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ARTICLE

Weight reduction added to CPAP decreases blood pressure and triglyceride level in OSA: Systematic review and meta-analysis

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Abstract

Obstructive sleep apnea (OSA) is associated with treatment-resistant hypertension and high cardiovascular risk. Continuous positive airway pressure (CPAP) fails to reduce cardiovascular risks consistently. Obesity and OSA show reciprocal association and they synergistically increase hypertension via different pathways. Our meta-analysis aimed to assess the cardiovascular benefits of combining weight loss (WL) with CPAP (vs. WL or CPAP alone) in OSA. Outcomes included systolic and diastolic blood pressure (BP) and blood lipid parameters. We explored Medline, Embase, Cochrane, and Scopus. Eight randomized controlled studies (2627 patients) were included. The combined therapy decreased systolic BP more than CPAP alone. Weighted mean difference (WMD) for CPAP + WL versus CPAP was −8.89 mmHg, 95% confidence interval (95% CI; −13.67 to −4.10, $p < 0.001$) for systolic BP. For diastolic BP, this decrease was not significant. In case of blood lipids, the combined treatment decreased triglyceride levels more than CPAP alone (WMD = −0.31, 95% CI −0.58 to −0.04, $p = 0.027$). On the other hand, addition of CPAP to WL failed to suppress BP further. The certainty of evidence according to GRADE was very low to moderate. In conclusion, our results showed that the addition of WL to CPAP significantly improved BP and blood lipid values in OSA. On the other hand, the addition of CPAP to WL could not significantly improve BP or blood lipid values. Review protocol: PROSPERO CRD42019138998.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Moderate to severe obstructive sleep apnea (OSA) is associated with obesity and increased cardiovascular risks. Positive pressure ventilation (CPAP) alone does not address these risks. The CPAP-induced reduction of blood pressure (BP) was shown to be around 2–3 mmHg, whereas no CPAP-induced weight loss (WL) was confirmed.

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WHAT QUESTION DID THIS STUDY ADDRESS?

Our meta-analysis aimed to assess the evidence with regard to the cardiovascular benefits (change in BP and blood lipids) of combining weight reduction intervention with CPAP in OSA.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Addition of efficient WL intervention to CPAP induces significant further reduction in systolic BP of ~ 8–9 mmHg. BP reduction elicited by the combination therapy could contribute to the suppression of cardiovascular risks. Additionally, WL improves the suppression of blood triglyceride levels as well.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

It is strongly recommended that patients with OSA characterized by overweight and hypertension should be treated by a combination of efficient weight loss intervention and CPAP. It could prevent the weight gain induced by CPAP therapy and efficiently decrease the cardiovascular risks of these high-risk patients.

INTRODUCTION

Obstructive sleep apnea (OSA) affects almost one billion people worldwide.[1,2] Moderate to severe forms of OSA are associated with an increased risk of cardiovascular and cerebrovascular diseases.[3] A comprehensive meta-analysis reported a positive association between OSA and therapy-resistant hypertension (odds ratio: 2.84 with 95% confidence interval [95% CI] 1.70–3.98).[4] Other studies also confirm the important role of OSA in the development of therapy-resistant hypertension, a major risk factor of cardiovascular mortality.[5–7] In addition to hypertension, other pathophysiological factors also aggravate the cardiovascular risks in OSA, including intermittent hypoxia with consequent sympathetic excitation, inflammation, oxidative stress, metabolic dysregulation, and concomitant obesity, to name just a few.[8–11] Obesity and OSA are closely inter-related diseases, because at least 60% of patients with OSA are obese.[9,12] On the one hand, obesity increases the risk of OSA, on the other hand, the metabolic dysregulation induced by OSA promotes weight gain.[9,13,14] Both OSA and obesity increases the risk of hypertension and that of other cardiovascular risk factors, such as dyslipidemia or diabetes mellitus (DM).[9,15] Although these two diseases show synergy in promoting hypertension, they act largely via different pathways.[6,9]

With regard to the prevention or treatment of hypertension and those of other cardiovascular risk factors in OSA, even the essential gold-standard therapy of this disease, continuous positive pressure ventilation (CPAP), was shown to be partially insufficient.[3,16] A large recent, meta-analysis concluded that CPAP is associated with a non-consistent reduction in cardiovascular outcomes in both primary and secondary prevention.[3] The CPAP-induced reduction of blood pressure (BP) was shown to be around 2–3 mmHg according to a comprehensive meta-analysis.[17] With regard to obesity in OSA, CPAP induced even a significant weight gain within 1–3 months, instead of the expected weight loss (WL), according to an earlier meta-analysis of 25 randomized controlled trials (RCTs; 3181 patients).[18] A large (2483 patients), recent, multicenter RCT also confirmed that CPAP could not reduce body weight over a mean follow-up period of 3.78 years.[19]

These findings indicate that CPAP alone does not address cardiovascular risk, hypertension, or being overweight sufficiently in OSA. We hypothesized that additional weight reduction intervention combined with CPAP may not only decrease body weight but also improve the BP and the cardiovascular health of the patients with OSA.[11,20]

In our systematic review and meta-analysis, we aimed to assess the available evidence with regard to the cardiovascular benefits, especially the effects on BP and blood lipids of combining weight reduction therapy with CPAP in OSA.

METHODS

Search strategy

We report our systematic review and meta-analysis in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[21] and those of the Cochrane handbook.[22] The protocol of our meta-analysis was registered in PROSPERO on June 14, 2019 (PROSPERO 2019 CRD42019138998). We performed searches in the following databases from inception to May

29, 2020: Medline, Embase, CENTRAL, and Scopus with the following key terms: ("sleep apnea" OR SAS OR OSA) AND (positive pressure ventilat* OR bilevel positive airway pressure OR continuous positive pressure OR BIPAP OR CPAP OR BPAP) AND (weight). We did not use any filters. After the selection, we manually screened the reference lists of included studies for other eligible articles.

Selection, eligibility, and data extraction

Following the systematic search process, two independent authors (D.K.K. and D.K.) eliminated duplicates from the pooled records. Publications were independently screened in three stages by two authors (D.K.K. and D.K.), by title, by abstract, and finally via screening by full-text. Any disagreements were solved by consensus with the help of a third author (M.B.). We included studies on adult patients with OSA, that measured BP and/or blood lipids. We included studies in which the intervention was a combination of CPAP and WL therapy compared with a control group with CPAP or WL therapy alone. They had to report data on BP or blood lipid parameters. We excluded studies focusing on children or adolescents and studies without control groups, case reports, overlapping populations, animal experiments, reviews, editorials, letters, notes, and conference abstracts without proper data. Two authors (D.K.K. and D.K.) extracted data from studies independently. Names of first authors, publication year, study design, interventions, duration of studies, baseline characteristics of populations, and parameters of cardiovascular risk factors were extracted. Cardiovascular risk factors included systolic and diastolic BP (SBP and DBP), C-reactive protein (CRP), serum levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TGs). Any disagreements were solved by a third author (M.B.).

Statistical analysis

For data synthesis, we have used the methods recommended by the working group of the Cochrane Collaboration.[22] Meta-analyses were performed, and the calculated effect sizes have been visualized in forest plots. Random effect model was used for meta-analyses with the DerSimonian and Laird weighting method. For our continuous outcomes (SBP and DBP, blood LDL, HDL, and TG levels) we have calculated weighted mean differences (WMDs) with 95% CIs to investigate the differences between the outcomes of the two pairs of groups (combined CPAP + WL vs. CPAP treatment or combined CPAP + WL vs. WL treatment, when available). Heterogeneity was tested with the χ^2 (chi-square) test and the I^2 statistics with the Q test. I^2 statistics represents the percentage of effect size heterogeneity that cannot be explained by random chance. If the Q test is significant, it implies that the heterogeneity among effect sizes reported in the analyzed studies are more diverse than it could be explained only by random error. We considered the Q test significant if $p < 0.1$. For meta-analyses the Stata 15 (Stata Corp) were applied. Due to the low number of available studies, the Egger's test for small-study effect could not be performed.

If per-protocol (PP) analyses were available for statistics, we used these data to include only the results of the adherent patients,[23] because a relatively large dropout rate (dietary nonadherence) characterizes the WL intervention studies. If appropriate PP data were not available, we used the data of the intention-to-treat (ITT) analyses. Additionally, we have also carried out sensitivity analyses using all available ITT data.

Risk of bias and quality of evidence

Risk of bias assessment was carried out independently by two authors (D.K.K. and M.B.) utilizing the revised Cochrane risk of bias tool 2 for randomized trials (RoB2 tool).[24] Any disagreements were solved by consensus. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of evidence.[25,26]

RESULTS

Results of the search and selection process

A total of 4358 records were identified through a systematic search in Medline, Embase, CENTRAL, and Scopus databases. Following the removal of duplicates, we screened 3829 publications by title and abstracts and 82 publications by full-text. The flow diagram of the search and selection process is shown in Figure 1 including reasons for exclusion. Eight randomized controlled studies representing 2627 patients met the criteria for inclusion and provided data for our meta-analyses. Three studies compared the combination therapy with CPAP,[27–29] three with WL,[30–32] and two studies compared the combination therapy with both CPAP and WL.[33,34] These two latter studies reported data of overlapping populations, therefore, we refrained from using both of them in the same analysis to avoid overrepresentation of any population.[33,34] The baseline characteristics of the analyzed populations are shown in Table 1. The analyzed eight studies enrolled both normotensive

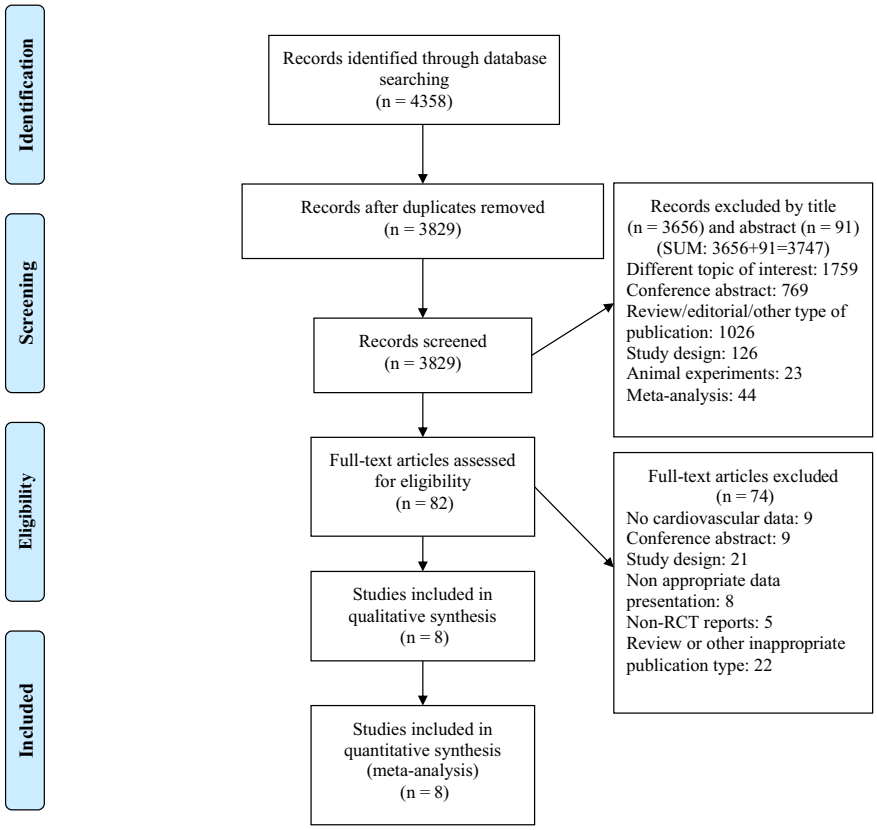

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart. RCT, randomized controlled trial

and patients with mild hypertension. Data in Table 1 also shows that the CPAP adherence of study participants exceeded 4 h/night (in at least 70% of the nights). The analyzed studies provided very little data on antihypertensive or lipid lowering medication of their study populations. Chirinos and coworkers reported 21%–25% antihypertensive treatment and 12%–13% statin use across the study groups.[33] In the study of Jain and coworkers, statin use reached 10%, and antihypertensive treatment was used for 16%–19% of the study populations.[34] The rest of the studies[27–32] failed to report data on antihypertensive drug or statin use.

Overt, diagnosed DM was among the exclusion criteria in some studies,[27–29,32] whereas in other two studies[33,34] type 1 DM and unstable type 2 DM were among the exclusion criteria. No data were provided about DM in case of the other two articles.[30,31]

Blood pressure lowering effects of the analyzed therapies

Our analyses showed that the combination (CPAP + WL) therapy decreased the normal or slightly higher SBP of patients with OSA more efficiently than CPAP therapy alone (WMD = −8.89 mmHg, 95% CI −13.67 to −4.10 mmHg, $p < 0.0001$; $I^2 = 84{,}2\%$, $p < 0.001$; see Figure 2). The decrease in DBP also favored the combination therapy, but these results were nonsignificant (WMD = −5.82 mmHg, 95% CI −14.26 to 2.63 mmHg, $p = 0.177$; $I^2 = 99.5\%$, $p < 0.0001$; see Figure 3).

With regard to the other arm of the analysis (CPAP + WL vs. WL), the BP lowering effects favored the combination therapy both for the SBP and the DBP values, but only the WMD of SBP approached the level of significance. Changes in systolic (WMD = −3.88 mmHg, 95% CI −7.78 to 0.02 mmHg, $p = 0.051$; $I^2 = 70.0\%$, $p = 0.019$) and DBP values (WMD = −3.47 mmHg, 95% CI −8.57 to 1.63 mmHg, $p = 0.182$; $I^2 = 97.1\%$, $p < 0.0001$) are shown in Figures 4 and 5. Our meta-analyses with regard to BP-lowering effects showed substantial-to-considerable heterogeneity.

Effects on blood lipid levels

On the CPAP versus CPAP + WL arm, we could analyze the changes of blood lipid levels, as well. We found that the combination therapy decreased the TG levels significantly more efficiently than CPAP alone (WMD = −0.31 mmol/L, 95% CI −0.58 to −0.04 mmol/L, $p = 0.027$; $I^2 = 84.6\%$, $p = 0.002$; Figure 6). Changes in blood LDL seemed to favor the combination therapy but not significantly (WMD = −0.12 mmol/L, 95% CI −0.27 to 0.03 mmol/L, $p = 0.11$; $I^2 = 99.6\%$, $p < 0.0001$; Figure S1).

TABLE 1 Baseline characteristics of the analyzed populations

Study	Group of intevrention	Study design	Duration, week	*N*	Percent of women (%)	Age, years	Blood pressure, mmHg		BMI, kg/m^2	Weight, kg		AHI (event/h)	Severity of OSA	CPAP adherence
							SBP	DBP		Baseline	End point			
Georgoulis et al. 2020[28]	CPAP	RCT	24	62	21	48 ± 10[c]	128 ± 12[c]	83 ± 10[c]	35.8 ± 6.3[c]	111 ± 22[c]	111 ± 20[c]	52 (31, 87)[d]	moderate to severe	28 (27, 42)[d] h/week
	CPAP + WL			59	29	50 ± 9.1[c]	136 ± 18[c]	88 ± 15[c]	34.8 ± 5.9[c]	108 ± 24[c]	99 ± 22[c]	60 (35, 81)[d]		24 (20, 40)[d] h/week
Moss et al. 2014[29]	CPAP	RCT	12	30		18-85[a]	127 ± 11[c]	72 ± 8[c]	39.8 ± 7[c]	118.3 ± 21.9[c]	117.9 ± 21[c]	15<		>75% nightly use; >4 h/night
	CPAP + WL			30		18-85[a]	132 ± 15[c]	75 ± 9[c]	38.9 ± 6.9[c]	117.4 ± 24.3[c]	115.2 ± 24.3[c]			
López-Padrós et al. 2020[27]	CPAP	RCT	52	16	6.3	52 (45–54)[d]			35.4 ± 2.9[c]	−0.1 ± 4.8[h]		69 ± 15.4[c]	severe	6.17 ± 1.65 h/day
	CPAP + WL			18	16.7	49.5 (46.2–52.8)[d]			34.5 ± 2.6[c]	−8.2 ± 5.9[h]		69 ± 23.9[c]		3.95 ± 1.87 h/day
Chirinos et al. 2014[33]	CPAP	RCT	24	39	38.5	51.8 ± 9.3[c]	129.7 ± 11.3[c]	80.8 ± 7.8[c]	38.2 ± 7.2[c]	112.3 ± 21.2[c]	0.5(−1.1, 2)[i]	44.7 ± 22.6[c]	Moderate to severe	>70% nightly use; >4 h/night
	CPAP + WL			24	45.8	50.8 ± 11.4[c]	123.8 ± 10.8[c]	75.7 ± 6.6[c]	37.7 ± 5.5[c]	114.7 ± 21.5[c]	−11.5(−13.5,−9.4)[i]	45.6 ± 25.5[c]		
	WL			27	51.9	50.9 ± 11.8[c]	125.8 ± 9.8[c]	77.6 ± 7.7[c]	38.3 ± 5.5[c]	112.5 ± 18.7[c]	−10.5(−12.4,−8.7)[i]	38.3 ± 17.5[c]		
Jain et al. 2017[34]	CPAP	RCT	24	45	40	48.9 ± 11.3[c]	129.1 ± 10.6[c]		40.7 ± 7.5[c]	0.48 (−1.04, 1.99)[g]		43.1 ± 21.3[c]	Moderate to severe	>70% nightly use; >4 h/night
	CPAP + WL			46	50	49.8 ± 12.1[c]	128.4 ± 10.2[c]		38.1 ± 6.3[c]	−11.76 (−13.81, −9.71)[g]		45.3 ± 26[c]		
	WL			48	38.5	49 ± 10.7[c]	124.8 ± 10.2[c]		37.2 ± 4.9[c]	−10.54 (−12.34, −8.73)[g]		38.3 ± 1.5[c]		
Monasterio et al. 2001[31]	CPAP + WL	RCT	24	66	19	53 ± 9[c]	126 ± 17[c]	81 ± 12[c]	29.4 ± 3.7[c]	0.1 ± 3.4[h]		20 ± 6[c]	Mild	4.8 ± 2.2[c] h/day
	WL			59	9	54 ± 9[c]	132 ± 17[c]	84 ± 11[c]	29.5 ± 3.3[c]	−2.7 ± 4.3[h]		21 ± 6[c]		
Lam et al. 2006[30]	CPAP + WL	RCT	10	34	21	45 ± 1[e]	127.9 ± 2.3[e]	77.0 ± 1.8[e]	27.6 ± 0.6[e]	75.8 ± 1.7[e]	74.6 ± 1.6[e]	23.8 ± 1.9[e]	Mild to moderate	4.2 ± 0.1[e] h/day
	WL			33	21	47 ± 1[e]	125.5 ± 3.5[e]	74.2 ± 2.4[e]	27.3 ± 0.6[e]	74.8 ± 2.3[e]	74.5 ± 2.2[e]	19.3 ± 1.9[e]		
Salord et al. 2016[32]	CPAP + WL	RCT	12	42	74	48.5 ± 8.6[b]	136 ± 18[c]	85 (80–91)[d]	45.7 ± 5[b]			68.3 (43–88)[d]	Severe	5.4 ± 1.6[c] h
	WL			38	71	44.6 ± 9.4[b]	145 ± 18[c]	90 (83–100)[d]	49.3 ± 6.6[b]			52.6 (37–78)[d]		

Note: [a]- range; [b]- median ± SD; [c]- mean ± SD; [d]- median (IQR); [e]- mean ± SEM; [f]- mean, [g]- mean change from baseline (95% confidence interval), [h]- mean change from baseline ±SD, [i]- median change from baseline (IQR).

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive pressure ventilation; DBP, diastolic blood pressure; *N*, number of the participants; OSA, obstructive sleep apnea; RCT, randomized controlled trial; SBP, systolic blood pressure; WL, weight loss.

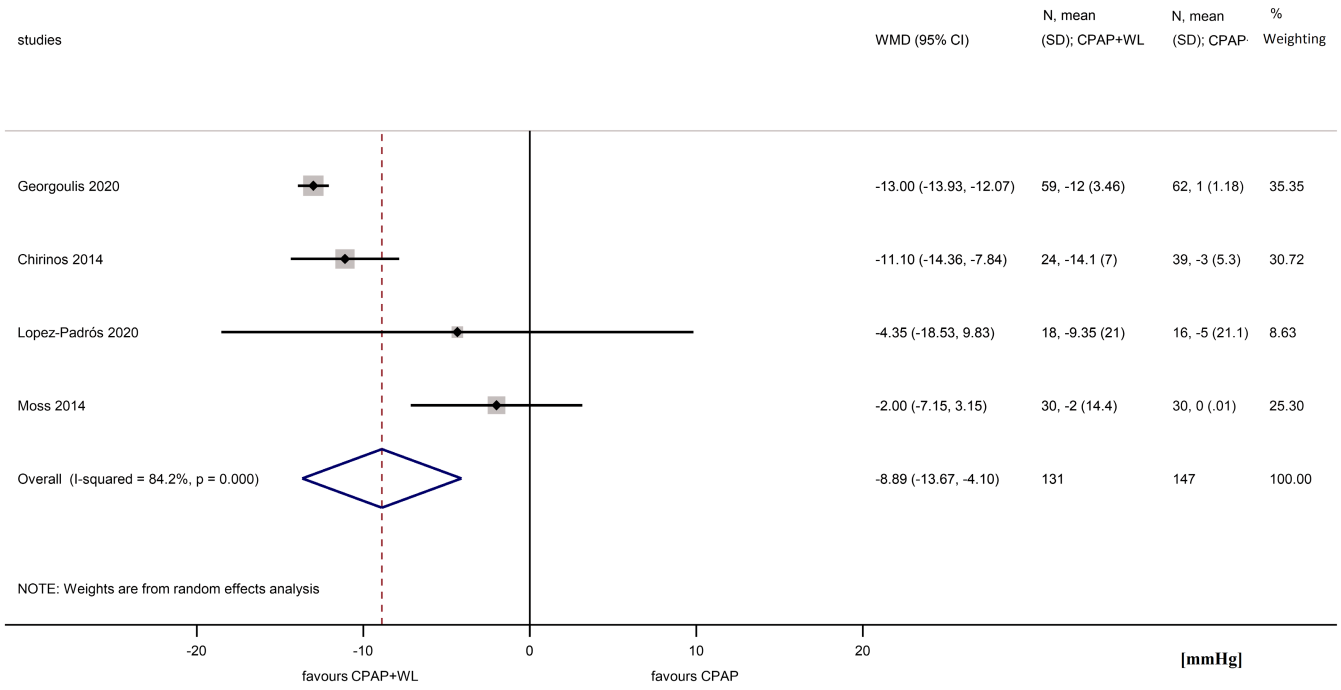

FIGURE 2 Forest plot representing reduction of systolic blood pressure (SBP) after CPAP + WL versus CPAP therapies. Squares show the weighted mean difference (WMD) of SBP after continuous positive pressure ventilation (CPAP) + weight loss (WL) versus CPAP therapies. The grey area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall WMD with its corresponding 95% CI. *N*, number of participants

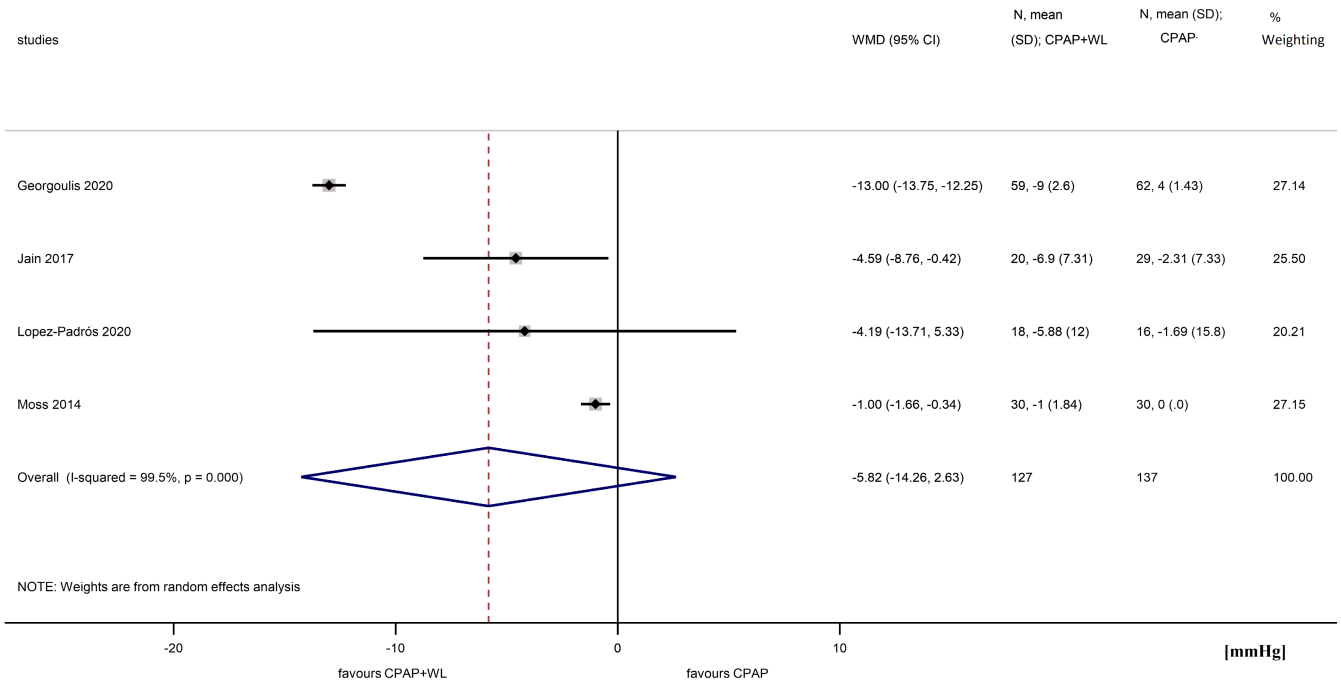

FIGURE 3 Forest plot representing reduction of diastolic blood pressure (DBP) after CPAP + WL versus CPAP therapies. Squares show the weighted mean difference (WMD) of DBP after continuous positive pressure ventilation (CPAP) + weight loss (WL) versus CPAP therapies. The grey area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall WMD with its corresponding 95% CI. *N*, number of participants

Changes in the HDL levels did not show any difference between the two therapies (WMD = 0.04 mmol/L, 95% CI −0.11 to 0.19 mmol/L, $p = 0.601$; $I^2 = 89.9\%$, $p < 0.0001$; Figure S2). Our meta-analyses with regard to blood lipid lowering effects showed substantial-to-considerable heterogeneity.

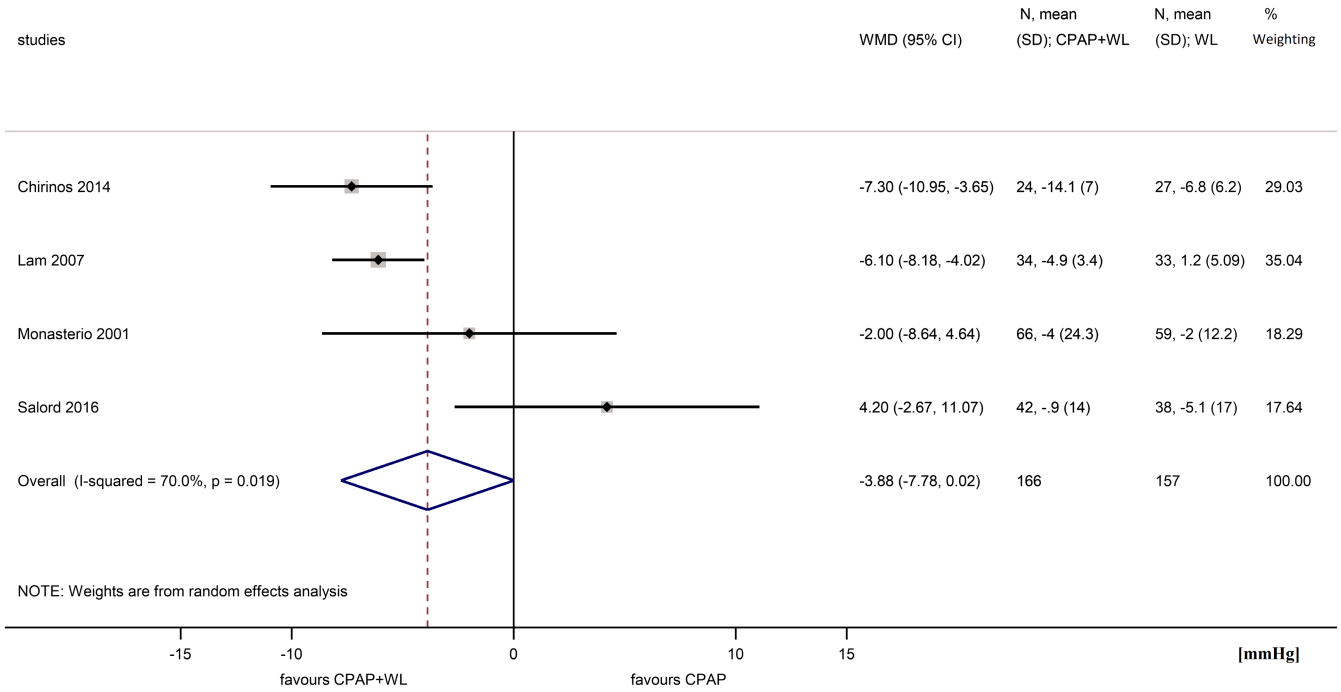

FIGURE 4 Forest plot representing reduction of systolic blood pressure (SBP) after CPAP + WL versus WL therapies. Squares show the weighted mean difference (WMD) of SBP after continuous positive pressure ventilation (CPAP) + weight loss (WL) versus WL therapies. The grey area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall WMD with its corresponding 95% CI. *N*, number of participants

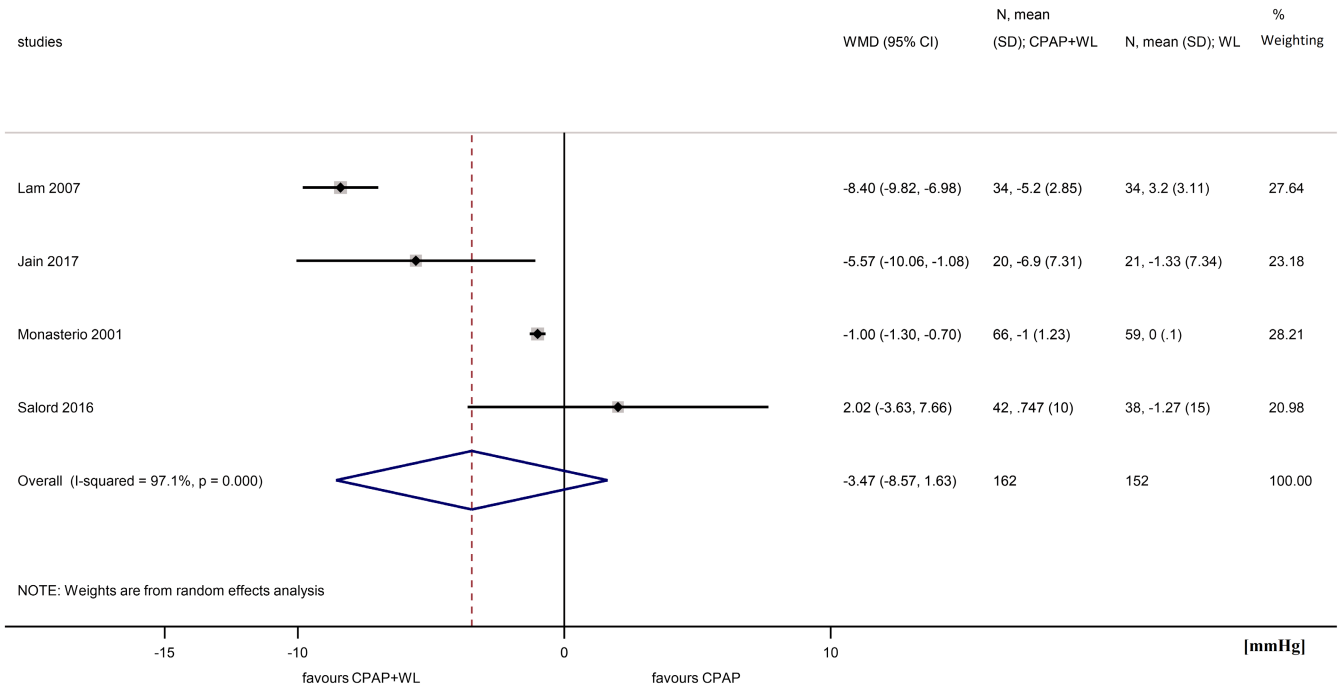

FIGURE 5 Forest plot representing reduction of diastolic blood pressure (DBP) after CPAP + WL versus WL therapies. Squares show the weighted mean difference (WMD) of DBP after continuous positive pressure ventilation (CPAP) + weight loss (WL) versus WL therapies. The grey area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall WMD with its corresponding 95% CI. *N*, number of participants

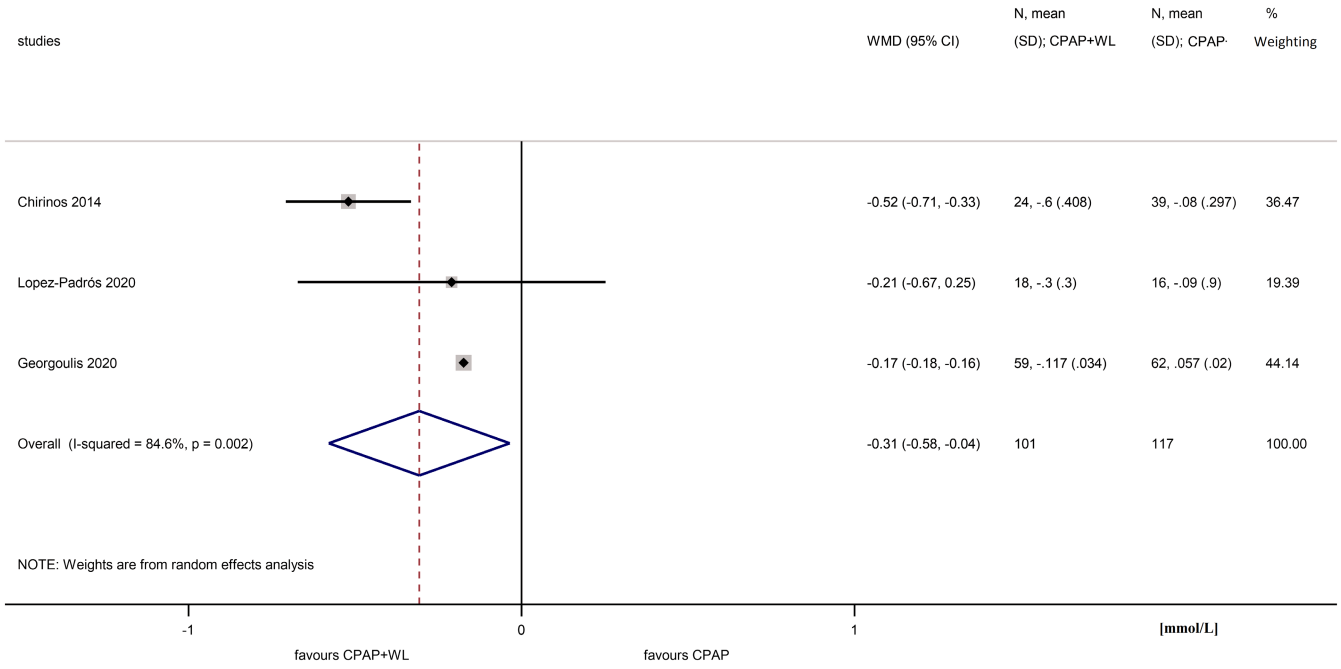

FIGURE 6 Forest plot representing reduction of blood triglyceride (TG) level after CPAP + WL versus CPAP therapies. Squares show the weighted mean difference (WMD) of blood TG level after continuous positive pressure ventilation (CPAP) + weight loss (WL) versus CPAP therapies. The grey area reflects the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (95% CIs). The diamond shows the overall WMD with its corresponding 95% CI. *N*, number of participants

Risk of bias assessment and quality of evidence

The results of the risk of bias assessments are shown in Table S1. We found a low risk of bias in several domains, such as randomization, deviations from the intended interventions, or measurement of the outcome. "Methods for randomization" were generally reported in detail with one exception.[30] "Blinding of participants" was not possible due to the interventions, but assessment of the outcomes (BP or blood lipid parameters) are not likely to be influenced by such knowledge. In the "Missing outcome data" category of the RoB2 tool, some concerns were identified in three of the eight studies.[29,31,32] However, it is not likely that these minor concerns could influence the results of the meta-analyses. In the "Selection of the reported results" category, some concerns were also found, because sufficiently detailed methods of data reporting and statistical analysis were not included in any of the published study protocols.

The overall quality of evidence of the analyzed data, based on the GRADE approach, is very low to moderate, summarized in Table S2. We had to downgrade the quality of evidence for all outcomes, because of the substantial and considerable heterogeneity of the results. For two outcomes (WL vs. CPAP + WL), indirectness was identified, because the mean body mass index (BMI) and BP values of the baseline population of one study[32] differed from those of all others. Serious imprecision was indicated by the wide CIs of various results.

With regard to sensitivity analyses using ITT data, they showed similar WMDs. Authors of the only study, in which only PP data were published,[27] emphasized that there was no difference between their ITT and PP results (online Supplementary Material Figures S3–S9).

DISCUSSION

Our systematic review and meta-analysis demonstrated that the addition of WL to CPAP decreased such major cardiovascular risk factors as the SBP and TG levels significantly stronger than CPAP alone (Figures 2 and 6). Based on our further analyses, we found that the combination therapy tended to improve both SBP and DBP and lipid parameters (except HDL) more than either individual therapy (CPAP or WL), as demonstrated by Figures 2–6 and by Figures S1–S2.

Our results are especially important, because therapy-resistant hypertension frequently develops in moderate or severe OSA, contributing to the cardiovascular mortality of these patients.[4–7] On the other hand, patients with OSA are also frequently overweight or obese[5,12] presenting a vicious circle, in which weight gain progressively increases as a consequence of OSA and it also further aggravates the severity of the sleep apnea.[5,9,12] Both

OSA and obesity are known independent risk factors of hypertension.[9,15]

The gold-standard therapy of OSA, CPAP cannot consistently normalize the BP.[3,16] Thus, additional therapeutic options are needed to reduce the cardiovascular risk of this patient group. Moreover, instead of the expected WL, CPAP failed to reduce the body weight over the course of several years.[19] The addition of weight reduction to CPAP succeeded to decrease the SBP significantly (as compared with exclusive CPAP therapy). Based on previous observations, a 10 mmHg decrease in SBP has been demonstrated to decrease the risk of cardiovascular diseases by 14%.[35] According to these prior reports, if the relative risk of cardiovascular diseases below 120 mmHg systolic pressure was 1, in the 120 to 129 mmHg range, it was 1.2 among male and 1.59 among female patients. These values increase with any further rise in SBP.[35] Thus, an addition of a weight reduction program to CPAP would be outstandingly important. Such a combination therapy efficiently decreases both the body weight and the BP in OSA.

OSA has been linked to increased risks of atherogenesis also via atherogenic changes in blood lipids.[36] Exclusive CPAP has been demonstrated to decrease LDL, but not TG.[37] Our results demonstrate that the combination of WL and CPAP also succeeded to improve the TG levels. An earlier review article demonstrated that each 0.1 mmol/L reduction showed a proportional change in risk ratio of 0.95.[38] Our meta-analysis demonstrated a WMD of −0.3 mmol/L decrease in TG level by the WL + CPAP therapy versus CPAP alone. The studies applying continuous long-term caloric restriction were the most efficient in decreasing both TG and LDL levels (favoring the combination therapy over CPAP alone).[28,33] Controversial changes were reported for HDL.[27–29] Overall, our analysis suggest that the addition of WL to CPAP could decrease the risk of atherogenesis further via improving lipid parameters.

With regard to inflammation indicator CRP, two studies demonstrated significantly stronger decrease following the combination therapy versus CPAP,[27,29] and a similar tendency was shown by a third study.[33] In the long run, even modest changes in the low-grade chronic inflammatory state of OSA may reduce the risk of cardiovascular complications.[9]

Our meta-analyses showed substantial to considerable heterogeneity. In the background, probably one of the most important factors was the variability of the applied WL programs. Certain studies applied continuous long-term caloric restriction (1200–1800 kcal/day depending on the initial body weights of participants) with training education and/or intervention that achieved a WL around 10% of the initial body weight.[28,33,34] These studies reported significantly improved BP reducing effects upon adding WL to CPAP.[28,33,34] One study started the WL program with a strict 600–800 kcal 15-day diet, followed by a 10-week 1200 kcal/day regime with a 1200–1800 kcal/day 9-month follow-up achieving comparable WL.[27] This latter study also reported significant BP lowering effects, albeit with a high variance.[27] On the other hand, some programs applying dietary counseling and some exercise training lead to minimal WL (<2% of initial mean body weight) and resulted in very modest results.[29] Unfortunately, the number of available studies did not allow subgroup analysis based on the type of WL intervention. Nevertheless, it is an important finding of our meta-analyses that significant additional WL (around 10% of initial body weight) is capable of improving the previously described, albeit modest BP-reducing effects of CPAP.[17] Our findings underline the importance of long-term caloric restriction-based WL programs added to the standard CPAP therapy of OSA. With regard to exclusive WL therapy in OSA, previous studies of the literature reported controversial results. Some researchers reported BP-reducing effects of efficient WL programs,[39–42] but others failed to demonstrate BP-lowering effects of even efficient dietary WL interventions or bariatric surgery in OSA.[37,43] In summary, our findings reinforce the recommendations of the American Thoracic Society urging clinicians to incorporate WL therapy along with CPAP for patients with OSA, also showing overweight or obesity.[44]

The other arm of our study, in which we analyzed the addition of CPAP to WL, also demonstrated favorable effects of the combination therapy (Figures 4, 5). The addition of CPAP improved the SBP and DBP somewhat in both the successful WL programs[33,34] and in those with modest WL,[30,31] except in patients with severe obesity and modest WL.[32] These findings are in accord with those of the comprehensive meta-analysis of Montesi and coworkers[17] that demonstrates the modest but significant BP-lowering effects of CPAP. In summary, this arm of our analysis also supports the application of combined CPAP + WL therapy in OSA to reduce cardiovascular complications.

Our meta-analysis was also challenged by limitations. The number of available studies reporting appropriate data and the number of included study participants were relatively low. Available studies did not report hard outcomes, such as cardiovascular mortality or major cardiovascular events. The studies reported BP values or blood lipid parameters measured at single time points before and after the treatment period. Antihypertensive treatments or their variations during the studies were not reported in an appropriate form for analysis. In addition, patients were characterized by different severity levels and durations of OSA and also by variable histories of CPAP treatment. We needed to use data both from "per-protocol"[27,33,34] and also from "intention-to-treat"[28–32] analyses, because of irreconcilable differences in data reporting of the included studies. This variability of the

studies (GRADE assessment; Table S2) and the variability of the WL interventions could contribute to the substantial and considerable heterogeneity of our analyses.

CONCLUSION

Our meta-analysis demonstrated that the addition of long-term caloric restriction (leading to an ~10% WL) to CPAP significantly improved the CPAP-induced reduction of SBP and also reduced the blood TG level of patients with OSA. Such benefits could contribute to the prevention of the numerous, severe cardiovascular complications of OSA.[45] Thus, our findings reinforce the recommendations of the American Thoracic Society urging clinicians to incorporate WL therapy along with CPAP for patients with OSA.[44] Due to the substantial to considerable heterogeneity of our results, future long-term prospective clinical trials would be needed to confirm the preventive value of the addition of efficient, long-term caloric restriction-based WL to CPAP for cardiovascular risks and also for major cardiovascular events or cardiovascular mortality.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. M.B., P.H., B.F., and A.S. designed the research. D.K.K. and D.K. performed the research. L.H., L.SZ., and N.G. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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