Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis

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This study identified age, blood pressure levels before treatment and hypoxic burden expressed by the minimum desaturation as potential predictors of blood pressure reduction in patients treated for obstructive sleep apnoea http://bit.ly/31LdrJA

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ABSTRACT The treatment for obstructive sleep apnoea (OSA) with continuous positive airway pressure (CPAP) or mandibular advancement devices (MADs) is associated with blood pressure (BP) reduction; however, the overall effect is modest. The aim of this systematic review and meta-analysis of randomised controlled trials (RCTs) comparing the effect of such treatments on BP was to identify subgroups of patients who respond best to treatment.

The article search was performed in three different databases with specific search terms and selection criteria. From 2289 articles, we included 68 RCTs that compared CPAP or MADs with either passive or active treatment. When all the studies were pooled together, CPAP and MADs were associated with a mean BP reduction of −2.09 (95% CI −2.78–−1.40) mmHg for systolic BP and −1.92 (95% CI −2.40–−1.43) mmHg for diastolic BP and −1.27 (95% CI −2.34–−0.20) mmHg for systolic BP and −1.11 (95% CI −1.82–−0.41) mmHg for diastolic BP, respectively. The subgroups of patients who showed a greater response were those aged <60 years (systolic BP −2.93 mmHg), with uncontrolled BP at baseline (systolic BP −4.14 mmHg) and with severe oxygen desaturations (minimum arterial oxygen saturation measured by pulse oximetry <77%) at baseline (24-h systolic BP −7.57 mmHg).

Although this meta-analysis shows that the expected reduction of BP by CPAP/MADs is modest, it identifies specific characteristics that may predict a pronounced benefit from CPAP in terms of BP control. These findings should be interpreted with caution; however, they are particularly important in identifying potential phenotypes associated with BP reduction in patients treated for OSA.

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Introduction

The relationship between sleep disordered breathing, especially obstructive sleep apnoea (OSA), and hypertension has been well investigated in both cross-sectional and longitudinal studies [1, 2]. Cardiorespiratory interaction includes the activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system as a response to intermittent hypoxia and arousals from sleep induced by obstructive apnoeic events [3].

Nonetheless, the strength of this association is somewhat mitigated by the presence of multiple confounding factors such as obesity that coexists in patients with OSA and comorbidities [4].

Since the late 1980s, various randomised controlled trials (RCTs) have assessed the effect of OSA treatment on blood pressure (BP). The results have been included in systematic reviews and meta-analyses showing a beneficial but modest overall treatment effect on both systolic BP and diastolic BP [5–8].

There are various explanations for this. 1) Compliance with OSA treatment, either in the form of continuous positive airway pressure (CPAP) or mandibular advancement devices (MADs), is often suboptimal. 2) Not all studies have assessed BP in the same way: it is well known that BP is a highly variable parameter and therefore measuring BP only during the consultation, without out-of-office BP measurements, does not allow a full description of a patient's 24-h BP profile, including night-time BP. 3) Treatments such as CPAP need to be properly titrated in order to establish an adequate air pressure able to control sleep disordered breathing without at the same time disturbing the patient's sleep. A study in obese patients with OSA has shown a direct relationship between CPAP pressure, patient discomfort and BP levels [9].

There is a need to better understand the effects of OSA treatments on BP since a better characterisation of patients who benefit most can help to tailor therapy according to the expected benefit to reduce BP and in general improve the patient's cardiovascular risk profile.

Thus, we undertook a systematic review and meta-analysis of RCTs comparing the effect of CPAP and/or MADs on BP with the aim of detecting subgroups and phenotypes of patients who respond best to treatment.

Methods

Study registration and literature search

The present systematic review and meta-analysis was conducted following the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and adheres to the PRISMA statement [10, 11], and has been registered at PROSPERO with identifier number CRD42018093961.

A systematic search was conducted including three databases, *i.e.* MEDLINE (from 1966 to December 31, 2018), Embase (from 1981 to December 31, 2018) and Web of Science (from inception to December 31, 2018), in order to identify all RCTs that evaluated the possible BP-lowering effect of either CPAP or MAD therapy in patients affected by OSA regardless of accompanying daytime somnolence or symptoms of unrefreshing sleep (key words and further details of the literature search are summarised in the supplementary material).

Trial eligibility

Studies were eligible for inclusion if they met the following criteria. 1) Adult patients >18 years old with OSA (>5 apnoeas/hypopnoeas per hour of sleep). 2) The diagnosis of OSA was obtained by full polysomnography or cardiorespiratory polygraphy. 3) BP was measured both before and after CPAP/MAD/other treatment. 4) The studies were RCTs with a control group. The following comparator groups were considered. a) "Passive control group treatment": either sham CPAP (when CPAP is used at a lower pressure than is needed to maintain airway patency) or sham MAD or oral tablets or non-structured conservative measures, such as weight reduction and counselling or usual care. b) "Active control group treatment": antihypertensive drugs or MADs. If there was more than one "passive control group" within the same RCT, the primary analysis was conducted *versus* the one we considered the most appropriate control group according to this rank: i) sham CPAP/MAD, ii) tablets and iii) conservative measures/usual care. When data were published more than once, the most recent and complete publication was considered. If overlapping samples were present, data of the largest study were used. If a report referred to a previous publication for the description of the study design, setting and patients' characteristics, we

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extracted these data. In case of doubt about overlapping patients, we decided to contact the original investigators for more detailed information. Minimum treatment duration was 2 weeks. 5) Comorbidities (*i.e.* heart failure) were not considered an exclusion criterium. However, patients with central apnoea syndromes (defined as non-obstructive apnoeas >50% of total apnoeic episodes) were excluded.

Two researchers (M.P. and C.F.) independently retrieved the studies. The strength of agreement in selecting the articles was measured by Cohen's κ coefficient with approximate standard errors; κ=0.41–0.60 indicated moderate agreement, κ=0.61–0.80 indicated strong agreement and κ⩾0.81 represented very strong agreement. Disagreements were resolved by consensus after discussion between C.F. and M.P.

Data extraction and outcomes

The main outcome of interest was the difference in BP change induced by OSA treatment (computed as BP at treatment end minus BP at baseline). Such difference was calculated as the BP change in the CPAP group minus the BP change in the control group. In our study, the main analysis was based on the inclusion of one BP estimate only for each study considered. When both "office" and ambulatory BP monitoring (ABPM) data were available, in the main meta-analysis we included the ABPM values: either the 24-h ambulatory BP values, or if unavailable, the ambulatory daytime BP values, or night-time BP values in case of absence of the daytime values. Moreover, we also calculated the overall summary BP differences for both office BP and 24-h ABPM by considering only the estimates related to the specific technique.

Other outcomes of interest were predictors of a favourable treatment response of BP to CPAP. More specifically the following sub-analyses were considered. 1) Analyses according to anthropometric characteristics (age, sex and body mass index (BMI)). 2) Analyses in selected groups based on BP levels or on different hypertension subtypes at baseline: i) subjects with controlled or uncontrolled average BP, ii) individuals taking antihypertensive drugs and iii) patients with resistant hypertension. 3) Analyses in selected groups according to sleep apnoea variables: i) patients with severe OSA (average apnoea–hypopnoea index (AHI) >30 events·h^{-1}), ii) average compliance >4 or <4 h per night, iii) studies based on oxygen saturation parameters (minimum arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) and time in bed spent with S_{pO_2} <90%), and iv) sleepy *versus* non-sleepy patients (according to an average Epworth Sleepiness Scale (ESS) score ⩾10 or <10, respectively).

Furthermore, to strengthen the main analysis, we performed other specific analyses. 1) An influence analysis, omitting one study at a time, to identify to what extent the results were influenced by a single study. 2) A cumulative meta-analysis, by adding studies one-by-one in chronological order to explore the temporal evolution of the effect size. Next, this procedure was repeated according to sample size to test if bias related to publication could affect the results. 3) Publication bias was evaluated through both funnel plots and the Egger test [12].

Quality assessment

To evaluate the methodological quality of the included studies we first used the Jadad scale [13]. Scores range from 0 (very poor) to 5 points (rigorous) and the following characteristics of RCTs were assessed: randomisation (1 point if the trial was randomised and an additional 1 point if a table of random numbers or computer-generated randomisation was used), double-blind design (1 point if it was a double-blind trial and an additional 1 point if the article specified how the double-blind was maintained) and follow-up reporting (1 point if the trial stated the numbers and reasons for withdrawal in each study group). However, we acknowledge that the Jadad score has some limitations as it does not include specific criteria useful to estimate the risk of bias and other methodological drawbacks. Thus, we added a self-made score which adds other items to the Jadad score: the way to maintain blindness (use of sham CPAP and sham MAD were considered better methods with respect to others), the presentation of the results of the "intention to treat" analysis and incomplete outcome data assessing. In addition to these aspects, that are common to all RCTs, we also took into account whether BP was among the primary outcomes. We considered the choice of the BP measurement methods as an index of the accuracy of the BP estimate provided by different studies. Finally, we considered an average use of CPAP ⩾4 h per night as an index of quality of the administered therapy.

The Jadad score and the additional comprehensive quality score were independently adjudicated by two investigators (A.G. and M.P.), and disagreements were resolved by consensus.

In subgroup analyses, studies with a comprehensive quality score <6 (low quality) were compared with studies with a score 6–8 (medium quality) and 9–11 (high).

Statistical analysis

We calculated mean net change in either systolic or diastolic BP from intervention with CPAP for each study. When the variability of the difference between BP changes induced by OSA treatment in the two groups was not directly available we calculated it by $SE=\sqrt{((SE_{CPAP})^2+(SE_{control})^2)}$ in the case of parallel study design, while in case of crossover studies $SE=\sqrt{((SD_{CPAP})^2+(SD_{control})^2-(2\times\rho\times SD_{CPAP}\times SD_{control}))}/\sqrt{(n)}$, where the value of the correlation coefficient (ρ) between the CPAP and the control group was calculated from collected data. Moreover, when the standard errors of the BP changes (BP at treatment end minus BP at baseline) were not directly available from the included data, we calculated them by $SE=\sqrt{((SD_{baseline})^2+(SD_{treatment\ end})^2-(2\times\rho\times SD_{baseline}\times SD_{treatment\ end}))}/\sqrt{(n)}$, where the value of the correlation coefficient (ρ) between pre-treatment and post-treatment BP was calculated from collected data. Mean changes of BP were reported in individual patients from randomisation to treatment end including between-patient variations (standard deviation, standard error or 95% confidence interval). If the data of interest were available only from a graph, software for digitalisation of graphs was used to extract the data (GetData Graph Digitizer version 2.26.0.20; www.getdata-graph-digitizer.com).

The differences of the BP changes were pooled by the random effects models proposed by DerSimonian and Laird [14]. The between-changes heterogeneity was tested by Cochrane's Q-test and quantified with the I^2 index [15].

A Cochrane's Q-test was computed to test, for each estimate, the statistical significance of the differences between strata.

For all tests, statistical significance was set at $p<0.05$ and the 95% confidence intervals were therefore presented. All statistical analyses were performed using RevMan version 5.3 (https://community.cochrane.org/help/tools-and-software/revman-5) and Stata version (StataCorp, College Station, TX, USA).

Results

Study selection

From a total of 4289 records identified through the literature search, a total of 68 studies were included in the main meta-analysis (figure 1). The agreement between researchers in selecting the articles was high (κ=0.94±0.02). Characteristics of the individual studies are summarised in supplementary table E1: in detail, 61 studies compared CPAP *versus* passive treatment, eight studies compared MADs *versus* passive treatment, five studies compared CPAP *versus* MADs and three studies compared CPAP *versus* drugs that have a BP-lowering effect [16–79].

Impact of OSA treatment on BP

Supplementary tables E2 and E3 summarise the studies and their overall net BP change for systolic and diastolic BP, respectively. CPAP was associated with a net average BP reduction when compared with passive treatment of −2.09 (95% CI −2.78–−1.40) mmHg for systolic BP and −1.92 (95% CI −2.40–−1.43) mmHg for diastolic BP. The BP change in response to CPAP did not differ significantly between office and ambulatory BP (figure 2). Similar results were obtained considering MAD treatment *versus* passive control with a systolic BP change of −1.27 (95% CI −2.34–−0.20) mmHg and a diastolic BP change of −1.11 (95% CI −1.82–−0.41) mmHg (supplementary figure E1). There was no significant difference between CPAP and MADs in their association with the change in systolic BP (0.26 (95% CI −1.07–1.60) mmHg) or diastolic BP (0.15 (95% CI −0.58–0.89) mmHg) (supplementary figure E2).

In three trials, CPAP was compared with drugs with an antihypertensive effect, even if among them only valsartan can be considered a specific antihypertensive agent. Given the high heterogeneity of the type of treatment and of the drugs being used, we decided not to include these data in the meta-analysis even if each of the drugs with a BP effect considered was superior to CPAP in reducing BP.

Cumulative meta-analysis, influence analysis, stratified analysis and publication bias

In the cumulative meta-analysis according to the time of publication and sample size, no clear trend was apparent (supplementary figures E3–E6). The influence analysis using the leave-one-out method, in which we recalculated the results of our meta-analysis each time leaving out one study, showed no significant differences in the overall results (supplementary figures E7 and E8). A stratified analysis considering the different quality of the RCTs showed a trend towards a greater BP reduction in studies with high quality compared with studies with lower quality, although this difference did not reach the level of statistical significance for either systolic or diastolic BP (supplementary table E4). Funnel plots of all the studies included in the meta-analysis for both systolic and diastolic BP did not show any significant asymmetry (supplementary figure E9). However, the Egger test was compatible with the presence of selection bias for both systolic and diastolic BP ($p<0.001$ and $p=0.04$, respectively).

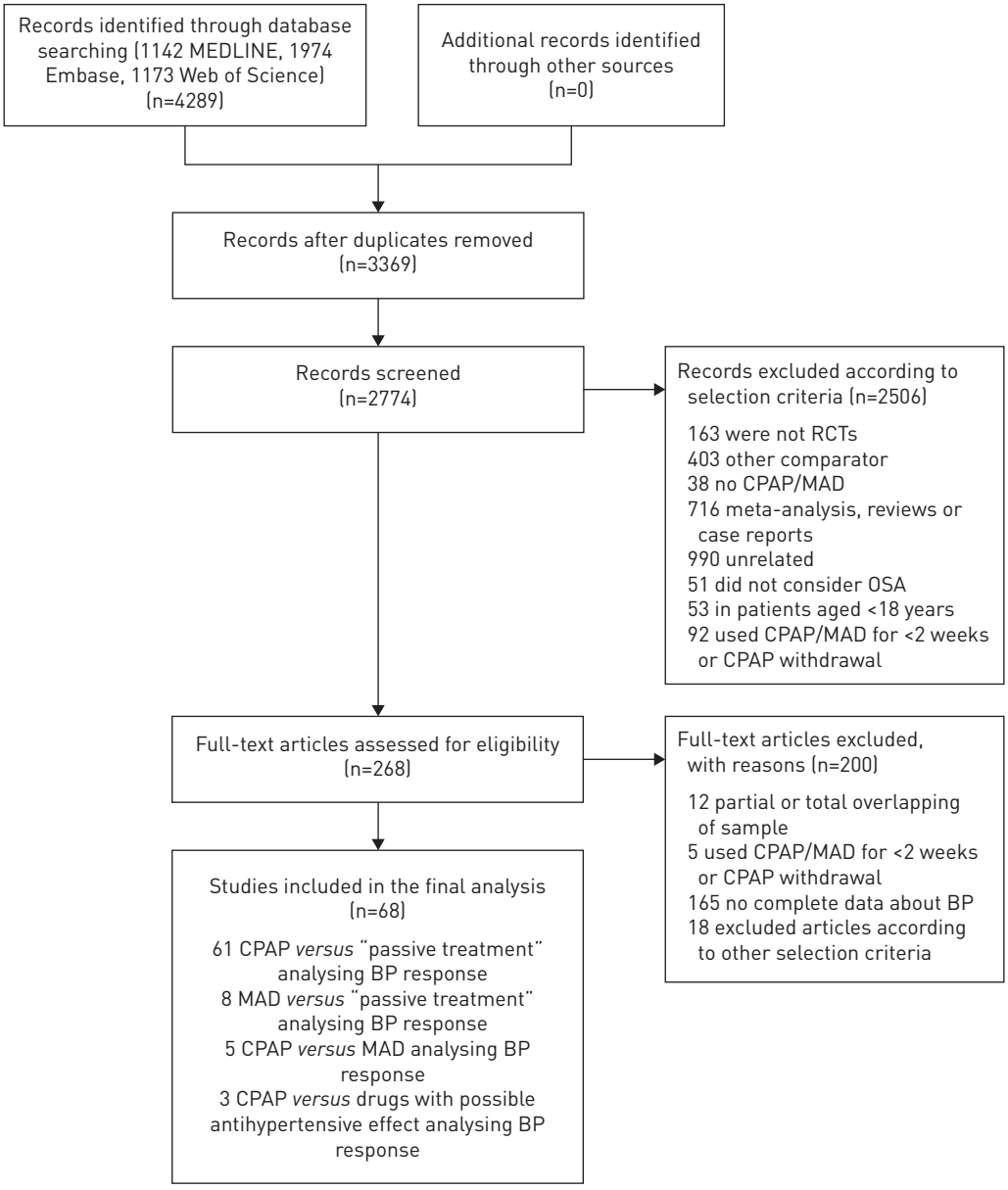


FIGURE 1 PRISMA flow diagram.

Subgroup analysis

Subgroup analysis in studies comparing CPAP versus *control considering all studies*

No significant differences in the treatment effect on BP were seen in the subgroup analysis dividing the studies according to different baseline characteristics such as sex (participants >80% or <80% males), BMI (BMI >30 or <30 kg·m^{-2}), compliance with CPAP (usage >4 or <4 h per night) and daytime sleepiness (ESS <10 or ⩾10 points). Patients aged 40–50 and 50–60 years exhibited a greater systolic BP reduction on CPAP treatment compared with patients aged >60 years. Also, in patients with severe OSA treated with CPAP, a greater diastolic but not systolic BP change was seen compared with patients with non-severe OSA. For systolic BP only, the change in BP was greater in treated patients with uncontrolled BP at baseline (figures 3 and 4).

Subgroup analysis of studies comparing CPAP versus *control considering office BP and ambulatory BP*

As for the entire cohort, patients aged 40–50 and 50–60 years exhibited a greater systolic and diastolic BP reduction in response to CPAP treatment compared with patients aged >60 years (figure 5). OSA

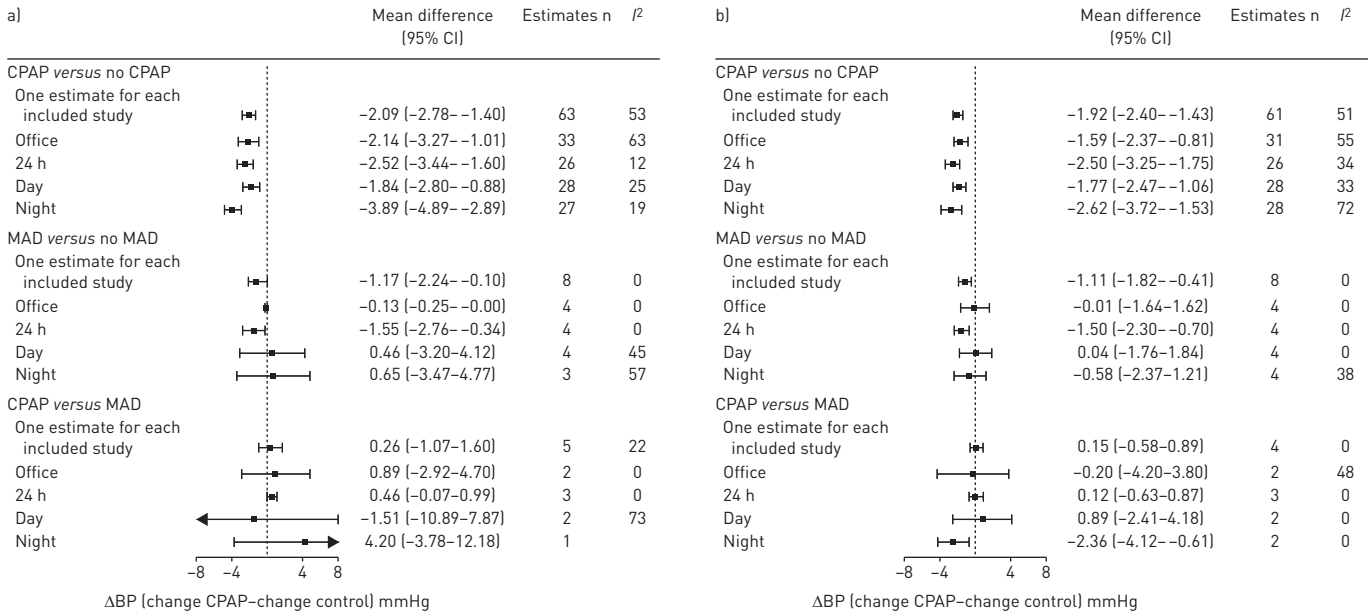


FIGURE 2 Overall a) systolic and b) diastolic blood pressure (BP) changes comparing continuous positive airway pressure (CPAP) *versus* passive treatment, mandibular advancement devices (MADs) *versus* passive treatment and CPAP *versus* MADs considering all studies together (office BP and ambulatory BP monitoring only).

treatment was associated with a significantly greater systolic BP reduction in trials including patients with daytime sleepiness (ESS >10 points) and in trials where BP was uncontrolled at baseline or in which participants were not on antihypertensive drugs. In the only three trials focusing on patients with OSA and heart failure, BP did not decrease on CPAP treatment.

OSA treatment effects on diastolic BP were larger in patients with severe OSA (AHI <30 events·h^{-1}) or with severe S_{pO_2} desaturations (minimum S_{pO_2} <77%) (supplementary figures E10–E13).

When considering studies on patients with heart failure, a significant difference was seen in terms of BP reduction: in three studies which enrolled only patients with heart failure (mean BP 129/75 mmHg), an increase of 5.82 mmHg was seen at follow-up compared with a reduction of −2.39 mmHg observed in the remaining 30 studies on patients without heart failure (mean BP 133/80 mmHg; p=0.009). Such a significant difference was observed only for systolic BP.

Considering only RCTs using ABPM, an average compliance with CPAP >4 h per night and patients with severe oxygen desaturations (minimum S_{pO_2} <77%) exhibited a greater ambulatory systolic BP reduction on treatment (figure 5).

Further explorative analyses

Due to the positive results obtained in the pre-specified subgroup of patients with uncontrolled BP at baseline and to be more adherent to what is usually done in RCTs evaluating the effect of antihypertensive drugs, we added further explorative analyses.

Considering the studies where hypertension status was a pre-specified inclusion criterion [27, 30, 39–41, 49–51, 57, 59, 61, 63, 69, 71, 74, 76], the BP change by CPAP was −2.72 (95% CI −3.66– −1.78) mmHg (I^2=0%) for systolic BP and −2.53 (95% CI −3.32– −1.73) mmHg (I^2=20%) for diastolic BP.

Furthermore, we have analysed the data including only trials with a minimum follow-up of 6 months considering two different cut-offs (24 and 26 weeks) [36, 40, 41, 50, 51, 57, 59, 61, 63, 69, 71, 74, 76]. Analysing RCTs (n=11) with a follow-up >24 weeks, the BP change was −0.49 (95% CI −2.46–1.49) mmHg (I^2=61%) for systolic BP and −1.06 (95% CI −1.94– −0.18) mmHg (I^2=20%) for diastolic BP. When considering only the five RCTs with a longer follow-up (⩾26 weeks), the BP change was −0.36 (95% CI −3.93–3.26) mmHg (I^2=75%) for systolic BP and −1.09 (95% CI −2.65–0.47) mmHg (I^2=31%) for diastolic BP. Furthermore, we re-analysed the data of the five studies with a follow-up of 24 weeks including hypertensive patients only and we found a mean change of −2.91 (95% CI −4.91– −0.91) mmHg (I^2=0%) for systolic BP and −2.26 (95% CI −3.66– −0.90) mmHg (I^2=0%) for diastolic BP, favouring CPAP.

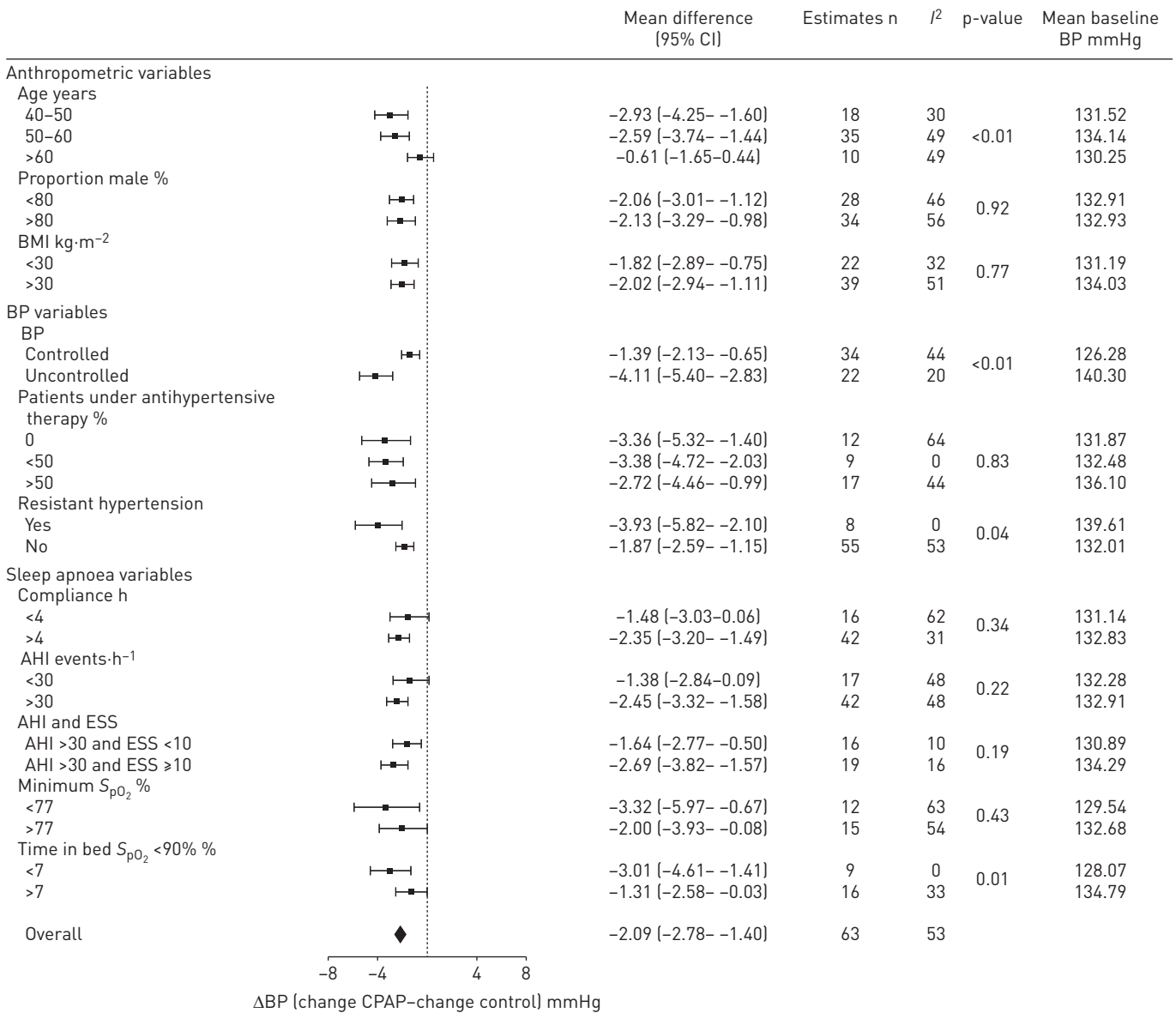


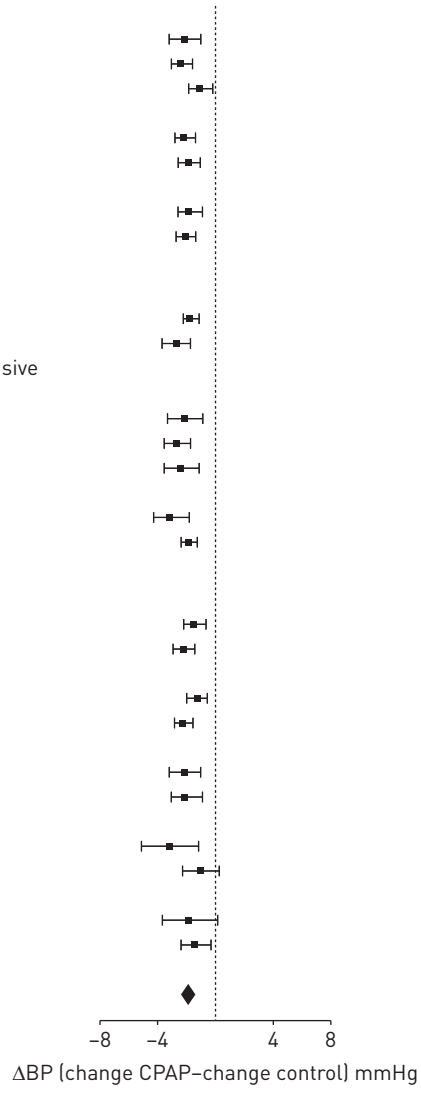
FIGURE 3 Stratified analysis of systolic blood pressure (BP) changes according to different subgroups comparing continuous positive airway pressure (CPAP) *versus* passive treatment considering all studies. BMI: body mass index; AHI: apnoea–hypopnoea index; ESS: Epworth Sleepiness Scale; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

In addition, we analysed the eight RCTs which specifically stated that BP-lowering medications remained constant between baseline and follow-up [30, 41, 49–51, 59, 69, 71]. We found that systolic BP (−2.63 (95% CI −3.80– −1.54) mmHg (I^2=0%)) as well as diastolic BP (−1.98 (95% CI −2.78– −1.18) mmHg (I^2=0%)) were lower in the CPAP arm compared with the placebo arm.

Lastly, with regard to dipping status, we analysed the data assuming a dipping cut-off of 50% at baseline (*i.e.* comparing studies with >50% dippers [23, 41, 43, 75] with studies with <50% dippers [50, 63, 70, 71]). For systolic BP, in studies (n=5) with <50% of dippers the BP change at follow-up was −1.24 (95% CI −3.27–0.78) mmHg and in studies (n=4) with >50% of dippers it was −4.18 (95% CI −7.76– −0.60) mmHg with a p-value for comparison of 0.16. For diastolic BP, in studies (n=5) with <50% of dippers the BP change at follow-up was −1.66 (95% CI −3.18– −0.14) mmHg and in studies (n=4) with >50% of dippers it was −2.98 (95% CI −5.59– −0.37) mmHg with a p-value for comparison of 0.39.

Discussion

This meta-analysis has demonstrated an overall modest but significant effect of OSA treatment (CPAP or MADs) on BP in an unselected OSA population, but has identified younger age, uncontrolled BP and



	Mean difference (95% CI)	Estimates n	I^2	p-value	Mean baseline BP mmHg
Anthropometric variables					
Age years					
40–50	−2.04 (−3.12– −0.97)	17	30		80.20
50–60	−2.32 (−3.07– −1.58)	35	51	0.08	81.51
>60	−1.03 (−1.91– −0.15)	9	68		77.82
Proportion male %					
<80	−2.10 (−2.80– −1.40)	26	59	0.56	80.05
>80	−1.79 (−2.53– −1.06)	34	45		81.14
BMI kg·m^{-2}					
<30	−1.74 (−2.54– −0.95)	22	37	0.64	81.25
>30	−1.99 (−2.64– −1.34)	38	57		79.93
BP variables					
BP					
Controlled	−1.66 (−2.22– −1.10)	44	56	0.08	78.90
Uncontrolled	−2.65 (−3.61– −1.70)	14	17		83.93
Patients under antihypertensive therapy %					
0	−2.10 (−3.25– −0.95)	12	44		80.74
<50	−2.63 (−3.56– −1.71)	9	0	0.77	80.93
>50	−2.33 (−3.53– −1.14)	17	49		81.33
Resistant hypertension					
Yes	−3.09 (−4.27– −1.90)	8	0	0.04	80.52
No	−1.76 (−2.28– −1.25)	53	52		81.49
Sleep apnoea variables					
Compliance h					
<4	−1.45 (−2.26– −0.64)	15	38	0.2	78.99
>4	−2.16 (−2.89– −1.43)	40	57		80.55
AHI events·h^{-1}					
<30	−1.23 (−1.96– −0.49)	16	18	0.06	79.90
>30	−2.17 (−2.81– −1.54)	41	52		80.65
AHI and ESS					
AHI >30 and ESS <10	−2.10 (−3.16– −1.04)	15	50	0.9	81.34
AHI >30 and ESS ⩾10	−2.00 (−3.10– −0.90)	18	57		79.62
Minimum S_{pO_2} %					
<77	−3.11 (−5.14– −1.09)	11	70	0.08	80.09
>77	−0.97 (−2.19–0.25)	15	43		79.19
Time in bed S_{pO_2} <90% %					
<7	−1.75 (−3.65–0.16)	8	52	0.71	77.05
>7	−1.34 (−2.34– −0.35)	16	56		81.71
Overall	−1.92 (−2.40– −1.43)	61	51		

FIGURE 4 Stratified analysis of diastolic blood pressure (BP) changes according to different subgroups comparing continuous positive airway pressure (CPAP) *versus* passive treatment considering all studies. BMI: body mass index; AHI: apnoea–hypopnoea index; ESS: Epworth Sleepiness Scale; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

severe OSA-related oxygen desaturations as positive predictors of a favourable BP response to OSA treatment.

The present study represents the most recent meta-analysis in the field including 68 RCTs in an updated version of our previous work published in 2014 [6]. Although the number of included studies has doubled, the results did not vary substantially, showing an average BP decrease of 2 mmHg in OSA treated with CPAP (or MADs) compared with the control group.

Nevertheless, despite that the overall effect size of BP reduction by OSA treatment is modest, it is important to note that a 2 mmHg decrease in either diastolic or systolic BP is associated with significant improvement in cardiovascular events and mortality in patients with hypertension [80]. However, as suggested by clinical trials in which CPAP was compared with drugs with known antihypertensive effect, the effect size of CPAP is lower compared with antihypertensive drugs.

Indeed, the high variability of results among RCTs on OSA treatment effects on BP raises the question whether a specific phenotype of patients might respond better to CPAP treatment compared with others.

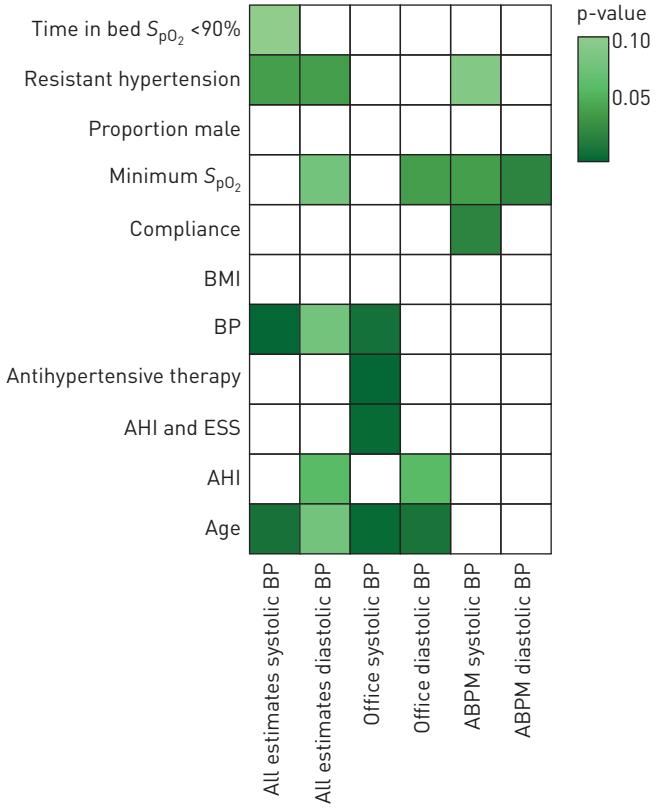


FIGURE 5 Heat map showing significant differences between subgroups according to different blood pressures (BPs). S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; BMI: body mass index; AHI: apnoea–hypopnoea index; ESS: Epworth Sleepiness Scale; ABPM: ambulatory BP monitoring.

Stratified analyses have identified characteristics that predict which patient could benefit most from CPAP therapy in terms of BP reduction. In particular, we identified uncontrolled baseline BP values pre-treatment as one of the main determinants of a favourable treatment response. Similarly, studies that also specifically included patients with either hypertension or resistant hypertension were more likely to show a greater BP reduction after OSA treatment.

This finding is clinically relevant as it indicates that OSA treatment by CPAP is expected to decrease BP especially in patients with uncontrolled hypertension. Such a result can be due in part to a regression towards the mean effect which, however, is minimised by the presence of a control group and depends on many other factors related to the way the RCT is designed and conducted, such as the precision of measurement but also the degree of variability of the biological measure studied. Most of the trials focused on one set of office BP measurements only, taken at the time of patient screening, without considering out-of-office values or a reassessment of office BP values over time to confirm eligibility. Moreover, this finding was not confirmed when considering ABPM measurements only.

Another determinant of BP response to OSA treatment was age: elderly patients tended to experience less BP reduction compared with patients aged <60 years. This important finding presumably reflects the time course of OSA disease, which is not routinely assessed in clinical trials. In addition, other pro-hypertensive mechanisms could be more difficult to counteract when consolidated with time and in the presence of hypertension-mediated organ damage, as commonly found in older patients.

This finding is somewhat consistent with the results of the large-scale, international Sleep Apnoea and cardioVascular Endpoints (SAVE) randomised trial where in high-risk patients with OSA (mean age 61.3 years), CPAP did not prevent serious cardiovascular events [65]. Interestingly, in the same trial, only a small non-sustained reduction in mean BP was observed, potentially explaining the lack of efficacy of CPAP use in reducing cardiovascular outcomes.

Of note, the results of the SAVE trial were influenced by compliance with CPAP treatment, which was overall suboptimal (3.3 h per night). A secondary analysis examining patients with CPAP use >4 h per night showed, at least in those patients, a reduced rate of cerebrovascular complications. Although such an analysis is not equivalent to a controlled study, it reinforces the concept that patients compliant to CPAP are more likely to fully experience the treatment benefits in terms of cardiovascular protection. Similarly, also in the present meta-analysis, when comparing studies with good compliance with those with poor

compliance assuming a cut-off of 4 h per night as an indicator of sufficient CPAP use, a mild statistically significant difference was seen at least when daytime BP was considered. This limited statistical significance could be due to the lack of individual patient data. Repeating the meta-analysis using individual patient data rather than aggregate data could improve the assessment of the association of CPAP use and BP response.

Compared with the most recent meta-analysis on this topic [8], our study included 17 more RCTs, adding considerably more power to assess the association between OSA treatment and BP response.

A major novel element of clinical interest in the present meta-analysis is the identification of responders among OSA patients with diagnosed hypertension by stratified analyses. Even if such results should be interpreted with caution, as they were derived from a meta-analysis and not from a specifically designed RCT, our meta-analysis identifies the subgroup(s) on which to concentrate future trials aimed at decreasing BP and putatively cardiovascular events in OSA patients.

It should also be considered that current guidelines and recommendations support the treatment of OSA with the aim of reducing BP, but do not define clear BP thresholds nor identify phenotypes of hypertensive patients in whom this approach could be most useful [81].

More recently, the Task Force of the American Academy of Sleep Medicine Clinical Practice Guidelines suggested clinicians to use positive airway pressure (PAP) therapy to treat OSA in adults with comorbid hypertension, but again without defining specific BP cut-offs [82]. Although the Task Force admitted that the overall quality of evidence, based on the critical outcome of mean arterial BP, was moderate due to imprecision, they concluded that in adult patients with OSA and comorbid hypertension, the benefits of PAP therapy compared with no PAP therapy likely outweigh the potential harms and burdens, and that the majority of well-informed patients would choose the intervention over no treatment.

While this view is understandable, it is important to note the following. 1) Almost half of the studies included in the present meta-analysis enrolled patients with mean office BP within normal limits. Such patients are less likely to experience a decrease of BP while on treatment; thus, in asymptomatic OSA patients, the indication for CPAP treatment should be carefully discussed with the patient. 2) Some patients with OSA might even experience an increase in BP with CPAP due to mask discomfort, fragmented sleep or hyperinflation of the chest in cases where the CPAP pressure is not titrated adequately [9, 83]. This is of crucial importance since some of the causes of the lack of BP decrease are reversible: mask leaks have been associated with a BP increase in subjects on CPAP treatment [9]; thus, a proper mask fitting could improve patient compliance. Furthermore, excessive PAP can overload the respiratory system enhancing sympathetic activation, while low PAP is responsible for residual OSA. 3) Insomnia is frequent in patients with OSA [84]; thus, periods of wake during the night might be responsible for the lack of nocturnal BP dipping. These aspects reinforce the concept that proper PAP titration can ensure adequate CPAP compliance and, conversely, that arousals from sleep and sleep quality are potential causes of nocturnal hypertension [85].

Among the subgroups of patients who might not benefit from CPAP treatment in terms of reducing BP are those with heart failure. Although the number of studies in patients with heart failure was rather small, BP tended to increase on CPAP compared with studies in patients without heart failure [25, 37, 55].

Another important finding of the present study is the impact of the baseline hypoxic burden on BP response to treatment. Considering both office and ABPM measurements, trials with a minimum S_{pO_2} <77% were associated with a greater BP drop at follow-up in treated patients, further supporting the role of intermittent hypoxia in the pathogenesis of OSA-related hypertension. The importance of hypoxic burden in patients with OSA has been recently confirmed by a study in which the magnitude of oxygen desaturations in OSA predicted cardiovascular mortality across populations [86]. Taken together, these data suggest that a better characterisation of OSA severity at baseline, focusing not only on the frequency but also on the depth and duration of sleep-related upper airway obstructions, can help in predicting a more favourable outcome for patients with OSA treated with CPAP. Quite unexpectedly, however, patients with AHI >30 events·h^{-1} did not seem to have a greater systolic BP-lowering effect by CPAP unless in the presence of important daytime somnolence (data not shown).

This meta-analysis has some limitations. Even if we applied a highly sensitive search strategy to identify all the eligible primary studies according to our inclusion criteria, we cannot exclude that some studies were missed. Some of the inclusion/exclusion criteria we applied can be considered as subjective; in particular, the choice of 2 weeks as the minimum time of treatment for an RCT to be included in the present meta-analysis could be seen as too restrictive, but we think that this is a minimum time requirement to see a stable antihypertensive effect by CPAP. However, the exploratory analysis of trials with at least 24–26 weeks of CPAP shows a possible loss of efficacy over time, even if the BP-lowering effect was

maintained at least in hypertensive patients. Even the inclusion of different types of BP measurements such as office or ABPM data could be criticised: this may have increased heterogeneity, but it did allow all studies to be incorporated into the analyses. Moreover, we have shown that the results in terms of both size and direction are almost similar in studies using either office or ABPM data. Another limitation is that our stratified analyses, even if well powered for most of the subgroups, cannot be as accurate as a meta-analysis including individual patient data so that the real effects of CPAP in the selected subgroups could have been either underestimated or overestimated. Nevertheless, the findings of the present meta-analysis give an important suggestion for future RCTs willing to focus on the use of CPAP to lower BP. Only two active treatments (CPAP and MADs) have been investigated while other treatments have been excluded, such as invasive/non-invasive electrical stimulation, which have been shown to be effective in reducing BP in patients with OSA [51, 87, 88]. However, only a few trials focusing on other interventions are available and these treatments are to be considered only in a subtype of patients with OSA. Moreover, we decided not to apply the stratified analysis for MAD trials since, in our opinion, there were only sparse data to provide meaningful results. Finally, based on the Harbord–Egger and the Begg–Mazumdar tests, publication bias cannot be excluded even if the shape of the funnel plot is fairly symmetrical.

Conclusions

Among patients with OSA, both CPAP and MADs are associated with reductions in BP. Subgroup analyses showed that especially patients with more elevated BP values pre-treatment and patients aged <60 years are more likely to exhibit a more pronounced BP-lowering effect in response to CPAP treatment. In addition, patients with severe oxygen desaturations experienced a greater BP reduction while on CPAP treatment, suggesting that not only the frequency but also the severity and duration of sleep-related respiratory events are important disease-characterising features.

Data about predictors of BP response to OSA treatment should be confirmed in future prospective RCTs that focus on selected phenotypes of patients with OSA in order to inform clinicians to implement more personalised treatment choices.

Conflict of interest: None declared.

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