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Effect of Sleep Surgery on Inflammatory Cytokines in Adult Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

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Objective: To evaluate whether sleep surgery is associated with inflammatory cytokine changes. This study hypothesizes cytokines may change after surgery in adult obstructive sleep apnea (OSA).

Study Design: Systematic review and meta-analysis.

Methods: The study protocol was registered on PROSPERO (CRD42020154425). Two authors independently searched PubMed, Embase, and Cochrane review databases from their inception to June 2021. The keywords used were sleep apnea, inflammatory markers, cytokines, and surgery. The effects of sleep surgery on the apnea–hypopnea index (AHI) and inflammatory cytokines were evaluated using a random-effects model. Both mean difference (MD) and standardized mean difference (SMD) of the changes in cytokines were calculated.

Results: Nine studies with 235 adults were included (mean age: 43 years; 82% were men). After sleep surgery, AHI significantly reduced by −11.3 events/h (95% confidence interval [CI], −15.8 to −6.9). In total, 8 and 6 studies were pooled for examining tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels, respectively. Sleep surgery significantly reduced TNF-α levels, with an MD of −2.8 pg/ml (95% CI, −5.1 to −0.6) and an SMD of −0.56 (95% CI, −0.85 to −0.27). Furthermore, sleep surgery reduced IL-6 levels, with an MD of −0.6 pg/ml (95% CI, −1.0 to −0.2) and an SMD of −0.66 (95% CI, −0.89 to −0.43). No covariates were identified to be correlated with cytokine changes in subgroup and meta-regression analyses. Funnel plots showed possible publication bias in current data.

Conclusions: In adults, OSA treatment with sleep surgery improves inflammatory cytokines.

Key Words: adult, cytokines, meta-analysis, sleep apnea syndromes, surgery, uvulopalatopharyngoplasty.

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated episodes of apnea and hypopnea due to upper airway collapse during sleep.[1,2] The consequences of untreated OSA are fragmented sleep, intermittent hypoxia, intrathoracic pressure swings, and increased sympathetic nervous activity.[1–3] This leads to the increased expression of several systemic inflammatory markers, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8), in patients with OSA.[4–9] Current evidence suggests that OSA is associated with a group of proinflammatory and prothrombotic factors crucial for atherosclerosis development.[10,11] These pathways may further contribute to increased risks of cardiovascular disease and stroke in patients with OSA.[12]

TNF-α is a multifunctional proinflammatory cytokine that plays crucial roles in diverse cellular processes, such as cell survival, proliferation, differentiation, and death.[13–17] TNF-α is associated with the pathogenesis of numerous diseases, including sepsis,[14] autoimmune disorders,[15] and cancer.[16] Furthermore, proinflammatory cytokines appear to be associated with OSA pathogenesis.[17] In a recent meta-analysis and meta-regression study, Imani et al revealed that adults with OSA had significantly higher serum and plasma TNF-α levels compared with healthy controls.[17]

IL-6 is produced at the inflammation site and plays a key role in the acute phase response.[18,19] The immediate and transient expression of IL-6 is generated in response to environmental stress, including infections and tissue injuries.[20] In addition, IL-6 exerts stimulatory effects on T and B cells, thus favoring chronic inflammatory responses.[19] The dysregulation of IL-6 production occurs in various autoimmune and chronic inflammatory diseases, such as rheumatoid arthritis.[20] Meta-analyses by Zhong et al[7] and Imani et al[8] have confirmed that

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serum and plasma IL-6 levels are higher in patients with OSA than in healthy controls.

According to 2017 clinical practice guidelines established by American Academy of Sleep Medicine, polysomnography is the gold standard diagnostic test for adult OSA.[2] Furthermore, polysomnography can reliably quantify the effects of treatment modalities on adult OSA.[1,2] Currently, effective treatments for adults with OSA include positive airway pressure, surgical modification of upper airways, and oral appliances.[1,21] In adults, OSA treatment with positive airway pressure reduces blood pressure and improves several cardiovascular and inflammatory markers.[1,22–24] Moreover, surgical modification of upper airways may improve cardiovascular and inflammatory parameters. A recent meta-analysis confirmed that sleep surgery for OSA resulted in a significant reduction in C-reactive protein levels in adults.[25] However, to the best of our knowledge, a meta-analysis is lacking on the effects of sleep surgery on inflammatory cytokines in adults with OSA.

This study evaluated the effects of sleep surgery on inflammatory cytokines in adults with OSA. We particularly assessed the degree of OSA based on polysomnography, TNF-α levels, and IL-6 levels before and after sleep surgery in adults with OSA. Subgroup analysis and meta-regression analysis were conducted to explore associations between OSA improvements and changes in cytokine levels after sleep surgery.

METHODS

Search Strategy

The study protocol was registered on PROSPERO (CRD42020154425).[26] The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[27] The following PICO elements were used: adults with OSA (patient or problem), sleep surgery (intervention or indicator), before and after sleep surgery (comparator), and cytokines (outcome). Two authors (Lee CH and Lin MT) independently searched PubMed, Embase, and Cochrane review databases for relevant articles published from database inception to June 2021. The reference sections of the selected studies were searched for additional articles. The keywords used were "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," "inflammatory markers," "inflammation," "cytokines," "tumor necrosis factor-alpha," and "interleukins." Studies in the English language only were included in this study. Table S1 presents a list of keywords and medical subject heading terms used in the search process. Table S2 provides the details of the search process in each database.

The inclusion criteria were as follows: patients aged >18 years; OSA diagnosis based on polysomnography (i.e., apnea–hypopnea index [AHI] > 5); and patients receiving sleep surgeries for OSA treatment. Cytokine levels were tested in the included patients before and after sleep surgery. The cytokines analyzed were TNF-α, IL-6, and IL-8.[4–9]

Sleep surgeries were classified into four categories according to a review article by Halle et al[28] and our previous meta-analysis[25]: (1) tracheostomy; (2) soft-tissue surgery (e.g., nasal surgery, uvulopalatopharyngoplasty, or multilevel surgery); (3) skeletal surgery (i.e., maxillomandibular advancement); and (4) hypoglossal nerve stimulation.

Studies not complying with the inclusion criteria were excluded. Letters to the editor and case reports were excluded. The databases were searched by two authors (Lee CH and Lin MT) independently and were reviewed by the two corresponding authors (Lin MT and Kang KT).

Quality Assessments

The quality of the included studies was measured using the Newcastle–Ottawa scale (NOS).[29] The NOS score ranged from 0 (lowest quality) to 9 (highest quality). The NOS score was assessed by two authors independently (Kang KT and Lin MT), and the disagreements were resolved through a consensus.

Statistical Analysis

We used Comprehensive Meta-Analysis Version 3.3.070 (2014, Biostat Inc., Englewood, NJ, USA) for the analysis. The preoperative value, postoperative value, and change value in age, gender, body mass index, cytokines, and AHI were meta-analyzed using the DerSimonian–Laird random-effects model. Two types of effect sizes were calculated in this meta-analysis: the weighted mean difference (MD) and weighted standard mean difference (SMD). The MD obtains difference in values for a specified outcome in the same natural unit, which is more clinically relevant, and more sensible to outliers. The SMD expresses the size of the intervention effect relative to the variability, which is less clinically relevant, and less sensible to outliers. Heterogeneity between included studies was evaluated using I^2 statistics, where a value of $I^2 > 50\%$ indicates substantial heterogeneity.[30]

The extent of changes in cytokines and AHI after sleep surgery between different subgroups (e.g., OSA improvement and risk of bias score) was compared using the mixed-effect models. Furthermore, the correlation between baseline AHI value and changes in cytokines after sleep surgery was explored using a mixed-effect meta-regression without additional covariate adjustment. Finally, a funnel plot was illustrated and with the Egger's intercept test was conducted to assess publication bias in the literature.[30] A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Literature Search

Figure 1 illustrates the flowchart of the literature search. The initial database search yielded 2297 studies. After duplicates were removed, 2129 studies were identified and further screened. After duplicates were removed, 2129 studies were identified and further screened. After screening, the full text of 28 studies was retrieved. Among these 28 studies, 19 studies were excluded with reasons (e.g., not adults, no surgical intervention, or no available data) (Fig. 1).[31,32] Finally, nine studies elaborating changes in cytokines after sleep surgery were included.[33–41]

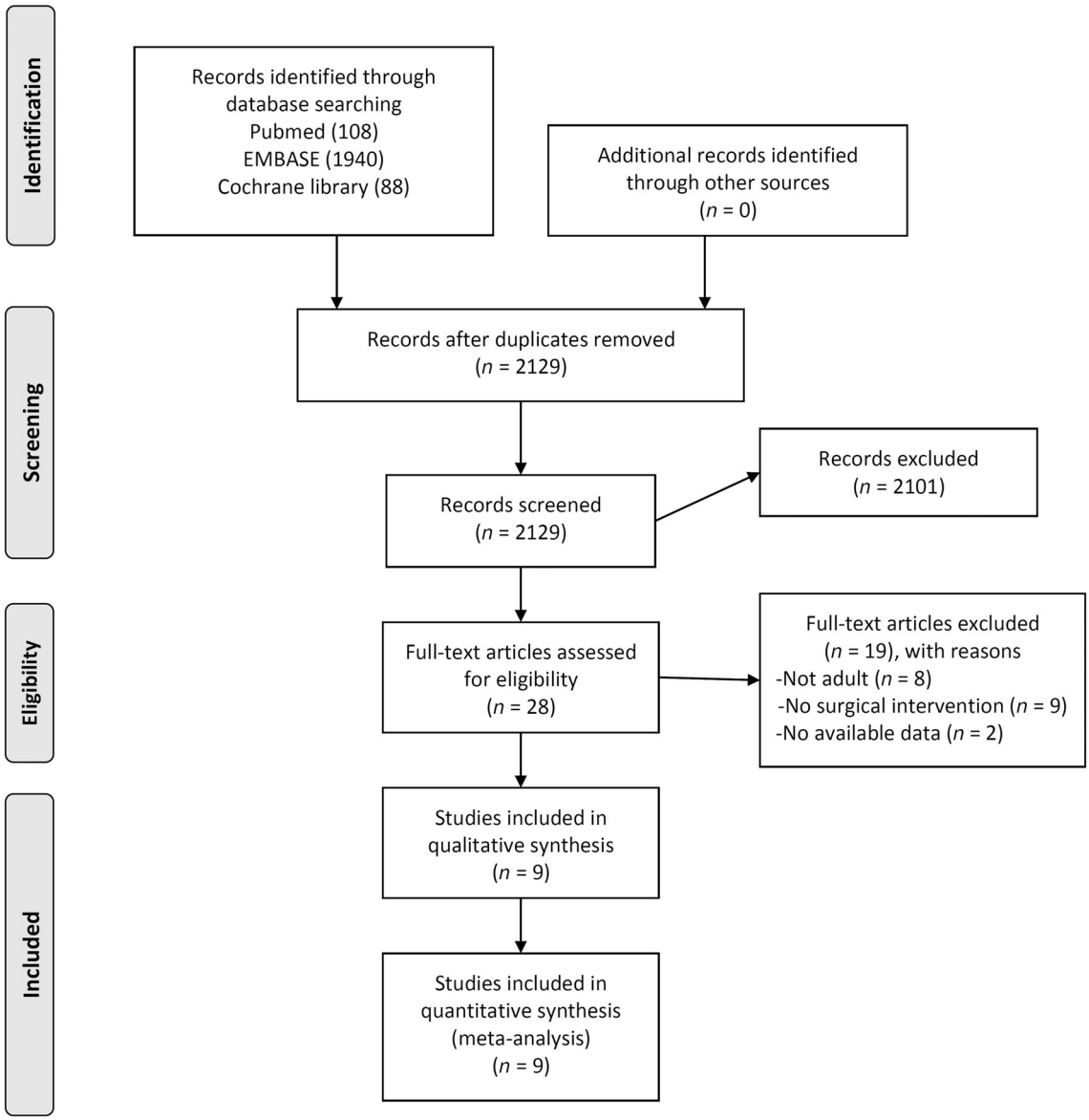

Fig. 1. Flow diagram of literature search.

Quality Assessment

The quality assessment of the included studies was conducted using the NOS, with scores ranging from 0 (lowest) to 9 (highest) points.[29] Table S3 lists the detailed NOS results. The NOS score was 3 in 1 study, 5 in 1 study, 6 in 6 studies, and 8 in 1 study.

Characteristics of Included Studies

Table I summarizes the characteristics of the included studies. In total, 9 studies with 235 adults with OSA were included.[33–41] The sample size ranged from 5 to 51, and the mean sample size was 26.1. The mean age was 43.0 (95% confidence interval [CI], 41.0–44.9) years. Men comprised 82% of the patients. The mean body mass index was 32.6 (95% CI, 28.4–36.9) kg/m^2.

Most included studies were case series studies. Only two studies by Constantinidis et al[34] and De Santis et al[38] were case–control studies. Soft-tissue sleep surgeries were performed in all studies, and none of the included studies performed tracheostomy, skeletal surgery, or hypoglossal nerve stimulation.[33–41] Multilevel surgery was performed in two studies,[36,37] and uvulopalatopharyngoplasty or nasal surgery was performed in the other seven studies.[33–35,38–41]

The scoring system for sleep studies was initially proposed by Rechtschaffen and Kales in 1968.[42] Subsequently, the American Academy of Sleep Medicine (AASM) announced the manual for scoring in 2007 (AASM 2007, Version 1.0).[43] Updated scoring manual was made by AASM in 2012.[44] In this meta-analysis, nine studies were included. Two studies used scoring system proposed by Rechtschaffen and Kales,[34,35] one study used the AASM 2007 criteria,[36] and three studies used the AASM 2012 criteria.[39–41] The

TABLE I.
Characteristics of Included Studies.

First author/Year	Country	N	Design	Surgery	Age, year	Male, %	BMI, kg/m^2	OSA definition	AHI Before surgery, events/h	AHI After surgery, events/h	Cytokine	Follow-up period
Kataoka/2004[33]	Japan	OSA: 27 non-OSA: 7 control: 4	Case series	UPPP, tonsillectomy, adenoidectomy	28.5	85.2%	NR	Apnea index >5	NR	NR	TNF-alpha	1 week
Constantinidis/2008[34]	Greece	24	Case–control	Septoplasty and UPPP	45.1	100%	30.5 (1.2)	AHI >5	23.2 (3.6)	9.8 (1.5)	TNF-alpha, IL-6, IL-1 beta	6 months
Li/2008[35]	China	5	Prospective cohort	UPPP, nasal surgery	NR	NR	NR	AHI >5	38,6 (19.3)	12.9 (15.6)	TNF-alpha IL-6, IL-10,	2 months
Eun/2010[36]	Korea	51	Case series	Multilevel surgery	42.6 (10.1)	100%	26.9 (3.3)	AHI >5	31.1 (21.3)	NR	TNF-alpha, IL-6,	4 weeks
Kezirian/2010[37]	USA	30	Prospective cohort study	Multilevel surgery	44.6 (10.6)	93.3%	30.1 (4.2)	AHI >5	44.9 (28.1)	27.8 (26.4)	IL-6	3 months
De Santis/2015[38]	Italy	14	Case–control	UPPP with or without septoplasty	41.8 (7.4)	65.4%	33.0 (5.2)	AHI >5	26.2 (12.1)	NR	TNF-alpha, IL-6,	6 months
Binar/2017[39]	Turkey	29	Prospective	Pharyngoplasty or palatoplasty	39 (9.5)	93.0%	NR	AHI >5	30.1 (20.5)	13 (12.4)	TNF-alpha	3 months
Mutlu/2017[40]	Turkey	25	Prospective	Uvulopalatal flap	46.2 (9.3)	56%	30.1 (4.4)	AHI >5	18.9 (8.4)	12.8 (6.6)	TNF-alpha	6 months
Bilal/2021[41]	Turkey	30	Case series	Expansion sphincter pharyngoplasty	44.3	66.7%	30.41	AHI >5	24.7	12.7	TNF-alpha IL-6, IL-8.	3 months

Note: Data were expressed as mean (SD).
AHI = apnea–hypopnea index; IL-1 beta = interleukin-1 beta; IL-6 = interleukin-6; IL-8 = interleukin-8; NR = not reported; OSA = obstructive sleep apnea; TNF-alpha = tumor necrosis factor-alpha; UPPP = uvulopalatopharyngoplasty.

other three studies did not specify the scoring system for sleep studies.[33,37,38]

In total, eight studies reported TNF-α levels,[33–36,38–41] and 6 studies reported IL-6 levels.[34–38,41] Only one study by Constantinidis et al[34] reported the IL-1 beta level, one study by Li et al[35] reported the IL-10 level, and one study by Bilal et al[41] reported the IL-8 level. Therefore, we were unable to conduct a meta-analysis for IL-1 beta, IL-8, or IL-10 levels. The follow-up period for included studies ranged from 1 week to 6 months.

Effect of Sleep Surgery on AHI

The weighted mean AHIs before and after surgery were 27.5 (95% CI, 21.7–33.4) and 13.2 (95% CI, 10.0–16.4) events/h, respectively. After sleep surgery, the weighted MD and SMD of the mean AHI were −11.3 (95% CI, −15.8 to −6.9) events/h (Fig. 2A) and −1.4 (95% CI, −2.2 to −0.7) (Fig. 2B), respectively. The heterogeneity of the pooled estimate was substantial for both MD ($I^2 = 87.2\%$) and SMD ($I^2 = 77.3\%$).

Effect of Sleep Surgery on Epworth Sleepiness Scale

In the field of sleep medicine, the Epworth sleepiness scale (ESS) is a widely used subjective measure of a patient's sleepiness.[45] The weighted mean ESS scores before and after surgery were 9.2 (95% CI, 7.5–10.9) and 5.4 (95% CI, 2.8–8.1), respectively. After sleep surgery, the weighted MD of the mean ESS was −4.5 (95% CI, −7.4 to −1.7), with substantial heterogeneity ($I^2 = 58.6\%$).

Effect of Sleep Surgery on TNF-α

Before surgery, the TNF-α concentration ranged from 3.64 to 180.3 pg/ml, and weighted mean TNF-α was 33.3 (95% CI, 27.7–39.0) pg/ml. After surgery, the TNF-α concentration ranged from 3.18 to 99.4 pg/ml, and the weighted mean TNF-α was 16.3 (95% CI, 12.4–20.1) pg/ml.

Figure 3 shows the changes in the MD and SMD of TNF-α after sleep surgery. After sleep surgery, the weighted MD and SMD of the mean TNF-α were −2.83 (95% CI, −5.07 to −0.59) pg/ml (Fig. 3A) and −0.56 (95% CI, −0.85 to −0.27) (Fig. 3B), respectively. The heterogeneity of the pooled estimate was substantial for both MD ($I^2 = 92.4\%$) and SMD ($I^2 = 51\%$).

Effect of Sleep Surgery on IL-6

Before surgery, the IL-6 concentration ranged from 0.45 to 71.4 pg/ml, and the weighted mean IL-6 concentration was 31.8 (95% CI, 18.0–45.6) pg/ml. After surgery, the IL-6 concentration ranged from 0.16 to 55.17 pg/ml,

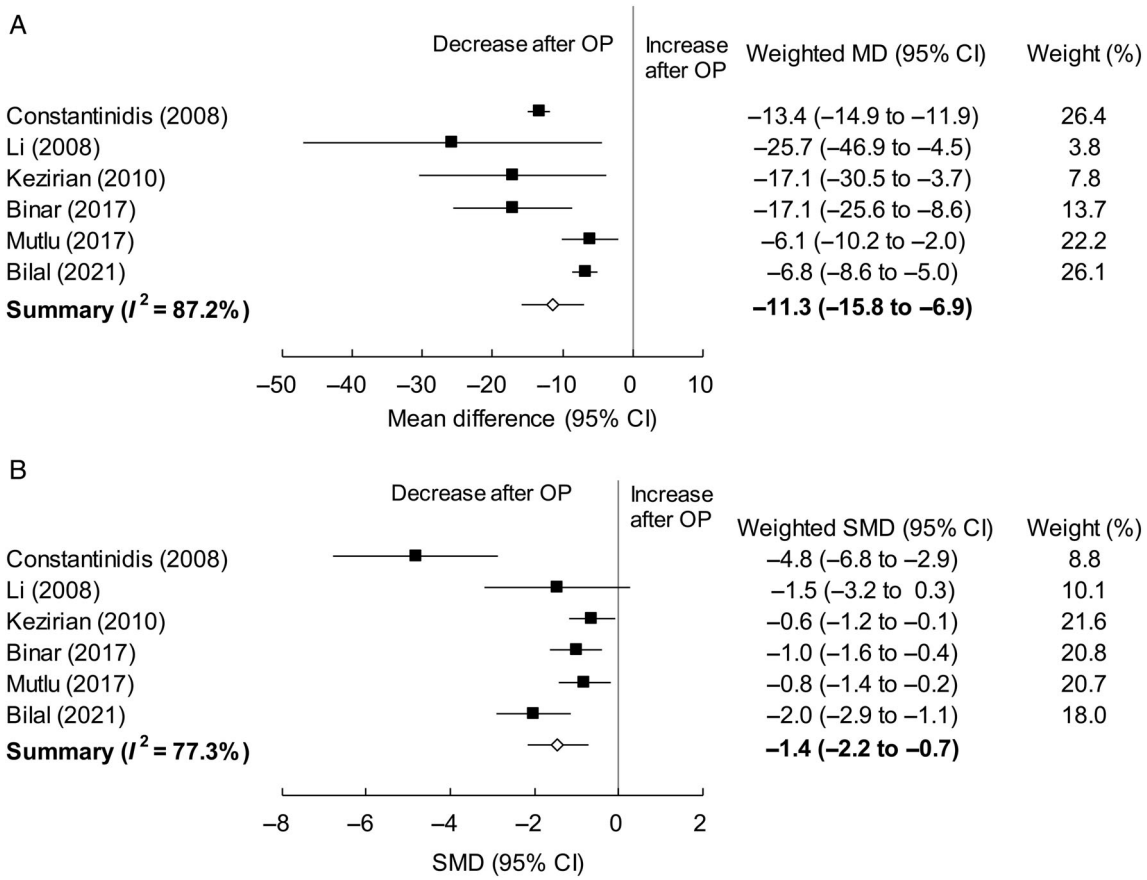

Fig. 2. Forest plot showing the changes in (A) mean difference and (B) standardized mean difference (SMD) of the apnea–hypopnea index (AHI) after sleep surgery.

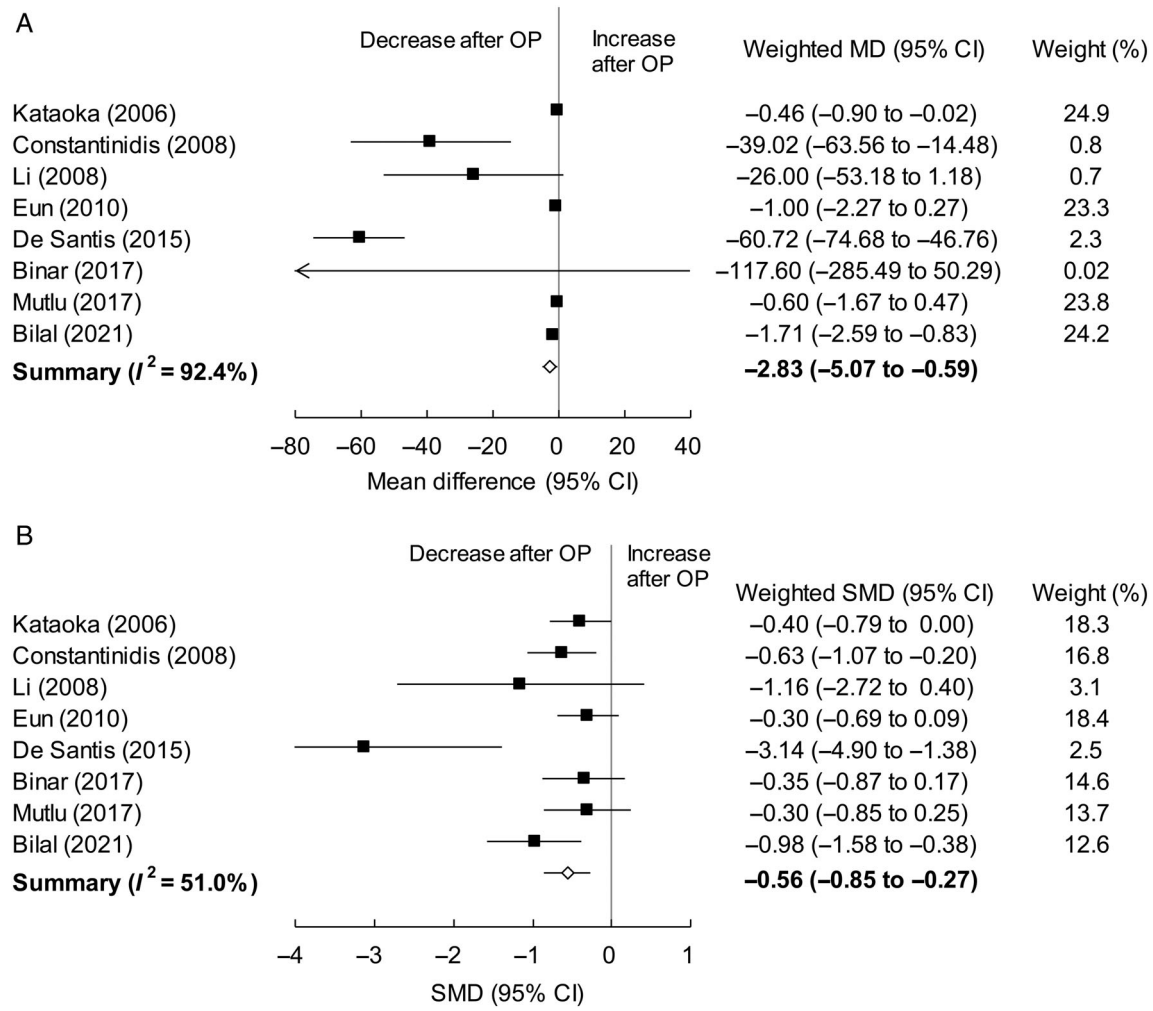

Fig. 3. Forest plot showing the changes in (A) mean difference and (B) standardized mean difference (SMD) of tumor necrosis factor-alpha (TNF-α) after sleep surgery.

and the weighted mean IL-6 concentration was 25.9 (95% CI, 17.1–34.6) pg/ml.

Figure 4 presents changes in the MD and SMD of the IL-6 concentration after sleep surgery. After sleep surgery, the weighted MD and SMD of the mean IL-6 concentration were −0.6 (95% CI, −1.03 to −0.17) pg/ml (Fig. 4A) and −0.66 (95% CI, −0.89 to −0.43) (Fig. 4B), respectively.

Subgroup Analysis: OSA Improvement

According to the literature, surgical success in patients with OSA is defined as a reduction in AHI by 50% or a postoperative AHI of <20 events/h.[46]

In this meta-analysis, a subgroup analysis was conducted according to the postoperative mean AHI reduction of >20 and <20 events/h. The change in the TNF-α concentration in patients with the mean AHI reduction of >20 events/h did not significantly differ from that in patients with the mean AHI reduction of <20 events/h (p for interaction = 0.54). Similarly, the change in the IL-6 concentration in patients with the mean AHI reduction of >20 events/h did not significantly differ from that in patients with the mean AHI reduction of <20 events/h (p for interaction = 0.56).

Furthermore, we compared the changes in TNF-α and IL-6 concentrations between patients with the mean AHI reduction of <50% and >50%. Analytic results demonstrated no significant differences in the changes in TNF-α and IL-6 between patients with the mean AHI reduction of <50% and >50% (p for interaction >0.05).

Subgroup Analysis: Risk of Bias

We performed additional analysis for studies with NOS ≥6 score. For studies with NOS ≥6 score, the changes in the MD and SMD of TNF-α after sleep surgery were −4.41 (95% CI, −7.99 to −0.84) pg/ml and −0.63 (95% CI, −1.11 to −0.15), respectively. The changes in the MD and SMD of IL-6 after sleep surgery were −2.31 (95% CI, −3.98 to −0.63) pg/ml and −0.64 (95% CI, −1.18 to −0.09), respectively. In high-quality studies, the TNF-α and IL-6 were significantly changed after sleep surgery in adult OSA.

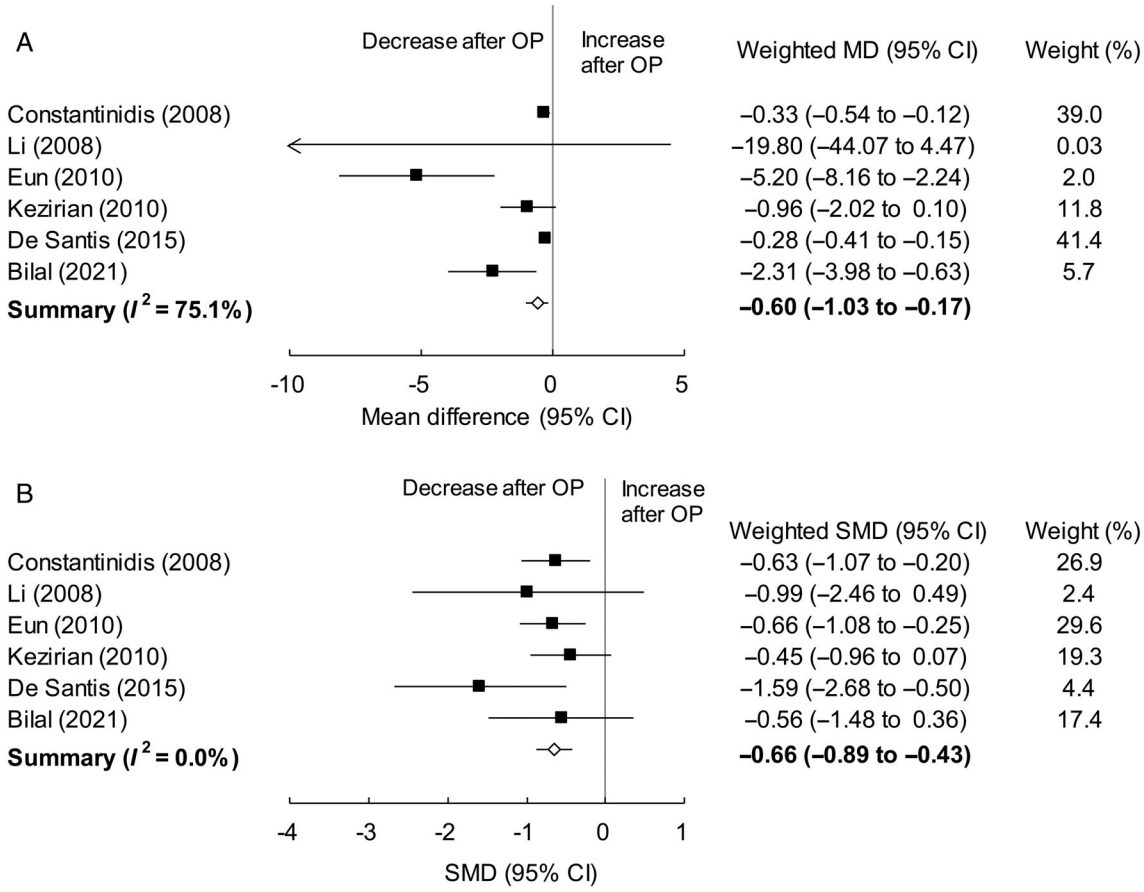

Fig. 4. Forest plot showing the changes in (A) mean difference and (B) standardized mean difference (SMD) of interleukin-6 (IL-6) after sleep surgery.

Meta-Regression Analysis

In the univariate meta-regression analysis, the outcome variables were changes in cytokine levels, and the explanatory variable was the baseline AHI. The results showed that the baseline AHI value was not significantly correlated with changes in the concentrations of TNF-α (regression coefficient [B] = −0.007; 95% CI = −0.101–0.088) and IL-6 (B = 0.016; 95% CI = −0.018–0.051).

Publication Bias

We plotted a funnel plot and used the Egger test to evaluate the publication bias. The funnel plots revealed apparent asymmetry. Given the limited number of included studies in this meta-analysis, the results showed a possible publication bias regardless of the significance of the Egger tests (Figures S1–S3).

Surgeries That Excluded Isolated Nasal Surgery

As far as the literature is concerned, the effect of nasal surgery alone on OSA is trivial.[47] In this meta-analysis, only one study enrolled patients with isolated nasal surgery.[33] After removing this article, we calculated the AHI change (Figure S4), TNF-α change (Figure S5), IL-6 change (Figure S6), and publication bias (Figures S7–S9). The weighted MD and SMD of the AHI change were −10.7 (95% CI, −15.3 to −6.2) events/h and −1.4 (95% CI, −2.2 to −0.7), respectively. The weighted MD and SMD of the TNF-α change were −2.64 (95% CI, −4.85 to −0.42) pg/ml and −0.55 (95% CI, −0.85 to −0.25), respectively. The weighted MD and SMD of the IL-6 change were −0.58 (95% CI, −0.99 to −0.16) pg/ml and −0.65 (95% CI, −0.88 to −0.42), respectively.

DISCUSSION

Adult OSA is associated with systemic inflammation and increases in several inflammatory cytokines.[4–9] Previous meta-analyses and review articles have reported that adults with OSA can be effectively treated with positive airway pressure[22–24] or oral appliance therapy,[48] which may also suppress inflammatory cytokines. However, the effects of sleep surgery on cytokines remain unclear. This meta-analysis is the first to estimate the effect size (i.e., MD and SMD change) of sleep surgery on TNF-α and IL-6 concentrations in adults with OSA. This meta-analysis identified that sleep surgery significantly reduced TNF-α (MD of −2.8 pg/ml and SMD of −0.56) and IL-6 (MD of −0.6 pg/ml and SMD of −0.66).

Adult OSA and Inflammatory Cytokines: TNF-α and IL-6

Associations of inflammatory cytokines with adult OSA have been studied for several years.[4,6–8,17] Among these inflammatory cytokines, TNF-α[4,6,9,17] and IL-6[4,7,8] have drawn great attention. In 2013, a meta-analysis by Nadeem et al identified that the standardized pooled MD between OSA and controls was 1.03 for TNF-α.[4] Updated meta-analysis by Cao et al. in 2020 showed a positive correlation between the TNF-α concentration and OSA severity, and aging significantly increased the effect size of the TNF-α concentration in patients with OSA.[9] Another meta-analysis by Imani et al revealed that compared with controls, adults with OSA had significantly higher serum and plasma TNF-α levels, with an MD of 10.22 and 5.9 pg/ml, respectively.[17]

IL-6 is one of the most significant inflammatory markers in adults with OSA.[4,7,8] In a meta-analysis in 2013, Nadeem et al determined that the standardized pooled MD between OSA and controls was 2.16 for IL-6.[4] In a meta-analysis in 2016, Zhong et al revealed that the serum IL-6 concentration was significantly higher in both adults and children with OSA.[7] In a recent meta-analysis in 2020, Imani et al reported significantly higher serum and plasma IL-6 concentrations among patients with OSA than among healthy controls.[8] Available data imply correlations between inflammatory cytokines and adults OSA.[4,6–8,17] Whether effective treatments for adult OSA result in improvements in inflammatory cytokines has been questioned.[22–24,44]

Cytokine Reduction After OSA Treatment: Positive Airway Pressure Versus Surgery Versus Oral Appliance

Some OSA patients need treatment alternatives to positive airway pressure.[49] In addition to positive airway pressure, surgeries and oral appliance have been proposed as OSA treatments.[48,50–61] Several surgical procedures, including nasal surgery,[52,53] uvulopalatopharyngoplasty,[54] multilevel surgery,[55,56] maxillomandibular advancement,[57,58] tracheostomy,[59] and hypoglossal nerve stimulation,[60,61] have been introduced based on patients' anatomy, and they have different surgical outcomes. Our recent meta-analysis in 2021 revealed that sleep surgery for OSA resulted in a significant reduction of C-reactive protein levels in adults.[25]

Currently, continuous positive airway pressure is widely considered one of the most effective treatments for adult OSA.[21] Previous meta-analyses have continually reported the beneficial effects of positive airway pressure treatment on cytokines in adult OSA.[22–24] In a meta-analysis, Xie et al reported a significant reduction in TNF-α and IL-6 levels after positive airway pressure, with SMDs of 0.478 and 0.299, respectively.[22] As for oral appliance, in a recent review article in 2021, Mecenas et al summarized limited scientific evidence showing that it may improve serum cytokine levels in adults with OSA.[48] In the present meta-analysis, we identified that sleep surgery significantly reduced the TNF-α concentration, with an MD of −2.8 pg/ml and an SMD of −0.56. Furthermore, sleep surgery decreased the IL-6 concentration, with an MD of −0.6 pg/ml and an SMD of −0.66. These findings highlight that OSA treatment can suppress inflammatory cytokines, with small to medium effect sizes.

In this meta-analysis, we were unable to clarify the factors associated with cytokine changes after sleep surgery. Our previous meta-analysis identified that OSA improvement was associated with C-reactive protein changes after sleep surgery.[25] By contrast, according to our analysis, OSA improvement was not significantly associated with cytokine changes. Notably, high heterogeneity was observed between included studies. The substantial heterogeneity may originate from disparities in surgical procedures, settings, countries, and follow-up period. Therefore, future studies should further clarify the factors determining cytokine changes after OSA treatment.

Inflammatory Cytokine Changes After Surgery: Clinical Relevant?

It is particularly challenging to evaluate what differences in the inflammatory cytokines are considered clinically relevant due to the difficulty of establishing "normal" versus abnormal" cytokine levels.[62,63] Cytokines vary greatly among individuals, and differ in a variety of disease conditions.[62,63] The recommended reference normal range of serum TNF-α is from non-detectable to 8.1 pg/ml.[64] The IL-6 level in healthy donors varied between 0 and 43.5 pg/ml, and the pooled estimate of IL-6 was 5.186 pg/ml.[65] In adults with OSA, the differences in cytokines between OSA and controls, and the effect size of positive airway pressure treatment on cytokine changes may provide information for the judgment. A 2013 meta-analysis by Nadeem et al identified that the standardized pooled MD between OSA and controls was 1.03 for TNF-α, and 2.16 for IL-6.[4] In a meta-analysis, Xie et al reported a significant reduction in TNF-α and IL-6 levels after positive airway pressure, with SMDs of 0.478 and 0.299, respectively.[22] The information may be helpful to interpret the clinical relevance of inflammatory cytokine changes after sleep surgery in adults with OSA.

Limitations and Future Directions

This meta-analysis has several limitations. First, relevant studies had small sample sizes with high heterogeneity, and a randomized controlled trial is lacking. Publication bias is high, and several confounding factors may affect surgical outcomes. Second, soft-tissue surgery was performed in all included studies. Consequently, we are unable to elucidate cytokine changes after tracheostomy, skeletal surgery, and hypoglossal nerve stimulation. Third, positive airway pressure for OSA may reduce cardiovascular event risks in adults.[66–68] Future studies can further explore associations between cytokine changes and major cardiovascular events in adults receiving sleep surgery for OSA.[69–71] Fourth, surgical efficacy may decrease over time.[72] Current studies only investigated short-term cytokine changes after sleep surgery. Thus, future studies are required on the long-term effects

of sleep surgery on cytokine changes. Fifth, recent randomized controlled trial showed improvement in the AHI after surgery was approximately 27 events/h.[73] Thus, the real effect of cytokine reduction may be much higher with contemporary surgical methodology. Sixth, patients with medical comorbidities, weight loss, or taking medications may affect inflammatory cytokine levels. However, included studies did not provide the relevant data. Seventh, the scoring criteria for sleep studies evolve over time, reflecting the advancement of knowledge toward the OSA.[42–44] Therefore, different authors may have applied different scoring systems and this discrepancy should be regarded as a limitation.

CONCLUSION

In adults with OSA, sleep surgeries improve OSA and reduce inflammatory cytokines, including TNF-α and IL-6. Future studies should further investigate linkages between inflammatory cytokines and cardiovascular outcomes in adults with OSA after sleep surgery.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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