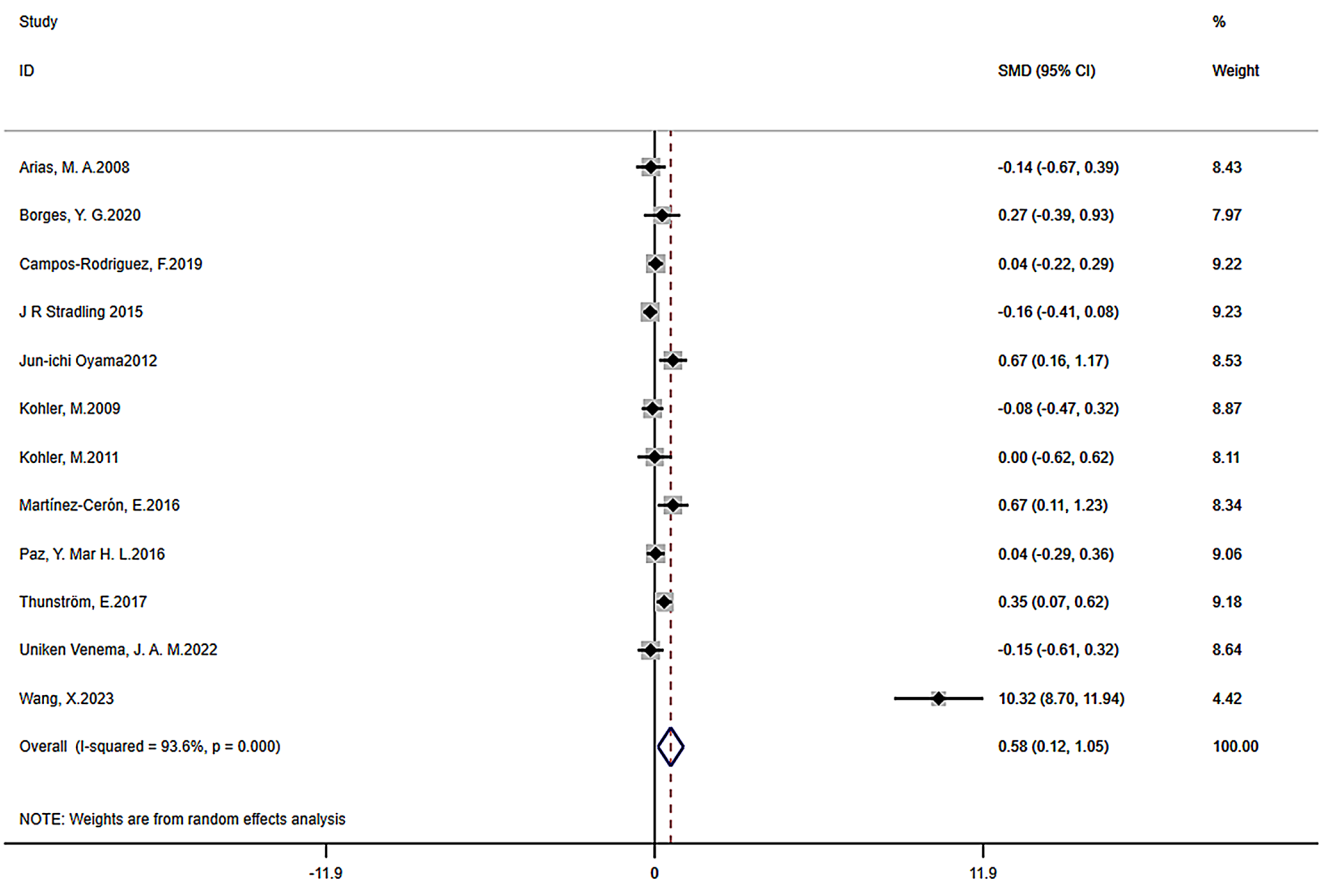

Fig. 3 Comparing IL-6 levels in the 12 included studies before and after CPAP therapy. Abbreviations: SMD, standardized mean difference; CI, confidence interval

[29] was the source of the unrobust results after the data merger.

Subgroup analysis of the IL-6 levels revealed no notable differences in IL-6 reduction when the patients were grouped by age, BMI, AHI, ESS, sample size, or region. A treatment duration of ≥3 months had a significant effect on the IL-6 concentration. Meta-regression analysis showed that duration of treatment, age, baseline ESS, and sample size may be the source of heterogeneity; however, subgroup analysis did not find the source of heterogeneity. However, the sensitivity analysis revealed that the paper by Wang et al. [29] was the source of the unrobust results.

Owing to the limited number of studies on IL-8 levels, meta-regression and subgroup analyses were not executed.

Subgroup analysis revealed that when the duration of treatment was ≥3 months and the AHI was >30, CPAP therapy significantly reduced the TNF-α levels. Meta-regression did not reveal the source of heterogeneity. The results of the sensitivity analysis were robust.

Publication bias

Publication bias was assessed for groups of studies that included≥10 articles. The Egger test ($p=0.078$) yielded consistent results, and there was no significant publication bias in the studies on CRP levels. However, the results of the Egger test ($p=0.031$) showed bias in the studies on IL-6 levels. However, this did not affect the overall findings according to the trim-and-fill analysis. (Online Resource: Fig. S2)

Discussion

Our meta-analysis evaluated how CPAP treatment affected the levels of various inflammatory markers in OSA patients, including TNF-α, IL-6, IL-8, and CRP. Because of their extensive research and potential substantial correlation between OSA and cardiovascular disease, we selected these inflammatory markers. OSA has been linked to genetic variations of TNF-α, IL-6, and CRP [32–34]. The results of this meta-analysis revealed that while CPAP did not lower IL-8 levels in patients with OSA, it did lower CRP, IL-6, and TNF-α levels. A previous meta-analysis revealed that

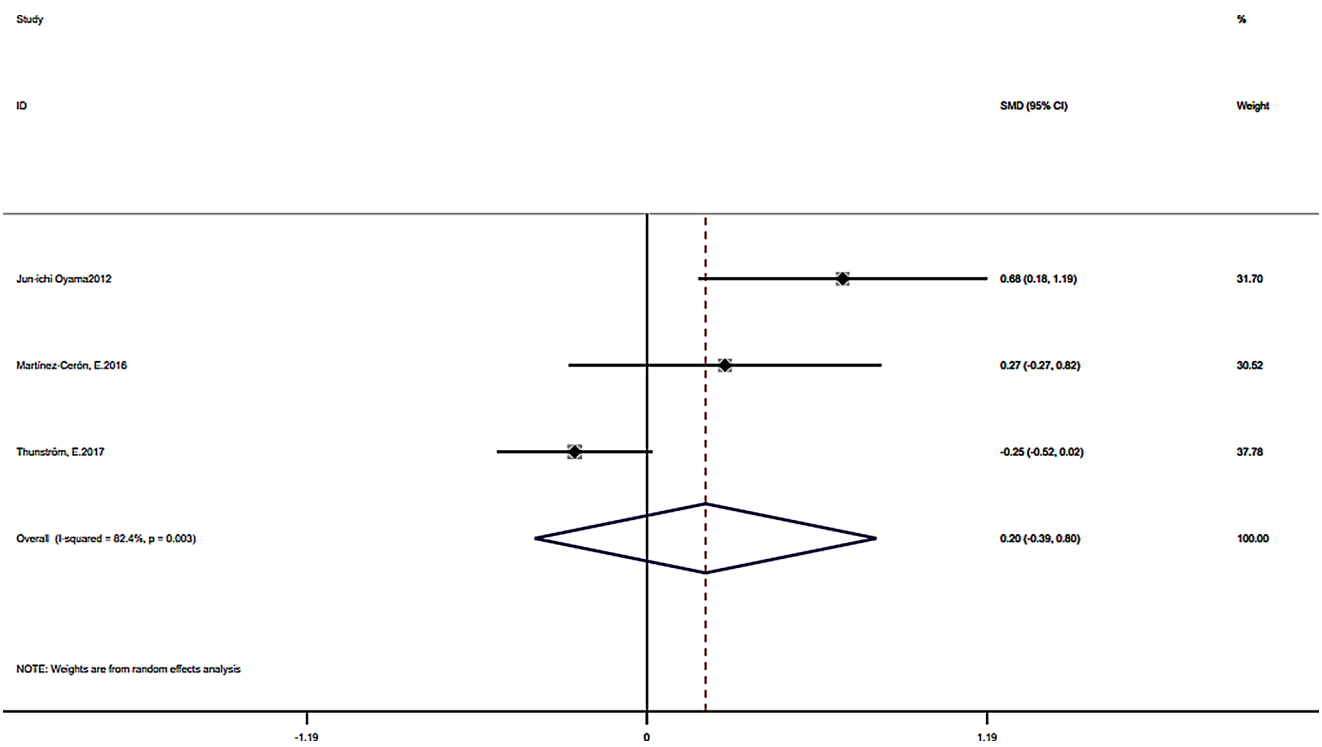

Fig. 4 Comparing IL-8 levels in the 3 included studies before and after CPAP therapy. Abbreviations: SMD, standardized mean difference; CI, confidence interval

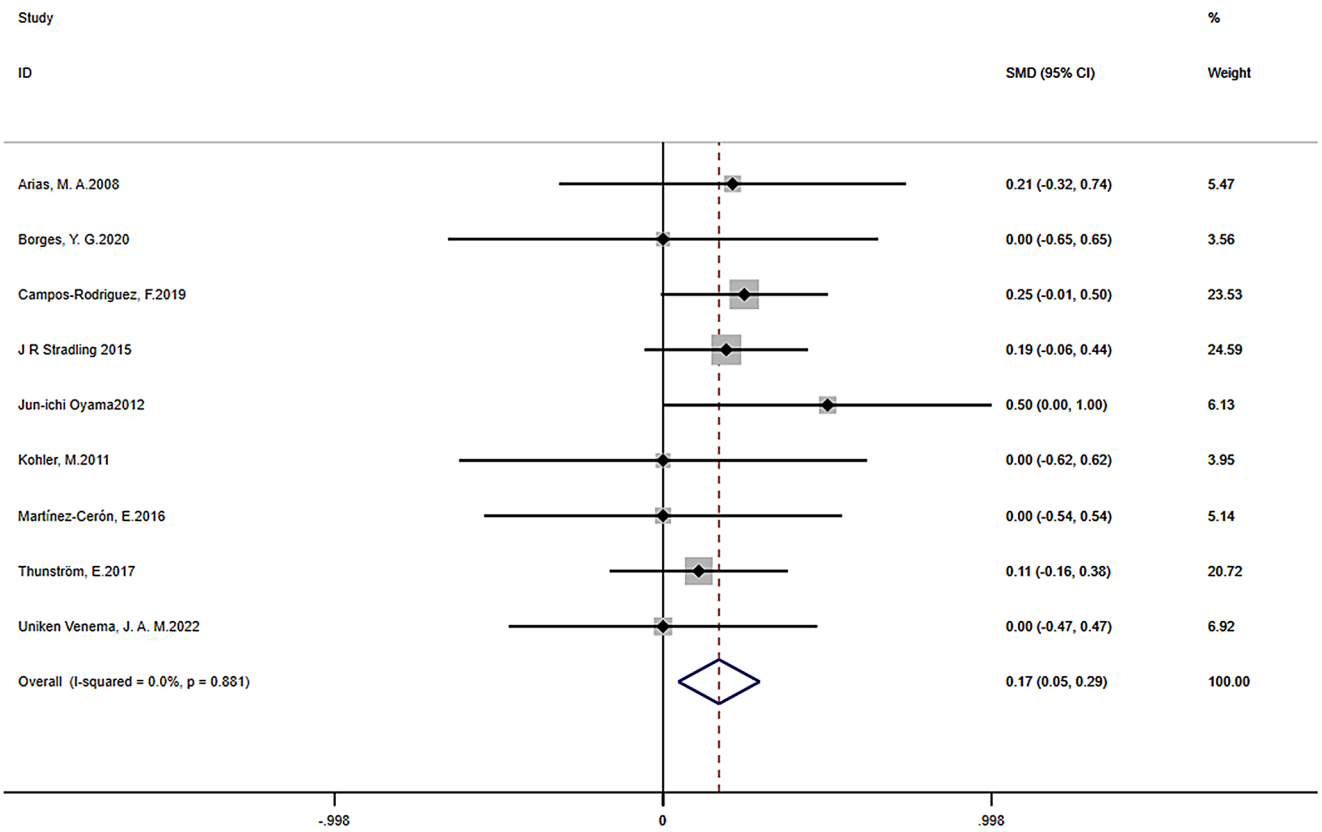

Fig. 5 Comparing TNF-α levels in the 9 included studies before and after CPAP therapy. Abbreviations: SMD, standardized mean difference; CI, confidence interval

CPAP therapy could improve IL-8 levels [11]; however, it included observational and prospective studies, which are more limited than RCTs by selection bias and confounding factors.

CPAP is considered the first choice of treatment for patients with OSA [1], but the effects of CPAP therapy on the levels of inflammatory markers remain controversial. For CRP, some studies have reported favorable outcomes [35–40], whereas others have reported no changes in the CRP levels after CPAP treatment [41–45]. Our meta-analysis, which included randomized controlled studies, revealed that CPAP therapy reduced CRP and IL-6 levels at least 3 months treatment in OSA patients. This result is consistent with a previous study [46]. Short-term treatment (<3 months) may be difficult to reveal the effect due to the delayed response of inflammatory state of CRP decline. In addition, the improvement of TNF-α levels is also dependent on long-term treatment, especially in patients with severe OSA (AHI>30 events/h), suggesting that the duration of treatment and disease severity jointly affect the level of inflammatory cytokines. A different conclusion was reached in a previous meta-analysis of randomized controlled studies [12], which suggested that CPAP therapy did not cause a reduction in TNF-α levels. However, another recent meta-analysis suggested that CPAP therapy could reduce TNF-α levels in OSA patients [47], although it included more than just RCTs.

We were surprised by the sensitivity analysis's non-robust results for IL-6 and CRP levels, which could be the consequence of a number of factors. First of all, it's possible that tiny sample sizes lacked sufficient confidence to fully disclose all of the treatment's possible advantages. In addition, CPAP treatment could reduce OSA symptoms, but may not have had substantial effects on inflammatory markers. Finally, a regional subgroup analysis revealed a small number of studies in Asian populations, but significant benefits to Asian patients. Thus, to validate these results, more well planned, extensive clinical trials involving Asian patients are required.

The beneficial effects of CPAP treatment can be influenced by a number of conditions. Among these, the length of treatment has a clinically significant impact in lowering inflammatory marker levels. Our findings showed that the CRP, IL-6 and TNF-α levels improved after 3 months or more of treatment. In addition, the treatment had beneficial effects on TNF-α levels in patients with severe OSA (AHI>30 events/h). Furthermore, most previous studies support the same conclusion [41, 48–51]. The CRP and IL-6 levels did not significantly differ depending on the duration of treatment. Furthermore, variations in mean age, BMI, AHI, ESS, length of therapy, and baseline inflammatory marker levels did not predict treatment differences based on the systemic inflammatory response, according to meta-regression analyses. Because subgroups were created after the fact and research averages rather than specific patients were used as information points, the meta-analysis's findings should be carefully considered. As a result, none of the requirements listed above may independently foresee how well CPAP treatment will work for chronic inflammation.

Although the separate components involved are still up for debate, obesity has been found to have a significant role in both causing and worsening chronic inflammation in OSA patients. Guilleminault C et al. [52] and Sharma SK et al. [30] even suggested that the increase in the CRP level could be attributed to obesity, but most studies reported that the increase in the CRP level was related mainly to OSA, not obesity [53–56]. The results of our meta-analysis revealed no discernible relationship between the change in CRP measurements and the BMI. Furthermore, no research have documented CRP changes consistent with the BMI for effective CPAP therapy. Following 3 months of CPAP therapy, there was no discernible difference in CRP levels between obese and nonobese OSA patients [31].

In addition to the inflammatory markers, oxidative stress has also been confirmed to be closely related to the pathophysiology of OSA. In the study by Tichanon et al. [57], after three months of CPAP treatment, oxidative stress, airway inflammation, AHI, ESS, systolic blood pressure, diastolic blood pressure and mean arterial pressure were all reduced in OSA patients. The significant reduction in mean arterial pressure after CPAP treatment may be due to the relief of endothelial dysfunction. The alleviation of endothelial inflammation in patients can improve ESS, revealing that longer treatment duration and better compliance may further reduce airway inflammation. This study also found that the malondialdehyde level in OSA patients was significantly reduced after treatment, indicating that CPAP can effectively inhibit the changes in the redox state related to OSA, reduce chronic intermittent hypoxia, and thereby reduce the generation of oxidative stress.

This study suggests that the anti-inflammatory effect of CPAP may be different depending on the traits or endotypes of OSA patients. The endotypes of OSA include different physiological mechanisms such as upper airway collapse tendency, low arousal threshold, high loop gain, or respiratory control instability [58]. Zinchuk et al. [59] suggested that the endotypes of OSA are associated with cardiovascular risk and may involve inflammatory pathways. We speculate that patients with severe nighttime hypoxia, patients with high baseline inflammation levels, and non-obese OSA patients may reduce inflammatory marker levels from CPAP therapy. Intermittent hypoxia drives inflammation by activating the nuclear factor-kappaB pathway, and improved oxygenation by CPAP therapy may directly inhibit this

pathway [50]. Patients with higher baseline CRP or IL-6 values may benefit more from the targeting of inflammatory pathways by CPAP therapy [53]. Obesity may obfuscate OSA specific effects through adipose tissue inflammation, while improvements in inflammation in non-obese patients are more likely to be attributed to CPAP itself [31]. Of course, further analysis of OSA endotypes combined with multi-omics data is needed in the future to achieve individual anti-inflammatory therapy for OSA patients.

The findings of our meta-analysis need to be regarded with some caution. Primarily although our analysis showed a great deal of variability, no clear factors were found. Heterogeneity may be clinical or methodological. In our study, all included studies were randomized controlled studies; therefore, methodological heterogeneity does not appear to be possible. According to the studies and patient data presented in Table S1, we found that clinical heterogeneity might be present. We then performed sensitivity, subgroup, and meta-regression analyses to investigate possible causes of heterogeneity. However, we did not find that variations in age, BMI, AHI, ESS, racially poor sample size, or duration of CPAP treatment were the exact sources of heterogeneity. Second, the impact of CPAP treatment on chronic inflammation was not the main outcome assessed in the majority of research. Furthermore, the results were susceptible to selection bias since the sample sizes were small, particularly for IL-8 levels. Third, the methods used to measure inflammatory markers in some studies were inconsistent, which has led to biased outcome indicators. Fourth, substantial variances were discovered in factors such patient characteristics, medications, marker measurements, treatment patterns, and treatment durations, even though the majority of studies have made an effort to account for possible confounders that could affect the levels of inflammatory indicators. Finally, the mean and SD values for some research were determined by analyzing the charts or computing the outcomes of the nonnormally distributed statistics (medians and quartile distances). Therefore, there may be a chance of inaccuracy because these statistics do not accurately reflect values derived from real research. These cautions might all result in inaccurate findings, lower statistical precision, or even deny our findings.

Conclusion

The results of this meta-analysis indicated that CPAP treatment can significantly reduce the levels of CRP, IL-6 and TNF-α in patients with OSA, but had no significant effect on IL-8 levels. The duration of treatment and the severity of OSA were the key factors influencing the alleviation of inflammation, while BMI revealed no significant correlation with the changes in inflammatory markers. However, this study still had some limitations. Firstly, the included studies had high heterogeneity, potentially due to variations in population characteristics, CPAP compliance and methods of detecting inflammatory factors. Secondly, because of the limited sample sizes used for the IL-8 analysis, selection bias might affect the findings. Finally, most studies did not systematically control for confounding factors, including drug use and comorbidities.

Given the strong link between OSA and cardiovascular diseases, future studies should examine how lowering chronic inflammation can improve cardiovascular risks related to OSA and clarify the association between the anti-inflammatory effects of long-term CPAP treatment and cardiovascular outcomes. More large-sample randomized multicenter controlled studies are needed in the future to explore the exact impact of CPAP treatment on inflammatory factors. Additionally, the synergistic effects of CPAP treatment combined with lifestyle and pharmacological therapies can also be explored.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11325-025-03348-6.

Author contributions QZ, SH and QL designed the study. QZ wrote the initial manuscript. Data collection and statistical analysis were carried out by QZ, QL, ZW, SC, and GC. SH gave the article a careful evaluation and made adjustments. Each author accepted the submitted version of the article and contributed to it.

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Data availability Without unnecessary hesitation, the authors will make the raw data that supports the results of this research open to the public.

Declarations

Ethical approval Ethical permission was not sought for this meta-analysis, as only pooled data from previously permitted individual studies were included.

Informed consent Every individual participant in the earlier research gave their informed permission.

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

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