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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

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

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Abstract

Purpose Obstructive sleep apnea (OSA) is associated with increased levels of systemic inflammatory markers, increased arterial stiffness, and endothelial dysfunction, which may lead to increased cardiovascular risk. We aimed to quantify the effects of continuous positive airway pressure (CPAP) on cardiovascular biomarkers and to establish predictors of response to CPAP.

Methods We searched PubMed and the Cochrane Library from inception to May 31, 2017. Randomized controlled trials (RCTs) assessing the efficacy of CPAP on high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), tumor necrosis factor- alpha (TNF-α), augmentation index (AIx), pulse wave velocity (PWV), and flow-mediated dilatation (FMD) in patients with OSA were selected by consensus.

Results We included 15 RCTs comprising 1090 patients in the meta-analysis. The pooled standard mean difference (SMD) of effect of CPAP on hs-CRP was − 0.64 (95% confidence interval (CI) − 1.19 to − 0.09; $P = 0.02$). CPAP was associated with a reduction in AIx of 1.53% (95% CI, 0.80 to 2.26%; $P < 0.001$) and a significant increase in FMD of 3.96% (95% CI 1.34 to 6.59%; $P = 0.003$). Subgroup analyses found CPAP was likely to be more effective in improving FMD levels in severe OSA patients or patients with effective CPAP use ≥ 4 h/night.

Conclusions Among patients with OSA, CPAP improves inflammatory marker hs-CRP, arterial stiffness marker AIx, and endothelial function marker FMD. These biomarkers may provide information related to response to treatment. Future studies will need to clarify the efficacy of these biomarkers in assessing cardiovascular risk reduction among OSA treated with CPAP.

Keywords Continuous positive airway pressure · Cardiovascular biomarker · Obstructive sleep apnea · Meta-analysis

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Introduction

OSA is characterized by recurring cessations or reductions in respiratory flow due to upper airway collapse during sleep [1]. The estimated prevalence of symptomatic OSA is about 4% in China [2] and 2 to 4% in Western countries [3]. The condition is associated with oxygen desaturation and arousals from sleep, which can lead to an increased expression of systemic inflammatory markers [4], increased arterial stiffness [5], derangement in endothelial function [6], and finally increases in blood pressure and risks of cardiovascular diseases.

Whether CPAP can improve these cardiovascular biomarkers in OSA patients remains conflicting. Besides, except for daytime symptom improvement, it is difficult to monitor the adequacy of treatment response. Although there were meta-analyses on the subject so far, studies included in those meta-analyses were self-control or observational studies, which were largely low-level evidence [7, 8]. Many additional RCTs have been published afterwards. Thus, the search for biomarkers and a comprehensive meta-analysis become critical. We, therefore, planned a meta-analysis comprising high-quality RCTs to assess whether CPAP can improve serum levels of inflammatory markers, arterial stiffness, and endothelial function in patients with OSA.

Methods

This meta-analysis was reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Online Resource 1).

Inclusion criteria

The studies must have randomized participants aged ≥ 18 years with a diagnosis of OSA (defined by an apnea-

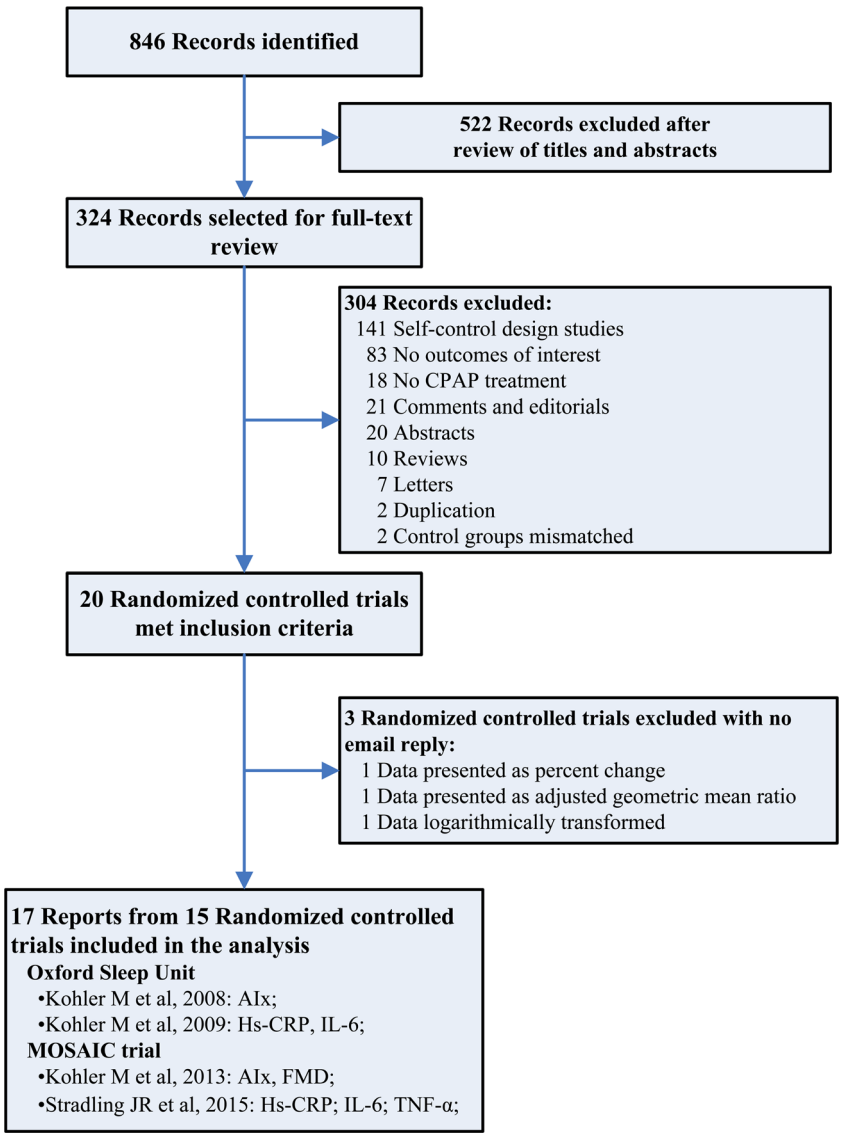


Fig. 1 Flowchart of literature search and study selection. AIx, augmentation index; CPAP, continuous positive airway pressure; FMD, flow-mediated dilatation; Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor-alpha

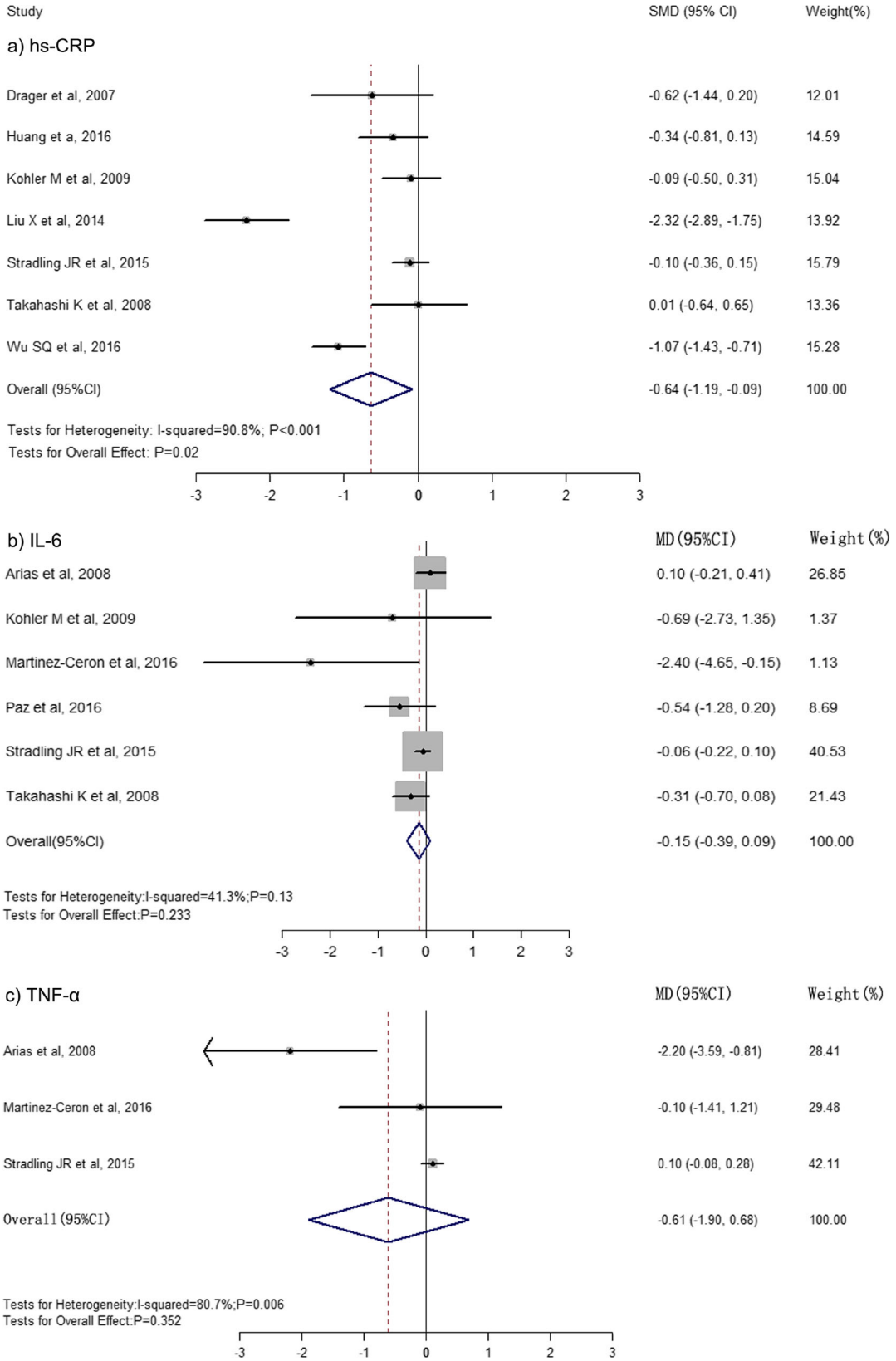
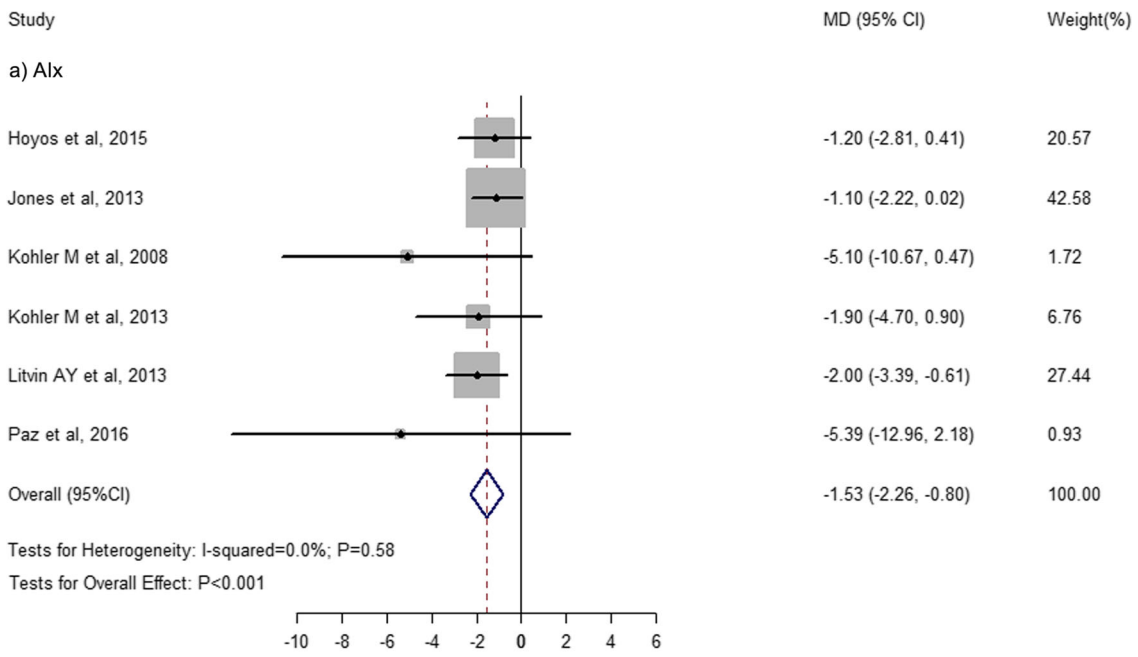
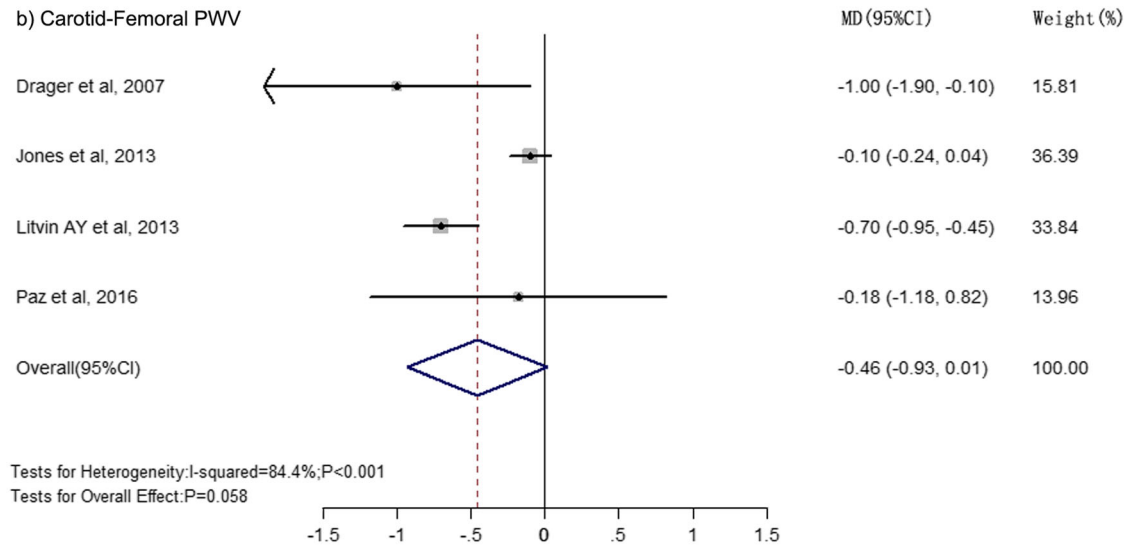
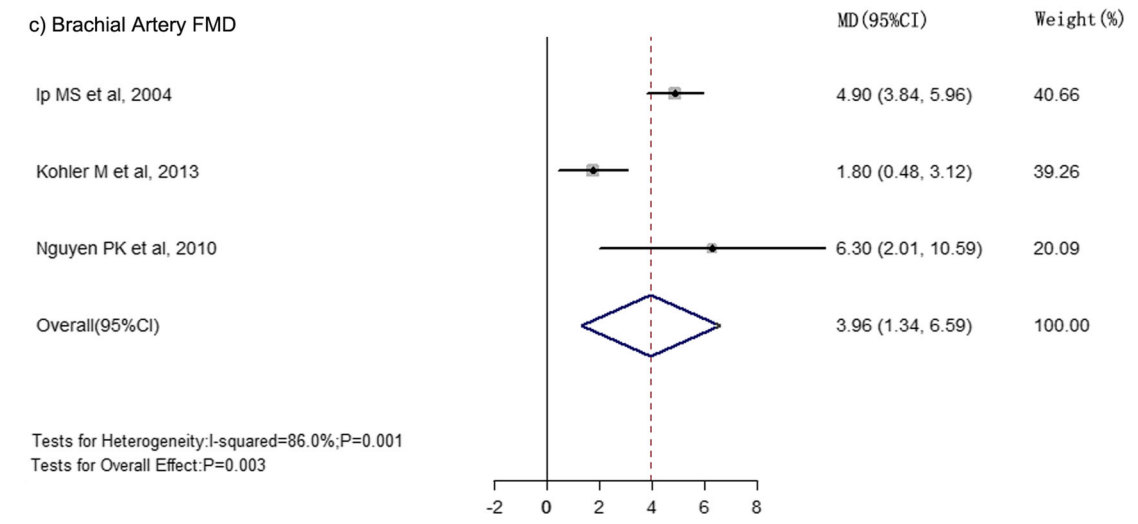


Fig. 2 Treatment effects on serum inflammatory markers of continuous positive airway pressure versus inactive control. CI, confidence interval; Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; MD, mean difference; SMD, standard mean difference; TNF-α, tumor necrosis factor-alpha


Study
MD (95% CI)
Weight(%)
a) AIx
Hoyos et al, 2015
-1.20 (-2.81, 0.41)
20.57
Jones et al, 2013
-1.10 (-2.22, 0.02)
42.58
Kohler M et al, 2008
-5.10 (-10.67, 0.47)
1.72
Kohler M et al, 2013
-1.90 (-4.70, 0.90)
6.76
Litvin AY et al, 2013
-2.00 (-3.39, -0.61)
27.44
Paz et al, 2016
-5.39 (-12.96, 2.18)
0.93
Overall (95%CI)
-1.53 (-2.26, -0.80)
100.00
Tests for Heterogeneity: I-squared=0.0%; P=0.58
Tests for Overall Effect: P<0.001
-10 -8 -6 -4 -2 0 2 4 6


b) Carotid-Femoral PWV
MD(95%CI)
Weight(%)
Drager et al, 2007
-1.00 (-1.90, -0.10)
15.81
Jones et al, 2013
-0.10 (-0.24, 0.04)
36.39
Litvin AY et al, 2013
-0.70 (-0.95, -0.45)
33.84
Paz et al, 2016
-0.18 (-1.18, 0.82)
13.96
Overall(95%CI)
-0.46 (-0.93, 0.01)
100.00
Tests for Heterogeneity:I-squared=84.4%;P<0.001
Tests for Overall Effect:P=0.058
-1.5 -1 -.5 0 .5 1 1.5


c) Brachial Artery FMD
MD(95%CI)
Weight(%)
Ip MS et al, 2004
4.90 (3.84, 5.96)
40.66
Kohler M et al, 2013
1.80 (0.48, 3.12)
39.26
Nguyen PK et al, 2010
6.30 (2.01, 10.59)
20.09
Overall(95%CI)
3.96 (1.34, 6.59)
100.00
Tests for Heterogeneity:I-squared=86.0%;P=0.001
Tests for Overall Effect:P=0.003
-2 0 2 4 6 8

◀ **Fig. 3** Treatment effects on arterial stiffness and endothelial function of continuous positive airway pressure versus inactive control. AIx, augmentation index; CI, confidence interval; FMD, flow-mediated dilatation; MD, mean difference; PWV, pulse wave velocity

hypopnea index (AHI) of ≥ 5/h) receiving CPAP treatment versus inactive control (e.g., sham CPAP or no treatment). Trials must also have measured and reported data on hs-CRP, IL-6, TNF-α, AIx, PWV, and FMD. If a particular patient population was reported in more than one publication, we selected the article that provided a complete data set. Both parallel and crossover RCTs published in full in any language will be considered for eligibility. Reviews, observational studies, and uncontrolled trials were excluded.

Search strategy

Literature was searched independently by two authors (Y.N. and T.S.Z.) using PubMed and the Cochrane Library without any restrictions from inception to May 31, 2017. We used the following search terms, both as MeSH terms and text words: sleep apnea, hypopnea, continuous positive airway pressure, inflammation, arterial stiffness, and endothelial function. The computerized search was supplemented by a manual search of the bibliographies of all retrieved articles.

Study selection and data extraction

Two authors (Y.N. and T.S.Z.) assessed the eligibility of studies. One author (Y.N.) extracted the relevant data from eligible studies, which was then independently checked by another author (T.S.Z.). Treatment effects were extracted directly from the studies along with standard errors (SE), 95% CI, or *P* values.

Summary statistics for the baseline data were also recorded, such as body mass index (BMI), AHI, oxygen desaturation index (ODI), Epworth Sleepiness Scale (ESS) score, and arterial oxygen saturation (SaO_2).

Two authors (Y.N. and T.S.Z.) evaluated the risk of bias in each study using the modified Jadad score [9]. We developed the evaluation criteria with score ranges from 0 to 7 points, with a higher score indicating higher study quality.

The primary outcomes were serum hs-CRP, IL-6, TNF-α, AIx, PWV, and FMD, and their inclusion in the analysis depended on the availability of adequate data. We used endpoint data rather than change data to maximize data availability.

Statistical methods

We used mean difference (MD) as a summary statistic when outcome measurements in all studies were made on the same scale, or the SMD when studies measured the outcomes in a variety of ways [10]. If treatment effects were not reported, the mean (SD) values for each outcome in each group at the end of follow-up were used to estimate treatment effects. For some of the outcomes including parallel and crossover trials, the SE of MD was needed to calculate the pooled effects. For parallel trials, when not available directly, the SE of MD were obtained from the SD for the measurements at the end of follow-up in each group. For crossover trials, they were obtained from 95% CIs for MD or imputation of SD achieved by assuming a particular correlation coefficient [11]. The correlation coefficient described how similar the measurements on CPAP therapy and control intervention were within a participant. We estimated the correlation in all crossover studies for which it was possible (i.e., those reporting SD, SE, or 95% CIs of treatment effects and the SD for the measurements at follow-up), and used the mean correlation to impute the treatment effect SE in studies for which estimation was not possible. To assess the sensitivity of our results to this correlation, we repeated the meta-analysis using some other correlations.

The summary statistics and 95% CIs were calculated using the inverse variance fixed-effect model and the DerSimonian and Laird random-effects model in Stata version 12.0 (StataCorp). The results were examined for heterogeneity by calculating the I^2 statistic, with values less than 25% indicating low, 25 to 50% indicating moderate, and greater than 50% indicating high heterogeneity [12].

We performed predefined subgroup analyses to explore potential sources of heterogeneity. When $I^2 \geq 25\%$, we used the hetred command in Stata to evaluate the change in between-study heterogeneity as one or more outlier studies were excluded from the calculations, which was developed by Patsopoulos [13]. Several predefined sensitivity analyses were performed to test the robustness of the results.

Potential reporting bias was explored by funnel plot and the Egger test. All analyses were conducted at the two-sided significance level of 0.05.

Results

Studies identified

Of 846 reports identified, we excluded 522 studies that were unrelated to our subject and 304 studies after detailed evaluation. In the 20 RCTs left, four studies offered the unsuitable data type [14–17]. We then contacted the corresponding authors by emails, but only one replied with data in need [17]. Besides, four reports were actually from two RCTs but analyzed different outcomes. Thus, 17 reports from 15 RCTs (1090 patients) of CPAP versus inactive control were included in this analysis (Fig. 1). Of 15 RCTs, four were crossover trials referred to outcomes of IL-6, TNF-α, AIx, and PWV (Online Resource 2: Table S1); eight were awarded a total score of ≥ 4 (Online Resource 2: Table S2).

Primary analyses

The mean estimated correlation for AIx across the three crossover trials for which it could be estimated was 0.95 (one study for 0.94 [18]; the other for 0.96 [19]). For crossover trials with measurements of IL-6, TNF-α, and PWV, the correlation could not be estimated. Therefore, we used the correlation 0.95 to impute SE of treatment effect in other crossover trials. Sensitivity analyses were undertaken to determine whether the overall results were robust to the use of imputed correlation coefficients by trying different values of correlation ($r = 0.68$, 0.5, 0.3, 0.1).

Seven RCTs involving 684 subjects were included in the analysis of hs-CRP. The pooled SMD of effect of CPAP was − 0.64 (95% CI − 1.19 to − 0.09; $P = 0.02$) (Fig. 2). Statistical heterogeneity across the RCTs was high ($I^2 = 90.8\%$), indicating that additional factors could affect the efficacy of intervention with CPAP in reducing serum hs-CRP.

Six RCTs with 546 subjects were included for the analysis of IL-6. The summary MD was − 0.15 (95% CI − 0.39 to 0.09; $P = 0.23$) (Fig. 2). There was an evidence of moderate heterogeneity ($I^2 = 41.3\%$).

For TNF-α, three RCTs were included with 311 individuals. Evidence synthesis for TNF-α showed that the treatment effect of CPAP was not statistically significant (MD − 0.61; 95% CI − 1.90 to 0.68; $P = 0.35$), with evidence of high heterogeneity ($I^2 = 80.7\%$) (Fig. 2).

In the meta-analysis of AIx including six RCTs with 520 participants, CPAP was associated with a reduction in AIx of − 1.53 (95% CI − 2.26 to − 0.80; $P < 0.001$) (Fig. 3). No evidence of statistical heterogeneity was found ($I^2 = 0.0\%$).

Four RCTs with 210 subjects were included for the analysis of PWV. The summary MD of PWV was − 0.46 (95% CI − 0.93 to 0.01; $P = 0.058$) (Fig. 3). There was an evidence of high heterogeneity ($I^2 = 84.4\%$).

In the meta-analysis of FMD, three RCTs were included with 111 participants, and CPAP was associated with a significant increase in FMD of 3.96% (95% CI 1.34 to 6.59%; $P = 0.003$) (Fig. 3). Statistical heterogeneity across the RCTs was high ($I^2 = 89.5\%$).

Subgroup analyses and sensitivity analyses

Pre-specified subgroup analyses of TNF-α found the RCT design and type of control might be the source of heterogeneity (Table 1). Similarly, the sensitivity analysis by hetred command found the RCT by Arias et al. [21] was the source of heterogeneity (Table 2). The heterogeneity has been due to the design differences, for it was the only one parallel RCT and used sham CPAP as a control group.

Subgroup analyses of PWV found the effective CPAP use might be the source of heterogeneity. Similarly, the sensitivity analysis by hetred command found the RCT by Jones et al. [18] was source of heterogeneity, which has been due to the < 4 h/night use of the CPAP device.

Subgroup analyses of FMD found the OSA severity and the effective CPAP use might be the source of heterogeneity. Similarly, the sensitivity analysis by hetred command found the RCT by Kohler et al. [25] was the source of heterogeneity, which has been due to the mild to moderate OSA patients and < 4 h/night use of the CPAP device.

Subgroup analyses did not find the source of heterogeneity for the estimates of hs-CRP and IL-6. However, sensitivity analyses using the hetred demand revealed that some studies were sources of heterogeneity. For hs-CRP, two studies were found to be the source of heterogeneity [22, 23]. The heterogeneity may have been due to several design differences, such as the inclusion of OSA patients with coronary heart diseases and older population [22], or larger population [23]. For IL-6, one RCT was the source of heterogeneity, which may have been due to the inclusion of OSA patients with type 2 diabetes and older patients [24].

Moreover, we found that CPAP was likely to be more effective in improving FMD levels in severe OSA patients or patients with effective CPAP use ≥ 4 h/night (Table 1). However, we did not find this relationship in other outcomes.

In pre-specified sensitivity analyses (Table 2), the effect size of each outcome changed little after analyses with fixed- or random-effects models. For IL-6, TNF-α, AIx, and PWV, the treatment effects did not change by using different values of correlation ($r = 0.68$, 0.5, 0.3, 0.1). These analyses indicated the robustness of our results.

Publication Bias

We found the result of the Egger test for AIx was significant ($P = 0.04$), indicating the funnel plot was not symmetrical (Online Resource 2: Fig. S1). This asymmetry may arise from study factors other than publication bias; i.e., participants in one trial had a lower mean AHI and ESS, and this trial reported the greatest reduction in AIx and the widest 95% CI [17].

Discussion

The present meta-analysis of RCTs shows CPAP treatment may cause a moderate decrease in the serum levels of inflammatory markers hs-CRP, but not IL-6 and TNF-α. However, two previous meta-analyses showed that CPAP therapy also improved serum levels of TNF-α and IL-6 [26, 27]. These meta-analyses included self-control or observational studies, which have limitations of selection bias, confounding factors, and weaker power of argument than RCTs.

Results indicate that CPAP is an effective intervention for the reduction of arterial stiffness outcome of AIx (1.53%) but not PWV in OSA patients. Previous meta-analyses only including observational or self-control studies found CPAP was

Table 1 Subgroup analyses of treatment effects of CPAP versus inactive control

	Hs-CRP				IL-6				TNF-a			
	Trials	SMD (95%CI)	I^2	*P* value*	Trials	MD (95%CI)	I^2	*P* value*	Trials	MD (95%CI)	I^2	*P* value*
OSA severity												
Mild to moderate	2	−0.16 (−0.38, 0.07)	0.0%	0.42	2	−0.16 (−0.53, 0.22)	34.5%	0.99	1	0.10 (−0.08, 0.28)	–	NA
Severe	5	−0.82 (−1.62, −0.03)	91.6%		4	−0.24 (−0.75, 0.27)	57.1%		2	−1.14 (−3.20, 0.92)	78.4%	
Effective CPAP use												
<4 h/night	1	−0.10 (−0.36, 0.15)	–	0.06	1	−0.06 (−0.22, 0.10)	–	0.64	1	0.10 (−0.08, 0.28)	–	NA
≥4 h/night	4	−0.21 (−0.47, 0.06)	0.0%	0.03	5	−0.28 (−0.71, 0.15)	51.4%		2	−1.14 (−3.20, 0.92)	78.4%	
Unclear	2	−1.68 (−2.90, −0.46)	92.4%	Reference	0	–	–		0	–	–	
RCT design												
Parallel	7	−0.64 (−1.19, −0.09)	90.8%	NA	5	−0.27 (−0.60, 0.06)	42.2%	0.34	2	0.10 (−0.08, 0.27)	0.0%	NA
Crossover	0	–	–		1	0.10 (−0.21, 0.41)	–		1	−2.20 (−3.59, −0.81)	–	
Type of control												
Sham CPAP	1	−0.09 (−0.50, 0.31)	–	0.51	3	−0.12 (−0.60, 0.35)	29.7%	0.78	1	−2.20 (−3.59, −0.81)	–	NA
Observation	6	−0.74 (−1.39, −0.09)	91.8%		3	−0.24 (−0.66, 0.18)	62.6%		2	0.10 (−0.08, 0.27)	0.0%	
Length of follow-up												
<4 weeks	0	–	–	0.26	0	–	–	0.38	0	–	–	NA
4–8 weeks	2	−0.07 (−0.41, 0.28)	0.0%		2	−0.32 (−0.71, 0.06)	0.0%		0	–	–	
≥8 weeks	5	−0.88 (−1.62, −0.15)	93.1%		4	−0.12 (−0.44, 0.21)	55.4%		3	−0.61 (−1.90, 0.68)	80.7%	

	AIx				PWV				FMD			
	Trials	MD (95%CI)	I^2	*P* value*	Trials	MD (95%CI)	I^2	*P* value*	Trials	MD (95%CI)	I^2	*P* value*
OSA severity†												
Mild to moderate	2	−2.32 (−4.95, 0.31)	0.0%	0.57	1	−0.18 (−1.18, 0.82)	–	0.69	1	1.80 (0.48, 3.12)	–	NA
Severe	4	−1.46 (−2.22, −0.71)	0.0%		3	−0.51 (−1.04, 0.03)	89.6%		2	4.98 (3.95, 6.01)	0.0%	
Effective CPAP use												
<4 h/night	2	−1.21 (−2.25, −0.17)	0.0%	0.44	1	−0.10 (−0.24, 0.04)	–	0.05	1	1.80 (0.48, 3.12)	–	NA
≥4 h/night	4	−1.84 (−2.87, −0.82)	0.0%		3	−0.69 (−0.93, −0.45)	0.0%		2	4.98 (3.95, 6.01)	0.0%	
Unclear	0	–	–		0	–	–		0	–	–	
RCT design												
Parallel	3	−2.83 (−5.20, −0.45)	0.0%	0.32	2	−0.62 (−1.42, 0.18)	29.8%	0.71	3	3.96 (1.34, 6.59)	86.0%	NA
Crossover	3	−.40 (−2.16, −0.63)	0.0%		2	−0.39 (−0.98, 0.20)	93.9%		0	–	–	
Type of control												
Sham CPAP	5	−1.50 (−2.26, −0.75)	0.0%	0.80	3	−0.36 (−0.86, 0.15)	87.9%	0.41	1	6.30 (2.01, 10.60)	–	NA
Observation	1	−1.90 (−4.70, 0.90)	–		1	−1.00 (−1.90, −0.10)	–		2	3.38 (0.34, 6.41)	92.3%	
Length of follow-up												
<4 weeks	1	−2.00 (−3.39, −0.61)	–	Reference	1	−0.70 (−0.96, −0.45)	–	0.46	0	–	–	NA
4–8 weeks	1	−5.10 (−10.67, 0.47)	–	0.37	0	–	–		1	4.90 (3.84, 5.96)	–	
≥8 weeks	4	−1.26 (−2.13, −0.40)	0.0%	0.44	3	−0.31 (−0.81, 0.20)	46.7%		2	3.57 (−0.74, 7.87)	74.1%	

NA not available or applicable

**P* values indicate whether the pooled estimate in each subgroup differs from a nominated reference subgroup

† Mild to moderate OSA defined as AHI/RDI < 30 or ODI < 20; severe OSA defined as AHI/RDI > 30 or ODI > 20 [20]

Table 2 Sensitivity analyses of treatment effects of CPAP versus inactive control

	Hs-CRP				IL-6			
	Trials	SMD (95%CI)	*P* value*	I^2	Trials	MD (95%CI)	*P* value*	I^2
Statistical model								
Random effects	7	− 0.64 (− 1.19, − 0.09)	0.02	90.8%	6	− 0.15 (− 0.39, 0.09)	0.23	41.3%
Fixed effects	7	− 0.49 (− 0.65, − 0.33)	NA	NA	6	− 0.08 (− 0.21, 0.04)	NA	NA
Correlation coefficient (r)								
$r = 0.95$	NA	NA	NA	NA	6	− 0.15 (− 0.39, 0.09)	0.23	41.3%
$r = 0.68$	NA	NA	NA	NA	6	− 0.20 (− 0.47, 0.07)	0.14	31.4%
$r = 0.5$	NA	NA	NA	NA	6	− 0.21 (− 0.49, 0.06)	0.13	30.2%
$r = 0.3$	NA	NA	NA	NA	6	− 0.22 (− 0.50, 0.06)	0.12	29.5%
$r = 0.1$	NA	NA	NA	NA	6	− 0.22 (− 0.50, 0.06)	0.12	29.1%
Analyses except								
Outlier study†	5	− 0.15 (− 0.34, 0.03)	0.10	0.0%	5	− 0.09 (− 0.24, 0.07)	0.28	10.3%
	TNF-a‡				AIx‡			
Statistical model								
Random effects	3	− 0.61 (− 1.90, 0.68)	0.35	80.7%	6	− 1.53 (− 2.26, − 0.80)	< 0.001	0.0%
Fixed effects	3	0.06 (− 0.11, 0.23)	NA	NA	6	− 1.53 (− 2.26, − 0.80)	NA	NA
Correlation coefficient (r)								
$r = 0.95$	3	− 0.61 (− 1.90, 0.68)	0.35	80.7%	6	− 1.53 (− 2.26, − 0.80)	< 0.001	0.0%
$r = 0.68$	3	0.09 (− 0.08, 0.26)	0.31	0.0%	6	− 1.64 (− 2.78, − 0.50)	0.01	0.0%
$r = 0.5$	3	0.09 (− 0.08, 0.27)	0.30	0.0%	6	− 1.66 (− 2.86, − 0.47)	0.01	0.0%
$r = 0.3$	3	0.09 (− 0.08, 0.27)	0.29	0.0%	6	− 1.67 (− 2.91, − 0.44)	0.01	0.0%
$r = 0.1$	3	0.09 (− 0.08, 0.27)	0.29	0.0%	6	− 1.68 (− 2.93, − 0.43)	0.01	0.0%
Analyses except								
Outlier study†	2	0.10 (− 0.08, 0.27)	0.28	0.0%	NA	NA	NA	NA
	PWV‡				FMD‡			
Statistical model								
Random effects	4	− 0.46 (− 0.93, 0.01)	0.06	84.4%	3	3.96 (1.34, 6.59)	0.003	86.0%
Fixed effects	4	− 0.25 (− 0.37, − 0.13)	NA	NA	3	3.77 (2.96, 4.58)	NA	NA
Correlation coefficient (r)								
$r = 0.95$	4	− 0.46 (− 0.93, 0.01)	0.06	84.4%	NA	NA	NA	NA
$r = 0.68$	4	− 0.41 (− 0.85, 0.02)	0.06	45.2%	NA	NA	NA	NA
$r = 0.5$	4	− 0.39 (− 0.82, 0.04)	0.07	32.3%	NA	NA	NA	NA
$r = 0.3$	4	− 0.38 (− 0.81, 0.04)	0.08	19.3%	NA	NA	NA	NA
$r = 0.1$	4	− 0.38 (− 0.80, 0.04)	0.08	11.0%	NA	NA	NA	NA
Analyses except								
Outlier study†	3	− 0.69 (− 0.93, − 0.45)	< 0.001	0.0%	2	4.98 (3.95, 6.01)	< 0.001	0.0%

AIx augmentation index, *CI* confidence interval, *FMD* flow-mediated dilatation, *Hs-CRP* high-sensitivity C-reactive protein; *IL-6* interleukin 6, *MD* mean difference, *NA* not available or applicable, *PWV* pulse wave velocity, *SMD* standard mean difference, *TNF-α* tumor necrosis factor-alpha

**P* value for effect size

† Source of heterogeneity found by sensitivity analyses: Liu et al. (2014) [22] and Wu et al. (2016) [23] for hs-CRP; Martinez-Ceron et al. (2016) [24] for IL-6; Arias et al. (2008) [21] for TNF-α; Jones et al. (2013) [18] for PWV; Kohler et al. (2013) [25] for FMD

‡ The summary statistic of TNF-a, AIx, PWV, and FMD studies is MD

also associated with statistically significant decrease in PWV [8, 28]. However, we believe more multi-center RCTs are needed to give a robust conclusion of PWV.

Results imply that CPAP treatment causes a strong and significant increase in endothelial function as measured by FMD (3.96%), which is consistent with a previous meta-analysis [7].

However, it included one RCT with CPAP withdrawal as control, which we do not think met the inclusion criteria.

Subgroup analyses indicated that CPAP was likely to be more effective in improving FMD levels in severe OSA patients or patients with effective CPAP use ≥ 4 h/night. We did not find this relationship in other outcomes. The results of sensitivity analyses support the robustness of our finding.

This analysis has a number of strengths. First, this is the first meta-analysis including all of RCTs on the subject so far. Eligible RCTs have been published as full-length original articles and were conducted within the past decade, minimizing any effect of secular trends and changes in medical practice. Second, our results have important clinical significance. Aside from daytime symptom improvement, these biomarkers may provide information related to response to treatment.

There are some limitations. First, limited RCTs were included in this meta-analysis, which may not reflect the real pooled effect size. Second, the absence of individual participant data might influence the accuracy of results. Third, given the absence of time of taking blood samples in some studies, we failed to discuss the potential effects of diurnal variation of hs-CRP, IL-6, and TNF-α on the pooled effect size. Last, according to a report by Lin YN et al., the OSA treatment follow-up regimen should base on the time-response characteristics of different indicators [29]. They infer that the time-response effects include 3 phases. However, the choice of indicators and the duration in each phase are still uncertain. As a result, in the present meta-analysis, we are unable to set up an acknowledged and specific time point for each measurement to conduct the precise analyses. There is an urgent need to perform further RCTs to confirm.

Conclusions

Among OSA patients, CPAP reduces serum inflammatory markers of hs-CRP and arterial stiffness outcome of AIx, and increases endothelial function outcome of FMD. The serum hs-CRP levels, AIx, and FMD may act as predictors of the adequacy of CPAP treatment response in OSA. However, future studies will need to clarify the efficacy of these biomarkers in assessing cardiovascular risk reduction among patients with OSA treated with CPAP.

Author contributions Drs. Y.N., M.Z., and Y.X.W. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Y.N., M.Z., T.S.Z., and Y.X.W. conceived and designed the study. Y.N. and T.S.Z. reviewed the scientific literature, did the statistical analysis, prepared all tables and figures, and wrote the first draft of the report. Y.N., T.S.Z., and W.W.W. contributed to acquisition of data and quality assessment. M.Z. and Y.X.W. reviewed and revised the article. All authors made a critical revision of the manuscript for key intellectual content.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was not necessary for this meta-analysis, as only identified pooled data from previously approved individual studies was used.

Informed consent Informed consent was obtained from all individual participants included in the study.

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