Changes in cortisol levels by continuous positive airway pressure in patients with obstructive sleep apnoea: meta-analysis of 637 individuals

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SUMMARY

Background: Obesity, obstructive sleep apnoea (OSA) and hypertension frequently coexist and are associated with elevated cortisol levels. Identification and treatment of such patients is important when investigating for suspected Cushing's syndrome and hypertension. Studies of the impact of continuous positive airway pressure (CPAP) on cortisol and blood pressure are limited by small sample size and show conflicting findings. We conducted a meta-analysis to document changes in the levels of cortisol and blood pressure in response to CPAP treatment of OSA.

Methods: Meta-analysis was conducted using RevMan (v5.3) and expressed in standardised mean difference (SMD) for catecholamines and mean difference (MD) for systolic (SBP) and diastolic blood pressure (DBP). The quality of the studies was evaluated using standard tools for assessing the risk of bias.

Results: A total of 22 studies met our search criteria; they consisted of 16 prospective cohort studies (PCS) that recruited 385 participants and six randomized control trials (RCT) totalling 252 participants. Range of mean age was 41-62yr and BMI 27.2-35.1kg/m^2. CPAP treatment reduced plasma cortisol levels in PCS: SMD = -0.28 (95%CI = -0.45 to -0.12), I^2 = 0%, p = 0.79 and in RCT: SMD = -0.39 (95%CI = -0.75 to -0.03), I^2 = 28.3%, p = 0.25. CPAP treatment reduced SBP by 5.4 mmHg (95% confidence interval =1.7-9.1) and DBP by 3.3 mmHg (95% confidence interval = 1.0-5.7). Inter-study heterogeneity was low for all studies. Bias in most RCT arose from the lack of blinding of participants and personnel.

Conclusion: CPAP treatment in individuals with OSA reduces cortisol levels and blood pressure.

INTRODUCTION

Obesity, obstructive sleep apnoea (OSA) and hypertension are common coexisting morbidities.[1,2] These conditions pose a number of secondary health complications such as cardiovascular disease[3] and other cardiometabolic disorders such as type 2 diabetes mellitus and chronic renal disease.[4,5] Studies in the US have indicated that 25% of men and 11% of women over 40 years have OSA.[6] Furthermore, between 30 and 50% of individuals with essential hypertension have OSA,[1,7] but many are not diagnosed.[8-10] The main treatment for moderate to severe OSA is continuous positive airway pressure (CPAP).

OSA results in hypothalamic-pituitary-adrenal (HPA) axis activation. Cortisol, one of the major stress hormones, is often elevated in patients with obesity,[11] OSA[12] and hypertension.[13] Although there is also evidence that cortisol induces hypertension[14] and promotes adipose tissue expansion,[15] the links between OSA, obesity and blood pressure are complex, and likely reciprocally related to each another.[16,17] A limited number of case reports or small studies[18,19] have shown that cortisol levels could be reduced to the reference range after CPAP treatment in pseudo-Cushing's syndrome; however, there exist no large scale studies. An earlier systematic review of the association between OSA and cortisol changes with CPAP treatment showed conflicting findings.[20] Moreover, given the clinical importance of the role of OSA on raised cortisol levels and hypertension, it is surprising that the assumption of CPAP to reduce cortisol levels and blood pressure has been based on such limited information. Therefore, a meta-analysis was needed to review current data and guide clinicians, especially when the clinical and biochemical diagnosis of hypercortisolism is often so

difficult. Here, we conducted such a meta-analysis to document changes in the levels of cortisol and blood pressure in response to treatment of OSA with CPAP.

METHODS

Search criteria

Two investigators, followed PRISMA[21] and Cochrane[22] guidelines, and performed independently a literature search of MEDLINE, Google Scholar and Cochrane Library Central Register of Controlled Trials databases up to March 2021 using the key terms (British or US usage and abbreviations, *e.g.* CPAP and OSA): obstructive sleep apnoea, continuous positive airway pressure and plasma and salivary cortisol, hydrocortisone, corticosteroid, cortisone, glucocorticoid, urinary free cortisol or over-night dexamethasone suppression test, and hypertension. No filters for language or data were used. The Boolean operators “AND” and “OR” were used to combine search terms. Relevant studies were hand-searched within these references.

Selection criteria

Studies examining the effect of CPAP on cortisol in the OSA population were included irrespective of age, sex, race, comorbidities, duration of CPAP and treatment. Studies that fit the inclusion criteria were prospective cohort studies (PCS) and randomised control trials (RCT). Studies were excluded if they did not present numerical data for cortisol at baseline and end-point.

Risk of bias

The quality of the reports was evaluated using the risk of bias in non-randomised studies of interventions (ROBINS-I) tool for PCS[23] and risk of bias assessed using

Cochrane Collaboration's tool for RCT.[24] The risk of bias for each report was rated independently from low, moderate, serious or critical by two authors and any discrepancies were resolved by reciprocal discussion.

Statistical analysis

Meta-analysis was performed using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). The standardised mean difference (SMD) was used to determine the effect size on cortisol to accommodate for a variety of ways they were measured. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study and was necessitated due to the different units in which cortisol levels were reported.[25] Negative values indicate a fall of the variable with the intervention. The mean difference (MD) was used on the original scale of measurement to determine the effect size on systolic (SBP) and diastolic blood pressure (DBP). Pooled estimates of outcomes were obtained via the DerSimonian and Laird method using a random effects model.[26] Statistical significance threshold was accepted as p <0.05. The I^2 statistic was used to assess heterogeneity of study results.[27]

RESULTS

After screening the literature, 22 studies comprising 647 participants met the above search criteria (**Figure 1**). A total of 335 subjects participated in the 15 PCS using plasma cortisol as outcome,[28-42] and 50 subjects in the only one PCS using salivary cortisol.[43] The three RCT using plasma cortisol as the outcome measure[44-66] contained 195 participants (105 in treatment groups and 90 controls), and the other three RCT

using salivary cortisol contained 57 participants (28 in treatment groups and 29 controls).[47-49]

The reported mean age ranged 31-62 yr, body mass index 29.6-46.9 kg/m^2, SBP 119-144 and DBP 66-93 mmHg (**Table 1A & B**). Baseline cortisol levels were variably reported in different units. The duration of CPAP treatment ranged from one day to 39 months in PCS and one day to six months in RCT (**Table 2A & B**). The remaining sleep study characteristics are presented in **Tables 1-2**.

CPAP treatment reduced ($p < 0.05$) the levels of plasma cortisol with in PCS: SMD = -0.28 (95%CI = -0.45 to -0.12), I^2 = 0%, p = 0.79 (**Figure 2**) as well as in RCT: SMD = -0.39 (95%CI = -0.75 to -0.03), I^2 = 28.3%, p = 0.25 (**Figure 3**). Including the one PCS study that used salivary cortisol[43] increased the SMD slightly: -0.34 (95%CI = -0.48 to -0.20), I^2 = 0%, p = 0.47 (**Supplementary Figure 1**). CPAP treatment also reduced the levels of salivary cortisol in RCT: SMD = -0.57 (95%CI = -1.11 to -0.03), I^2 = 0%, p = 0.56 (**Supplementary Figure 2A**), as well as the levels of plasma and salivary cortisol presented together: SMD = -0.42 (95%CI = -0.67 to -0.16), I^2 = 0%, p = 0.50 (**Supplementary Figure 2B**).

Blood pressure was reported in six studies totalling 104 participants (**Table 2**).[29,32,36,44,49] CPAP treatment led to a blood pressure reduction: mean values for SBP were 5.4 mmHg (95%CI = 1.7-9.1 mmHg) (**Figure 4A**) and of DBP were 3.3 mmHg (95%CI = 1.0-5.7 mmHg) (**Figure 4B**). There was no evidence of inter-study heterogeneity (I^2 = 0%).

Bias risk for PCS was evaluated using the ROBINS-I tool (**Figure 5A**). There was no evidence of bias due to confounding factors or in selection of participants. Five studies were considered to suffer bias due to deviations from intended interventions as CPAP treatment was less than a week. Missing data were assessed to cause a moderate risk of bias in seven studies.[35,37,38,39,42,43] None of the studies had bias in measurement of outcomes. There was insufficient information from any of the studies for assessing bias in selection of the reported result.

Risk of bias for the RCT assessed by random sequence generation (**Figure 5B**) showed a high risk in the majority of studies since they were not blinded,[45-49] except one study which provided sham CPAP to the control group.[44] Two studies were at risk of incomplete outcome data (baseline blood pressure).[46,48] All of the studies used intention-to-treat analysis but lacked information of selective reporting bias as they did not mention the study protocol. The duration of CPAP treatment in the study by Nakamura was only one night.[45]

DISCUSSION

In this meta-analysis of data from 637 participants with OSA, we observe that CPAP treatment significantly reduced both plasma and salivary cortisol levels as well as both SBP and DBP. These findings provide important information to clinicians. Individuals undergoing investigation for suspected Cushing's syndrome and for those with hypertension would benefit from an initial screening for OSA such as the Epworth sleepiness score and proceed to a sleep study if indicated. If OSA is present, CPAP treatment may help avoid false positive diagnosis of Cushing's syndrome (pseudo-Cushing's syndrome) and lower blood pressure.

The impact of CPAP on cortisol and blood pressure has been debatable because of conflicting findings between studies. A number of factors could contribute to these discrepancies, primarily the wide variation in study designs and small sample sizes. For example, the duration of CPAP treatment varied from days to months. The minimum time for CPAP to fully lower the levels of cortisol is not known but one day of CPAP, as performed by two studies,[33,44] would be unlikely to have a significant effect on the HPA axis. Studies such as Gaspar et al showed the level of cortisol measured at 4 months (46.5 ng/ml) was virtually identical to that measured after 24 months (46.9 ng/ml) of CPAP treatment.[38]

We found most studies used plasma cortisol, with some using salivary cortisol as outcome measures. Excluding the study using salivary cortisol from the rest of the forest plot in PCS, or splitting the six RCT into plasma and salivary cortisol studies showed CPAP had very similar effects on the reduction of cortisol measured from both sources. Observations from the present study complement our recent meta-analysis showing catecholamines and blood pressure were also reduced by CPAP treatment.[50,51] The reduction of 5.4 mmHg of SBP and 3.3 mmHg DBP by CPAP in the present study was remarkably similar to the results observed in our previous meta-analysis of CPAP and catecholamines.[50] These findings together suggest that CPAP reduces stress induced by OSA. In response, secretion of stress hormones such as cortisol and catecholamines are also decreased. The relative contribution of these two hormones towards lowering blood pressure is not certain as most studies do not measure both cortisol and catecholamines simultaneously in the studies of the impact of CPAP on OSA and blood pressure.

As expected for a meta-analysis, certain limitations were identified in this study. These include differences in methods of measuring cortisol as described above. In addition, most studies did not document blood pressure after CPAP treatment. Furthermore, the reduction in blood pressure is small regarding clinical importance, but this provides an important insight into the underlying mechanisms linking OSA with the stress hormone cortisol and hypertension, which could be reversed to a certain extent by CPAP. There were also varying methods applied to control groups in the RCT, the majority received no treatment while only a few received sham CPAP treatment. This may introduce a risk of bias since sham CPAP treatment may exert greater influences on the participants[52] which may underestimate the effect of CPAP itself on cortisol and blood pressure. Due to the nature of the study, it is probably impossible to disguise sham CPAP from patients as most of them are able to recognise whether sham CPAP or therapeutic CPAP were prescribed. Despite the well-known high prevalence of women with OSA, most studies did not recruit a sufficient number of female participants, therefore the findings from this study should not be extrapolated to the female population. Details on compliance to CPAP was not reported by most studies. Ideally, data confirming adherence with minimum of five hours a night is necessary for effectiveness. Furthermore, there was also a lack of data confirming that CPAP is effective in overcoming the obstructions with a reduction in the apnea-hyponea index.

In conclusion, CPAP treatment in individuals with OSA reduces cortisol levels and blood pressure. Identification and treatment of such patients is important when investigating for suspected Cushing’s syndrome and hypertension.

Conflict of interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval

This study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author contribution

TSH created the study concept and design. TSH and GK-D reviewed the literature. GK-D performed data collection and data analysis under the guidance of TSH. TSH wrote the first draft of the manuscript. CHF and TSH edited subsequent versions. PM, DF and CHF commented on the manuscript. All authors checked, interpreted the results, and approved the final manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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LEGENDS

Figure 1. QUOROM (quality of reporting of meta-analyses) flow chart of literature search.

Figure 2. Changes in plasma cortisol levels with and without continuous positive airway pressure treatment in prospective cohort studies.

Figure 3. Changes in plasma cortisol with and without continuous positive airway pressure treatment in randomised control trials.

Figure 4. Changes in systolic (**A**) and diastolic (**B**) blood pressure with and without continuous positive airway pressure treatment.

Figure 5. Risk of bias of prospective cohort studies evaluated by ROBINS-I tool (**A**) and risk of bias of randomised control trials evaluated by Cochrane Collaboration's tool (**B**).

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Figure 1.

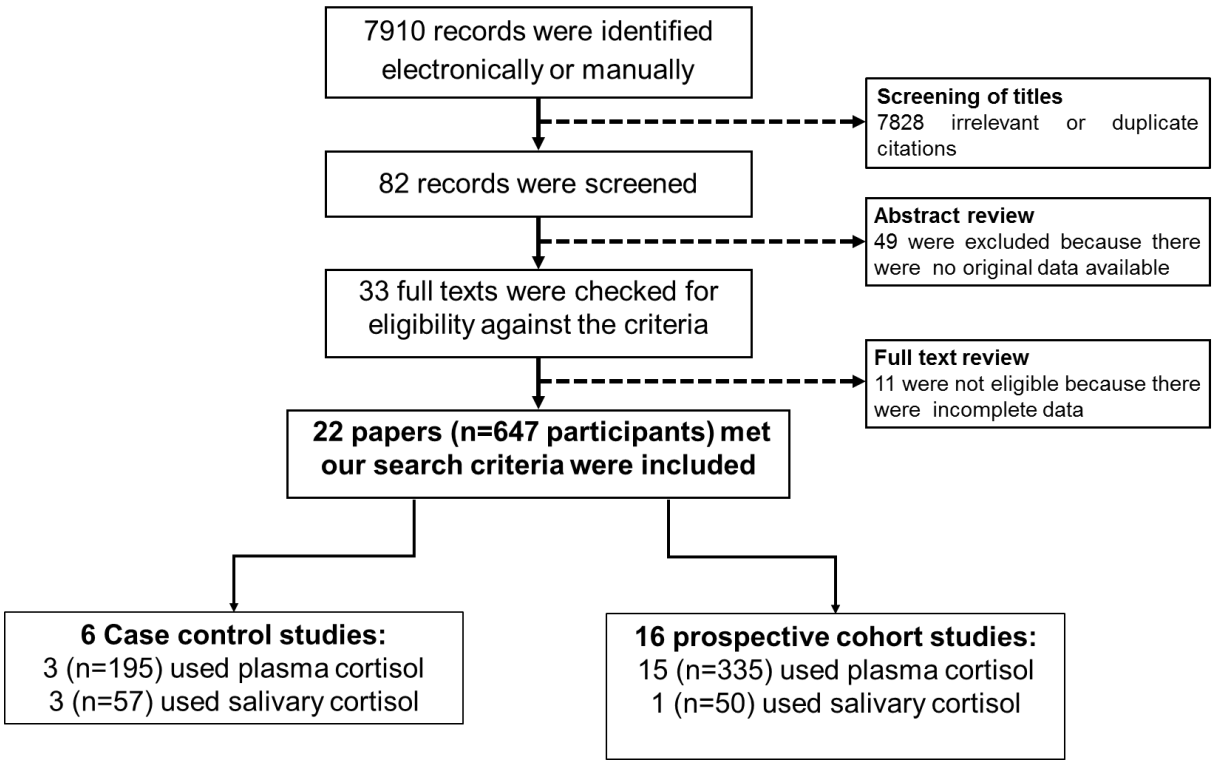

7910 records were identified electronically or manually
Screening of titles
7828 irrelevant or duplicate citations
82 records were screened
Abstract review
49 were excluded because there were no original data available
33 full texts were checked for eligibility against the criteria
Full text review
11 were not eligible because there were incomplete data
22 papers (n=647 participants) met our search criteria were included
6 Case control studies:
3 (n=195) used plasma cortisol
3 (n=57) used salivary cortisol
16 prospective cohort studies:
15 (n=335) used plasma cortisol
1 (n=50) used salivary cortisol

Figure 2.

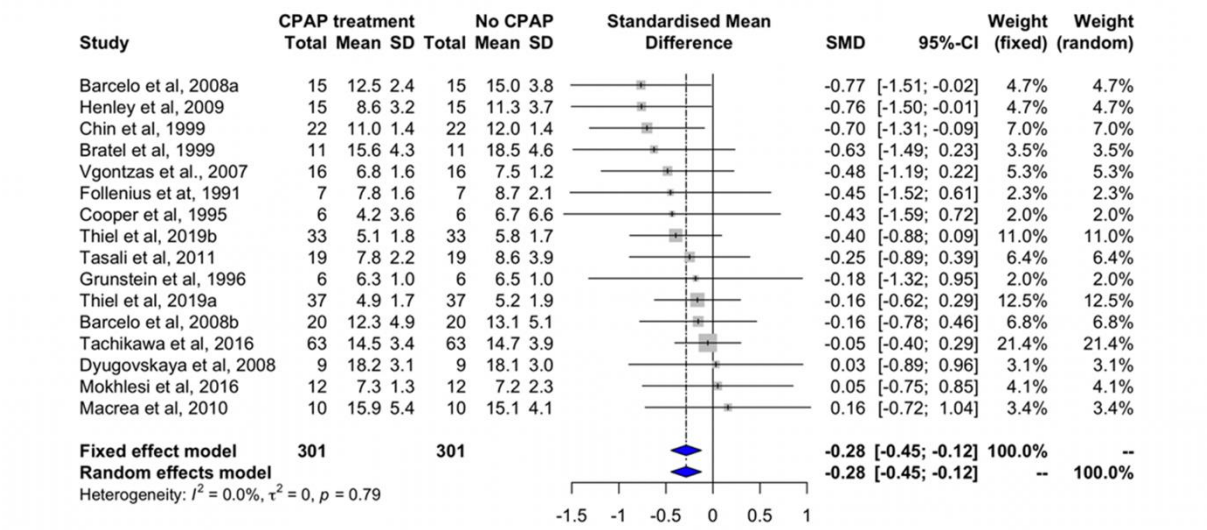

Study
CPAP treatment Total Mean SD
No CPAP Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed)
Weight (random)
Barcelo et al, 2008a 15 12.5 2.4 15 15.0 3.8 -0.77 [-1.51; -0.02] 4.7% 4.7%
Henley et al, 2009 15 8.6 3.2 15 11.3 3.7 -0.76 [-1.50; -0.01] 4.7% 4.7%
Chin et al, 1999 22 11.0 1.4 22 12.0 1.4 -0.70 [-1.31; -0.09] 7.0% 7.0%
Bratel et al, 1999 11 15.6 4.3 11 18.5 4.6 -0.63 [-1.49; 0.23] 3.5% 3.5%
Vgontzas et al., 2007 16 6.8 1.6 16 7.5 1.2 -0.48 [-1.19; 0.22] 5.3% 5.3%
Follenius et at, 1991 7 7.8 1.6 7 8.7 2.1 -0.45 [-1.52; 0.61] 2.3% 2.3%
Cooper et al, 1995 6 4.2 3.6 6 6.7 6.6 -0.43 [-1.59; 0.72] 2.0% 2.0%
Thiel et al, 2019b 33 5.1 1.8 33 5.8 1.7 -0.40 [-0.88; 0.09] 11.0% 11.0%
Tasali et al, 2011 19 7.8 2.2 19 8.6 3.9 -0.25 [-0.89; 0.39] 6.4% 6.4%
Grunstein et al, 1996 6 6.3 1.0 6 6.5 1.0 -0.18 [-1.32; 0.95] 2.0% 2.0%
Thiel et al, 2019a 37 4.9 1.7 37 5.2 1.9 -0.16 [-0.62; 0.29] 12.5% 12.5%
Barcelo et al, 2008b 20 12.3 4.9 20 13.1 5.1 -0.16 [-0.78; 0.46] 6.8% 6.8%
Tachikawa et al, 2016 63 14.5 3.4 63 14.7 3.9 -0.05 [-0.40; 0.29] 21.4% 21.4%
Dyugovskaya et al, 2008 9 18.2 3.1 9 18.1 3.0 0.03 [-0.89; 0.96] 3.1% 3.1%
Mokhlesi et al, 2016 12 7.3 1.3 12 7.2 2.3 0.05 [-0.75; 0.85] 4.1% 4.1%
Macrea et al, 2010 10 15.9 5.4 10 15.1 4.1 0.16 [-0.72; 1.04] 3.4% 3.4%
Fixed effect model 301 301 -0.28 [-0.45; -0.12] 100.0% --
Random effects model -0.28 [-0.45; -0.12] -- 100.0%
Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.79
-1.5 -1 -0.5 0 0.5 1

Figure 3.

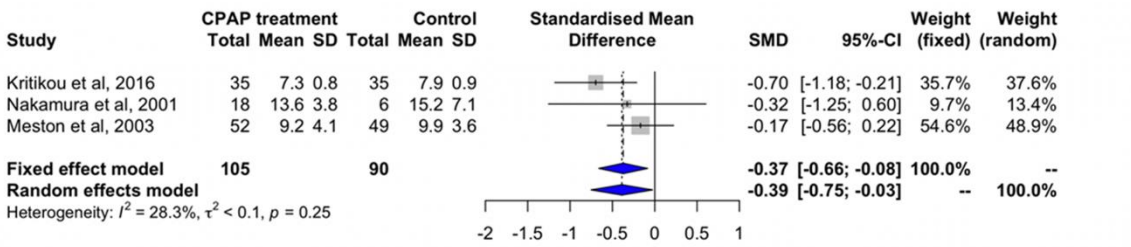
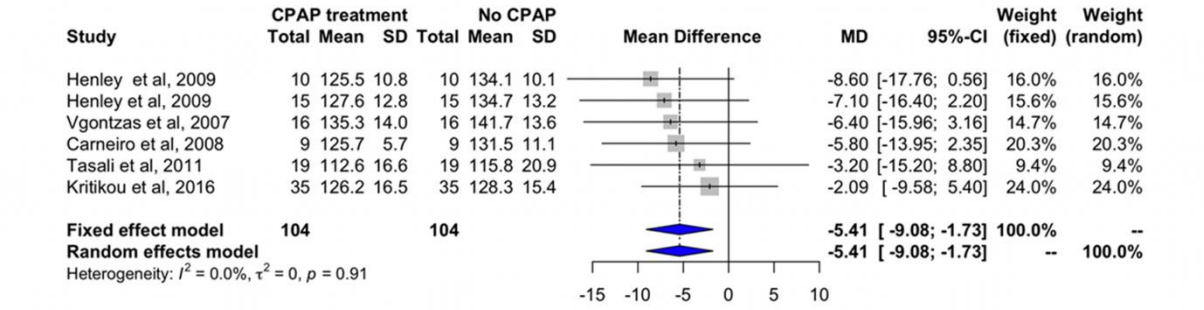

Study
CPAP treatment Total Mean SD
Control Total Mean SD
Standardised Mean Difference
SMD 95%-CI
Weight (fixed)
Weight (random)
Kritikou et al, 2016 35 7.3 0.8 35 7.9 0.9 -0.70 [-1.18; -0.21] 35.7% 37.6%
Nakamura et al, 2001 18 13.6 3.8 6 15.2 7.1 -0.32 [-1.25; 0.60] 9.7% 13.4%
Meston et al, 2003 52 9.2 4.1 49 9.9 3.6 -0.17 [-0.56; 0.22] 54.6% 48.9%
Fixed effect model 105 90 -0.37 [-0.66; -0.08] 100.0% --
Random effects model -0.39 [-0.75; -0.03] -- 100.0%
Heterogeneity: I^2 = 28.3%, τ^2 < 0.1, p = 0.25
-2 -1.5 -1 -0.5 0 0.5 1

Figure 4.

(**A**)


Study
CPAP treatment Total Mean SD
No CPAP Total Mean SD
Mean Difference
MD 95%-CI
Weight (fixed)
Weight (random)
Henley et al, 2009 10 125.5 10.8 10 134.1 10.1 -8.60 [-17.76; 0.56] 16.0% 16.0%
Henley et al, 2009 15 127.6 12.8 15 134.7 13.2 -7.10 [-16.40; 2.20] 15.6% 15.6%
Vgontzas et al, 2007 16 135.3 14.0 16 141.7 13.6 -6.40 [-15.96; 3.16] 14.7% 14.7%
Carneiro et al, 2008 9 125.7 5.7 9 131.5 11.1 -5.80 [-13.95; 2.35] 20.3% 20.3%
Tasali et al, 2011 19 112.6 16.6 19 115.8 20.9 -3.20 [-15.20; 8.80] 9.4% 9.4%
Kritikou et al, 2016 35 126.2 16.5 35 128.3 15.4 -2.09 [-9.58; 5.40] 24.0% 24.0%
Fixed effect model 104 104 -5.41 [-9.08; -1.73] 100.0% --
Random effects model -5.41 [-9.08; -1.73] -- 100.0%
Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.91
-15 -10 -5 0 5 10

(**B**)

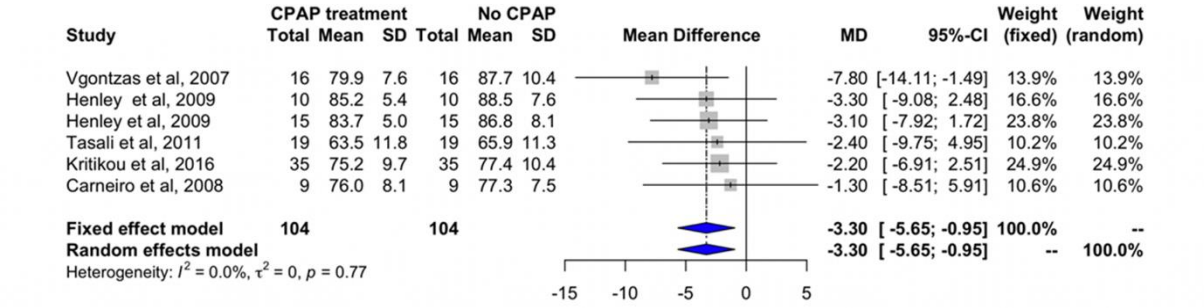

Study
CPAP treatment Total Mean SD
No CPAP Total Mean SD
Mean Difference
MD 95%-CI
Weight (fixed)
Weight (random)
Vgontzas et al, 2007 16 79.9 7.6 16 87.7 10.4 -7.80 [-14.11; -1.49] 13.9% 13.9%
Henley et al, 2009 10 85.2 5.4 10 88.5 7.6 -3.30 [-9.08; 2.48] 16.6% 16.6%
Henley et al, 2009 15 83.7 5.0 15 86.8 8.1 -3.10 [-7.92; 1.72] 23.8% 23.8%
Tasali et al, 2011 19 63.5 11.8 19 65.9 11.3 -2.40 [-9.75; 4.95] 10.2% 10.2%
Kritikou et al, 2016 35 75.2 9.7 35 77.4 10.4 -2.20 [-6.91; 2.51] 24.9% 24.9%
Carneiro et al, 2008 9 76.0 8.1 9 77.3 7.5 -1.30 [-8.51; 5.91] 10.6% 10.6%
Fixed effect model 104 104 -3.30 [-5.65; -0.95] 100.0% --
Random effects model -3.30 [-5.65; -0.95] -- 100.0%
Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.77
-15 -10 -5 0 5

Figure 5.

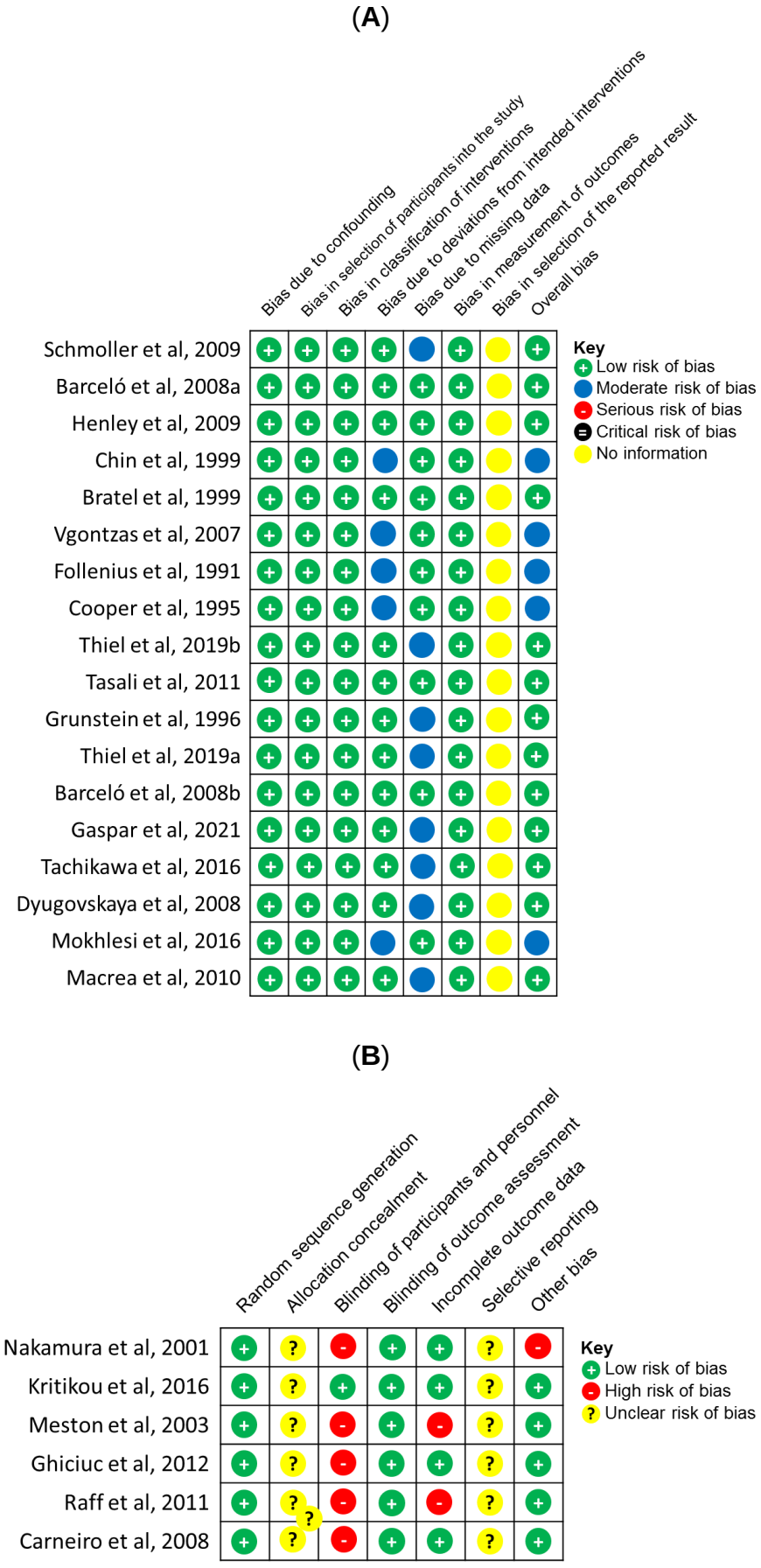

(A)
Bias due to confounding
Bias in selection of participants into the study
Bias in classification of interventions
Bias due to deviations from intended interventions
Bias due to missing data
Bias in measurement of outcomes
Bias in selection of the reported result
Overall bias
Schmoller et al, 2009
Barceló et al, 2008a
Henley et al, 2009
Chin et al, 1999
Bratel et al, 1999
Vgontzas et al, 2007
Follenius et al, 1991
Cooper et al, 1995
Thiel et al, 2019b
Tasali et al, 2011
Grunstein et al, 1996
Thiel et al, 2019a
Barceló et al, 2008b
Gaspar et al, 2021
Tachikawa et al, 2016
Dyugovskaya et al, 2008
Mokhlesi et al, 2016
Macrea et al, 2010
Key
Low risk of bias
Moderate risk of bias
Serious risk of bias
Critical risk of bias
No information
(B)
Random sequence generation
Allocation concealment
Blinding of participants and personnel
Blinding of outcome assessment
Incomplete outcome data
Selective reporting
Other bias
Nakamura et al, 2001
Kritikou et al, 2016
Meston et al, 2003
Ghiciuc et al, 2012
Raff et al, 2011
Carneiro et al, 2008
Key
Low risk of bias
High risk of bias
Unclear risk of bias

Table 1A. Baseline physiological characteristics of participants in prospective cohort studies.

		Mean ± standard de		
	Sex (M/F)	**Age (years)**	**BMI (kg/m^2)**	**SBP**
Prospective cohort studies				
Schmoller et al (2009)[43]	47/3	55.1±1.6	35.4±0.9	
Barceló et al (2008)[28]	22/0	49.0±6.0	32.0±3.0	13
Henley et al (2009)[29]	15/0	51.2±2.7	36.1±1.3	134
Chin et al (1999)[30]	29/2	50.3±3.4	29.6±1.3	130
Bratel et al (1999)[31]	16/0	51.3±3.7*	32.0±1.6*	143
Vgontzas et al (2007)[32]	16/0	48.1±5.6	37.5±5.7	141
Follenius et al (1991)[33]	7/0	40.0±1.0	35.8±2.9	1
Cooper et al (1995)[34]	6/0	50.8±11.9	37.6±5.5	14
Thiel et al (2019)[35]	27/6	60.9±10.8	34.6±5.8	
Tasali et al (2011)[36]	0/19	31.2±1.2	46.4±2.4	115
Grunstein et al (1996)[37]	8/0	56.9±8.6	33.0±7.0	
Gaspar et al, (2021)[38]	34/0	54.6±1.8	31.3±0.8	
Thiel et al (2019)[35]	31/6	62.0±10.6	32.7±6.5	
Barceló et al (2008)[28]	22/0	50.0±5.0	31.0±4.0	14
Tachikawa et al (2016)[39]	51/12	60.6±10.0	27.9±3.8	
Dyugovskaya et al (2008)[40]	8/1	48.0±7.6	33.7±7.1	
Mokhlesi et al (2016)[41]	6/6	54.6±10.2	37.7±8.7	
Macrea et al (2010)[42]	14/0	57.0±2.8*	32.0±1.4*	

CPAP, continuous positive airway pressure; M/F, male/female; BMI, body mass index; SBP and DBP, systolic and diastolic blood pressure; *±SEM.

Table 1B. Baseline physiological characteristics of participants in randomised control trials.

		Mean ± standard deviation			
	Sex (M/F)	**Age (years)**	**BMI (kg/m^2)**	**SBP (mmHg)**	**DBP (mmHg)**
RCT using plasma cortisol					
CPAP treatment					
Nakamura et al (2001)[44]	18/0	49.0±2.2	29.9±1.2	119±3.8	84.0±2.8
Kritikou et al (2016)[45]	19/16	55.5±6.6	28.5±0.6	128.3±2.6	77.4±1.8
Meston et al (2003)[46]	52	40-60	--	--	--
Control group					
Nakamura et al (2001)[44]	6/0	47.7±5.4	30.3±1.6	--	--
Kritikou et al (2016)[45]	20/17	53.3±5.9	27.3	122.8±13.7	75.0±7.8
Meston et al (2003)[46]	49	40-60	--	--	--
RCT using salivary cortisol					
CPAP treatment					
Ghiciuc et al (2012)[47]	10/0	53.0±3.0	32.3±0.7	127±2	76±2
Raff et al (2011)[48]	9	47.0±9.0	33.8±6.2	--	--
Carneiro et al (2008)[49]	9/0	40.1±2.8	46.9±2.0	133.1±3.3	79.6±1.3
Control group					
Ghiciuc et al (2012)[47]	7/0	51.0±3.0	32.1±0.6	117±3	69±4
Raff et al (2011)[48]	9	47.0±9.0	33.8±6.2	--	--
Carneiro et al (2008)[49]	13/0	38.8±3.3	42.8±1.3	127.6±2.3	76.1±1.9

RCT, randomised control trial; CPAP, continuous positive airway pressure; M/F, male/female; BMI, body mass index; SBP and DBP, systolic and diastolic blood pressure.

Table 2A. Baseline sleep study characteristics of participants in prospective cohort studies.

		Mean ± standard deviation				
	CPAP duration	**ODI (events/hr)**	**TSat$_{90}$ (%)**	**LSat O_2 (%)**	**AHI (events/hr)**	**ESS**
Prospective cohort studies						
Schmoller et al (2009)[43]	3 months	49.5±2.8		92.2±0.4	59.6±2.0	
Barceló et al (2008)[28]	3 months	--	--	69±12	52±19	16±3
Henley et al (2009)[29]	93.8±2.2 days	45.3±9.4	--	--	55.0±5.8	11.7±1.2
Chin et al (1999)[30]	3-4 days	--	47.4±8.1	54.2±4.1	59.4±6.9	--
Bratel et al (1999)[31]	6-10 months	39.2±7.0	--	85.2±1.6	43.3±4.7	--
Vgontzas et al (2007)[32]	4 days	--	--	72.4±2.1	53.3±7.0	--
Follenius et al (1991)[33]	1 day	--	--	84.2±3.6	91±9	--
Cooper et al (1995)[34]	3 days	--	31±23	67±19	60±15	--
Thiel et al (2019)[35]	2 weeks	49.4±25.1	--	--	50.6±24.9	7.5±3.4
Tasali et al (2011)[36]	8 weeks	12.4±3.4	--	--	24.3±5.5	--
Grunstein et al (1996)[37]	2-9 years	--	--	80±5	62±9	--
Gaspar et al, (2021)[38]	4 months	--	22.4±4.3	76.8±1.9	45.7±4.5	9.8±0.7
Thiel et al (2019)[35]	2 weeks	50.0±19.3	--	--	51.8±20.0	7.0±3.5
Barceló et al (2008)[28]	3 months	--	--	81±8	48±16	4±3
Tachikawa et al (2016)[39]	3 months	--	16.8±20.3	76.5±8.3	42.2±19.9	8.7±5.3
Dyugovskaya et al (2008)[40]	8.5±4.1 months	--	--	--	8.8±8.4	--
Mokhlesi et al (2016)[41]	1 week	--	--	--	41.0±29.9	--
Macrea et al (2010)[42]	11-39 months	--	37.0±12.0*	77.0±3.0*	28±6.2* (AI)	--

CPAP, continuous positive airway pressure; ODI, oxygen desaturation index; TSat$_{90}$, <90% saturation index; LSat O_2, lowest (minimum) O_2 saturation; AHI, apnoea-hypopnoea index; ESS, Epworth sleepiness scale; AI, arousal index;*±SEM.

Table 2B. Baseline sleep study characteristics of participants in randomised control trials.

	CPAP duration	ODI (events/hr)	$TSat_{90}$ (%)	LSat O_2 (%)	AHI (events/hr)	ESS
RCT using plasma cortisol						
CPAP treatment						
Nakamura et al (2001)[44]	1 day	--	32.5±3.4	61.2±3.2	53.8±3.8	--
Kritikou et al (2016)[45]	2 months	--	--	82.1±1.1	38.5±2.7	--
Meston et al (2003)[46]	1 month	--	--	--	--	--
Control group						
Nakamura et al (2001)[44]	--	--	--	--	--	--
Kritikou et al (2016)[45]	--	--	--	90.3±4.6	2.3±1.9	--
Meston et al (2003)[46]	--	--	--	--	--	--
RCT using salivary cortisol						
CPAP treatment						
Ghiciuc et al (2012)[47]	3-6 months	58.4±9,4	--	68.5±4.3	63.5±9.3	12.9±1.2
Raff et al (2011)[48]	2 weeks	--	--	--	30.8±32.1	8.9±3.4
Carneiro et al (2008)[49]	3 months	--	--	--	65.7±9.9	--
Control group						
Ghiciuc et al (2012)[47]	--	4.9±0.8	--	87.6±1.5	2.6±0.5	4.0±0.8
Raff et al (2011)[48]	--	--	--	--	30.8±32.1	10.7±4.3
Carneiro et al (2008)[49]	--	--	--	--	3.2±0.5	--

RCT, randomised control trial; CPAP, continuous positive airway pressure; ODI, oxygen desaturation index; $TSat_{90}$, <90% saturation index; LSat O_2, lowest (minimum) O_2 saturation; AHI, apnoea-hypopnoea index; ESS, Epworth sleepiness scale.

SUPPLEMENTARY MATERIAL

Figure 1. Changes in plasma cortisol levels with and without CPAP treatment in prospective cohort studies, including one salivary cortisol study by Schmoller et al.[43]

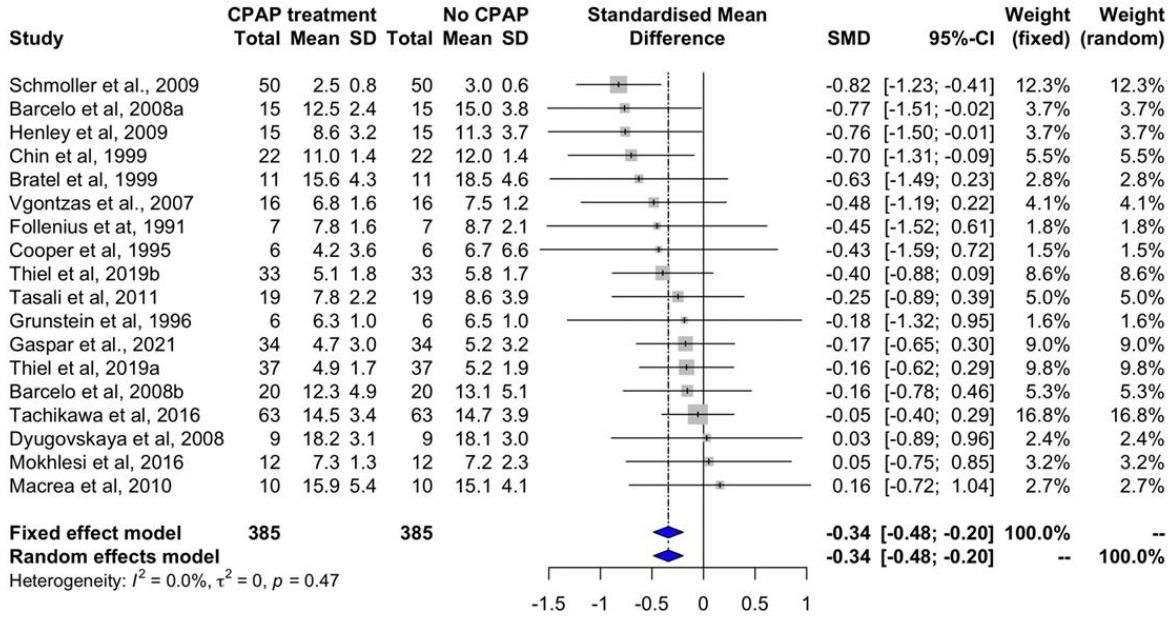
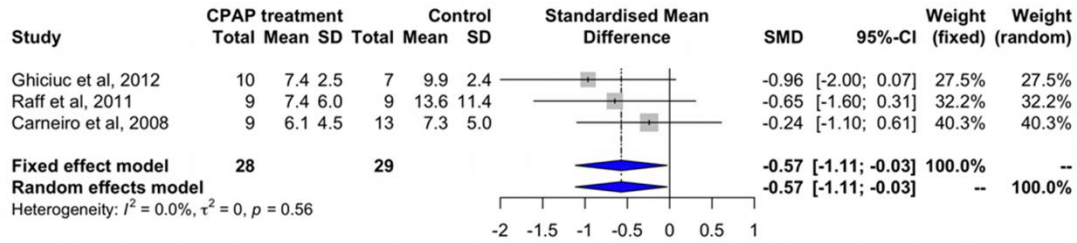


Figure 2. Changes in salivary cortisol only (**A**) and in plasma cortisol and salivary cortisol presented together (**B**), without and with CPAP treatment in RCT.

(**A**)



(**B**)