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Effect of Sleep Surgery on C-Reactive Protein Levels in Adults With Obstructive Sleep Apnea: A Meta-Analysis

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Objectives/Hypothesis: To evaluate associations between sleep surgery and CRP (C-reactive protein) levels in adults with obstructive sleep apnea (OSA).

Study Design: Meta-analysis.

Methods: Two authors independently searched PubMed, Medline, EMBASE, and Cochrane review databases until July 2019. The keywords used were sleep apnea, OSA, sleep apnea syndromes, surgery, C-reactive protein (CRP), and inflammatory markers. The effects of sleep surgery on CRP levels were examined using a random-effects model.

Results: Nine studies with 277 patients were analyzed (mean age: 46.5 years; 92% men; mean sample size: 30.8 patients). The mean change in the apnea–hypopnea index (AHI) after surgery was significantly reduced by −21.1 (95% confidence interval [CI], −28.4 to −13.7) events/hr. Overall, sleep surgery resulted in a significant reduction of CRP levels in patients with OSA (standardized mean difference [SMD] = −0.39, 95% CI, −0.67 to −0.11). Patients with postoperative AHI reduction >20 events/hr achieved a greater reduction in CRP than those with AHI reduction <20 events/hr (SMD: −0.72 vs. −0.14, *P* for heterogeneity = .007). According to subgroup analysis, differences in the CRP levels after surgery were nonsignificant in the different countries (i.e., United States vs. other countries), CRP types (i.e., CRP vs. high-sensitivity CRP), surgical procedures (i.e., pharyngeal surgery vs. other surgical procedures), and follow-up period (i.e., <6 vs. >6 months).

Conclusions: Sleep surgery for OSA resulted in a significant reduction of CRP levels in adults. The beneficial effect of surgery on CRP levels is greater in patients with large improvement in OSA (i.e., AHI reduction >20 events/hr) after sleep surgery.

Key Words: Adult, C-reactive protein, meta-analysis, sleep apnea syndromes, surgery, uvulopalatopharyngoplasty.

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INTRODUCTION

Obstructive sleep apnea (OSA) in adults is a respiratory disorder caused by complete or partial airway obstruction during sleep, leading to considerable physiological disturbances with various clinical effects.[1–3] In adults, untreated OSA is associated with an increased risk of cardiovascular events.[2,3] Therefore, early diagnosis and proper treatment of OSA are imperative.

C-reactive protein (CRP) is a serum marker of inflammation.[4] CRP is associated with incident myocardial infarction, stroke, peripheral arterial disease, sudden cardiac death, and OSA.[5–9] Several meta-analyses have reported that patients with OSA had significantly higher CRP levels than did those without OSA.[6–9] Growing bodies of evidence suggest an association of elevated CRP levels with OSA and cardiovascular complications[5-9]; nevertheless, whether treatments for OSA reduce CRP levels is unclear.

Currently, continuous positive airway pressure (CPAP) therapy is considered one of the most effective treatments for OSA.[10] Treatment of OSA with CPAP therapy is associated with a reduction in CRP levels.[11–14] However, not all patients had favorable compliance with CPAP therapy.[15] Therefore, patients who are intolerant of CPAP therapy may eventually receive surgical interventions.[16–18] However, the effect of surgical procedures on CRP levels in adults with OSA remains unclear.[19]

The aim of this study was to evaluate whether sleep surgery affects CRP levels in adults with OSA. Furthermore, we conducted a subgroup analysis to compare changes in CRP levels with respect to country, CRP measurement type, surgical procedure, and follow-up period. Different surgical procedures may engender different degrees of improvement in OSA; accordingly, we also

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examined the associations between postoperative OSA changes and CRP reductions.

MATERIALS AND METHODS

Search Strategy

This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and the recommendations of the Meta-analysis of Observational Studies in Epidemiology group.[20] Regarding the search strategy applied in this study, the following PICO elements were used: adults with OSA (patient or problem), sleep surgery (intervention or indicator), before and after sleep surgery (comparator), and CRP levels (outcome). Two authors independently searched PubMed, MEDLINE, EMBASE, and Cochrane review databases for articles published until July 2019. Moreover, the reference sections of the selected articles were searched for additional articles. The following keywords were used in the search: "sleep apnea," "OSA," "obstructive sleep apnea," "sleep apnea," "sleep apnea syndromes," "nasal surgical procedures," "uvulopalatopharyngoplasty," "UPPP," "hyoid suspension," "tongue surgery," "Tongue base surgery," "radiofrequency ablation," "maxillomandibular advancement," "tracheostomy," "multilevel surgery," "upper airway stimulation," "hypoglossal nerve stimulation," "surgical procedures, operative," "robotic surgical procedures," "surgery," "CRP," "C-reactive protein," "inflammation," "inflammatory markers," and "cardiovascular risk factors." Only studies published in English were considered. Supporting Table 1 in the online version of this article lists the keywords used in the search process. Supporting Table 2 in the online version of this article lists the details of the search process used for each database.

The study inclusion criteria were as follows: studies should include patients aged >18 years, the OSA diagnosis should be confirmed through polysomnography studies (i.e., apnea-hypopnea index [AHI] >5), included patients should have undergone surgical procedures for OSA treatment, and pre- and post-operative CRP levels should be measured and reported. Anatomical features, disease severity, and comorbidities vary considerably among patients with OSA; hence, no standard surgical procedure for OSA exists.[19] After a careful review of relevant articles, we classified OSA surgery into 1) soft tissue surgery (e.g., nasal surgery, uvulopalatopharyngoplasty, or tongue base surgery); 2) skeletal surgery (e.g., maxillomandibular advancement); 3) tracheostomy; and 4) nerve stimulation.[19]

Studies that included patients who had received both surgery and CPAP therapy or received surgery and weight loss intervention were excluded. Case reports, abstracts, and letters to the editor were also excluded. The initial search was conducted by two reviewers independently (K.-T.K. and W.-C.H.) and was assessed by the two corresponding authors (M.-T.L. and W.-C.H.).

Quality Assessments

The methodological assessment of the article quality in this meta-analysis entailed using the relevant section of the Newcastle-Ottawa Scale (NOS).[21] Quality scores ranged from 0 (lowest) to 9 (highest). The toolset was adapted to each article separately by two authors (K.-T.K. and M.-T.L.), and disagreements were resolved through consensus.

Statistical Analysis

We analyzed the data using Comprehensive Meta-Analysis Version 3.3.070 (Biostat Inc., Englewood, New Jersey, U.S.A., 2014). The effects of surgery on CRP levels in adults with OSA were evaluated using the DerSimonian–Laird random-effects model. Statistical heterogeneity among studies was assessed using I^2 statistics, which measured the proportion of overall variation attributable to between-study heterogeneity. I^2 values of >25%, >50%, and >75% indicate mild, moderate, and high heterogeneity, respectively.[22]

Subgroup analyses were performed to evaluate changes in CRP levels in different countries (i.e., United States vs. other countries), CRP types (i.e., CRP vs. high-sensitivity CRP), and surgical procedures (i.e., pharyngeal surgery vs. other surgical procedures), and follow-up periods (i.e., <6 vs. >6 months). Another subgroup analysis was performed to compare CRP reduction levels with respect to OSA improvement degree. The correlations between continuous factors (including body mass index [BMI], preoperative AHI, preoperative CRP levels, and AHI improvements) and CRP changes were explored using a mixed-effect meta-regression analysis. Changes in CRP levels among studies in different subgroups were compared using mixed-effect models. Potential publication bias was illustrated using a funnel plot and assessed using the Egger intercept test.[22] A two-sided P value of <.05 was considered statistically significant.

RESULTS

Search Process

The initial literature search yielded 1090 studies. After the exclusion of duplicates, 885 studies remained. Among the studies, 31 were published as full-text articles and were thus assessed in this meta-analysis. Eleven studies described adults with OSA who received surgery and provided CRP measurements.[23–33] However, two studies by Marvisi et al. and Vicente et al. did not provide raw data required for meta-analysis[23,24]; their corresponding authors were contacted, but the data were still unavailable. Therefore, only nine studies were considered for the final analysis (Fig. 1).[25–33]

Quality Assessment

The quality of the included studies was assessed using the NOS,[21] ranging from 0 (lowest) to 9 (highest) points. Supporting Table 3 in the online version of this article provides details regarding the NOS scores used for quality assessment. The NOS score was 8 for five studies and 9 for the remaining four studies.

Basic Data

Table I lists the baseline characteristics of the nine included studies (277 patients).[25–33] All nine studies were retrospective or prospective case series; only one study included a normal control group.[30] No randomized controlled study was found among the included studies. None of the studies compared CRP levels between surgical and nonsurgical treatments (e.g., CPAP therapy). The mean (range) sample size was 30.8 (15–73) patients.

Of the included studies, one was conducted in Japan,[25] one in China,[29] two in Taiwan,[28,30] two in Turkey,[31,32] and three in the United States.[26,27,33] The mean patient age was 46.5 ± 6.1 years, and 92% of the

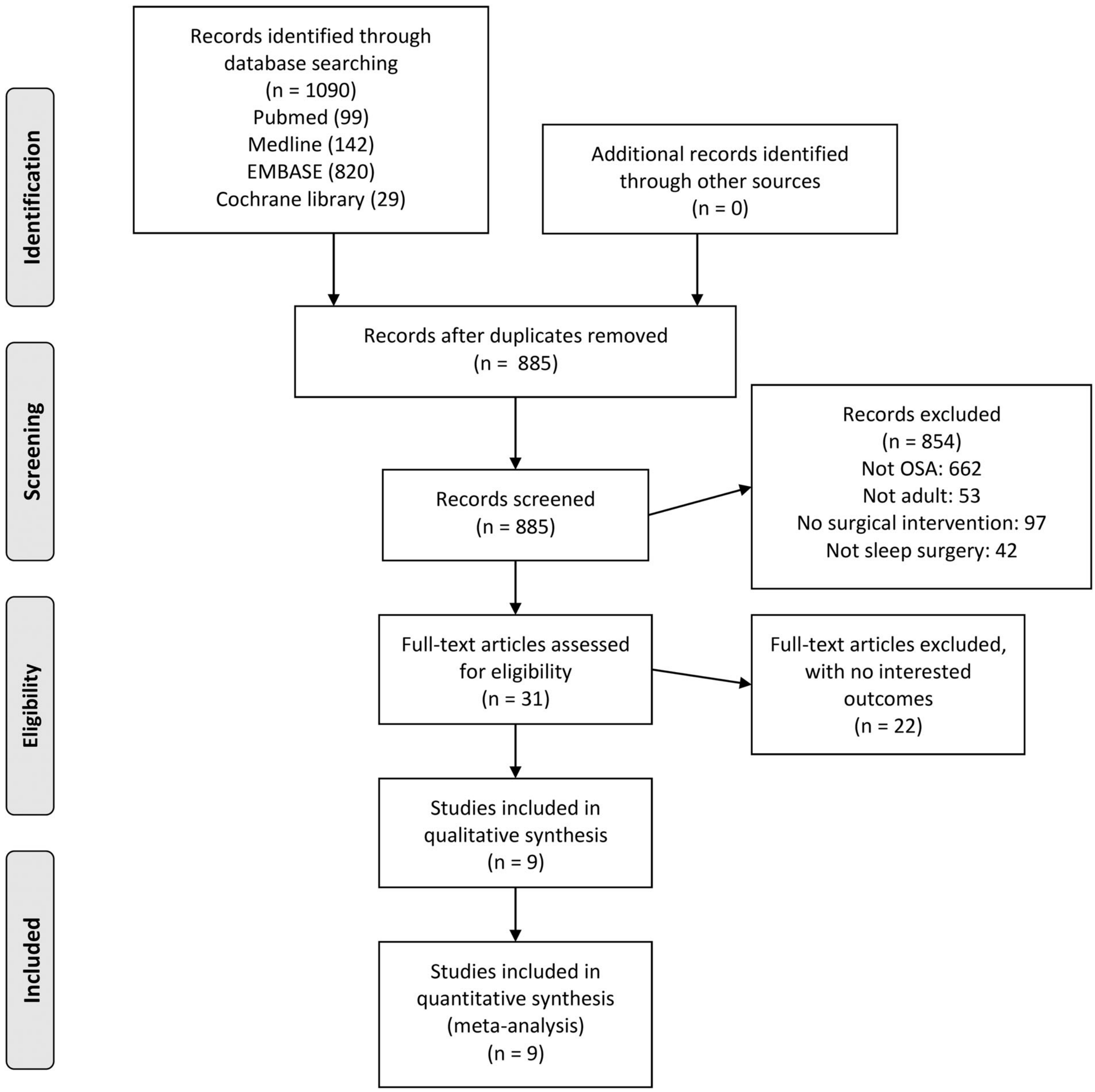

Fig 1. Flow diagram of literature search. OSA = obstructive sleep apnea.

patients were men. The mean BMI was 28.6 ± 1.4 kg/m^2. Soft tissue surgery was performed in eight studies (e.g., nasal, pharyngeal, or tongue base surgery)[25–32]; skeletal surgery (i.e., maxillomandibular advancement) was performed in only one study.[33] No study reported the use of tracheostomy or nerve stimulation for OSA.

All studies reported the AHI before and after surgery. The synthesized AHI (95% confidence interval [CI]) was 39.7 (30.8–48.6) events/hr before surgery and 16.7 (12.3–21.2) events/hr after surgery. The mean change in synthesized AHI (95% CI) after surgery was −21.1 (−28.4 to −13.7) events/hr, indicating a significant reduction; the corresponding SMD (95% CI) was −1.14 (−1.56 to −0.72). The follow-up periods ranged from 2 months to 208 days.

Effect of Surgery on CRP Levels

Overall, the results revealed that the CRP level was significantly reduced after surgery, with the SMD (95% CI) being −0.39 (−0.67 to −0.11) (Fig. 2).[25–33] I^2 was 78.8%, indicating high heterogeneity across the included studies.

Subgroup analysis with exclusion of nasal surgeries. After excluding nasal surgeries, the results showed that the CRP level was significantly reduced after surgery, with the SMD (95% CI) being −0.36 (−0.57 to −0.14). I^2 was 58.2%, indicating moderate heterogeneity across the included studies.

Subgroup analysis with respect to country, CRP type, surgery type, and follow-up period. The SMD (95% CI) for CRP levels was −0.27 (−0.53 to −0.01) for

TABLE I.
Characteristics of Included Studies*.

First Author/Year	Country	N	Study Design	Surgery	Age, Year	Male, %	BMI	ESS	AHI Before Surgery	AHI After Surgery	Marker	Follow-Up Period
Kinoshita/2006[25]	Japan	15	Case series	UPPP	42.8	14/15 = 93%	27.9 (2.8)	NR	47.9 (23.7)	15.6 (14.5)	hs-CRP	3 months
Friedman/2006[26]	USA	30	Case series	UPPP. Tongue base, pillar implant	49.5	24/30 = 80%	30.4 (4.3)	NR	48.4 (24.9)	24.7 (12.2)	hs-CRP	2 months
Kezirian/2010[27]	USA	30	Prospective case series	Multilevel Surgery	44.6	28/30 = 93%	30.1 (4.2)	NR	44.9 (28.1)	27.8 (26.4)	hs-CRP	208 days
Lee/2011[28]	Taiwan	30	Prospective case series	Relocation pharyngoplasty	39.5	29/30 = 97%	27.5 (4.5)	10.8 (4.2)	46.2 (22.9)	17.9 (13.6)	hs-CRP	6 months
Zheng/2016[29]	China	73	Prospective case series	Nasal and palatal surgery	54.9	57/73 = 78%	27.5 (3.2)	16.3 (3.5)	42.7 (12.9)	20.8 (9.8)	CRP	6 months
Lin/2016[30]	Taiwan	21	Prospective cohort	Multilevel Surgery	40.1	18/21 = 86%	26.2 (3.4)	NR	38.8 (19.9)	25.2 (20.9)	hs-CRP	3 months
Binar/2017[31]	Turkey	23	Prospective case series	Expansion sphincter pharyngoplasty	37	51/53 = 96%	27.9 (3.5)	11.8 (5.6)	32.4 (20.9)	11.8 (11.0)	hs-CRP	3 months
Mutlu/2017[32]	Turkey	25	Prospective case series	uvulopalatal flap	25	14/25 = 56%	30.1 (4.4)	NR	18.9 (8.4)	12.8 (6.6)	CRP	6 months
Boyd/2019[33]	USA	30	Prospective case series	Maxillomandibular advancement	45.9	19/30 = 63%	30 (5.8)	13.3 (4.9)	39.6 (26.5)	7.9 (7.5)	hs-CRP	6.7 months

*Data in BMI, ESS, AHI were present as mean (standard deviation).
AHI = apnea-hypopnea index; BMI = body mass index; CRP = C-reactive protein; ESS = Epworth Sleepiness Scale; hs-CRP = high-sensitivity C-reactive protein; NR = not reported; UPPP = uvulopalatopharyngoplasty.

studies conducted in the United States. This SMD was not significantly different from that observed for studies conducted in other countries (SMD = −0.45; 95% CI −0.86 to −0.04) (P for interaction = .47).

Seven studies measured serum high-sensitivity CRP,[25–28, 30,31,33] and two studies measured serum CRP.[29,32] The SMD (95% CI) for high-sensitivity CRP levels was −0.28 (−0.46 to −0.10), which was not significantly different from that for serum CRP levels (SMD = −0.71; 95% CI, −1.66 to 0.24) (P for interaction = .38).

The studies applied several surgical procedures, including uvulopalatopharyngoplasty,[25] tongue base surgery,[26] multilevel surgery,[27,30] relocation pharyngoplasty,[28] nasal surgery,[29] expansion sphincter pharyngoplasty,[31] uvulopalatal flap,[32] and maxillomandibular advancement.[33] The subgroup analysis results revealed that the SMD for CRP levels did not differ significantly between the different surgical procedures (P for interaction = .79).

Five studies had a follow-up period of ≥6 months,[27–29,32,33] and four studies had a follow-up period of <6 months.[25,26,30,31] The subgroup analysis results indicated that the SMD for CRP levels for studies with a follow-up period of ≥6 months was not significantly different from that for those with a follow-up period of <6 months (SMD: −0.43 vs. −0.33, P for interaction = .72).

Subgroup analysis—degree of OSA improvement. Surgical success has traditionally been defined as a 50% reduction in AHI and/or an AHI of <20 events/hr.[34] We compared changes in CRP levels in patients with different degrees of OSA improvement: 1) mean AHI reduction >50% versus mean AHI reduction <50% after surgery; 2) mean AHI reduction >20 events/hr versus mean AHI reduction <20 events/hr after surgery; and 3) mean AHI <20 events/hr versus mean AHI >20 events/hr after surgery.

The SMD for changes in postoperative CRP levels in patients with a mean AHI reduction of >50% did not differ significantly from that for those in patients with a mean AHI reduction of <50% (SMD: −0.48 vs. −0.28, P for interaction = .46). The SMD for changes in postoperative CRP levels in patients with a mean AHI of <20 events/hr did not differ significantly from that for those with a mean AHI of >20 events/hr (SMD: −0.54 vs. −0.25, P for interaction = .31). Notably, patients with a postoperative AHI reduction of >20 events/hr achieved a significantly greater reduction in CRP than did those with an AHI reduction of <20 events/hr (SMD: −0.72 vs. −0.14, P for interaction = .007) (Fig. 3).

Meta-regression analysis. In the univariate meta-regression analysis, the outcome variables were the SMD in CRP levels and covariates, including baseline BMI, AHI, CRP levels, and AHI improvements. The results revealed that the baseline BMI (regression coefficient [B] = 0.07; 95% CI = −0.13 to 0.26), preoperative AHI (B = −0.02; 95% CI = −0.05 to 0.01), preoperative CRP levels (B = −0.08; 95% CI = −0.19 to 0.04), and AHI improvements (B = 0.01; 95% CI = −0.02 to 0.05) were not correlated with the degree of CRP changes.

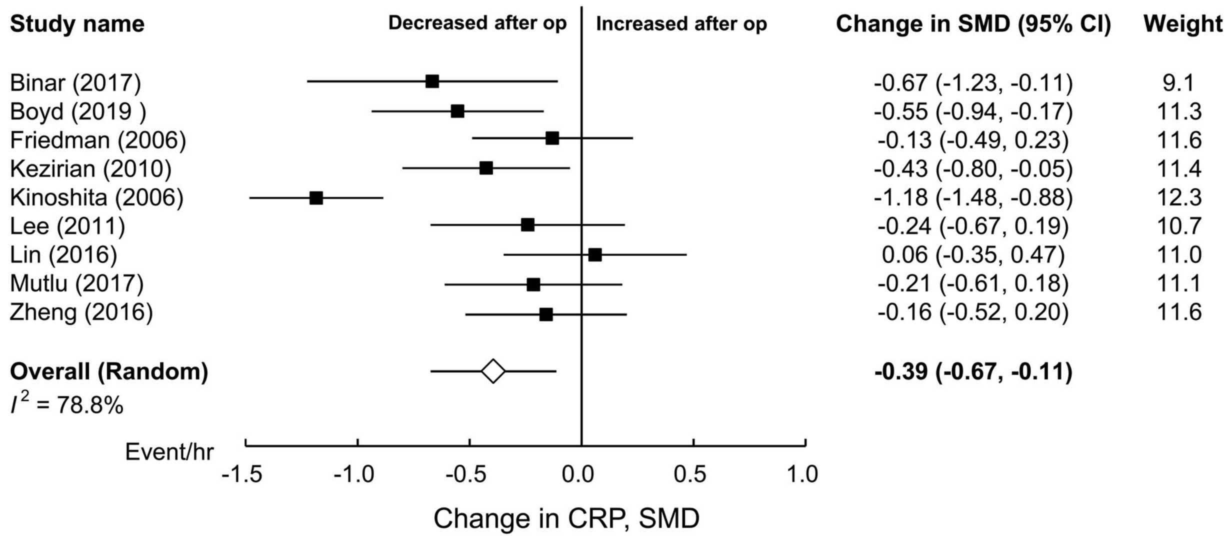

Fig 2. Forest plot showing the standardized mean difference (SMD) in C-reactive protein (CRP) levels after surgery. CI = confidence interval.

Publication Bias

A funnel plot was used to plot the SMD for changes in CRP levels (Fig. 4), and the Egger test was applied to test publication bias. The test results indicated no apparent publication bias ($P = .24$).

DISCUSSION

This meta-analysis elaborated on the current research gap regarding the effects of sleep surgery on CRP levels in patients with OSA. Our results reveal that sleep surgery results in a significant reduction in CRP levels in adults with OSA (SMD: 0.39). Although our analysis results reveal no correlation between AHI improvements and CRP changes, they indicate a significant reduction in CRP levels only in patients with considerable improvements in OSA (i.e., reduction of AHI >20 events/hr) after surgery. Thus, the relationship between CRP changes and AHI improvement may not be linear but have a threshold effect. These findings highlight the role of sleep surgery in reversing CRP levels in patients with OSA. Clinically, patients with OSA and elevated CRP levels can receive surgical treatment to alleviate both sleep apnea and abnormal CRP levels.[28,35]

Cardiovascular Implications of CRP Levels in Adults

CRP is a nonspecific acute-phase response to most forms of inflammation.[4] In the mid-1990s, CRP immunoassays exhibiting greater sensitivity than those in routine use indicated that increased CRP levels, even within the

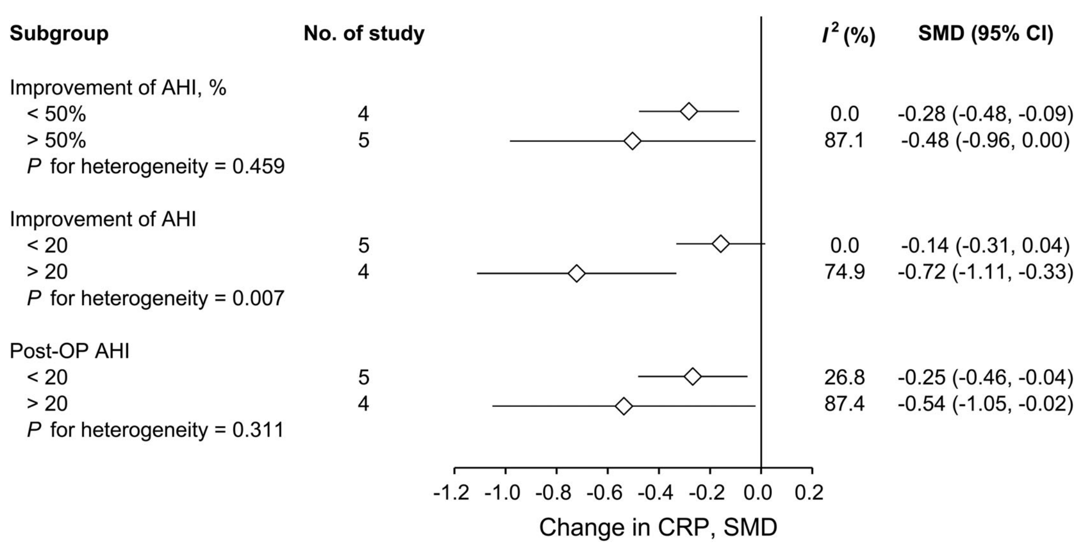

Fig 3. Forest plot comparing the standardized mean difference (SMD) in C-reactive protein (CRP) among patients with different degree of obstructive sleep apnea improvement. (A) Mean apnea–hypopnea index (AHI) reduction >50% versus <50% after surgery; (B) mean AHI reduction >20 versus <20 events/hr after surgery; (C) mean AHI <20 versus >20 events/hr after surgery. CI = confidence interval.

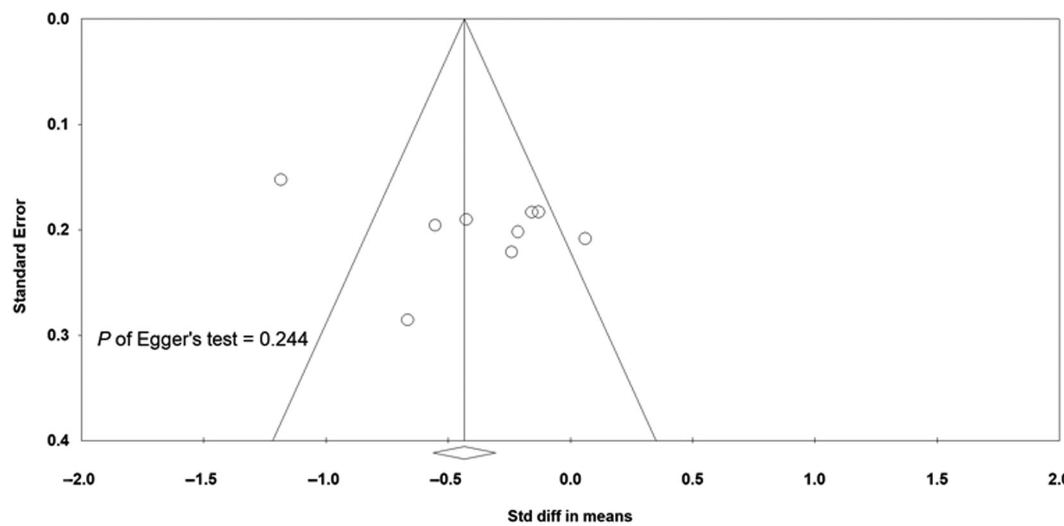

Fig 4. Funnel plot showing publication bias may not be apparent across studies.

range previously considered normal, may predict future cardiovascular events.[4] Ridker used widely available high-sensitivity assays and demonstrated that CRP levels of <1, 1–3, and >3 mg/L correspond to low, moderate, and high risks of future cardiovascular events.[5] Ridker et al. performed a large nested case–control study and reported CRP to be a predictor of the risk of cardiovascular events.[36] Several studies have demonstrated that CRP is associated with incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death.[5,36,37] Kaptoge et al. conducted an individual-participant meta-analysis and reported CRP levels to be associated with the risk of coronary heart disease, ischemic stroke, vascular mortality, and death due to several cancers and lung disease.[38] These findings focus on the clinical implications of CRP levels for cardiovascular disease detection and prevention.

Associations Between OSA and Elevated CRP Levels

Elevated CRP levels have been observed in patients with OSA.[39] Nadeem et al. conducted a meta-analysis and reported that CRP levels were higher in patients with OSA than in controls, with the corresponding SMD being 1.77.[6] Subsequent meta-analyses[7-9] have demonstrated robust associations between OSA and elevated CRP levels, confirming the finding of Nadeem et al. Additionally, the severity of OSA was found to be correlated with the elevation of CRP levels.[40] Elevated CRP levels in patients with OSA also increase cardiovascular risks.[41,42] Therefore, appropriate treatment strategies for resolving OSA and reducing CRP levels among these patients may prevent further cardiovascular events.

Effects of CPAP on CRP in OSA Patients

CPAP remains the first-line therapy for OSA.[43,44] A study reported CPAP to reduce elevated CRP levels in patients with OSA.[45] Friedman et al. conducted a meta-analysis and revealed that CPAP treatment led to a significant reduction in CRP levels (17.8%).[11] Moreover, Guo et al. performed a meta-analysis and indicated that the overall SMD in CRP levels measured before and after CPAP therapy was 0.64.[12] In the present study, the overall SMD corresponding to the reduction in CRP levels due to sleep surgery was modest (i.e., 0.39); it was not as large as the SMD for the reduction in CRP levels due to CPAP therapy alone. Although CPAP therapy is effective in diminishing CRP levels in patients with OSA, compliance with CPAP therapeutic regimens is relatively low.[15,44] A study indicated that over a period of 20 years, the overall CPAP nonadherence rate was 34.1%, and improvement over time was nonsignificant.[46] Therefore, sleep surgery may play a role in treating OSA and reducing CRP levels in these patients.

Effects of Sleep Surgery on OSA and CRP

The effectiveness of sleep surgery in treating OSA remains controversial.[34,47] Several surgical procedures have been proposed, including nasal surgery,[48,49] uvulopalatopharyngoplasty,[50] pharyngeal surgery,[51] tongue base surgery,[52] multilevel surgery,[53,54] maxillomandibular advancement,[55,56] hyoid surgery,[57] tracheostomy,[58] and hypoglossal nerve stimulation.[59,60] Studies have described disparities in the outcomes of different surgical procedures[61]; accordingly, the identification of predictive factors for poor outcomes and appropriate selection of patients are critical.[62,63]

No consensus has been reached regarding the effects of sleep surgery on CRP levels in adults with OSA.[25–33] The present study is the first to conduct a meta-analysis of CRP levels after surgery in adults with OSA. Available data from mainly small and observational studies suggest that surgical treatment of OSA may improve CRP levels. Overall, sleep surgery can engender a significant SMD reduction in CRP levels in patients with OSA (SMD:

0.39). The present meta-analysis highlighted the beneficial effects of sleep surgery on both OSA and CRP levels.

Factors Associated With CRP Change After Surgery

Predicting outcomes after surgical procedures in adult patients with OSA has been receiving increasing attention.[62,63] An anatomy-based system may predict surgical outcomes effectively and provide information to facilitate adequate case selection for counseling patients before sleep surgery.[62] For example, the Friedman stage and hyoid position are pertinent predictors of surgical outcomes following uvulopalatopharyngoplasty.[63] However, factors associated with cardiovascular endpoints after sleep surgery are not adequately understood.[19] The present meta-analysis also explored the associations between OSA improvement and CRP reduction. Traditionally, surgical success has been defined as an AHI reduction of 50% and/or an AHI of <20 events/hr.[34] In our meta-analysis, patients with a considerable improvement in OSA after surgery (i.e., AHI reduction of >20 events/hr) exhibited a more prominent decrease in the CRP levels than did other patients. Additionally, we found that CRP reduction may not be associated with differences in country, surgery type, CRP type, or follow-up duration. These findings may serve as a catalyst for future studies.

Limitations and Future Directions

This meta-analysis has some limitations. First, most of the included studies were retrospective observational case series.[25–29,31–33] Only one study included a control group.[30] Additionally, available data were of small sample sizes, which raises a concern for selection bias. Therefore, a large prospective randomized trial is highly recommended to further investigate the effects of surgery on cardiovascular outcomes.[64] Second, study populations were highly heterogeneous across studies, including race, age, sex, obesity, surgical procedure, and OSA improvement degree. Surgical selection bias may affect the cardiovascular effects of surgery.[19] For example, pharyngeal surgery may be appropriate for mild OSA, whereas tracheostomy, maxillomandibular advancement, and hypoglossal nerve stimulation surgery are usually reserved for patients with moderate to severe OSA. Third, data linking changes in CRP levels after surgery with future major cardiovascular events are limited.[65] Future studies are required to evaluate whether sleep surgery results in a reduction in major cardiovascular events and mortality.[66–68] Fourth, the efficacy of surgery for OSA may decrease over time,[69,70] and the long-term effects of sleep surgery on cardiovascular outcomes in patients with OSA remain unclear.[71,72] Sixth, the number of patients is relatively small, indicating potential selection bias. Seventh, this meta-analysis addressed an association of lower CRP levels with sleep surgery. However, causal relationship between CRP levels and sleep surgery is not established and required future studies.

CONCLUSION

Sleep surgery in patients with OSA significantly ameliorated OSA, with the mean AHI decreasing by 21.1 events/hr and CRP levels decreasing significantly (SMD: 0.39). Patients with a considerable improvement in OSA after surgery exhibited a prominent decrease in CRP levels. The findings of this study demonstrate the beneficial effects of sleep surgery on both OSA and CRP levels.

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