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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Impact of continuous positive airway pressure therapy on renin–angiotensin–aldosterone system in obstructive sleep apnea: an updated systematic review and meta-analysis

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Abstract

Purpose While continuous positive airway pressure (CPAP) reduces cardiovascular risk in obstructive sleep apnea (OSA), its effects on renin–angiotensin–aldosterone system (RAAS) modulation remain controversial. This meta-analysis investigates CPAP's differential impacts on RAAS components and identifies responsive patient subgroups.

Methods Sixteen studies were included in the systematic review and eight (231 patients) in the meta-analysis. Primary outcomes included plasma aldosterone concentration (PAC), plasma renin activity (PRA), and angiotensin II (AngII) changes. Subgroup analyses examined age, BMI, and CPAP duration thresholds, with meta-regression assessing moderating factors.

Results CPAP significantly reduced PAC (d + of -0.72, 95% CI -1.39 to -0.05, $p = 0.036$), though statistical significance was attenuated in adjusted models, and improved daytime hemodynamics: systolic BP (d + -0.81), diastolic BP (d + -1.30), and heart rate (d + -1.61). Notably, patients < 50 years showed marked PAC reduction (d + -1.12, 95% CI -1.88 to -0.35), as did those with CPAP adherence ≥ 3 months (d + -0.88, 95% CI -1.86 to 0.09). No significant changes occurred in PRA ($p = 0.917$), plasma renin concentration ($p = 0.463$), or AngII ($p = 0.058$) in the overall cohort. Meta-regression revealed no significant associations between age, BMI, or CPAP duration and RAAS changes (all $p > 0.05$).

Conclusion CPAP demonstrates selective RAAS modulation – significantly lowering PAC – alongside pronounced hemodynamic benefits, even though overall renin and AngII levels did not change significantly. Younger patients (< 50 years) and those maintaining ≥ 3 months therapy show aldosterone responsiveness, suggesting duration-dependent physiological effects. These findings highlight CPAP's potential role in targeted RAAS modulation and underscore the need for personalized treatment strategies in OSA management.

Keywords Angiotensin · Renin · Hyperaldosteronism · Blood pressure · CPAP

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Introduction

Obstructive sleep apnea (OSA) is a chronic, sleep-related breathing disorder commonly found alongside obesity and resistant hypertension [1, 2]. It is characterized by periodic narrowing and obstruction of the pharyngeal airway during sleep [3]. Left untreated, OSA leads to heightened cardiovascular risk [4], consequently amplifying morbidity and mortality rates. This association is believed to be mediated by the presence of metabolic syndrome, particularly hypertension, which exerts deleterious systemic effects [5].

Aldosterone is a key hormone in the mineralocorticoid pathway and plays an essential role in regulating the salt and water balance, controlling blood pressure, and facilitating cardiovascular remodeling [6]. Elevated aldosterone levels are associated with an increased risk of cardiovascular events and mortality [7]. There is growing evidence indicating a connection between OSA and dysregulation of the renin–angiotensin–aldosterone system (RAAS) [8]. RAAS activation plays an important role in the relationship between OSA and hypertension, especially in resistant hypertension. Therefore, the Endocrine Society recommends screening for primary aldosteronism among patients with OSA and hypertension [9]. However, beyond its well-established role in hypertension, RAAS dysregulation also contributes to OSA severity and may increase cardiovascular morbidity and mortality [8], underscoring the importance of identifying treatments that can ameliorate RAAS disturbances regardless of a patient's hypertension status.

The physiological link between OSA and RAAS dysregulation involves several key mechanisms. During episodes of apnea, intermittent hypoxia and hypercapnia occur, triggering a sympathetic nervous system response that increases blood pressure and heart rate [5]. This heightened sympathetic activity stimulates the release of renin, initiating the RAAS cascade and leading to increased production of angiotensin II (AngII) and aldosterone [8]. AngII, a potent vasoconstrictor, further elevates blood pressure by promoting vascular constriction and enhancing sodium retention, while aldosterone promotes fluid retention and potassium excretion, exacerbating hypertension [7]. Additionally, oxidative stress and inflammation, which are also increased in OSA, can enhance RAAS activity by stimulating the expression of angiotensin-converting enzyme (ACE) and other components of the RAAS pathway [10]. Understanding these mechanisms is crucial for developing targeted therapeutic strategies to mitigate the cardiovascular risks associated with OSA.

Continuous positive airway pressure (CPAP) therapy, currently regarded as the gold standard treatment, has been proven to enhance sleep parameters, alleviate OSA symptoms, improve quality of life, and mitigate neurocognitive impairment [11]. Moreover, its use has shown effectiveness in reducing various cardiovascular disease risk markers, both in short- and long-term therapy [12], with evidence supporting a 31% reduction in cardiovascular events with CPAP use compared with non-use [13]. Despite these apparent beneficial effects, the extent to which CPAP therapy can mitigate RAAS dysregulation remains unclear, and previous studies have yielded conflicting results.

Two earlier meta-analyses, encompassing eight and five studies, respectively, showed contradictory findings regarding changes in plasma aldosterone concentration (PAC) with CPAP therapy in patients with OSA [14, 15]. Notably, both meta-analyses focused solely on aldosterone and did not assess upstream RAAS components such as plasma renin activity (PRA) and AngII. OSA influences RAAS activation at multiple levels, and CPAP may exert differential effects on renin, AngII, and aldosterone. Limiting analyses to PAC alone provides an incomplete picture. It is biologically plausible that renin and AngII respond differently to CPAP than aldosterone and evaluating all three biomarkers is therefore essential to understand the broader impact of CPAP on RAAS modulation.

Given the unresolved debate, we conducted an updated systematic review and meta-analysis to evaluate the effects of CPAP on RAAS in patients with OSA. In contrast to prior meta-analyses focusing only on aldosterone, our study examined aldosterone, renin (activity and concentration), and AngII to provide a more comprehensive picture of CPAP's impact on RAAS modulation and its cardiovascular implications. To refine the analysis, we planned subgroup evaluations (e.g., excluding patients with resistant hypertension to see if CPAP's RAAS effects extend beyond severe hypertension). Additionally, meta-regression analyses were performed to explore whether BMI, age, and CPAP duration influenced RAAS outcomes. Since RAAS plays a crucial role in regulating blood pressure and heart rate, the outcomes of these studies that reported them were also analyzed.

Methods

This meta-analysis was conducted in accordance with the PRISMA guidelines, and the checklist is provided in Supp Table 1.

Search strategy

A comprehensive search of all English-language medical literature, from 1980 through December 2024, was conducted using PubMed, CINAHL, and OVID to capture all relevant studies examining RAAS changes in adults with confirmed OSA. The search included the following terms:

"PAP", "positive airway pressure", "CPAP", "continuous positive airway pressure", "aldosterone", "renin angiotensin aldosterone system", and "RAAS". The exact search string used in PubMed was: (PAP OR "positive airway pressure" OR CPAP OR "continuous positive airway pressure") AND (aldosterone OR "renin angiotensin aldosterone system" OR RAAS). Additionally, the reference lists of relevant studies were screened to identify any additional articles that might have been missed. For studies with unavailable full texts or insufficient data, the authors were contacted via email to request additional information.

Study selection

Studies were included if they met the following criteria: i) participants aged ≥ 18 years regardless of hypertension status; (ii) OSA diagnosis confirmed via polysomnography, respiratory polygraphy, or peripheral arterial tonometry; and iii) reported aldosterone levels and/or other RAAS-related parameters before and after CPAP therapy. The primary outcome was changes in aldosterone levels, while the secondary outcomes included PRA, plasma renin concentration (PRC), AngII level, urine aldosterone, and aldosterone-to-renin ratio (ARR). The exclusion criteria were review articles, conference abstracts, theses, and studies involving participants receiving treatment for primary aldosteronism.

The search results were imported into Endnote, where duplicates were removed before two independent reviewers (HHL and AY) screened the titles and abstracts. Discrepancies were resolved through consensus. Data extraction, including demographic characteristics, OSA severity, and RAAS parameters, was independently performed by HHL and AY using a standardized data extraction form. Wherever numerical data were unavailable, values were estimated using PlotDigitizer.

Quality assessment

Two reviewers (HHL, WHK) independently assessed study quality using the Newcastle–Ottawa Scale (NOS) for cohort studies, and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for randomized controlled trials (RCT). The NOS assigns up to 9 stars across selection, comparability, and outcome domains. We considered studies with ≥ 3 stars in selection, ≥ 1 star in comparability, and ≥ 2 stars in outcome domains as good quality, consistent with inclusion criteria for meta-analysis. The RoB 2 assesses five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Discrepancies between the two reviewers were resolved by consensus.

Statistical analysis

The extracted data were summarized and analyzed using SPSS version 29 (SPSS Inc., Chicago, IL, USA). The heterogeneity of the trials was assessed using the I-squared (I^2) statistic, with values greater than 50% indicating substantial heterogeneity. A random effects model (Restricted Maximum Likelihood) was applied in cases of significant heterogeneity; otherwise, a fixed-effects model was used. Heterogeneity (I^2) for each pooled analysis is reported with the results; a random-effects model was used for outcomes showing substantial heterogeneity. Publication bias was evaluated using the Egger's regression test. Cohen's d (d+) was used to determine the standardized mean difference before and after CPAP therapy, with an effect size greater than 0.8 or less than −0.8 considered large.

Results

Our initial search identified 419 articles, comprising 154 from PubMed, 149 from CINAHL, and 116 from OVID. Following thorough screening of titles, abstracts, and full texts, and removal of duplicate publications, 41 articles were identified. Among these, 24 articles were further excluded: six were review articles, one was a case report, seven had incomplete data, three had an overlap cohort, and seven assessed outcomes different from the objectives of this research (Fig. 1 outlines the study selection process). A total of 16 studies were included in the systematic review. The demographic data of all the included studies and their reported outcomes are shown in Tables 1, 2 and 3. Baseline OSA severity ranged from moderate to severe across studies, and approximately 50% of patients were hypertensive in most cohorts (Table 1). CPAP intervention duration varied widely (from a single night to 12 months), with mean duration ~ 103 days. Not all studies measured every RAAS component; 11 studies reported aldosterone, seven on PRA, three on AngII, and three on PRC, as summarized in Tables 2 and 3.

A total of 231 participants from eight articles were included in the meta-analysis. Among them, 85.8% were males. All included articles were prospective studies, of which four were RCTs [16–19]. Among these studies, all examined PAC [16–26], whereas two reported AngII levels before and after CPAP use [23, 25, 26]. Four studies compared PRA [16, 20–22, 24–26] while two studies reported PRC [19, 23, 27] with CPAP therapy. Two studies evaluated changes in 24-h urine aldosterone with CPAP treatment [25, 28]. Five studies reported changes in blood pressure [17, 18, 23, 24, 26] and three on heart rate [22, 23, 26] changes pre- and post-CPAP in patients with OSA. The sample size

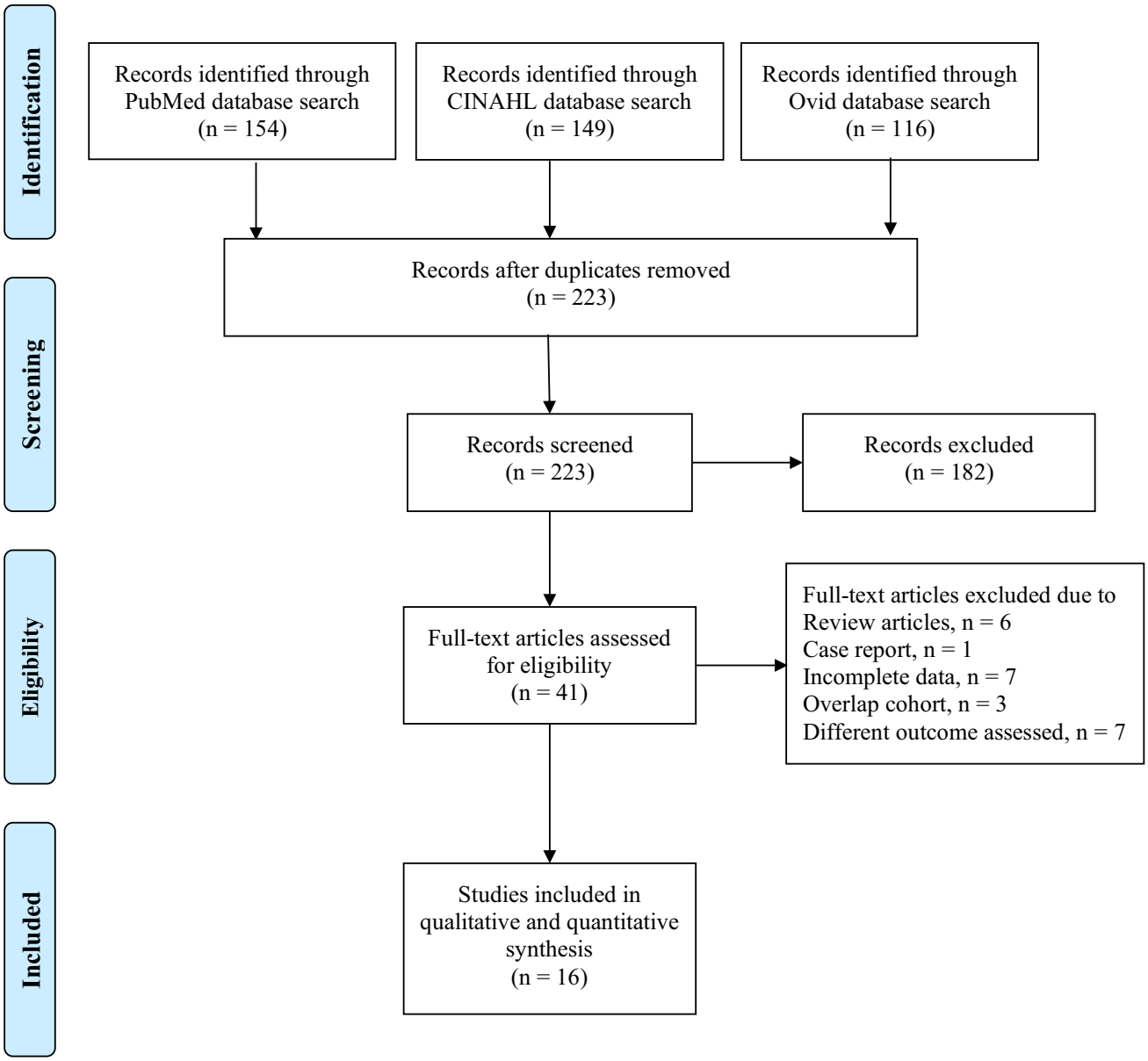


Fig. 1 Study design

ranged from 11 to 54. The quality assessment scores for cohort studies (NOS) and RCTs (RoB 2) included in the meta-analysis are presented in Supp Tables 2a and 2b.

Descriptive statistics

The pooled mean ± SD age of the patients with OSA was 52.8 ± 7.0, with a mean BMI of 32.5 ± 4.1 kg/m^2. The average duration of CPAP therapy was 103 days (range, 1–420 days).

In the two studies which reported changes in 24-h urine aldosterone levels following CPAP treatment, among 117 patients with OSA and resistant hypertension, there was no significant reduction in urinary aldosterone excretion between the CPAP treatment and control groups in the intention-to-treat analysis, although in the per-protocol analysis, those who received CPAP treatment demonstrated a significant reduction in aldosterone excretion compared to the control group after a 6-month period ($p = 0.027$) [28]. In a separate study of 20 patients with OSA and type 2 diabetes, the use of CPAP for 7 days did not lead to a significant reduction in urinary aldosterone levels [25]. Similarly, Barcelo et al. reported a non-significant reduction in ARR and the number of patients with hyperaldosteronism after 12 months of CPAP treatment among 51 patients with OSA [24].

Table 1 Demographic data of included studies

Ref	Country	Study design	Mean age	Gender M:F	Background	Mean AHI or ODI	CPAP duration	CPAP daily use, hour	Control group/ intervention	Primary outcome
CPAP duration < 3 months										
Follenius [20]	France	Prospective single arm	40 ± 1	7:0	Severe OSA	91 ± 9	1 night	-	Nil	CPAP increased renin and aldosterone release
Rodenstein [21]	Belgium	Prospective single arm	50 ± 9	11:1	OSA (AHI > 15/h)	81.3 ± 41.7	3 nights	-	Nil	No change in renin and aldosterone with CPAP
Meston [16]	UK	Prospective 2-arm, RCT	NA	52:0	OSA (ODI > 10/h)	NA	1 month > 4 h/ night	4.6 ± 2.4	OSA (ODI > 10/h)/ Sham CPAP	CPAP and placebo both increased aldosterone
Lacedonia [17]	France	Prospective single arm, cross-over	57 ± 8	23:0	OSA (AHI > 15/h) + HPT	29 ± 17.6	8 weeks, > 3 h/ night	4.8 ± 2.1	OSA (AHI > 15/h) + HPT/ Valsartan	CPAP and valsartan both reduced aldosterone and BP
Thunstrom [19]	Turkey	Prospective 2-arm, RCT	58.9 ± 4.8	37:17	OSA (AHI ≥ 15/h) + HPT	28.3 ± 12.4	6 weeks, > 4 h/ night	5 (3.2–6.3)	HPT non-OSA/ Losartan	Add-on CPAP decreased aldosterone
Nicholl (male group) [44]	Canada	Prospective single arm	49 ± 2	10:19	OSA (ODI ≥ 15/h)	NA	4 weeks, > 4 h/ night, > 70% for 4 weeks	6.4 ± 0.2	Nil	CPAP decreased aldosterone with AngII infusion in men
Nicholl (female group) [44]			50 ± 4							
Thiel [27]	Switzerland	Prospective 2-arm, RCT	62 ± 10.6	31:6	OSA (AHI/ODI ≥ 20/h)	51.8 ± 20	2 weeks, > 4 h/ night > 80% of all days	-	OSA/No CPAP	No change in renin and aldosterone
Zhang [25]	China	Prospective 2-arm, non-RCT	51.2 ± 7.4	18:2	OSA (AHI ≥ 15/h) + T2DM	40.1 ± 21.1	1 week	5.7 ± 1.2	T2DM non-OSA/No therapy	CPAP decreased renin, aldosterone, but still higher than control group No difference in AngII and urinary aldosterone
Nicholl (moderate NH group) [26]	Canada	Prospective single arm	48 ± 3	20:10	OSA (ODI ≥ 15/h)	NA	4 weeks, > 4 h/ night	6.4 ± 0.3	Nil	CPAP decreased urine protein, SBP, DBP, MAP, NE, aldosterone excretion. No difference in renin
Nicholl (severe NH group) [26]			49 ± 3					6.3 ± 0.4		CPAP decreased DBP, NE, aldosterone. No difference in SBP, MAP, renin
CPAP duration ≥ 3 months										
Saarelainen [22]	Finland	Prospective single arm	47 (37–55)	11:0	OSA (AI > 20/h) + HPT	55 ± 26	3 months, > 4 h/ night	-	Nil	CPAP decreased aldosterone and HR CPAP decreased BP at 3 weeks but not at 3 months
Moller [23]	Denmark	Prospective 2-arm, non-RCT	49	22:0	OSA (AHI ≥ 10/h)	28.7 ± 3.5	14 months, > 4 h/ night, > 70% of all days	-	Healthy non-OSA/No CPAP	CPAP decreased renin, AngII and BP

Table 1 (continued)

Barcelo (group with MS) [24]	Spain	Prospective 2-arm, non-RCT	52 ± 8	51:0	OSA (AHI ≥ 10/h) + MS	53 ± 24	12 months, > 4 h/night	-	Healthy non-OSA/No CPAP	CPAP decreased aldosterone
Barcelo (group without MS) [24]			49 ± 9		OSA (AHI ≥ 10/h) + no MS	45 ± 18				
Lloberes [18]	Spain	Prospective 2-arm, RCT	58.3 ± 9.4	25:11	OSA (AHI ≥ 15/h) + RHPT	50.1 ± 21.6	3 months, 75% used > 4 h/night	5.6 ± 1.5	OSA (AHI > 15/h) + RHPT/No CPAP	CPAP decreased aldosterone and night DBP in WCRH CPAP decreased 24-h BP in TRH
Torre (BP responder group) [45]	Spain	Prospective single arm	54 (50.8–63)	38:0	OSA (AHI ≥ 15/h) + RHPT	48.5 (31.5–59)	3 months, > 4 h/night	5.5 (4.9–6.5)	Nil	CPAP decreased ARR
Torre (BP non-responder group) [45]			60 (52–66)			34.5 (22.2–47.8)		5.5 (4.5–6)		
de Souza [28]	Brazil	Prospective 2-arm, RCT	60.8 ± 8	21:36	Moderate to severe OSA + RHPT	35 (24–54)	6 months, > 4 h/night	-	Moderate to severe OSA + RHPT/No CPAP	Optimal CPAP decreased urinary aldosterone
Joyeux-Faure [46]	France	Prospective 2-arm, RCT	60 ± 10	28:9	OSA (AHI > 15/h) + RHPT	37.6 (25.4–51.8)	6 months, > 3 h/night	3.9 (0.6–5.8)	OSA (AHI > 15/h) + RHPT/Sham CPAP	No change in renin and aldosterone with CPAP Sham CPAP increased aldosterone CPAP decreased BP and HR

Abbreviations: *AHI* Apnea-hypopnea index; *CPAP* Continuous positive airway pressure; *NOS* Newcastle Ottawa Scale; *OSA* Obstructive sleep apnea; *AI* Apnea index; *HPT* Hypertension; *SHBG* Sex hormone binding globulin; *IGF-1* Insulin-like growth factor 1; *TSH* Thyroid stimulating hormone; *AngII* Angiotensin II; *MS* Metabolic syndrome; *RHPT* Resistant hypertension; *WCRH* White coat resistant hypertension; *TRH* True resistant hypertension; *BP* Blood pressure; *DBP* Diastolic blood pressure; *FF* Filtration fraction; *NE* Norepinephrine; *T2DM* Type 2 diabetes; *NH* Nocturnal hypoxemia; *SBP* Systolic blood pressure; *MAP* Mean arterial pressure; *RPF* Renal plasma flow; *GFR* Glomerular filtration rate

Table 2 Changes of plasma aldosterone concentration and plasma renin activity before and after CPAP treatment

Ref	PAC, pmol/L				PRA, ng/ml/h			
	Pre-CPAP	Post-CPAP	Absolute difference of means	*p*	Pre-CPAP	Post-CPAP	Absolute difference of means	*p*
Follenius [20]	221.9±27.7	332.9±47.2	111.0	<0.05	1.50±0.30	3.0±0.70	1.5	<0.05
Rodenstein [21]	339.8±179.8	339.8±140.1	0	NS	1.39±1.38	2.37±3.64	0.98	NS
Saarelainen [22]	392.0±147.0	313.0±72.0	−79.0	0.046	0.97±0.55	0.91±0.54	−0.06	NS
Meston [16]	321.0±121.0	411.0±125.0	90.0	<0.001	2.69±2.45	2.67±2.23	−0.02	0.880
Moller [23]	175.0±22.4	172.0±16.0	−3.0	NS				
Barcelo [24]	463.3±241.3	329.5±260.8	−113.8	0.012	1.40±1.10	1.30±0.90	−0.1	0.765
Lacedenia [17]	285.0±238.0	201.0±142.0	−84.0	<0.05				
Lloberes (WCRH group [18]	724.0±310.7	524.3±281.0	−199.7	0.041				
Lloberes (TRH group) [47]	593.5±241.3	629.7±249.7	−63.8	0.182				
Thunstrom [19]	130.0±100.0	105.0±72.0	−25.0	0.147				
Joyeux-Faure [46]	216.4 (113.7, 610.3)	258.0 (188.6, 391.1)	41.6	0.540	1.11 (0.72, 3.79)	0.82 (0.58, 3.59)	−0.29	0.340
Zhang [25]	522.8±187.9	365.1±136.3	−127.7	0.00	1.33±1.22	0.88±0.94	−0.45	0.03
Nicholl (moderate OSA group) [26]	157.0±24.0	108.0±12.0	−49.0	0.011	0.86±0.14	0.79±0.11	−0.07	0.40
Nicholl (severe OSA group) [26]	196.0±38.0	110.0±15.0	−86.0	0.023	1.44±0.40	1.08±0.22	−0.36	0.80

Data presented in mean±SD or median (IQR)

CPAP Continuous positive airway pressure; *PAC* Plasma aldosterone concentration; *PRA* Plasma renin activity; *WCRH* White coat resistant hypertension; *TRH* True resistant hypertension

Table 3 Changes of plasma renin concentration and angiotensin II before and after CPAP treatment

Ref	PRC, μIU/mL				AngII, pg/mL			
	Pre-CPAP	Post-CPAP	Absolute difference of means	*p*	Pre-CPAP	Post-CPAP	Absolute difference of means	*p*
Moller [23]	24.0±4.5	20.0±4.2	−4.0	NS	14.5±2.7	12.3±1.8	−2.1	NS
Thunstrom [19]	30.8±38.0	28.2±30.0	−2.6	0.165				
Thiel [27]	54.6±100.7	69.0±123.2	14.4	NS				
Zhang [25]					74.8±32.1	67.2±35.7	−7.6	0.320
Nicholl (moderate OSA group) [26]					17.0±1.0	16.0±1.0	−1.0	NS
Nicholl (severe OSA group) [26]					23.0±3.0	23.0±5.0	0.0	NS

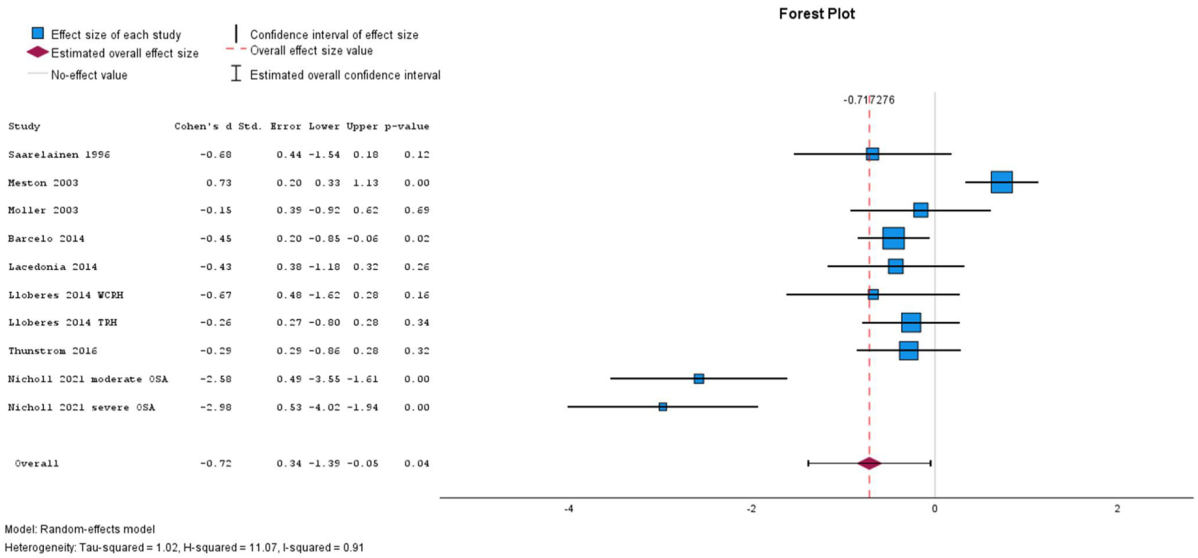
Data presented in mean±SD

CPAP Continuous positive airway pressure; *PRC* Plasma renin concentration; *AngII* Angiotensin II; *OSA* Obstructive sleep apnea

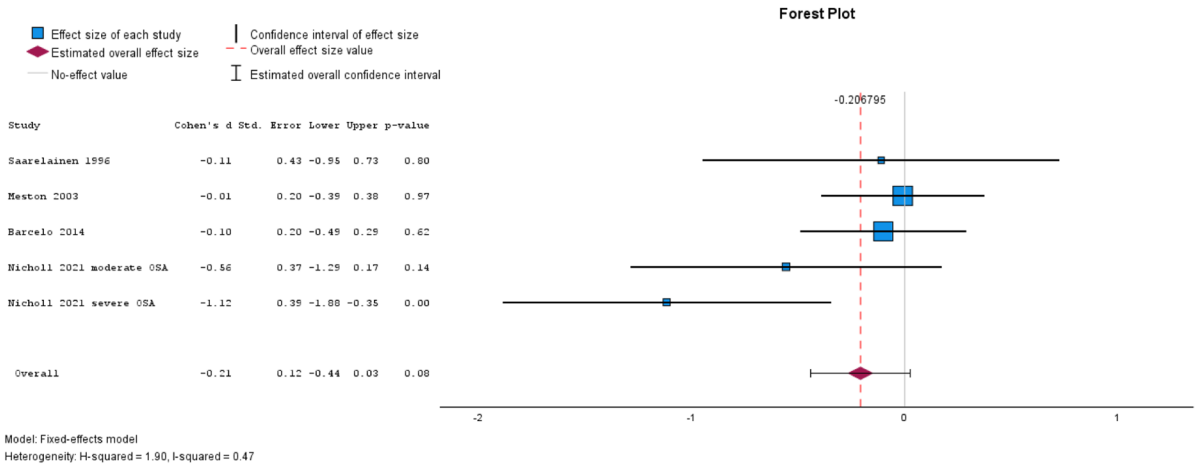
Among the four RCTs, two studied patients with newly diagnosed OSA and hypertension [17, 19]. One study that randomized patients to receive either CPAP or Valsartan for eight weeks demonstrated a significant reduction in PAC among those who received CPAP to levels similar to those receiving Valsartan [17]. Conversely, in the second study, with a larger sample size, in which patients received Losartan for 6 weeks before being randomized to receive CPAP or without, the addition of CPAP did not lead to significant changes in RAAS hormones compared to the control group [19]. Meston et al. randomized 101 newly diagnosed male patients with OSA to one month duration of CPAP ($n=52$) vs sham CPAP ($n=49$) and demonstrated no significant difference in changes of PAC in between both groups [16]. Among patients with OSA and resistant hypertension, only those with white-coat resistant hypertension demonstrated a significant reduction in aldosterone levels, but not among those with true resistant hypertension [18].

Meta-analysis

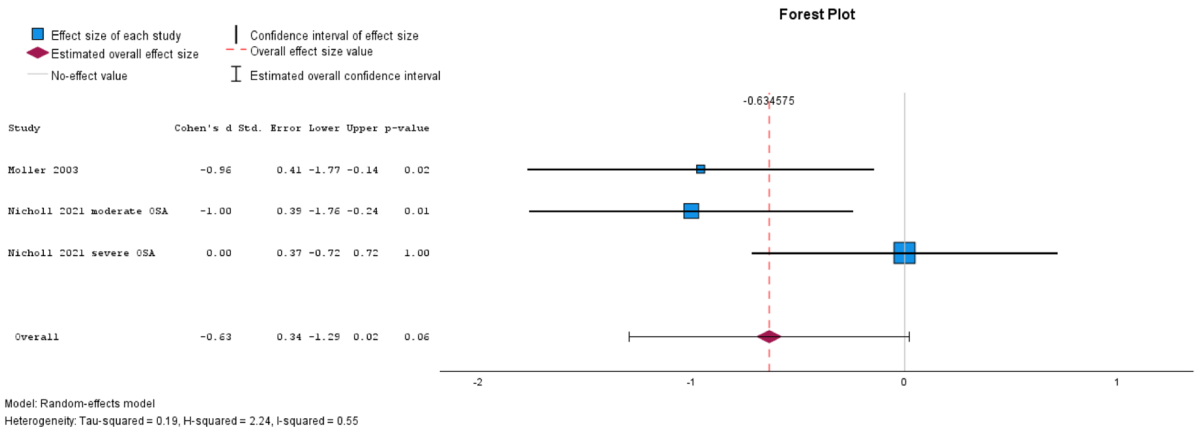
Only studies in which CPAP was used for more than four weeks were included in the meta-analysis. CPAP use resulted in a significant reduction in PAC in the overall population, with a pooled mean effect size estimate, d+of −0.72 (95% CI −1.39 to −0.05, $p=0.036$) (Egger's bias indicator 1.685, $p=0.051$) (Fig. 2a). However, no significant changes were observed in PRA [pooled d+of −0.21 (95% CI −0.44 to 0.03, $p=0.082$) (Egger's bias indicator 0.459, $p=0.289$)] (Fig. 2b), PRC [pooled d+of −0.45 (95% CI −1.27 to 0.37, $p=0.286$) (Egger's bias indicator not generated due to small



a Changes of plasma aldosterone concentration with CPAP use



b Changes of plasma renin activity changes with CPAP use



c Changes of angiotensin II with CPAP use

Fig. 2 **a** Changes of plasma aldosterone concentration with CPAP use. **b** Changes of plasma renin activity with CPAP use. **c** Changes of angiotensin II levels with CPAP use

number of studies)], and AngII levels [pooled d+of −0.64 (95% CI −1.29 to 0.02, $p=0.058$) (Egger's bias indicator 6.935, $p=0.411$)] (Fig. 2c).

Due to the heterogeneity of the study population included in the four RCTs, a meta-analysis was not performed to assess whether the changes in PAC with the use of CPAP were significant compared to the non-CPAP group.

Subgroup analysis

A subgroup analysis was performed to determine whether there was any significant change in PAC among patients without resistant hypertension. After excluding patients with true resistant hypertension [18], the reduction in PAC with CPAP use was no longer significant ($p=0.065$).

Subsequently, an additional analysis was performed to determine the factors influencing the effect of CPAP on PAC and PRA in the subgroups, excluding potential confounding factors (Tables 4 and 5). Studies were stratified by median age (<50 vs≥50 years), obesity (mean BMI<35 vs≥35 kg/m^2), and CPAP duration (short-term<3 months vs longer-term≥3 months), based on study characteristics and clinical relevance. CPAP therapy was effective in improving PAC among those who were younger (<50 years) and those with a longer duration of CPAP (≥3 months).

Meta-regression analysis

Meta-regression analysis demonstrated that age ($p=0.825$), BMI ($p=0.502$), and CPAP duration ($p=0.916$) did not significantly influence changes in PAC. Similarly, these factors (age, $p=0.802$; BMI, $p=0.812$; CPAP duration, $p=0.812$) did not significantly affect PRA levels.

Blood pressure and heart rate

Among the included studies which also reported changes of blood pressure and heart rate with CPAP use, pooled data demonstrated a significant reduction in daytime systolic blood pressure [pooled d+of −0.81 (95% CI −1.49 to −0.14, $p=0.017$) (Egger's bias indicator 0.902, $p=0.462$)], daytime diastolic blood pressure [pooled d+of −1.30 (95% CI of −2.34 to −0.26, $p=0.014$) (Egger's bias indicator 1.052, $p=0.541$)], and heart rate [pooled d+of −1.61 (95% CI −2.25 to −0.98, $p<0.001$) (Egger's bias indicator −4.967, $p=0.374$)]. However, there was no significant change seen in nighttime systolic blood pressure [pooled d+of −0.14 (95% CI −0.34 to 0.74, $p=0.207$) (Egger's bias indicator 1.19, $p=0.883$)] and nighttime diastolic blood pressure [pooled d+of −1.33 (95% CI −3.01 to 0.35, $p=0.121$) (Egger's bias indicator −0.181, $p=0.98$)] with CPAP use.

Table 4 Subgroup analysis for plasma aldosterone concentration

Subgroup	No. of studies	No. of patients	Heterogeneity (I^2, %)	d+(95% CI)	*p*
Age, years					
<50	4	65	90.7	−1.56 (−2.92 to −0.19)	0.026
≥50	3	126	88.9	−0.04 (−0.82 to 0.74)	0.924
BMI, kg/m^2					
<35	4	113	91.9	−0.84 (−1.86 to 0.18)	0.105
≥35	3	78	95.9	−0.93 (−3.05 to 1.18)	0.386
CPAP duration, months					
<3	4	105	96.3	−1.27 (−3.00 to 0.47)	0.153
≥3	3	101	0	−0.41 (−0.68 to −0.13)	0.004

Table 5 Subgroup analysis for plasma renin activity

Subgroup	No. of studies	No. of patients	Heterogeneity (I^2, %)	d+(95% CI)	*p*
Age, years					
<50	3	41	34.4	−0.62 (−1.07 to −0.17)	0.007
≥50	2	103	0	−0.05 (−0.33 to 0.22)	0.701
BMI, kg/m^2					
<35	2	66	14.7	−0.20 (−0.54 to 0.14)	0.252
≥35	3	78	69.1	−0.37 (−1.05 to 0.31)	0.287
CPAP duration, months					
<3	3	82	69.8	−0.49 (−1.14 to 0.16)	0.139
≥3	2	62	0	−0.10 (−0.45 to 0.25)	0.573

d+: Cohen's d; *CI* Confidence interval; *BMI* Body mass index; *CPAP* Continuous positive airway pressure

Discussion

The present meta-analysis indicates that CPAP therapy led to a significant reduction in PAC but did not significantly alter PRA, PRC, or AngII in the overall OSA population, highlighting the selective RAAS modulation effect of CPAP. However, when studies of patients with resistant hypertension were excluded, the reduction in PAC was no longer significant. This suggests that the initial observed changes may be influenced by the underlying hypertension severity or degree of RAAS dysregulation, rather than CPAP therapy alone. This also underscores the possibility of other mechanisms contributing to the modulation of RAAS disturbances in these patients in addition to the underlying OSA.

The near-significant improvement in PAC suggests that CPAP may only partially mediate reductions in PAC. This could be due to incomplete normalization of sympathetic overactivity, a key driver of PAC synthesis [29], and heterogeneity across studies in baseline PAC levels, OSA severity, co-morbidities and CPAP duration. Furthermore, the loss of significance after excluding participants with resistant hypertension indicates that the observed effect may have been driven by this subgroup, who may experience greater autonomic dysregulation [30] and derive more benefit from CPAP therapy.

In addition, the effect sizes in subgroup analyses indicated by Cohen's d were large, with p-values approaching significance, suggesting a possible meaningful physiological impact and a potential trend toward RAAS modulation with CPAP therapy. Notably, individuals younger than 50 years and those on CPAP for > 3 months showed an improvement in PAC, suggesting that age and longer CPAP adherence may enhance RAAS responsiveness, possibly because of greater hormonal adaptability in younger individuals. Older adults demonstrate blunted responses to RAAS stimuli most likely due to age-related declines in RAAS hormone secretion and activity [31, 32]. Nevertheless, the meta-regression analysis did not identify age, BMI, or CPAP duration as significant contributors to PAC or PRA changes. Other unidentified confounding factors may have influenced the RAAS adaptation, leading to the initial positive effect observed in the analysis. It is also important to note that genetic polymorphisms may also contribute to these observations. In our previous meta-analysis, significant differences in AngII levels were observed only among Asian patients with OSA compared to healthy controls [8], suggesting that ethnic variations may play a role in RAAS regulation and should be considered in future studies. While these effect sizes quantify the magnitude of changes in RAAS biomarkers and CPAP therapy, they may not fully reflect the clinical impact. Hence, absolute differences in the mean of the RAAS values should be considered, as they provide a more meaningful context regarding the physiological relevance and potential clinical significance of the findings.

Significant improvements in daytime blood pressure and heart rate were observed with CPAP use, although no changes were observed in nocturnal blood pressure. This indicates that CPAP may primarily improve daytime hemodynamic regulation rather than nocturnal blood pressure patterns. OSA is strongly linked to arterial hypertension, which is potentially driven by autonomic dysfunction [33]. The use of CPAP has been demonstrated to improve daytime sympathetic nerve activity [34], which may have contributed to the observed improvements in daytime blood pressure and heart rate. Furthermore, since RAAS activity surges in the early morning, CPAP therapy may have a greater impact on attenuating this surge, leading to a more pronounced reduction in daytime blood pressure and heart rate, while nocturnal blood pressure remains largely unchanged. CPAP's primary therapeutic effect is to alleviate OSA-related sequelae arising from nocturnal apneic events and hypoxemia. The absence of nocturnal blood pressure improvement may reflect incomplete correction of apneic events or the influence of co-morbidities such as obesity and resistant hypertension, potentially explaining the limited RAAS improvement. Given that nocturnal blood pressure is a strong predictor of cardiovascular risk, these findings suggest that CPAP alone may be insufficient to fully reverse nocturnal hypertension and the associated cardiovascular risks, highlighting the need for combined therapeutic strategies.

Since the improvement in blood pressure and heart rate was more pronounced than the changes in RAAS hormones with CPAP therapy, this also suggests that the observed blood pressure reduction and cardiovascular risk mitigation observed with the use of CPAP in earlier studies may be driven by other mechanisms and pathways beyond RAAS modulation alone. Indeed, CPAP treatment has been shown to reverse endothelial dysfunction [35], reduce levels of C-reactive protein and proinflammatory cytokines [36–38], and increase nitric oxide levels, which is a vasodilator and key determinant of metabolic and vascular health [39, 40]. Furthermore, other mechanisms, such as hyperleptinemia and hyperinsulinemia, observed in obese patients [41], which may not be alleviated by CPAP, could potentially contribute to RAAS activation. Nevertheless, the current meta-analysis demonstrated a significant improvement in PAC following CPAP treatment in the overall cohort, which may elucidate, at least in part, the observed decreases in daytime blood pressure and heart rate documented in this study.

Our study findings were similar to those of an earlier meta-analysis by Deng et al. [14]. In the subgroup and separate analyses, variations in multiple potential confounders did not have a significant effect on PAC levels. However, the meta-analysis included studies with patients on aldosterone receptor blockers and those who received CPAP for < 4 weeks, which may have affected the outcomes. Although Yang et al. similarly reported a significant reduction in aldosterone levels with longer duration of CPAP use and lower BMI, their meta-analysis was limited by the number of studies included [15].

Given the heightened cardiovascular risks associated with both OSA and hyperaldosteronism, it is imperative to explore adjuvant treatment approaches in addition to CPAP therapy, which can further improve the RAAS activity in patients with OSA. Moreover, hyperaldosteronism not only contributes to the development of resistant hypertension

[10] but also likely contributes to the high occurrence of nocturnal hypertension and non-dipping blood pressure profile in this cohort of patients [42], both of which are linked to increased mortality risks [43].

Our study had several limitations. First, the inclusion of only English-language publications may have introduced selection bias. Second, as the majority of the study population were males, our findings may have limited generalizability to female patients, who may exhibit different OSA pathophysiology, RAAS regulation, and cardiovascular responses to CPAP. However, it is worth noting that OSA is more prevalent in males. Additionally, the relatively short duration of CPAP therapy in most studies may have been insufficient to observe maximal changes in RAAS biomarkers or blood pressure. The limited availability of data and study heterogeneity also restricted our ability to perform meta-analysis for all RAAS parameters and these results should be interpreted with caution. This includes urinary aldosterone excretion, ARR, and the prevalence of hyperaldosteronism with CPAP therapy as well as RCTs comparing the effect of CPAP use on RAAS between treated and untreated patients. Furthermore, the substantial heterogeneous diagnostic criteria for OSA and different study designs of the included studies may have contributed to variability in effect sizes and restricted the extrapolation of our conclusions.

Moreover, variability in OSA diagnostic criteria, differences in study designs, small sample sizes, inconsistent CPAP adherence reporting, and heterogenous RAAS measurement techniques may have contributed to variability in effect sizes and limit the generalizability of our conclusion. Many studies were conducted in specific geographical locations, further restricting broader applicability. Finally, several pooled analyses demonstrated high heterogeneity ($I^2 > 90\%$), indicating that the magnitude and direction of effect may vary considerably across the included studies due to differences in population characteristics, study design, or intervention protocols. While subgroup analyses were performed, the results were generally non-significant and should be interpreted cautiously. These findings are exploratory, and intended to generate hypotheses rather than provide definitive conclusions.

Nevertheless, to our knowledge, this is the first meta-analysis to evaluate CPAP's effects on multiple RAAS components (aldosterone, renin, and AngII) in OSA. By using strict inclusion criteria (excluding patients on RAAS-altering medications or very short CPAP trials) and performing detailed subgroup analyses, we attempted to isolate CPAP's direct effects on the RAAS, addressing key limitations of earlier studies. We also explored age, BMI, and CPAP duration as potential moderators through meta-regression. These approaches provide a more nuanced understanding of how CPAP may influence hormonal pathways in OSA. Additionally, we aggregated CPAP's impact on blood pressure and heart rate across studies, linking hormonal changes to clinical outcomes.

Conclusion

In conclusion, while CPAP did not significantly lower renin and AngII levels in patients with OSA overall, it did reduce PAC and improved blood pressure, indicating some RAAS modulation. Patients who are younger or use CPAP longer may derive greater aldosterone lowering, though this needs confirmation. Our findings underscore the complexity of the OSA-RAAS interaction and the need for larger, well-controlled studies. In the meantime, clinicians should continue to treat OSA to gain its cardiovascular benefits and consider additional therapies for patients with persistent RAAS activation.

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Data availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study is a systematic review and meta-analysis of previously published studies and does not involve any new data collection involving human participants; therefore, ethical approval was not obtained.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Patient consent This article does not contain any studies with human participants performed by any of the authors.

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